CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505 (b)(1)
Application Number(s)	NDA 213217
Priority or Standard	Priority
Submit Date(s)	June 27, 2019
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Division/Office	Division of Hematology Products/Office of Hematology and Oncology Products
Review Completion Date	November 14, 2019
Established/Proper Name	Zanubrutinib
(Proposed) Trade Name	BRUKINSA
Pharmacologic Class	Kinase inhibitor
Code name	BGB-3111
Applicant	BeiGene USA
Dosage form	Capsules
Applicant proposed Dosing Regimen	160mg orally twice daily, approximately every 12 hours
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Mantle cel llymphoma
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Mantle cell lymphoma
Recommended Dosing Regimen	160mg orally twice daily or 320mg once daily

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OPQ=Office of Pharmaceutical Quality, OPDP=Office of Prescription Drug Promotion, OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology, DEPI= Division of Epidemiology, DMEPA=Division of Medication Error Prevention and Analysis, DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADCC	Antibody-Dependent Cell Cytotoxicity
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
AUC	Area Under the Curve
BCR	b-cell Antigen Receptor
BLA	biologics license application
BLK	B Lymphocyte Kinase
BMX	Bone Marrow Kinase on Chromosome X
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BRK	Breast Tumor Kinase
BTK	Bruton tyrosine kinase
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
CLL	Chronic Lymphocytic Leukemia
CMC	chemistry, manufacturing, and controls
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CT	computed tomography
DHOT	Division of Hematology Oncology Toxicology
DLBCL	Diffuse Large B-Cell Lymphoma
DMC	data monitoring committee
ERBB4	ErbB-B2 Receptor 4
ECG	electrocardiogram
eCTD	electronic common technical document
EFD	Embryo-Fetal Development
EGFR	Epidermal Growth Factor Receptor
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

FDG	fluorodeoxydlucose
FGR	Gardner-Rasheed Feline Sarcoma Viral Oncogene Homolog
FOB	Functional Observational Battery
FRK	Fyn-Related Kinase
GALT	Gut-Associated Lymphoid Tissue
GCP	good clinical practice
GD	Gestational Day
GI	Gastrointestinal
GLP	Good Laboratory Practice
GRMP	good review management practice
hERG	Human Ether-A-Go-Go-Related Gene
IC	Inhibitory Concentration
ICH	International Conference on Harmonisation
IFN-γ	Interferon Gamma
IND	Investigational New Drug
IRC	Independent Review Committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
ITK	IL-2-Inducible T Cell Kinase
LCK	Lymphocyte Cell-Specific Protein-Tyrosine Kinase
LD	Lethal Dose
LIMK1	LIM Kinase 1
MedDRA	Medical Dictionary for Regulatory Activities
MCL	Mantle Cell Lymphoma
MEK2	Mammalian Extracellular Signal-Regulated Kinase
MIPI	Mantle Cell Lymphoma International Prognostic Index
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NK	Natural Killer
NME	new molecular entity
NZW	New Zealand White
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PET	positron-emission tomography
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment

PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PPND	Pre- and Postnatal Development
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RBC	Red Blood Cell
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
TEC	Transient Erythroblastopenia of Childhood
TK	Toxicokinetics
TXK	Tyrosine-protein kinase
WBC	White Blood Cell

1 Executive Summary

1.1. Product Introduction

Established Name: Zanubrutinib, BGB-3111
Proprietary Name: BRUKINSA
Applicant: BeiGene, Ltd.
Pharmacologic Class: Kinase inhibitor
Mechanism of Action: Forms a covalent bond with cysteine residue (Cys 481) in the Bruton Tyrosine Kinase (BTK) active site, resulting in irreversible inactivation of the kinase.

Applicants Proposed Indication: For the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.

Proposed Dosage and Administration: 160mg orally twice daily.

Zanubrutinib, a new molecular entity (NME), is a Bruton Tyrosine Kinase (BTK) inhibitor. The BTK pathway is involved in the development, maintenance, and progression of B-cell malignancies hematologic malignancies. The recommended dose of zanubrutinib is 160 mg orally twice daily (BID) or 320mg orally once daily (b) (4) until disease progression or unacceptable toxicity.

The recommended dosing of zanubrutinib is modified from the Applicant's proposed dose of 160mg twice daily to include the dosing regimen of 320mg once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of zanubrutinib under 21 CFR 314.510 Subpart H for the indication "for treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy." The recommended dose is 160mg orally twice daily or 320mg once daily.

The recommendation is based on the efficacy findings from two studies as well as the safety data from an additional 3 studies. . The primary study supporting efficacy, BGB-3111-206, was a single-arm, multicenter study (NCT NCT3206970) that was conducted in China and enrolled 86 patients who had received at least one prior therapy for mantle cell lymphoma. Efficacy was supported by subpopulation of study BGB-3111-AU-003 which included 32 patients with previously treated mantle cell lymphoma. The median age for the study populations was 62 years (range, 34 to 86 years) and the median number of prior therapies was 2 (range, 1 to 4). Characteristics were similar between the two studies with regards to prior therapies, and disease characteristics. Patients who received prior treatment with BTK inhibitors were excluded from both studies. Zanubrutinib was administered orally at a dose of 160mg twice

daily in study 206 and either 160mg twice daily or 320mg once daily in study 003 until disease progression or unacceptable toxicity. Tumor response was assessed according to the 2014 Lugano Classification for Non-Hodgkin's Lymphoma. Subjects on study 206 were required to have PET scans for evaluation of disease response, while on study 003 tumor assessment was based on CT/MRI primarily. In study 003, PET scans were not required. l. The determination of efficacy was based on the overall response rate per independent review committee assessment of 84% (95% CI: 74, 91) for study 206 and 84% (95% CI: 67, 95) for study 003. The median duration of response was 19.5 months (95% CI: 16.6, NE) with median follow-up from treatment start to study discontinuation of 18.4 months for study 206. The median duration of response was 18.5 months (95% CI: 12.6, NE) with median follow-up from treatment start to study discontinuation of 18.8 months for study 003. Fifty-nine percent of patients (95% CI: 48, 70) in study 206 achieved a complete response (CR), while on study 003 the CR rate was 22% (95% CI: 9, 40).

Section 21 CFR 314.510 addresses approval based on clinical endpoints other than survival or irreversible morbidity. Accelerated approval is subject to the requirement that the Applicant study the drug further to verify and describe its clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcome.

The rationale for the recommendation of accelerated approval for zanubrutinib is founded upon the following considerations:

- Uncertainty as to the relationship of ORR and DOR to the ultimate outcome of overall survival. Although the ORR was 84% per independent review committee assessment, 22% of patients discontinued treatment due to progressive disease.
- Because multiple therapies are approved for mantle cell lymphoma, a comprehensive characterization of the efficacy of anti-neoplastic agents, targeted agents, disease course, and determination of adequacy of long-term follow up is important. Questions remain regarding the treatment of mantle cell lymphoma such as optimal use of single and combination treatments, characterization of disease course (nodal, extranodal sites, BM involvement), and evaluation of treatment effect on time-to-event endpoints including progression free survival and overall survival.

All disciplines agreed with the approval recommendation of zanubrutinib or did not identify any outstanding issues that precluded the approval recommendation. In summary, the review team concluded that the overall response rate of 84% in two separate studies with a median duration of response of 19.5 months in study 206 and 18.5 months in study 206 constitutes substantial evidence of effectiveness.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Zanubrutinib is a Bruton's Tyrosine Kinase (BTK) inhibitor which forms a covalent bond with cysteine residue (Cys481) in the BTK active site, leading to inhibition of BTK enzymatic activity.

Mantle cell lymphoma is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma. Current therapeutic options for patients with relapsed or refractory disease consists of single-agent or combination regimens with overall response rates ranging from approximately 20% to 90%. However, the median PFS and OS are generally less than two years. There are two BTK inhibitors that have received accelerated approval for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy based on overall response rates of 66-81% and median duration of response of 17.5+ months; however, the clinical benefit remains to be verified and described in an ongoing confirmatory trial. Effective agents are still needed for the treatment of relapsed or refractory mantle cell lymphoma.

The effectiveness of zanubrutinib was demonstrated in a single-arm, multicenter study (BGB-3111-206) conducted in China of single-agent zanubrutinib 160mg administered twice daily until disease progression or unacceptable toxicity in 86 patients with relapsed or refractory mantle cell lymphoma who had failed to achieve at least a partial response to prior therapy. Efficacy was supported by a second single-arm study BGB-3111-A-003 conducted globally which evaluated 32 patients with R/R MCL treated at the recommended indicated dose of 160mg BID or 320mg once daily. The median age from the two trials was 62 years (range: 34 to 86 years) and the median number of prior therapies was 2 (range, 1 to 4). Patients who received prior treatment with BTK inhibitors were excluded from the studies. Tumor response was assessed according to the Lugano Classification for Non-Hodgkin's Lymphoma (2014). The primary endpoint, overall response rate as assessed by and independent review committee, was 84% (95% CI: 74, 91) for the 206 study and 84% (95% CI: 67, 95) for the 003 study. The median duration of response was 19.5 months (16.6, NE) for 206 and 18.5 (12.6, NE) for 003. In study 206, 59% of patients achieved a complete response (CR) and 22% of patients in study 003 achieved a complete response.

Zanubrutinib demonstrated an acceptable safety profile for the intended population. The safety profile was supported by analysis of a combined safety database of 629 patients with hematological malignancies including 118 patients with relapsed and refractory MCL who were treated at the dose of either 160mg twice daily or 320mg once daily. In patients with R/R MCL (n=118), the median duration of treatment was 17.5 months (range, 0.2 to 34) and the most common adverse reactions (≥20% of patients) were anemia, thrombocytopenia, neutropenia, upper respiratory infection, rash, bruising, diarrhea, and cough. Dose discontinuations due to any adverse reactions were reported in 7% of patients, most commonly due to infections.

Events of clinical interest were identified based on preclinical findings, data from clinical studies, and pharmacological effects associated with BTK inhibitors, including hemorrhage, infections, cytopenias, atrial fibrillation or flutter, and second primary malignancies. In the combined safety database (n=629), bleeding of any kind to include bruising and petechiae, occurred in approximately 50% of patients. Major hemorrhage occurred in 3% of patients. Grade 3 or higher infections occurred in 30% of patients. Grade 3 or 4 cytopenias, including neutropenia (20%), anemia (6%) and thrombocytopenia (7%) based on AEs and laboratory measurements, also occurred. Second primary malignancies, including non-skin carcinomas, occurred in 9% of patients, and atrial fibrillation and flutter occurred in 2% (combined) of patients in the combined safety database population (n=629).

In summary, it is concluded that the overall response rate of 84% in two separate studies with a median duration of response of 19.5 and 18.5 months constitutes substantial evidence of effectiveness. Based on the available evidence, zanubrutinib demonstrated a favorable safety profile for the intended population. The safe use of zanubrutinib can be managed through accurate labeling and routine hematology and oncology care. Therefore, the benefit-risk profile is favorable to support approval of zanubrutinib under 21 CFR 314.510 Subpart H for the indication "for treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Relapsed and refractory mantle cell lymphoma is a serious and life-threatening illness with an overall poor prognosis.	Relapsed and refractory mantle cell lymphoma is a serious and life-threatening disease.
Current Treatment Options	• There is limited disease control with either combination chemotherapy (ORRs of 58%-93%) and median progression free survival of < 2 years or single agents (ORRs of 26%-31%) and median OS < 2 years. • Other BTK inhibitors received accelerated approval for patients with mantle cell lymphoma who have received at least one prior therapy based on a demonstrated ORR of 66-81% with median duration of response of at least 17.5 months.	There is a need for effective agents for the treatment of R/R MCL.

Benefit	• Study 206 was a single-arm, multicenter trial that enrolled 86 patients with mantle cell lymphoma who had received at least one prior therapy demonstrated an ORR of 84% (95% CI: 74, 91) per IRC assessment using the 2014 Lugano Classification for Non-Hodgkin Lymphoma. • Study 003, which included 32 patients with mantle cell lymphoma who had received at least one prior therapy and were treated at either 160mg twice daily or 320mg once daily demonstrated an ORR of 84% (95% CI: 67, 95) per IRC assessment using the 2014 Lugano Classification for Non-Hodgkin Lymphoma. • The complete response rate was 59% (95% CI: 48, 70) for study 206 and 22% (95% CI: • The median duration of response was 19.5 months (16.6, NE) in study BGB-3111-206 and 18.5 months (12.6, NE) in study BGB-3111-003	There is substantial evidence of effectiveness for zanubrutinib as a treatment for patients with mantle cell lymphoma who have received at least one prior therapy. The Applicant has an ongoing confirmatory trial to verify and describe the clinical benefit.
Risk and Risk Management	• In patients with relapsed and refractory MCL who received either 160mg BID or 320mg once daily (n=118), the most common adverse reactions (≥20% of patients) were neutropenia, thrombocytopenia, upper respiratory tract infection, anemia, rash, diarrhea, and bruising. (Hematological adverse reactions based on both laboratory and hematological adverse reactions) • Dose discontinuations due to any adverse reactions were reported in 7% of patients, respectively. • Serious adverse events occurred in 31% of patients. The most common SAE was pneumonia (12%) and hemorrhage (5%). • Grade ≥ 3 adverse reactions occurred in 47% of patients with neutropenia (15%) being the most common hematological event and pneumonia (10%) the most common non-hematological adverse reaction. • Four of the eight deaths on study were considered possibly related	Based on available evidence, the overall safety profile of zanubrutinib is acceptable for the intended population. The current USPI includes warnings and precautions for infections to include opportunistic infections, hemorrhage, cytopenias, atrial fibrillation and atrial flutter and second primary malignancies.

	to zanubrutinib therapy. Causes of death were due to infection, intracerebral hemorrhage, and two of unknown cause. • Adverse events of clinical interest include hemorrhage, infection, cytopenias, atrial fibrillation and flutter and second primary malignancies. • In the combined safety database (n=629), overall bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients. • Grade 3 or higher infections occurred in 23% of patients in combined safety database(n=629). • Grade 3 or 4 cytopenias, including neutropenia (27.0%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements occurred in the combined safety database population(n=629). • Second primary malignancies including non-skin carcinomas occurred in 9% of patients with hematological malignancies in the combined safety database of 629 patients. • Atrial fibrillation and flutter occurred in 2%% of patients in the combined safety database population(n=629).	

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	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		
	☐	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 were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

X
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Cross Discipline Team Leader

X
Margret Merino, MD
Clinical Reviewer

2 Therapeutic Context

2.1. Analysis of Condition

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma (NHL) that represents 3-10% (SEER 2017) of all new non-Hodgkin lymphomas cases per year. The estimated incidence of MCL is 0.51 to 0.55 cases per 100,000 persons in the US. Most patients present with aggressive, disseminated disease and there is a 2.5:1 male-to-female predominance with a median age at diagnosis of 64 years.[1,2] Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes due to the incurability of the disease with conventional chemotherapy and a more aggressive disease course in most patients. Overall, the prognosis for patients who are diagnosed with mantle cell lymphoma is poor, with the median duration of remission after standard chemoimmunotherapy regimens of 1.5-3 years and the median overall survival is 3-6 years.[3]

Patients can be classified into low, intermediate, and high-risk categories based on the MCL international prognostic index (MIPI) which incorporates age, performance status, LDH, and leukocyte count. The MIPI as well as the simplified MIPI has been validated in several studies as having prognostic significance for patients with MCL. Patients with intermediate and high risk MIPI scores have a median OS of less than 5 years.[4] Additional features that have been more recently identified to be associated with a more unfavorable prognosis include tumor cell proliferation rate (Ki-67 expression) as well as blastoid cytology. A subset of patients with leukemic nonmodal MCL have a disease that behaves more indolently, although these patients are generally treated similarly to other patients with MCL.[5]

Molecularly, mantle cell lymphoma is characterized by the chromosomal translocation t(11;14)(q13;q32) which juxtaposes the proto-oncogene CCND1 at 11q13 to the immunoglobulin heavy chain complex(IGHV) at chromosome 14q32 and results in over-expression of cyclin D1 and cell cycle dysregulation. Cyclin D1 promotes mantle cell lymphomagenesis due to its function in the cell cycle and regulation of cyclin-dependent kinases (CDK4 and CDK6)[5].

Clinically, patients often present with disseminated disease and extranodal involvement is common. A subset of patients present with disease involvement of the gastrointestinal tract.

There is no curative therapy for MCL with the exception of rare patients who achieve long-term disease-free survival after allogeneic stem cell transplantation. The median overall survival in patents with newly diagnosed high-risk MCL is 3-4 years with no plateau in the survival curve. First-line treatments include multi-agent chemotherapy regimens; however, almost all patients will eventually relapse. For patients with relapsed and refractory disease, the median overall survival for these patients treated with monotherapy is 1-2 years.[3,5]

2.2. Analysis of Current Treatment Options

Therapeutic options for patients who have mantle cell lymphoma that has relapsed or is refractory to standard therapies include salvage combination chemotherapy or chemoimmunotherapy regimens and targeted therapies. There is no standard accepted therapy for patients with relapsed mantle cell lymphoma who have relapsed after initial treatment. Bortezomib and lenalidomide are the only approved (regular) treatments for relapsed and refractory MCL with overall response rate (ORRs) of 31% and 26%, respectively. Ibrutinib (a first-generation BTK inhibitor), received accelerated approval in 2013 for relapsed and refractory mantle cell lymphoma based on an ORR of 66% (Ibrutinib USPI). Acalabrutinib, (a second generation BTK inhibitor) received accelerated approval for patients with mantle cell lymphoma who have received at least one prior therapy in 2017 based on an ORR of 81% in a single arm trial (Acalabrutinib USPI). The table below provides summaries of the trials supporting regulatory actions for these agents. Confirmatory trials are ongoing for both ibrutinib and acalabrutinib.

Table 1: FDA Approved Drugs for the Treatment of MCL

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Study Design	Efficacy Results
Bortezomib	R/R MCL	2015 Regular Approval	1.3mg/m2/ dose intravenously twice weekly for two weeks followed by 10 day rest	N=155 Single arm	ORR 31% CR 8% DOR 9.2 mo
Lenalidomide	R/R MCL	2013 Regular Approval	25mg orally once daily on days 1-21 of repeated 28 day cycles	N=134 Single-Arm	ORR 26% CR 7.5% DOR 16.6 mo
Ibrutinib	R/R MCL	2013 Accelerated Approval	560 mg orally daily until disease progression or unacceptable toxicity	N=111 Single Arm	ORR 66% CR 21% DOR 17.5 mo
Acalabrutinib	R/R MCL	2017 Accelerated Approval	100mg orally twice daily until disease progression or unacceptable toxicity	N = 124 Single Arm	ORR 80% CR (40%) mDOR NR (Median follow up 15.2 months)

Source: USPI, Bortezomib, Lenalidomide, Ibrutinib, Acalabrutinib

There are several other therapies that are used in both the front-line and relapsed setting. The decision as to which therapeutic option chosen often depends upon underlying co-morbidities, prior therapies, and the patient's potential for stem cell transplant. Accepted therapies include single agents such as bendamustine or rituximab and combination therapies such as bendamustine-rituximab (BR), rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD) alone or in combination with rituximab (R-Hyper CVAD) (NCCN Guidelines, 2019).[7]

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Zanubrutinib is a new molecular entity and is currently not marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The table below summarizes the key regulatory activities for zanubrutinib.

Table 2: Summary of Agency Interactions in the MCL Development Program

Date	Event Summary
May 12, 2016	EOP1 meeting to discuss results of BCB-3111-AU-003 (phase 1 study) and obtain input on registrational pathways for zanubrutinib for MCL, (b) (4) indications
June 23, 2016	Orphan Drug Designation granted for mantle cell lymphoma.
April 5, 2017	Type C meeting to discuss developmental plan for zanubrutinib in (b) (4)
June 23, 2016	Orphan Drug Designation granted for mantle cell lymphoma.
December 7, 2017	Type C CMC specific meeting regarding starting materials, drug substance and drug product specifications, manufacturing sites, and stability data
August 31, 2018	Type C meeting to discuss plans for NDA submission for MCL based on the BGB-3111-206 and BGB-3111-AU-003 study. At that time the agency recommended a minimum of 12 month follow up for responders to document durability of response.
January 9, 2019	Breakthrough Therapy Designation granted for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
February 7, 2019	discuss the study design for a pivotal and confirmatory Phase 3 Study (BGB-3111-306) in Mantle Cell Lymphoma. This will be granted as a teleconference
April 15, 2019	The Applicant received written responses and feedback was provided to Applicant on the proposed content and format of an NDA for zanubrutinib for the treatment of patients with mantle cell lymphoma who had received at least one prior therapy.
May 30, 2019	Pre-NDA meeting was held with the Agency.
June 27, 2019	NDA 213217 Submitted

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for Study BGB-3111-206 at two clinical sites: Site #29615 (Henan Cancer Hospital, Zhengzhou, China) and Site #20601 (Jun Zhu, Beijing, China). These sites were selected based on highest patient accrual and high rate of treatment response. The Applicant BeiGene, Ltd. was also audited. Refer to OSI review in DARRTS. Clinical trial oversight and monitoring by the Applicant appeared to be adequate. Clinical site inspections did identify issues related to study conduct or data quality.

4.2. Product Quality

No significant issues. Refer to Integrated Quality Review.

4.3. Clinical Microbiology

No significant issues. Refer to Integrated Quality Review.

4.4. Devices and Companion Diagnostic Issues

There were no devices or companion diagnostic issues with this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical development program for zanubrutinib was conducted in various cellular assay systems, and in the mouse, rat, rabbit, and dog, to evaluate the drug's pharmacology, pharmacokinetics, general toxicology, reproductive and developmental effects, and genotoxic potential. Zanubrutinib (also known as BGB-3111) is an inhibitor of Bruton tyrosine kinase (BTK).

BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways, and is expressed in B-cells, myeloid cells, mast cells, and platelets. BTK signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Chronic activation of the BCR pathway is involved in the proliferation and cell survival of various B-cell malignancies. The established pharmacological class for zanubrutinib is kinase inhibitor.

In vitro biochemical assays demonstrated that zanubrutinib inhibited BTK with an IC_{50} of 0.3 nM. Cell-free assays demonstrated that zanubrutinib binds covalently to cysteine 481 in the ATP pocket of BTK. In kinase selectivity screens, 1 μM zanubrutinib inhibited the following kinases by >70%: BRK, BLK, BMX, FGR, FRK, ERBB4, LIMK1, MEK2, TEC, EGFR, LCK ITK, and TXK. The in vitro cell-based activity of zanubrutinib on BTK was evaluated in mantle cell lymphoma (MCL) cell lines and showed that BTK was inhibited with an IC_{50} of 1.8 nM. In vitro activity was evaluated on a panel of 23 hematologic cancer cell lines. Zanubrutinib demonstrated the most prominent growth inhibitory activity on 3 MCL cell lines and a diffuse large B-cell lymphoma (DLBCL) cell line. In a secondary pharmacology study, zanubrutinib inhibited rituximab-induced ADCC activity with an IC_{50} of 24.7 μM, approximately 35-times the human C_{max} at the recommended dose of 160 mg twice daily.

Safety pharmacology studies assessed the effects of zanubrutinib on the cardiovascular, central nervous system (CNS), and respiratory function. Zanubrutinib had no toxicologically-significant effects on cardiovascular function in a cardiovascular study in telemetered dogs, and had no effects on neurobehavioral function, temperature, or respiratory function in CNS and respiratory studies conducted in male rats.

Repeat-dose studies were conducted to assess the toxicity of zanubrutinib. Zanubrutinib was administered once daily to rats and dogs in studies up to 6 months in rats and 9 months in dogs. The studies were conducted using the oral route of administration, which is consistent with the intended clinical route of administration. Drug-related findings included increased white blood cells (WBCs) and differentials, multi-organ inflammation, GI tract necrosis, multi-organ hemorrhage, and lymphoid depletion. The findings were more prominent in the rat, particularly those in the pancreas (e.g. fibrin deposit and hemorrhage).

In the 26-week study in rats, zanubrutinib was administered by oral gavage at 30, 100, 300, or 1000 mg/kg/day with a 4-week recovery period. The 1000 mg/kg/day dose caused mortality and unscheduled euthanasia. Findings in animals with early mortality included decreased activity, difficulty breathing, ataxia, GI tract necrosis, lymphoid depletion, adrenal hypertrophy, and splenic infiltration. In surviving animals, a multi-organ inflammatory response was noted that involved the lung, pancreas, and muscle, in addition to increases in WBCs and differentials. Other findings included the presence of blood in the urine, a low incidence of hemorrhage in the thymus and kidney, pancreatic fibroplasia and hemorrhage, and skeletal muscle degeneration. In the 39-week study in dogs, zanubrutinib was administered orally at doses of 10, 30, or 100 mg/kg/day with a 4-week recovery period. As noted in the rat repeat-dose study, inflammatory responses were observed, including elevated WBCs and differentials. Other findings in the dog included lymphoid depletion and reduced red blood cells (RBCs) and lineages, which may be at least partially related to bleeding noted on histopathology.

A fertility and embryo-fetal development study was conducted in rats with zanubrutinib administered once daily at doses of 30, 100, or 300 mg/kg/day, starting 28 days prior to pairing and through mating in males, and starting 14 days prior to pairing through Gestation Day (GD) 7 in females. No effects on fertility were observed but increased in post-implantation loss and abnormal sperm morphology was noted at the high dose level. Exposure at 300 mg/kg/day is approximately 10 times the human clinical dose based on the body surface area at the recommended human dose.

In an embryo-fetal development study in female rats, once daily administration of zanubrutinib at 30, 75, or 150 mg/kg/day on GD 6-17 resulted in fetal heart malformations in the form of 2- or 3-chambered hearts. Maternal exposure at 30 mg/kg/day was approximately 5 times the human clinical exposure based on AUC at the recommended human dose. Zanubrutinib steady-state daily AUC is 2200 ng·h/mL following administration of the approved recommended dosage of 160 mg twice daily. In an embryo-fetal development study in female rabbits, once daily administration of zanubrutinib at 30, 70, or 150 mg/kg/day on GD 6-18 resulted in elevated post implantation loss at the 150 mg/kg/day level. Maternal exposure at 150 mg/kg/day was approximately 31 times the human clinical exposure based on AUC at the recommended dose.

In a pre- and postnatal development (PPND) study in rats, pregnant females were administered zanubrutinib at 30, 75, or 150 mg/kg/day from GD6 to lactation day (LD) 17. All dosing levels were associated with adverse ocular findings, including cataracts and corneal opacity in the offspring. Maternal exposure at 30 mg/kg/day was approximately 5 times the human clinical exposure at the recommended human dose of 160 mg twice daily, based on AUC. No toxicokinetic (TK) data was available in the PPND study, thus the AUC from the rat EFD study (which included a dose level of 30 mg/kg/day) was used for animal-to-human exposure comparisons.

Zanubrutinib was not mutagenic in the in vitro bacterial reverse mutation test or clastogenic in either the in vitro chromosomal aberrations assay or in the in vivo bone marrow micronucleus assay in rats. No carcinogenicity studies have been conducted or are required to support marketing of zanubrutinib for the current indication.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of zanubrutinib for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary pharmacology

A. In vitro studies

Kinase selectivity profiling, irreversibility of binding, and IC_{50} determination was conducted for BGB-3111 in cell-free systems. The kinase selectivity profiling was conducted with 1 μM of BGB-3111 on a panel of 342 human kinases (Study R01-BIOL-148), including a subset of 9 that have a cysteine residue in a position comparable to cysteine 481 on BTK where BGB-3111 binds. Of the 342 kinases tested, 13 were inhibited by BGB-3111 by more than 70%. In a separate cell-free system, BGB-3111 was found to bind BTK covalently, with an IC_{50} of 0.3 nM.

Table 3: BGB-3111 Inhibitory Values on Kinases with Inhibition Greater than 70%

Kinase	BRK	BLK	BTK	BMX/ HER4	TXK	ERBB4/ HER4	FRK/ PTK5	MEK2	EGFR	TEC	FGR	ITK	LCK
Inhibition (%)	99	99	98	98	96	96	91	86	86	79	76	76	73

In a separate study, a cell-based system was used to determine BGB-3111's IC_{50}. In mantle cell lymphoma (MCL) cell lines, BTK autophosphorylation on tyrosine 223 was inhibited by BGB-3111 with an IC_{50} of 1.8 nM. A cell-based BTK occupation assay also demonstrated that BGB-3111 forms a covalent bond on cysteine 481. In vitro activity was evaluated with a panel of 23 leukemic cell lines treated with BGB-3111 for 6 days. The most prominent growth inhibition was observed in 3 MCL cell lines (REC-1, Mino, and JeKo-1), with IC_{50}s in the range of 0.36 to 20 nM and a diffuse large B-cell lymphoma (DLBCL) cell line (TMD8), with an IC_{50} of 0.54 nM.

Three metabolites of zanubrutinib (BGB-7941, BGB-10719, and BGB-4013) were investigated for their activity against BTK in cell-free and cell-based systems. Zanubrutinib inhibited the recombinant BTK activity with an IC_{50} of 0.21 nM while the IC_{50}s of the metabolites were 0.76 nM, 3879 nM, and >10μM for BGB-7941, BGB-4013, and BGB-10719, respectively. Cell-based assays for receptor occupancy, BTK inhibition, and proliferation inhibition were also conducted.

As summarized in the table below, only BGB-7941, a monooxidated zanubrutinib metabolite, had inhibitory activity comparable to zanubrutinib.

Table 4: Zanubrutinib Metabolite Characterization

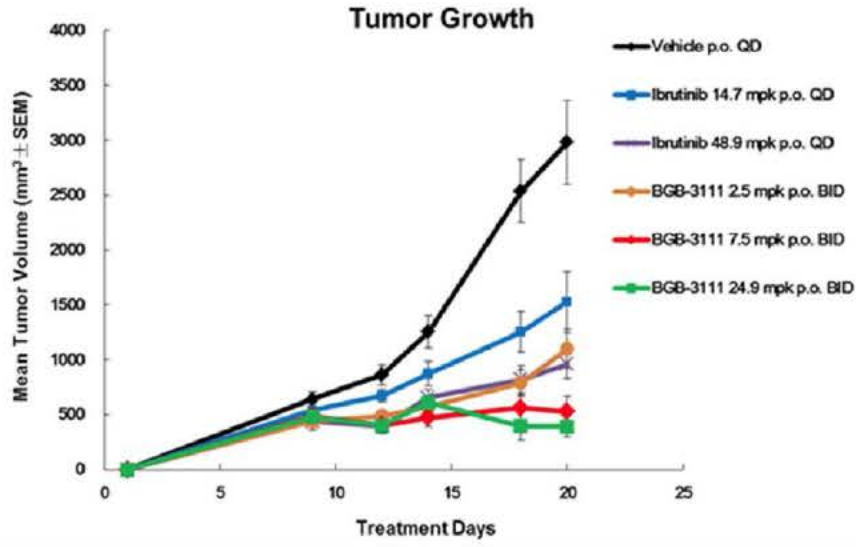
Compound	IC_{50} (nM)			
	rBTK Inhibition	Cellular BTK Inhibition	Cellular BTK Occupation	REC-1 Proliferation
BGB-3111	0.21	2.8	1.5	0.52
BGB-7941	0.76	5.2	3.6	5.9
BGB-4013	3879	Not Detectable (ND)	ND	ND
BGB-10719	>1000	ND	ND	ND

BGB-3111: zanubrutinib; rBTK: recombinant BTK enzyme.

B. In vivo studies

The in vivo activity of BGB-3111 was evaluated in a subcutaneous xenograft model of MCL, using the REC-1 cell line. Three days following cell line inoculation, mice were treated with zanubrutinib orally twice daily at 2.5, 7.5, or 24.9 mg/kg for 20 days. Zanubrutinib induced dose-dependent suppression of xenograft growth.

Figure 1: Effect of BGB-3111 on Rec-1 Mcl cell line xenograft growth (excerpted from study report RO1-VIVO-118)



Secondary Pharmacology

BTK inhibitors may antagonize antigen-dependent cell-mediated cytotoxicity (ADCC) of the kind central to the therapeutic effect of anti-CD20 antibodies used in treating B cell malignancies.

BGB-3111 was evaluated for its effect on in vitro anti-CD20 antibody-induced ADCC. The Mino human MCL cell line was the target cell. Mino cells were treated with zanubrutinib prior to co-incubation with the NK92MI natural killer (NK) cell line and the rituximab anti-CD20 antibody. Cell death was measured by lactose dehydrogenase activity after 5 hours of incubation. NK cell activity was determined by NK cell interferon gamma (IFN-γ) secretion measured after 24 hours of incubation. BGB-3111 decreased rituximab-induced ADCC with an IC_{50} of 24.7 μM and decreased IFN-γ secretion with an IC_{50} of >1 μM. These levels are higher than mean steady-state C_{max} of 314 ng/mL (0.7 μM) reached with the current recommended dose of BGB-3111 at 160 mg twice daily.

Safety Pharmacology

A. Central Nervous System
In a GLP study, Sprague Dawley (SD) rats (5/sex/group) were administered a single oral dose of BGB-3111 (30, 100, or 300 mg/kg) or vehicle (0.5% methylcellulose in water). Viability and clinical observations were made twice daily, while body weights were determined prior to testing day and on testing day prior to dosing. The CNS functional observation battery (FOB), including sensory, motor, behavior, and rectal temperatures, was measured at predose, 0.5, 2, and 24 hours after dosing. There were no mortalities and BGB-3111 had overall no significant effects on neurobehavioral function or rectal temperature up to 24 hours following a single oral administration at doses up to 300 mg/kg.

B. Respiratory
Sprague Dawley rats (10/sex/group) were administered a single oral dose of BGB-3111 (30, 100, or 300 mg/kg) or vehicle (0.5% methylcellulose in water). Viability and clinical observations were made twice daily while body weights were determined prior to testing day and on testing day prior to dosing. Respiratory measurements, including tidal volume, respiratory rate, and derived minute volume, were taken for 15 minute periods 0.5, 2, and 24 hours after dosing. There were no mortalities, and BGB-3111 had no overall significant effects on respiratory function up to 24 hours following a single oral administration at doses up to 300 mg/kg.

C. Cardiovascular
Telemetry-instrumented Beagle dogs (1/sex/group) were orally administered BGB-3111 (10, 30 or 100 mg/kg) or vehicle (0.5% methylcellulose in water) on days 1, 4, 7, and 10. Each dog received a dose following a Latin-Square Crossover design with a 3-day washout between administrations. Viability and clinical observations were made twice daily, while body weights were determined prior to testing day and on testing day prior to dosing. Blood pressure, heart rate, and ECG waveforms were read for 2 hours prior to each dose and for 24 hours after each dose. There were no mortalities but 1 female vomited 4 hours after receiving the high dose. BGB-3111 had no significant effects on cardiovascular function following single doses of up to 100 mg/kg.

5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Pharmacokinetic Studies of BGB-3111 in Beagle Dogs after Single- and Multiple-Dose Administrations of BGB-3111 (3D_RN016120)</td><td>Beagle dogs were given single oral doses of 2.5 mg/kg and 25 mg/kg and 7 daily doses of 7.5 mg/kg
• Oral bioavailability ranged from 45% to 50%.
• T_{max} ranged from 1.4 hours to 3.9 hours.
• $T_{½}$ ranged from 0.42 hours to 0.67 hours.</td></tr>
<tr><td>Pharmacokinetic Studies of BGB-3111 in Sprague-Dawley Rats after Single- and Multiple-Dose Administrations of BGB-3111 (3D_RN016119)</td><td>SD rats were given single oral doses of 10 mg/kg and 100 mg/kg and 7 daily doses of 30 mg/kg
• Oral bioavailability ranged from 9.3% to 41%.
• T_{max} ranged from 0.33 hours to 1.2 hours.
• $T_{½}$ ranged from 1.2 hours to 2.6 hours.</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Equilibrium Dialysis Determination of Bound Fraction of BGB-3111 in Human, Monkey, Dog, Rat and Mouse Plasma (3D_RN016124)</td><td>
<table>
<tr><th rowspan="2">Species</th><th>Plasma Protein Binding (%)</th></tr>
<tr><th>0.5 µM- 15 µM</th></tr>
<tr><td>Human</td><td>93.5-95</td></tr>
<tr><td>Monkey</td><td>92.6-94.7</td></tr>
<tr><td>Dog</td><td>93.1- 93.6</td></tr>
<tr><td>Rat</td><td>94.7-97.9</td></tr>
<tr><td>Mouse</td><td>94.6-95.2</td></tr>
</table>
</td></tr>
<tr><td>Red Blood Cell Distribution of BGB-3111 in Whole Blood of Humans, Dogs and Rats (3D_RN016123)</td><td>
<table>
<tr><th rowspan="2">Species</th><th>Blood-to-Plasma Ratios</th></tr>
<tr><th>0.3 µM- 30 µM</th></tr>
<tr><td>Human</td><td>0.75-0.84</td></tr>
<tr><td>Dog</td><td>0.73-0.79</td></tr>
<tr><td>Rat</td><td>0.77-1.4</td></tr>
</table>
</td></tr>
<tr><td>Determination of BGB-3111 in Sprague-Dawley Rat Organ Tissues after a Single Oral Administration of BGB-3111 (3D_RN016121)</td><td>
<table>
<tr><th rowspan="2">Tissue</th><th colspan="3">Mean Rat Tissue Concentration (ng/g or ng/mL) of BGB-311 Over Time</th></tr>
<tr><th>0.25 hrs</th><th>2 hrs</th><th>8 hrs</th></tr>
<tr><td>Plasma</td><td>1136</td><td>824</td><td>80.8</td></tr>
<tr><td>Heart</td><td>1626</td><td>1295</td><td>91.7</td></tr>
<tr><td>Liver</td><td>17237</td><td>8983</td><td>530</td></tr>
<tr><td>Spleen</td><td>720</td><td>654</td><td>52.0</td></tr>
<tr><td>Lung</td><td>635</td><td>559</td><td>43.2</td></tr>
<tr><td>Kidney</td><td>2299</td><td>2076</td><td>246</td></tr>
<tr><td>Brain</td><td>32.9</td><td>41.7</td><td>0</td></tr>
<tr><td>Stomach</td><td>32480</td><td>19389</td><td>1521</td></tr>
<tr><td>Small Intestine</td><td>28202</td><td>1795</td><td>776</td></tr>
<tr><td>Testicle</td><td>13.6</td><td>45.7</td><td>25.4</td></tr>
<tr><td>Ovary</td><td>970</td><td>1248</td><td>98.1</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>Fat</td><td>586</td><td>845</td><td>54.6</td></tr>
<tr><td>Muscle</td><td>418</td><td>664</td><td>33.3</td></tr>
<tr><td>Thymus</td><td>344</td><td>477</td><td>41.2</td></tr>
<tr><td>Skin</td><td>288</td><td>487</td><td>45.1</td></tr>
<tr><td>Submandibular Lymph Nodes</td><td>481</td><td>618</td><td>49.7</td></tr>
</table>
</td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>Metabolite Identification of BGB-3111 in Liver Microsomes of Different Species and in Sprague-Dawley Rats after Oral Administration (3D_RN016126)</td><td>
<table>
<tr><th rowspan="2">Metabolite (modification)</th><th colspan="5">BGB-311 Metabolite Presence in Liver Microsomes</th></tr>
<tr><th>Human</th><th>Monkey</th><th>Dog</th><th>Rat</th><th>Mouse</th></tr>
<tr><td>M1 (monooxidation)</td><td>X</td><td>X</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>M2 (monooxidation)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M3 (dehydration)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M4 (monooxidation)</td><td>X</td><td>X</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>M5 (monooxidation)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M6 (N-dealkylation)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M7 (carboxylation)</td><td>X</td><td>X</td><td>-</td><td>X</td><td>X</td></tr>
<tr><td>M8 (carboxylation)</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>M9 (monooxidation)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M10 (carboxylation)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M11 (dehydration)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table>
</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Excretion of [^{14}C]BGB-3111 Following a Single Oral Administration to Sprague-Dawley Rats (RTC00954)</td><td>
<table>
<tr><th colspan="4">[^{14}C]BGB-3111 Recovery %</th></tr>
<tr><th>Bile</th><th>Urine</th><th>Feces</th><th>Cage Rinse/Wash</th></tr>
<tr><td>39.55</td><td>1.88</td><td>57.28</td><td>0.33</td></tr>
</table>
</td></tr>
<tr><td>TK data from general toxicology studies
BGB-3111: 26-Week Repeated Oral Dose Toxicity and Toxicokinetics Study in Rats with 6-Week Recovery (180-0193-TX)</td><td>Rats:
• Higher exposures in females compared to males
• Slightly higher exposures on D182 compared to D1
• T_{max} increasing with increased doses, indicating potential for saturation of absorption at high doses</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>BGB-3111: 39-Week Repeated Oral Dose Toxicity and Toxikinetics Study in Beagle Dogs with 6-Week Recovery Period (180-0192-TX)</td><td>
• Less than dose-proportional increases in exposures, particularly at higher doses, also suggesting saturation of absorption

Dogs:
• Exposures were comparable in males and females
• Increases in exposures were generally dose proportional and T_{max} remained at approximately 1 h for all.

BGB-3111 TK Parameters in 26-Week Repeat-Dose Study in Rats
<table>
<tr><th>Dose (mg/kg/d)</th><th>Study Day</th><th>Sex</th><th>C_{max} (ng/mL)</th><th>T_{max} (h)</th><th>$AUC_{0\text{-}24h}$ (h*ng/mL)</th></tr>
<tr><td rowspan="4">30</td><td rowspan="2">1</td><td>M</td><td>1320</td><td>0.5</td><td>4420</td></tr>
<tr><td>F</td><td>3240</td><td>0.5</td><td>8140</td></tr>
<tr><td rowspan="2">182</td><td>M</td><td>1960</td><td>0.5</td><td>6600</td></tr>
<tr><td>F</td><td>4420</td><td>0.5</td><td>9320</td></tr>
<tr><td rowspan="4">100</td><td rowspan="2">1</td><td>M</td><td>5150</td><td>0.5</td><td>23500</td></tr>
<tr><td>F</td><td>6240</td><td>0.5</td><td>26400</td></tr>
<tr><td rowspan="2">182</td><td>M</td><td>3740</td><td>0.5</td><td>26500</td></tr>
<tr><td>F</td><td>8340</td><td>2.0</td><td>36000</td></tr>
<tr><td rowspan="4">300</td><td rowspan="2">1</td><td>M</td><td>5670</td><td>0.5</td><td>38300</td></tr>
<tr><td>F</td><td>11900</td><td>2.0</td><td>104000</td></tr>
<tr><td rowspan="2">182</td><td>M</td><td>6980</td><td>2.0</td><td>52100</td></tr>
<tr><td>F</td><td>17200</td><td>2.0</td><td>87300</td></tr>
<tr><td rowspan="4">1000</td><td rowspan="2">1</td><td>M</td><td>8200</td><td>2.0</td><td>82800</td></tr>
<tr><td>F</td><td>14900</td><td>2.0</td><td>159000</td></tr>
<tr><td rowspan="2">182</td><td>M</td><td>11000</td><td>1.0</td><td>170000</td></tr>
<tr><td>F</td><td>11400</td><td>4.0</td><td>195000</td></tr>
</table>

BGB-3111 TK Parameters in 39-Week Repeat-Dose Study in Dogs
<table>
<tr><th>Dose (mg/kg/d)</th><th>Study Day</th><th>Sex</th><th>C_{max} (ng/mL)</th><th>T_{max} (h)</th><th>$AUC_{0\text{-}24h}$ (h*ng/mL)</th></tr>
<tr><td rowspan="6">10</td><td rowspan="2">1</td><td>M</td><td>2520</td><td>0.8</td><td>5350</td></tr>
<tr><td>F</td><td>1920</td><td>0.8</td><td>5210</td></tr>
<tr><td>180</td><td>F</td><td>2470</td><td>0.5</td><td>5910</td></tr>
<tr><td>181</td><td>M</td><td>2510</td><td>0.8</td><td>5770</td></tr>
<tr><td rowspan="2">272</td><td>M</td><td>2290</td><td>0.8</td><td>5950</td></tr>
<tr><td>F</td><td>2470</td><td>0.8</td><td>5660</td></tr>
<tr><td rowspan="6">30</td><td rowspan="2">1</td><td>M</td><td>6060</td><td>1.0</td><td>17700</td></tr>
<tr><td>F</td><td>6660</td><td>1.0</td><td>16900</td></tr>
<tr><td>180</td><td>F</td><td>4910</td><td>1.0</td><td>14700</td></tr>
<tr><td>181</td><td>M</td><td>4940</td><td>1.0</td><td>13800</td></tr>
<tr><td rowspan="2">272</td><td>M</td><td>4800</td><td>1.0</td><td>13200</td></tr>
<tr><td>F</td><td>5330</td><td>0.5</td><td>12400</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td rowspan="6">100</td><td rowspan="2">1</td><td>M</td><td>13900</td><td>1.0</td><td>57700</td></tr>
<tr><td>F</td><td>16500</td><td>1.0</td><td>59700</td></tr>
<tr><td>180</td><td>F</td><td>12300</td><td>1.0</td><td>45600</td></tr>
<tr><td>181</td><td>M</td><td>11200</td><td>1.0</td><td>42300</td></tr>
<tr><td rowspan="2">272</td><td>M</td><td>11500</td><td>1.0</td><td>41500</td></tr>
<tr><td>F</td><td>10400</td><td>1.0</td><td>36900</td></tr>
</table>
</td></tr>
<tr><td>TK data from reproductive toxicology studies
BGB-3111: Oral Embryo-Fetal Developmental Toxicity Study in Rats
180-0161-TX

BGB-3111: Oral Embryo-Fetal Developmental Toxicity Study in Rabbits
180-0167-TX</td><td>
<table>
<tr><th colspan="4">BGB-111 Exposure in Oral Embryo-fetal Developmental Toxicity Study in Rats</th></tr>
<tr><th>Dose (mg/kg)</th><th>30</th><th>75</th><th>150</th></tr>
<tr><td>AUC_{0-24} (ng.h/mL)</td><td>11200</td><td>34600</td><td>45000</td></tr>
<tr><td>Relative Exposure (multiples of 2200*)</td><td>5.09</td><td>15.73</td><td>20.45</td></tr>
</table>
<table>
<tr><th colspan="4">BGB-111 Exposure in Oral Embryo-fetal Developmental Toxicity Study in Rabbits</th></tr>
<tr><th>Dose (mg/kg)</th><th>30</th><th>70</th><th>150</th></tr>
<tr><td>AUC_{0-24} (ng.h/mL)</td><td>21600</td><td>52500</td><td>69200</td></tr>
<tr><td>Relative Exposure (multiples of 2200*)</td><td>9.82</td><td>23.86</td><td>31.45</td></tr>
</table>
* In patients, BGB-3111 steady-state daily AUC is approximately 2200 ng·h/mL following administration of the approved recommended dosage of 160 mg BID.
</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

Study title/ Study number: 26-Week Repeated Oral Dose Toxicity and Toxicokinetics Study in Rats with 6-Week Recovery/180-0193-TX

Key Study Findings:

- Mortality was observed at the high dose of 1000 mg/kg/day during the first 9 days of treatment. Toxicities in the high dose included erosion, necrosis, or ulceration of the GI tract and thymus.
- Multi-organ inflammatory response was observed and included that in the lung, pancreas, and muscles. Consistent with these findings, there were increases in WBCs and differentials.
- Other findings included pancreatic hemorrhage and fibroplasia, skeletal myofiber degeneration, and thyroid gland hypertrophy.

Conducting laboratory and location (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 30, 100, 300, 1000 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in 10 mL of purified water
Species/Strain:	Rat/Sprage Dawley
Number/Sex/Group:	20 (0, 30, 100, 300 mg/kg/day), 10 (1000 mg/kg/day), 4-8 (TK group)
Age:	7 weeks
Satellite groups/ unique design:	N/A
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>1000 mg/kg/day: All animals were either found dead or euthanized between days 6 and 9. Notable changes included body weight loss and reduced food intake. Observed signs included cold to touch, hunched posture, decreased activity, atonia and abnormal gait, soft or tan stool, nasal and ocular discharge. Macroscopic/microscopic changes included GI tract necrosis, ulcers, or hemorrhage, lymphoid depletion, zona fasciculata hypertrophy in the adrenals, and histiocytic spleen infiltration.

No test article-related deaths occurred at the other doses.

Due to mortality at the 1000 mg/kg dose, parameters below are described for the 30-300 mg/kg dose levels)</td></tr>
<tr><td>Clinical Signs</td><td>Dose-dependent salivation, nasal and ocular discharge; red/ brown material around the mouth and nose (300 mg/kg/day group); abnormal stool (300 mg/kg group). These observations generally resolved by the end of the recovery period.</td></tr>
<tr><td>Body Weights</td><td>Reduction in body weight relative to the control arm was seen in all dose groups by the end of the dosing phase, was dose-dependent and more evident in males: (-10/0.2, -6/1, -12/-1 for 30, 100, and 300 mg/kg, respectively, in M/F).</td></tr>
<tr><td>Ophthalmoscopy</td><td>No BGB-3111-related changes were observed.</td></tr>
<tr><td>Hematology</td><td>
<table>
<tr><th colspan="7">% differences compared to controls by end of dosing phase</th></tr>
<tr><th>Dose (mg/kg)</th><th colspan="2">30</th><th colspan="2">100</th><th colspan="2">300</th></tr>
<tr><th>Sex</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>WBC</td><td>-</td><td>↑44</td><td>-</td><td>↑27</td><td>↑33</td><td>↑63</td></tr>
<tr><td>NEUT</td><td>-</td><td>↑59</td><td>-</td><td>↑75</td><td>↑149</td><td>↑211</td></tr>
<tr><td>MONO</td><td>-</td><td>↑73</td><td>-</td><td>↑48</td><td>↑58</td><td>↑71</td></tr>
<tr><td>EOS</td><td>-</td><td>↑84</td><td>-</td><td>↑42</td><td>↑48</td><td>↑85</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry</td><td>
<table>
<tr><th colspan="7">% differences compared to controls by end of dosing phase</th></tr>
<tr><th>Dose (mg/kg)</th><th colspan="2">30</th><th colspan="2">100</th><th colspan="2">300</th></tr>
<tr><th>Sex</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>ALT</td><td>-</td><td>-</td><td>-</td><td>↑85</td><td>↑52</td><td>↑51</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Total protein</td><td>↓7</td><td>↓5</td><td>↓7</td><td>↓6</td><td>↓10</td><td>↓9</td></tr>
<tr><td>Globulin (G)</td><td>↓10</td><td>↓7</td><td>↓13</td><td>↓9</td><td>↓16</td><td>↓13</td></tr>
<tr><td>A/G</td><td>↑6</td><td>↑5</td><td>↑13</td><td>↑6</td><td>↑12</td><td>↑8</td></tr>
<tr><td>K</td><td>↓15</td><td>↓15</td><td>↓14</td><td>↓16</td><td>↓15</td><td>↓15</td></tr>
<tr><td>Total Cholesterol</td><td>-</td><td>↑23</td><td>-</td><td>↑35</td><td>-</td><td>↑37</td></tr>
<tr><td>Triglycerides</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↓25</td><td>↓14</td></tr>
</table>
</td></tr>
<tr><td>Urinalysis</td><td>BGB-3111-related changes in male urine at the end of the dosing phase included incidences of glucose, turbidity, and blood at all dose levels and urobilinogen at 300 mg/kg/day. Female urine had incidences of turbity, blood and urobilinogen at 300 mg/kg/day.</td></tr>
<tr><td>Gross Pathology</td><td>Observations at the end of the dosing period included mandibular lymph node enlargements or discolorations (2 rats) and pituitary gland lesions (1 rat) in females dosed with 100 and 300 mg/kg/day. Testicular lesion and a small thymus was noted in males dosed with 100 and 300 mg/kg/day.</td></tr>
<tr><td>Organ Weights</td><td>Effects were mainly seen at the 300 mg/kg dose.
Organ weight relative to brain weight: % change from control
<table>
<tr><th>Dose (mg/kg)</th><th colspan="2">300</th></tr>
<tr><th>Sex</th><th>M</th><th>F</th></tr>
<tr><td>Adrenals</td><td>-</td><td>19</td></tr>
<tr><td>Heart</td><td>-6</td><td>13</td></tr>
<tr><td>Liver</td><td>-</td><td>14</td></tr>
<tr><td>Kidneys</td><td>11</td><td>13</td></tr>
<tr><td>Thyroids</td><td>-</td><td>56</td></tr>
</table>
</td></tr>
<tr><td>Histopathology</td><td>BGB-3111-related findings were observed in the pancreas (fibroplasia, hemorrhage, fibrin deposition, pigmented macrophages, mononuclear cell infiltrates), lung (macrophage infiltrates), adrenal (angiectasis), thyroid (follicular cell hypertrophy), and skeletal muscle (degeneration, mononuclear cell infiltration), low incidence hemorrhage (thymus, kidney), effects were most prominent at the high dose of 300 mg/kg.</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose.
-: indicates no noteworthy drug-related changes.
*: only statistically significant changes are reported in the table.
A: albumin; G: globulin;.

Study title/ Study number: 39-Week Repeated Oral Dose Toxicity and Toxicokinetics Study in Beagle Dogs with 6-Week Recovery Period/180-0192-TX

Key Study Findings

- Inflammatory responses detected on clinical pathology (increased in WBCs and differentials, increased fibrinogen) were most evident in males at the end of the dosing phase (Week 39) and in females at the interim evaluation (Week 26).
- The inflammatory response together with reduced erythrocytes, hemoglobin, hematocrit suggest bleeding in animals and may explain increased platelet levels.
- Histopathology showed lymphoid depletion and low incidence bleeding in multiple organs.

Conducting laboratory and location: (b) (4)

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10, 30, or 100 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	BGB-3111 in 0.5% (w/v) methylcellulose in purified water/0.5% methylcellulose in water
Species/Strain:	Dog/Beagle
Number/Sex/Group:	6
Age:	6 to 9 months
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	One death at high dose was considered not drug related and was due to jejunum torsion with severe diffuse hemorrhage
Clinical Signs	Clinical observations made at all doses included salivation, unkempt fur, abnormal stool, alopecia, scab, skin redness, swelling, and rash. Skin thickening was noted at ≥30 mg/kg/day. With the exception of the unkempt fur in the 100 mg/kg/day group, observations resolved by the end of the recovery period.
Body Weights	BGB-3111-related weight loss of <20% was noted at all doses. These differences resolved by the end of the recovery period.
Ophthalmoscopy	Conjunctiva hyperemia was noted at 30 and 100 mg/kg/dose and was reversible.
ECG	No BGB-3111-related effects were noted.
Hematology	**% differences compared to control by end of dosing phase (Week 39)**

Dose (MKD)	10		30		100	
Sex	**M**	**F**	**M**	**F**	**M**	**F**
RBC	-	-	↓13	-	↓21	↓14
HGB	-	-	↓17	-	↓22	↓14
HCT	-	-	-	-	↓19	↓12
WBC	-	-	-	↑10	↑91	↑25
NEUT	-	-	-	-	↑120	-
MONO	-	-	↑170	↑42	↑244	↑79
PLT	-	↑27	↑39	↑42	↑68	↑42
MPV	-	↓14	-	↓12	↓17	↓13

Of note, in females changes in the WBCs and differentials were more prominent during Week 26 (data not shown) when compared to Week 39 data above.

Clinical Chemistry	**% differences compared to controls by end of dosing phase (Week 39)**

Dose (MKD)	10		30		100	
Sex	**M**	**F**	**M**	**F**	**M**	**F**
FIB	-	-	↑66	-	↑102	-*
AST	-	-	↑40	-	↑85	↑52

	TP	-	-	↓14	↓13	↓23	↓22
	ALB	-	-	↓33	↓16	↓44	↓32
	TBIL	-	-	-	-	↓47	-
	GLU	-	-	-	-	↓13	-
	UREA	-	↓24	↓26	↓32	↓37	↓40
	Ca	-	-	↓10	-	↓14	↓10
	TCHO	↓25	-	↓29	↓40	↓31	↓43
	A/G	-	-	↓36	-	↓42	↓23
	Week 26 data shows 67% increase						
Urinalysis	Unremarkable						
Gross Pathology	Unremarkable						
Organ Weights	Trends in prostate weight reductions were noted while significant reductions in ovary weight were noted at all doses at the end of the dosing period. No significant differences were noted by the end of the recovery period.						
Histopathology	Mild and minimal microscopic findings were noted in the small intestines (GALT lymphoid depletion; all dose levels), lymph nodes (erythrophagocytosis; all dose levels), ovaries and uterus (inactive; 30 and 100 mg/kg doses); GI hemorrhage of minimal severity seen in 1 animal at the 30 mg/kg dose and in another animal (also minimal) at the 10 mg/kg dose; 1 animal had hemorrhage (minimal) in urinary bladder. Minimal mandibular lymph node erythrophagocytosis continued to be evident at the end of the recovery period.						

-: indicates no noteworthy drug-related changes.
ALB: albumin; A/G: albumin/globulin; FIB: fibrinogen; MPV: mean platelet volume; TBIL: total bilirubin; TCHOL: total cholesterol; TP: total protein

General toxicology; additional studies

BGB-3111: 28-Day Repeated Oral Dose Toxicity and Toxicokinetics Study in Rats with 28-day Recovery Period (Study 180-0064-TX)

BGB-311 was administered by oral gavage at doses of 50, 100, or 500 mg/kg/day once daily for at 28 days to SD rats. Toxicities (independent of the dose) included scab/swelling around the nose and mouth, salivation and soft stool, increase in neutrophils and multi-organ inflammation, increase in liver and spleen weight relative to body weight, and reduced prostate weight, presence of RBCs in urine, pancreatic hemorrhage and fibroplasia, and lymphoid depletion.

BGB-3111: 28-Day Repeated Oral Dose Toxicity and Toxicokinetics Study in Beagle Dogs with 28-day Recovery Period (Study 180-0059-TX)

BGB-311 was administered by oral gavage at doses of 10, 30, or 100 mg/kg/day once daily for 28 days to Beagle dogs. Toxicities (independent of the dose) included sporadic vomiting, soft stool, yellow ocular discharge, and increased salivation. No BGB-3111-related changes in hematology, urinalysis, or serum chemistry were observed. There were no histopathological findings.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: BGB-3111: Bacterial Reverse Mutation Assay/180-0135-GT

Key Study Finding:

- BGB-3111 did not increase the number of revertant colonies in tester strains with or without metabolic activation.

GLP compliance: Yes.
Test system: Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537, and Escherichia Coli strain WP2 uvrA in the presence or absence (at concentrations up to 5000 μg/plate) of rat liver S9 extract (at concentrations up to 5000 μg/plate).
Study is valid: Yes.

In Vitro Assays in Mammalian Cells

Study title/ number: In Vitro Chromosomal Aberration Assy in Chinese Hamster Ovary Cells/180-0136-GT

Key Study Finding:

- BGB-3111 did not induce chromosome aberrations in Chinese Hamster Ovary cells with or without metabolic activation.

GLP compliance: Yes.
Test system: Chinese Hamster Ovary cells +/- S9 activation. Drug concentrations in non-activated conditions were 5 to 80 μg/mL for 3 and 22 hours of incubation. S9-activated conditions ranged from 10 to 60 μg/mL for 3 hours.
Study is valid: Yes.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Bone Marrow Micronucleus Assay by Oral Gavage in Rats/180-0137-GT

Key Study Finding:

- BGB-3111 did not increase the frequency of micronucleated polychromatic erythrocytes in rats after oral administration.

GLP compliance: Yes.
Test system: Sprague Dawley rats were administered a single oral dose of zanubrutinib a doses ranging from 500 mg/kg to 2000 mg/kg. Necropsies were conducted 24 or 48 hours later.
Study is valid: Yes.

Other Genetic Toxicity Studies:
None.

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Oral Study on Fertility and Early Embryonic Development to Implantation in Rats/180-0196-DR

Key Study Findings

- No effects on fertility was noted in female rats but there was increased post-implantation loss at the high dose of 300 mg/kg.
- No effects on fertility was noted in male rats but morphological abnormalities were noted in sperm at the high dose of 300 mg/kg (approximately 10 times the human recommended dose of 160 mg twice daily, as calculated by body surface area).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes.

Methods

Dose and frequency of dosing:	30, 100, and 300 mg/kg/day. Males were dosed daily from 4 weeks before and throughout the mating period. Females were dose daily from 2 weeks prior to mating to Gestation Day (GD) 7.
Route of administration:	Oral gavage.
Formulation/Vehicle:	Methylcellulose (0.5% w/v) in purified water.
Species/Strain:	Rat/Crl:CD
Number/Sex/Group:	24
Satellite groups:	Six/sex were available for possible replacements
Study design:	Rats were paired 1:1 for a 2-week mating period. Males were euthanized for necropsy between days 55 and 58 while mated females were euthanized on GD15.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings

Mortality	No BGB-3111-related deaths were noted.
Clinical Signs	Soft stools were noted in the 300 mg/kg/day group while material was noted around the noses of mid- and high-dose animals.
Body Weights	Unremarkable
Necropsy findings	Unremarkable effects on the number of animals mating, number of pregnancy, estrous cycle, number of corpora lutea or number of implantations. Increased post-implantation loss of 12% was noted at the high dose of 300 mg/kg; the corresponding number was 6% in the control group.

Dose (mg/kg)	0	30	100	300
No evaluated	24	24	24	24
Mean no of live conceptus	16	16	16	15
No of dead conceptus	1	1	1	2
Post-implantation loss (%)	6.1	4.3	5.6	12.6

Sperm analysis

There was a dose-dependent increase in abnormal morphology in the sperm of treated males.

Table 5: Incidence of Abnormal Sperm Morphology

Dose mg/kg/day	0	30	100	300
Abnormal Sperm Incidences (%)	1.5	2.1	1.8	3.1

Embryo-Fetal Development

Study title/ number: Oral Embryo-Fetal Developmental toxicity in Rats/180-0161-TX

Key Study Findings

- Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. One litter each were affected at the low (30 mg/kg) and mid (75 mg/kg) doses and 2 litters were affected at the high dose of 150 mg/kg.
- The lowest dose of 30 mg/kg/day is approximately 6 times the exposure (AUC) in patients receiving the recommended dose of 320 mg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 30, 75, or 150 mg/kg/day from GD6 to GD17
Route of administration: Oral
Formulation/Vehicle: Methylcellulose (0.5% w/v) in purified water
Species/Strain: Rat/Crl:CD
Number/Sex/Group: 32 females/group
Satellite groups: Seven mated females were retained for possible replacement.

Study design:	Pregnant rats received zanubrutinib daily during GD days 6 through 17. Euthanization, caesarean and necropsies were performed on GD20.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	There were no unscheduled necropsies.
Clinical Signs	Unremarkable.
Body Weights	Unremarkable.
Necropsy findings Cesarean Section Data	No drug-related changes were seen in number of corpora lutea or uterine endpoints (resorption, implantation)
Necropsy findings Fetal	LD: One fetus (out of 338 fetuses/24 litters) presented with a 3-chambered heart. MD: One fetus (out of 372 fetuses/25 litters) presented with a 2-chambered heart. HD: Five fetuses (5 of 323 fetuses/23 litters) presented with a 3-chambered hearts. These findings were in 2 litters

LD: low dose; MD: mid dose; HD: high dose

Study title/number Oral Embryo-Fetal Developmental toxicity in Rabbits/180-0167-TX

Key Study Findings

- BGB-3111 administered at the highest dose of 150 mg/kg/day (40 times the patient exposure) resulted in post-implantation loss. This dose was associated with adverse maternal effects as indicated by 36% reduction in food consumption and 3% reduction in body weight

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	30, 70, or 150 mg/kg/day for GD6 to GD18
Route of administration:	Oral
Formulation/Vehicle:	Methylcellulose (0.5% w/v) in purified water.
Species/Strain:	Rabbits/NZW
Number/Sex/Group:	39

Satellite groups:	Four female mated rabbits were used for possible replacement prior to and including GD6
Study design:	Pregnant rabbits were given daily oral doses of BGB-3111 from GD6 through GD18. Euthanization/cesarean/necropsy was performed on GD29
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	There were no BGB-311-related mortalities.
Clinical Signs	Dose-dependent inappetence, decreased food consumption and defecation.
Body Weights	Unremarkable.
Necropsy findings Cesarean Section Data	Increased post-implantation loss of 9% compared to control (3%) was noted at the high dose.
Necropsy findings Fetal	LD: Unremarkable. MD: Unremarkable. HD: Unremarkable. The number of females with viable fetuses on GD29 was 19 out of 35 for each of the dosed compared to 23 out of 35 for the control group.

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/ number: BGB-3111: Pre- and Postnatal Development Toxicity Study in Rats/180-0228-DR

Key Study Findings

- Offspring (F1) from the middle and high dose groups had decreased body weights preweaning.
- In the F1 generation, all dose levels were associated with adverse ocular findings, including no or incomplete response to mydriatic, cataract, corneal opacity, invisible intraocular structure, and unclear fundus.
- The low dose of 30 mg/kg/day is approximately 6 times the AUC in patients receiving the recommended dose. For animal-to-human AUC comparison, TK data from the EFD study in rats was used, as doses given to animals are the same in the EFD and PPND studies.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes.

Methods

Dose and frequency of dosing:	30, 75, and 150 mg/kg/day
Route of administration:	Oral
Formulation/Vehicle:	Methylcellulose (0.5 w/v) in purified water.
Species/Strain:	Rat/Crl:CD
Number/Sex/Group:	24
Satellite groups:	Eleven mated females were used for possible replacement before and including GD6.
Study design:	Mated females were dosed from GD6 to lactation day (LD) 21.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	Less weight gain was noted during the first week at the mid and high dose levels for males and the high dose level for females.
F1 Generation	Reduced body weight of about 6% at 75 and 150 mg/kg dose levels, as compared to control animals (preweaning). Eye abnormalities (no response to mydriatic, incomplete pupil dilation, cataract, intraocular structure not visible or fundus unclear, cornea opacity) were observed on ophthalmic examination and occurred at a frequency of 14 out of 45 pups (11 out of 22 litters) at the low dose, 13 out of 50 pups (13 out of 24 litters) at the medium dose, and 21 out of 50 pups (18 out of 22 litters) at the high dose. **Findings in the eyes**

Dose (mg/kg)	**0**	**30**	**75**	**150**
Ophthalmological changes				
No of pups (litters) examined	38 (19)	45 (22)	50 (24)	50 (22)
No of pups (litters) affected	10 (8)	14 (11)	13 (13)	21 (18)
% of pups (litters) affected	26% (42%)	31% (50%)	26% (54%)	42% (82%)
Changes noted on clinical observation				

<table>
<tr><td></td><td>
<table>
<tr><td>No of pups affected</td><td>-</td><td>2</td><td>3</td><td>5</td></tr>
<tr><td>Description of finding</td><td>-</td><td>Large and white material in the eye; starting on PND 14</td><td>Eye protruding, big eye, cataract; starting on PND 16</td><td>Eye protruding, big eye, cataract, white material in the eye; starting on PND 14</td></tr>
</table>
No drug-related effects were noted on learning and memory, estrus cycle, or fertility parameters.

The male fertility index was 92% in the high dose group compared to 100% in all other groups. The female mating and fertility indices were 97% and 93% for the middle and high dose groups, respectively, relative to 100% in the control group.</td></tr>
<tr><td>F2 Generation</td><td>N/A</td></tr>
</table>

5.5.5. Other Toxicology Studies

Studies with Impurities

In-Silico Assessment of Mutagenicity of Impurities in BGB-311 (00-IMPURITY-3111)

BGB-3111 impurities were evaluated with in-silico modeling for their mutagenic potential. Impurities (b) (4) were determined to have potentially mutagenic properties but tested negative with the Ames assay.

There are no impurities of concern.

X

Simon Williams, PhD
Primary Reviewer

X

Haleh Saber, PhD
Nonclinical Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking accelerated approval of zanubrutinib for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The proposed dosing regimen is 160 mg orally twice daily with or without food.

Evidence to support the efficacy and safety of zanubrutinib in patients with relapsed or refractory MCL is based on two ongoing clinical trials (BGB-3111-206 and BGB-3111-AU-003). Patients with relapsed or refractory MCL treated with a zanubrutinib total daily dose of 320 mg [administered as either 160 mg twice daily (BID) or 320 mg once daily (QD)] exhibited durable objective responses with an overall response rate of 84% in both studies and median duration of response of 18.5-19.5 months. Zanubrutinib pharmacokinetics (PK) and pharmacodynamics (PD) were assessed in both efficacy trials and multiple supportive trials in patients with other hematologic malignancies. Additional safety data was also collected in supportive trials in patients with other hematologic malignancies.

Zanubrutinib demonstrated linear PK across the dose range studied and resulted in near complete BTK occupancy in blood and target tissue (lymph nodes) at doses of 160 mg BID and 320 mg QD. Zanubrutinib is primarily metabolized by CYP3A4. The dose of zanubrutinib should be reduced when used with a concomitant moderate or strong CYP3A inhibitor. Use of zanubrutinib with moderate or strong CYP3A inducers should be avoided. In addition, the dose of zanubrutinib should be reduced to 80 mg twice daily in patients with severe hepatic impairment. No dose adjustments are recommended for patients with mild or moderate hepatic impairment or renal impairment. Exposure-response for efficacy showed a positive trend over the range of exposure in patients with MCL, but there was no significant effect. Exposure-response for safety did not identify any significant relationships between zanubrutinib exposure and safety events. Both exposure-response analyses were limited by the small number of patients treated with doses below the recommended dosing regimen.

Recommendations
The Office of Clinical Pharmacology has reviewed the information contained in NDA 213217. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations and comments are summarized below.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	In Study BGB-3111-206, 86 previously treated patients with MCL received zanubrutinib 160 mg orally twice daily. The overall response rate (CR + PR) was 83.7% and median duration of response was 19.5 months. In Study BGB-3111-AU-003, 32 previously treated patients with MCL received zanubrutinib at either 160 mg orally twice daily or 320 mg orally once daily. The ORR was 84.4% and median duration of response was 18.5 months.

General dosing instructions	The recommended dose of zanubrutinib is 160 mg taken orally twice daily or 320 mg taken orally once daily with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	*Hepatic Impairment:* The recommended dose of zanubrutinib is 80 mg orally twice daily for patients with severe hepatic impairment. *Drug Interactions:* Zanubrutinib is a CYP3A substrate. Reduce the dose of zanubrutinib to 80 mg once daily when co-administered with a strong CYP3A inhibitor. Reduce the dose of zanubrutinib to 80 mg twice daily when co-administered with a moderate CYP3A inhibitor. Avoid concomitant use of zanubrutinib with moderate or strong CYP3A inducers.
Labeling	In addition to the Applicant's proposed starting dose of 160 mg twice daily, the starting dose of 320 mg once daily was included as a starting dose option, supported by safety and efficacy data from Study BGB-3111-AU-003. Other additions to the Applicant's proposed labeling include dose reduction in patients with severe hepatic impairment and avoidance of concomitant use with a moderate CYP3A inducer.

Post-Marketing Requirement (PMR) or Commitment (PMC)
The following issues should be addressed in post-marketing studies:

1. PMR: Conduct an analysis evaluating the pharmacokinetics and safety of zanubrutinib when administered with concomitant CYP3A4 inhibitors (including ciprofloxacin, diltiazem, erythromycin, fluconazole, posaconazole, voriconazole, and clarithromycin) utilizing data from ongoing studies (including but not limited to Studies BGB-3111-AU-003, BGB-3111-214, BGB-3111-215, BGB-3111-302, and BGB-3111-306). Evaluate the effect of each inhibitor on both the C_{max} and AUC of zanubrutinib and assess the safety (including adverse events, dose modifications, dose interruptions, and dose discontinuations) of the recommended dose modifications before, during, and after the concomitant dosing period. Submit a final report including PK and safety data and analyses from Studies BGB-3111-AU-003, BGB-3111-214, BGB-3111-215, BGB-3111-302, and BGB-3111-306.
2. PMC: Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of zanubrutinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Zanubrutinib exhibited dose-proportional increases in exposure (C_{max} and AUC) across the dose range of 40 to 320 mg.

Absorption
The absolute bioavailability of zanubrutinib was not determined. The median t_{max} was 2 hrs after oral administration of zanubrutinib. Gastric acid reducing agents had no clinically meaningful effect on absorption of zanubrutinib.

Distribution
Zanubrutinib is approximately 94.2% bound to human plasma proteins *in vitro*, independent of concentration. Zanubrutinib was 94.0-94.9% bound to plasma proteins in subjects with normal hepatic function or mild to moderate hepatic impairment. In patients with severe hepatic impairment and low baseline albumin, zanubrutinib plasma protein binding decreased to 91.3%. The blood-to-plasma ratio for zanubrutinib is 0.7 – 0.8.

Elimination
The mean terminal elimination half-life of zanubrutinib is 2 – 4 hours. Based on population PK analyses, the geometric mean (%CV) apparent clearance of zanubrutinib is 182 (37%) L/h and steady-state volume of distribution is 881 (95%) L.
Metabolism: Zanubrutinib is primarily metabolized by CYP3A4.
Excretion: In a human mass balance study, 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 (<1% unchanged).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommend dose of zanubrutinib is 160 mg taken orally twice daily or 320 mg taken orally once daily, with or without food.

Therapeutic Individualization

Hepatic Impairment: The recommended dose of zanubrutinib for patients with severe hepatic impairment is 80 mg orally twice daily. No dose adjustments are recommended for mild or moderate hepatic impairment.

Drug Interactions:
The dose of zanubrutinib should be modified when co-administered with CYP3A inhibitors or inducers.

- Strong CYP3A inhibitor: 80 mg zanubrutinib once daily
- Moderate CYP3A inhibitor: 80 mg zanubrutinib twice daily
- Moderate or strong CYP3A inducer: Avoid concomitant use

Outstanding Issues

The magnitude of interaction between zanubrutinib and CYP3A inhibitors varies for different concomitant medications and doses. Additional PK and safety data will be collected during the continued development of zanubrutinib and analyzed to further inform appropriate dose modifications due to drug interactions with specific drugs (see Post-Marketing Requirements).

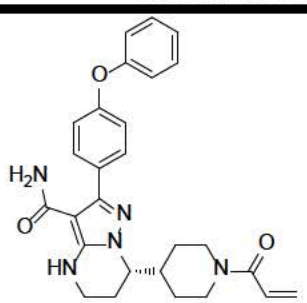
Moderate CYP3A inducers are predicted to decrease zanubrutinib exposure by a median of approximately 60%. A clinical study to determine appropriate dosing recommendation for zanubrutinib in combination with moderate CYP3A inducers will be conducted (see Post-Marketing Commitments).

There are no other outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general pharmacology and pharmacokinetics of zanubrutinib is provided below.

<table>
<tr><th colspan="2">General Information</th></tr>
<tr><td>Chemical structure and major physical and chemical properties</td><td> 
Molecular weight: 471.55 Daltons
pKa: 3.33
LogP: 4.21 (1-octanol and pH 8 buffer)
Zanubrutinib is poorly soluble in aqueous solutions with solubility ranging from 0.042 mg/mL in pH 8 phosphate buffer to 0.193 mg/mL in pH 1.2 hydrochloric acid buffer.</td></tr>
<tr><td>Route of administration and formulation</td><td>Zanubrutinib is supplied as 80 mg capsules for oral administration. The proposed commercial formulation was utilized throughout development.</td></tr>
<tr><td>Mechanism of action</td><td>Zanubrutinib is a Bruton's tyrosine kinase (BTK) inhibitor. Zanubrutinib covalently binds to cysteine 481 of BTK and inhibits its autophosphorylation at tyrosine 223, resulting in inactivation of the kinase.</td></tr>
<tr><th colspan="2">Dose and Adverse Events</th></tr>
<tr><td>Therapeutic dose and exposure</td><td>The proposed dosing regimen is 160 mg orally twice daily or 320 mg orally once daily 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>
</table></td></tr>
</table>

<table>
<tr><td></td><td colspan="2"><table>
<tr><td>160 mg PO BID (n=55)</td><td>314 (46.3%)</td><td>2,295 (36.6%)</td></tr>
<tr><td>320 mg PO QD (n=29)</td><td>543 (50.5%)</td><td>2,180 (41.0%)</td></tr>
</table>
After a single dose of 480 mg orally in healthy volunteers, the geometric mean (%CV) C_{max} was 406 (31%) ng/mL and $AUC_{0\text{-}inf}$ was 3,060 (26%) h·ng/mL.</td></tr>
<tr><td>Maximum tolerated dose (MTD)</td><td colspan="2">The MTD was not reached. Zanubrutinib total daily dose of up of 320 mg orally (administered as either 160 mg twice daily or 320 mg once daily) were evaluated in patients with B-cell malignancies, including relapsed or refractory MCL.</td></tr>
<tr><td>Major adverse events</td><td colspan="2">The most common adverse reactions (≥20%) were decreased neutrophil count, decreased platelet count, upper respiratory tract infection, decreased white blood cell count, decreased hemoglobin, rash, bruising, diarrhea and cough. Fatal and serious infections, including opportunistic infections, have occurred.</td></tr>
<tr><td colspan="3">Pharmacokinetic (PK) Features</td></tr>
<tr><td>Range of linear PK</td><td colspan="2">40 mg to 320 mg orally once daily</td></tr>
<tr><td>Absorption</td><td colspan="2">Absolute bioavailability of zanubrutinib was not determined.
Median t_{max} = 2 hrs
There is no clinically significant food effect on zanubrutinib. Co-administration of zanubrutinib with a high-fat meal increased C_{max} by 3% and decreased $AUC_{0\text{-}inf}$ by 7%. Co-administration of zanubrutinib with a low-fat meal increased C_{max} by 51% and $AUC_{0\text{-}inf}$ by 12%.</td></tr>
<tr><td rowspan="3">Distribution</td><td>V_{ss}/F</td><td>Geometric Mean (%CV): 881 (95%) L</td></tr>
<tr><td>Protein binding (%)</td><td>In vitro: 94.2%, concentration independent
In vivo:
• Normal hepatic function: 94.9%
• Mild hepatic impairment: 94.9%
• Moderate hepatic impairment: 94.0%
• Severe hepatic impairment: 91.3%</td></tr>
<tr><td>Blood to plasma ratio</td><td>0.7-0.8</td></tr>
<tr><td>Elimination</td><td>Route</td><td>Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, approx. 87% of the dose was recovered in feces (38% unchanged) and 8% in urine (<1% unchanged). Hepatic metabolism via CYP3A4 is the major route of elimination.</td></tr>
</table>

<table>
<tr><td></td><td>Terminal half-life</td><td>Mean: 2-4 hours</td></tr>
<tr><td></td><td>CL/F</td><td>Geometric Mean (%CV): 182 (37%) L/h</td></tr>
<tr><td>Metabolism</td><td colspan="2">Zanubrutinib is metabolized by CYP3A4.
Zanubrutinib is a weak inducer of CYP3A4 and CYP2C19 in vivo.
Zanubrutinib induces CYP2B6 in vitro.</td></tr>
<tr><td>Transporters</td><td colspan="2">Zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib inhibits P-gp.
Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.</td></tr>
<tr><td rowspan="2">Intrinsic Factors</td><td>Hepatic impairment</td><td>Zanubrutinib exposure increases in subjects with hepatic impairment. Increases in unbound exposure exceed increases in total exposure due to decreased protein binding in patients with severe hepatic impairment. The increase in zanubrutinib C_{max} and AUC observed in subjects with hepatic impairment relative to normal hepatic function is summarized below.
<table>
<tr><td></td><td colspan="2">C_{max}</td><td colspan="2">AUC</td></tr>
<tr><td></td><td>Total</td><td>Unbound</td><td>Total</td><td>Unbound</td></tr>
<tr><td>Mild</td><td>5%</td><td>16%</td><td>11%</td><td>23%</td></tr>
<tr><td>Moderate</td><td>53%</td><td>81%</td><td>21%</td><td>43%</td></tr>
<tr><td>Severe</td><td>28%</td><td>136%</td><td>60%</td><td>194%</td></tr>
</table></td></tr>
<tr><td>Other</td><td>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 140 kg), or mild or moderate renal impairment (creatinine clearance [CLcr] ≥ 30 mL/min as estimated by Cockcroft-Gault).
The effect of severe renal impairment (CLcr < 30 mL/min) and dialysis on zanubrutinib pharmacokinetics is unknown.</td></tr>
<tr><td>Extrinsic Factors</td><td>Drug interactions – effect of other drugs on zanubrutinib</td><td>CYP3A inhibitors:
Co-administration with itraconazole (strong CYP3A inhibitor) increased zanubrutinib C_{max} by 157% and $AUC_{0\text{-}inf}$ by 278%.
Co-administration with moderate CYP3A inhibitors (diltiazem, erythromycin, or fluconazole) is predicted to increase zanubrutinib C_{max} by 151-284% and AUC</td></tr>
</table>

		by 157-317%, depending on the concomitant drug and dose. CYP3A inducers: • Co-administration with rifampin (strong CYP3A inducer) decreased the zanubrutinib C_{max} by 92% and $AUC_{0\text{-}inf}$ by 93%. • Co-administration with efavirenz (moderate CYP3A inducer) is predicted to decrease zanubrutinib C_{max} by 58% and AUC by 60%.
	Drug interactions – effect of zanubrutinib on other drugs	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%. P-gp substrates: Co-administration of multiple doses of zanubrutinib increased digoxin (P-gp substrate) C_{max} by 34% and AUC by 11%.
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 600 patients enrolled in 9 studies. Baseline ALT (on CL/F) and health status (patient vs healthy volunteer; on CL/F and Vc/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 a statistically significant impact on the PK of zanubrutinib.	
Pharmacodynamic (PD) Features		
PD Studies	QT/QTc Interval	No clinically relevant QT prolongation
	BTK occupancy	Median BTK occupancy in PBMCs 100% after either 160 mg BID or 320 mg QD. Median BTK occupancy in lymph nodes 94% after 320 mg QD and 100% after 160 mg BID.
Exposure-Response Analyses	*Efficacy:* There was no significant relationship between zanubrutinib exposure and overall response rate.	

	Safety: There were no significant relationships between zanubrutinib exposure and adverse events including cytopenias, infections, and bleeding.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness in patients with mantle cell lymphoma (MCL) comes from Study BGB-3111-206. In this Phase 2, single-arm, open-label study, 86 adult patients with MCL who have received at least one prior therapy were enrolled and treated with zanubrutinib at a dose of 160 mg PO BID. The objective response rate (ORR; complete response + partial response) was 83.7% with a median duration of response of 19.5 months. 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 is provided by Study BGB-3111-AU-003. This study is a Phase 1 dose escalation and expansion study in patients with B-cell malignancies including 37 patients with MCL. Thirty-two of the 37 patients were treated with a total daily zanubrutinib dose of 320 mg [administered as either 160 mg BID (n=14) or 320 mg QD (n=18)]. The ORR in these patients was 84.4% with a median duration of response of 18.5 months. Both ORR and duration of response were similar for the 160 mg BID and 320 mg QD regimens (see **Table 3**). There was no clinically meaningful difference in response between the two regimens. Refer to Section 8.1.2 for a detailed review of efficacy results.

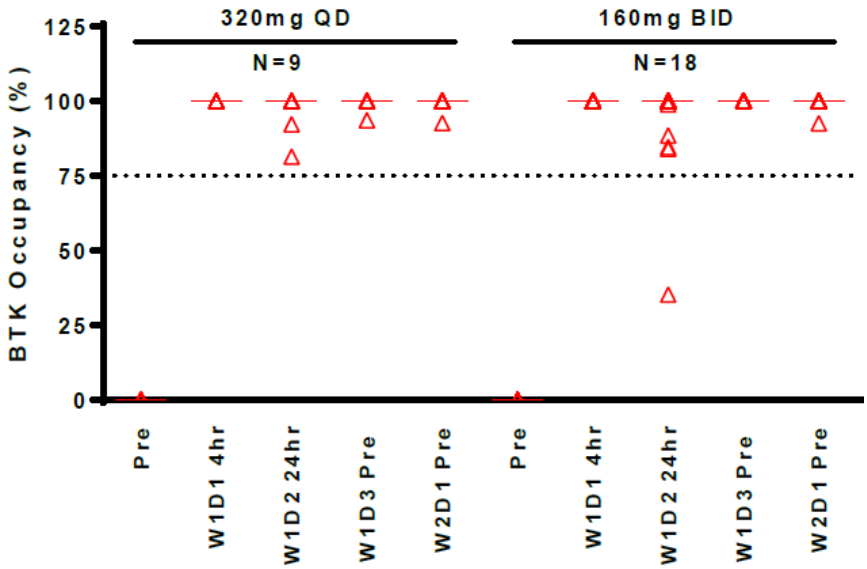
Table 3: Response to Treatment with Zanubrutinib 160 mg BID Compared to 320 mg QD

	Zanubrutinib 160 mg BID (n=14)	**Zanubrutinib 320 mg QD (n=18)**	**Overall (n=32)**
Overall Response Rate, n (%)	12 (85.7%)	15 (83.3%)	27 (84.4%)
Complete Response, n (%)	4 (28.6%)	4 (22.2%)	8 (25%)
Partial Response, n (%)	8 (57.1%)	11 (61.1%)	19 (59.4%)
Duration of Response (months), median (95% CI)	14.7 (7.1, 18.5)	NE (2.9, NE)	18.5 (12.6, NE)

Source: BGB-3111-AU-003 CSR, Table 14.2.1.9.1.1

BTK occupancy was evaluated in both peripheral blood mononuclear cells (PBMCs) and lymph nodes after treatment with zanubrutinib in patients with B-cell malignancies in Study BGB-3111-AU-003. For either 320 mg QD or the 160 mg BID, median BTK occupancy in PBMCs was 100% at all post-dose timepoints evaluated (see **Figure 1**).

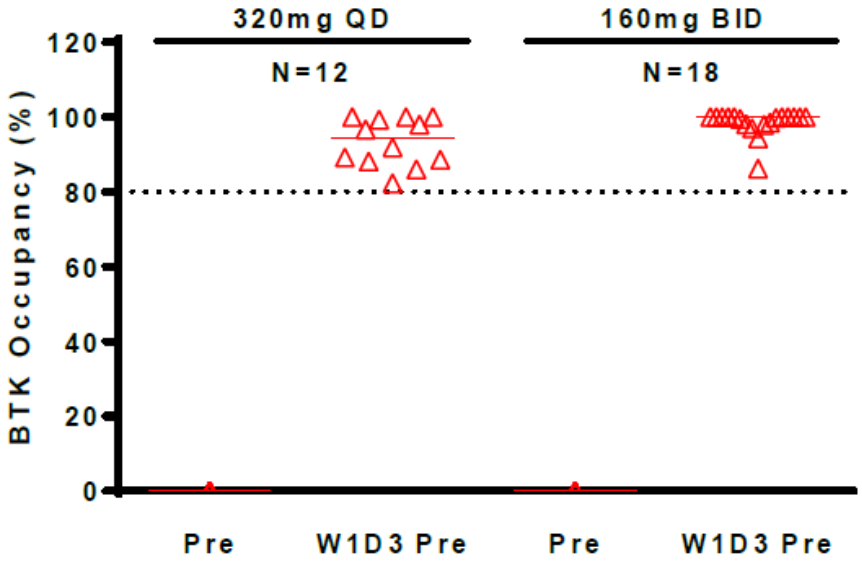
Figure 1: BTK Occupancy in PBMCs After Administration of Zanubrutinib by Dosing Regimen



Source: BGB-3111-AU-003-PD-01 CSR, Figure 7.4.2

BTK occupancy in lymph nodes was >80% in all samples evaluated regardless of dose with a median of 94% in patients treated with 320 mg QD and a median of 100% in patients treated with 160 mg BID (see **Figure 2**). These 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).

Figure 2: BTK Occupancy in Lymph Nodes After Administration of Zanubrutinib by Dosing Regimen



Source: BGB-3111-AU-003-PD-01 CSR, Figure 7.4.3

While the zanubrutinib C_{max} was higher after administration of 320 mg QD relative to 160 mg BID, the steady-state AUC and C_{min} were similar for both dosing regimens (see **Table 4**).

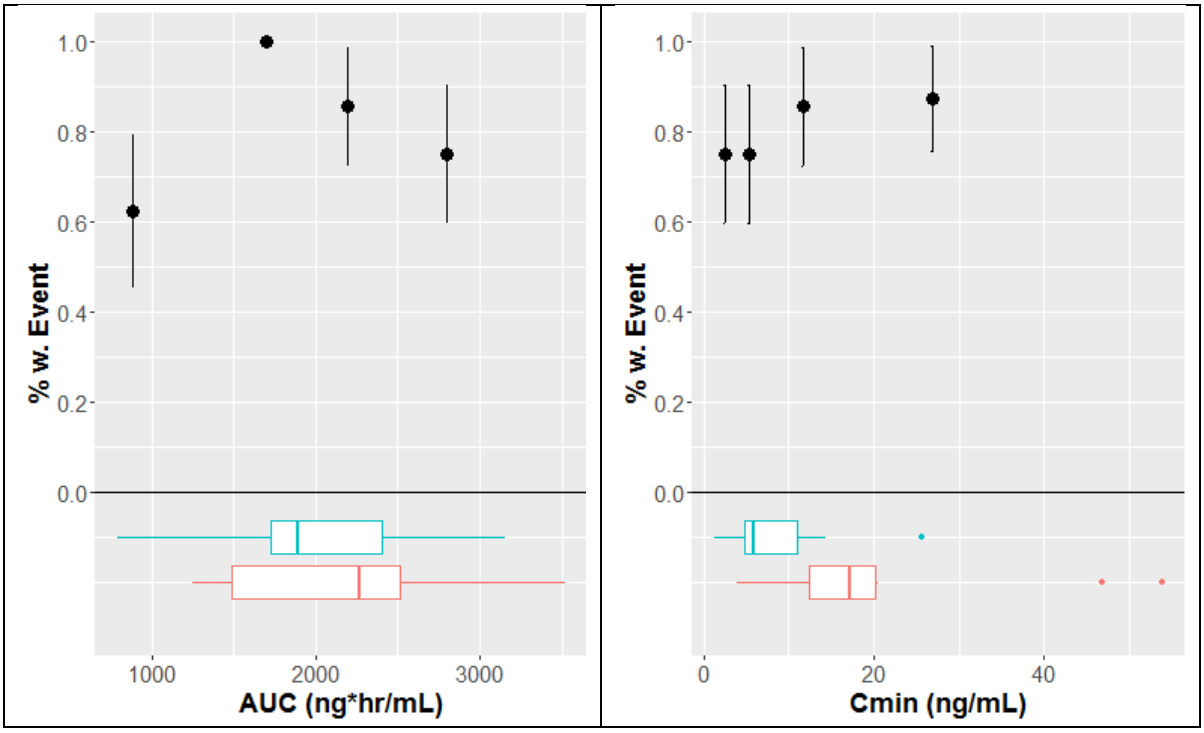
Table 4: Zanubrutinib Exposure After Administration of 160 mg BID or 320 mg QD

	Zanubrutinib 160 mg BID	Zanubrutinib 320 mg QD
Steady-state C_{max} (ng/mL), geometric mean (%CV)	314 (46.3%)	543 (50.5%)
Steady-state AUC_{0-24} (h·ng/mL), geometric mean (%CV)	2,295 (36.6%)	2,180 (41.0%)
Steady state C_{min} (ng/mL), mean (%CV), median	14.1 (110%), 9.6	6.8 (152%), 4.1

Source: FDA Analysis (C_{max} and AUC) and BGB-3111-AU-003 CSR, Table 14.4.1.34 (C_{min})

An exploratory exposure-response analysis was performed using pooled data from Studies BGB-3111-206 and BGB-3111-AU-003. This analysis is limited by the small number of subjects who received doses less than 320 mg per day (n=5). However, there was no significant relationship between zanubrutinib exposure (either $AUC_{0-24,ss}$ or C_{min}) and probability of objective response (see **Figure 3**). Given the overlap in exposure between the two dosing regimens, the exposure-response analysis further supports the use of either 160 mg BID or 320 mg QD as a starting dose. Refer to **Section 19.5.1** for a detailed review of the exposure-response efficacy analysis.

Figure 3: Probability of ORR (IRC) versus Steady-State AUC (left) and C_{min} (right) in Study BGB-3111-AU-003



Notes: Distribution of zanubrutinib exposures are shown for 160 mg BID (red) and 320 mg QD (blue) in the box plots at the bottom of each plot
Source: FDA Analysis, Section 19.5.1

Exploratory exposure-response analysis for safety conducted using pooled data from studies BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, and BGB-3111-206 was similarly limited by the small number of patients treated with doses less than 320 mg per day (n=12 of 597 in safety population). In this analysis, there were no apparent relationships between zanubrutinib exposure and adverse events including grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 infections/infestations, grade ≥ 3 anemia, secondary primary malignancies, atrial fibrillation and flutter, major bleeding events and any bleeding events. Additional FDA analysis utilizing observed zanubrutinib C_{max} yielded similar results. Refer to **Section 19.5.1** for a detailed review of the exposure-response safety analysis.

No remarkable difference in adverse events between the two regimens in the safety population in Study BGB-3111-AU-003 (including patients with both MCL and other B-cell malignancies; see **Table 5**) were observed. Refer to Section 8.2 for a detailed review of safety results.

Table 5: Summary of Treatment-Emergent Adverse Events by Zanubrutinib Dose Regimen

	Zanubrutinib 160 mg BID (n=269)	**Zanubrutinib 320 mg QD (n=95)**
Patients with at least one TEAE, n (%)	262 (97.4%)	94 (98.9%)
Grade 3 or higher	157 (58.4%)	47 (49.5%)
Serious	118 (43.9%)	36 (37.9%)
Leading to death	18 (6.7%)	2 (2.1%)
Leading to treatment discontinuation	30 (11.2%)	10 (10.5%)
Leading to dose reduction	17 (6.3%)	2 (2.1%)
Patients with at least one AESI	232 (86.2%)	88 (92.6%
Grade 3 or higher	121 (45.0%)	34 (35.8%)
Serious	75 (27.9%)	20 (21.1%)

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

In a thorough QT study, a single oral dose of 480 mg zanubrutinib did not result in any clinically meaningful change in the QTc interval and there was no zanubrutinib concentration-QTc relationship. It is important to note that the observed zanubrutinib C_{max} (406 mg/L) in the thorough QT study was lower than the C_{max} in patients treated with 320 mg QD in Study BGB-3111-AU-003 (543 mg/mL). However, no clinically relevant effect of zanubrutinib on the QTc interval was observed even up to the maximum therapeutic exposure achieved in patients in Study BGB-3111-AU-003. Refer to QT-IRT Review (DARRTS ID 4412389) and QT-IRT Consult Memo for detailed review of the effect of zanubrutinib on the QTc interval.

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

Yes. The proposed zanubrutinib dose of 160 mg BID resulted in a high ORR and durable responses in patients with MCL who have received at least one prior therapy. In addition, a dosing regimen of 320 mg QD is an appropriate alternative starting dose for the general patient population based on the PK, PD, safety, and efficacy data as described above.

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

Hepatic Impairment: The dose of zanubrutinib should be decreased to 80 mg PO BID in patients with severe hepatic impairment. This recommendation is based on the results of a dedicated hepatic impairment study (BGB-3111-107) conducted in subjects with normal hepatic function (n=11) and mild (n=6), moderate (n=6), and severe (n=6) hepatic impairment classified by Child-Pugh which evaluated the total and unbound exposure of zanubrutinib after a single oral dose of 80 mg. Blood samples for PK analysis were collected up to 48 hours after administration and zanubrutinib PK parameters were calculated using noncompartmental methods.

A summary of total and unbound zanubrutinib exposure in subjects by hepatic function is shown in **Table 6**.

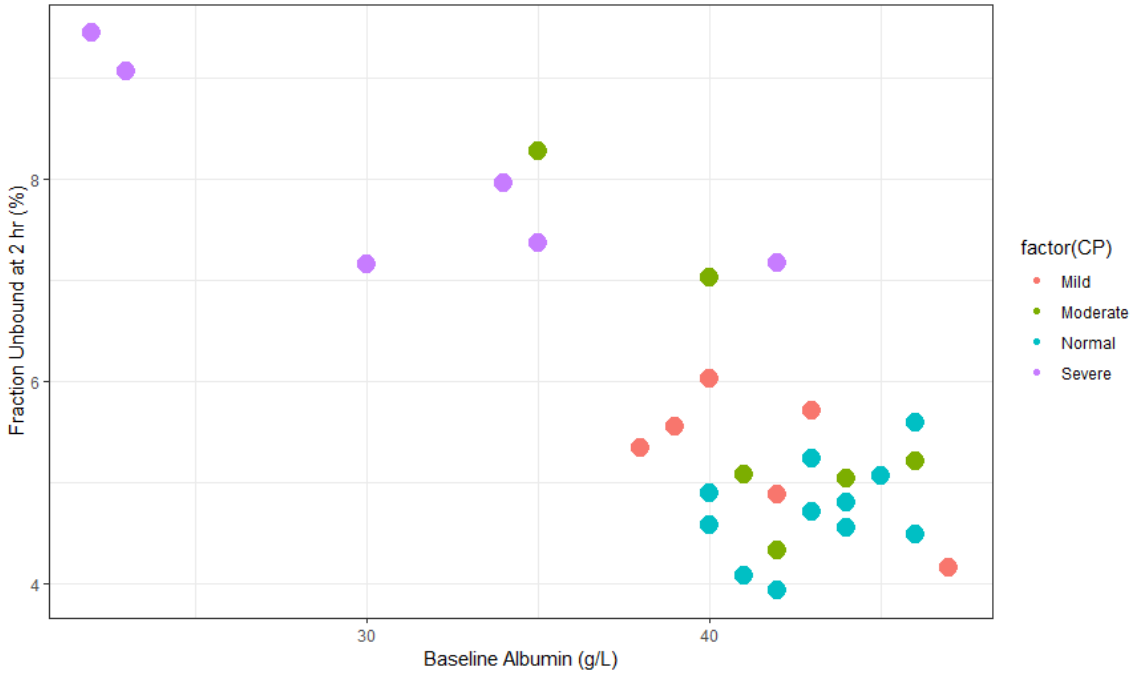
Table 6: Summary of Zanubrutinib Exposure in Subjects with Normal Hepatic Function or Hepatic Impairment Classified by Child-Pugh

Hepatic Function	Zanubrutinib Exposure				Increase Compared to Normal			
	C_{max} (ng/mL)		$AUC_{0\text{-}inf}$ (ng·h/mL)		C_{max}		AUC	
	Total	Unbound	Total	Unbound	Total	Unbound	Total	Unbound
Normal	162.8 (39.2%)	7.7 (44.7%)	683.1 (41.4%)	32.2 (44.3%)				
Mild	171.4 (33.0%)	8.9 (40.1%)	761.5 (27.1%)	39.5 (31.9%)	5%	16%	11%	23%
Moderate	249.1 (24.9%)	13.9 (35.3%)	825.9 (42.2%)	46.1 (41.3%)	53%	81%	21%	43%
Severe	209.1 (19.1%)	18.1 (25.1%)	1095 (18.1%)	94.7 (32.2%)	28%	136%	60%	194%

Source: BGB-3111-107 CSR, Tables 14.2.2.1 and 14.2.2.2

As shown in **Table 6**, subjects with hepatic impairment had higher zanubrutinib exposure relative to subjects with normal hepatic function. The increase in total zanubrutinib exposure was ≤60% relative to subjects with normal hepatic function for all degrees of hepatic impairment. However, patients with low baseline albumin, including patients with severe hepatic impairment, had even higher unbound zanubrutinib fraction relative to patients with normal hepatic function (see **Figure 4**).

Figure 4: Zanubrutinib Fraction Unbound by Baseline Albumin

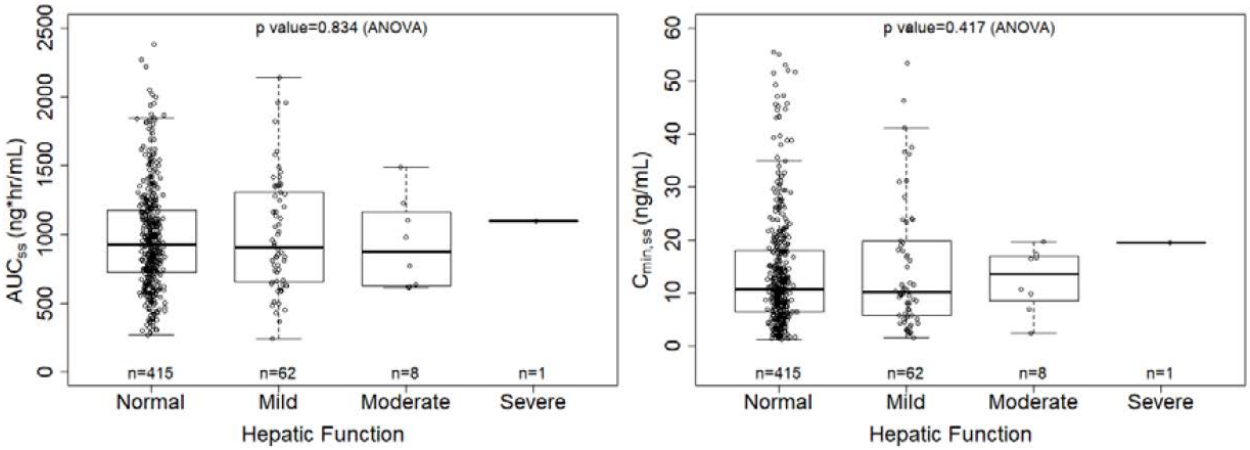


Source: FDA Analysis

Characteristic of this relationship, the increase in unbound zanubrutinib exposure was greater than the increase in total zanubrutinib exposure, particularly in patients with severe hepatic impairment. These results support a dose reduction in patients with severe hepatic impairment. A dose of 80 mg PO BID to match the unbound zanubrutinib exposure in patients with normal hepatic function is recommended. Given the degree of variability observed in the pharmacokinetics of zanubrutinib, dose reduction is not necessary for patients with mild or moderate hepatic impairment.

In the population PK analysis, ALT was a significant covariate on the clearance of zanubrutinib with higher ALT associated with lower clearance. However, the impact of ALT on zanubrutinib exposure was relatively small compared to the overall variability and was therefore not clinically meaningful within the population studied. As shown in **Figure 5**, simulated steady-state total zanubrutinib exposure (AUC and C_{min}) were similar between patients with normal hepatic function (n=415) and mild (n=62) or moderate (n=8) hepatic impairment, further supporting a lack of dose modification in patients with mild or moderate hepatic impairment. The population PK analysis did not provide additional information to support dose modification in patients with severe hepatic impairment as the dataset included only a single patient with severe hepatic impairment by NCI Criteria.

Figure 5: Simulated Steady-State Exposure of Zanubrutinib by Hepatic Function Classified by NCI Criteria

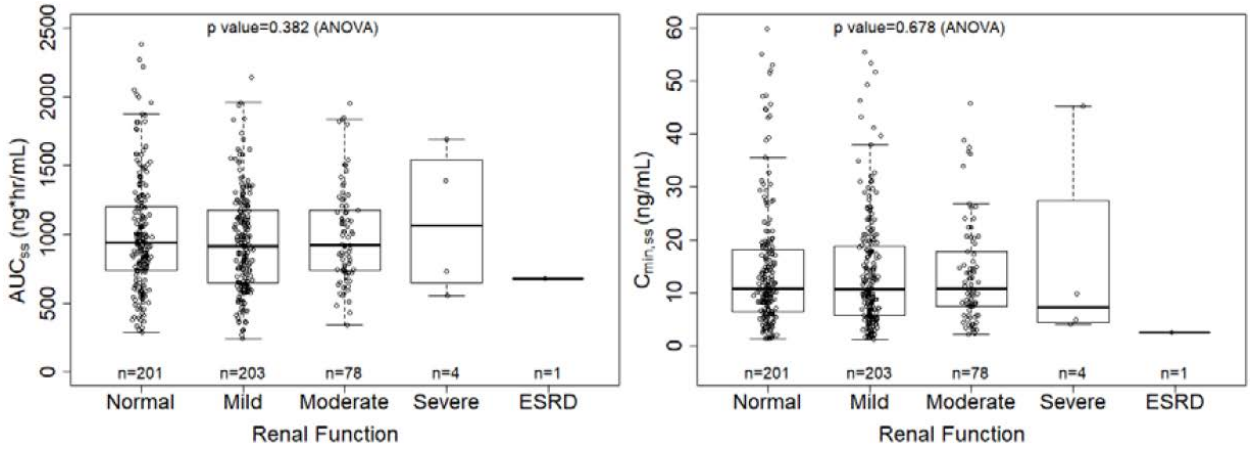


Source: BGB-3111-CP-002 Population PK Report, Figure 18

Renal Impairment:

Creatinine clearance was not a significant covariate on either clearance or volume of zanubrutinib in the population PK analysis (see Section 19.5.1). As shown in **Figure 6**, simulated steady-state total zanubrutinib exposure (AUC and C_{min}) were similar in patients with normal renal function (CrCL ≥90 mL/min; n=201) and mild (CrCL 60-89 mL/min; n=203) or moderate (CrCL 30-59 mL/min; n=78) renal impairment. There was limited data available from patients with severe renal impairment (CrCL 15-29 mL/min; n=4) or end-stage renal disease (CrCL <15 mL/min; n=1).

Figure 6: Simulated Steady-State Exposure of Zanubrutinib by Renal Function



Source: BGB-3111-CP-002 Population PK Report, Figure 19

Other Factors: The impact of age (age 19 to 90 years), sex, race (Asian, Caucasian, and Other), and body weight (36 to 140 kg) on zanubrutinib PK was evaluated in the population PK analysis. No clinically significant differences were identified based on these factors. See **Section 19.5.1** for a detailed review of the population PK analysis.

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

Food Effect: Zanubrutinib can be administered with or without food. The Applicant conducted a randomized, cross-over study (BGB-3111-103) to evaluate the effect of food (both low-fat and high-fat meals) on the PK of zanubrutinib in healthy subjects. In each treatment period, subjects were administered a single dose of 320 mg zanubrutinib after fasting or a meal. Subjects were fasted for 10 hours before and 4 hours after administration. Both a high-fat/high-calorie meal (~1,000 kcals with ~50% from fat) and a low-fat/low-calorie meal (~388 kcals with ~30% from fat) were evaluated.

Eighteen subjects were enrolled and 14 subjects completed all three treatment periods. The administration with a low-fat meal increased the zanubrutinib C_{max} by 51% and the AUC by 12% relative to the fasting condition. However, the administration with a high-fat meal increased the zanubrutinib C_{max} by 3% and decreased AUC by 7%. The food effect on zanubrutinib PK is not clinically meaningful and zanubrutinib was administered with or without food in the pivotal efficacy studies.

Drug Interactions:

Effect of Other Drugs on Zanubrutinib

CYP3A Inhibitors:

Zanubrutinib is a substrate of CYP3A. The Applicant conducted a clinical study (BGB-3111-104) to determine the effect of multiple doses of a strong CYP3A4 inhibitor (itraconazole) on the PK of a single dose of zanubrutinib in 18 healthy subjects. Blood samples for PK analysis were collected up to 48 hours after administration and zanubrutinib PK parameters were calculated using noncompartmental methods. The effect of co-administration of itraconazole 200 mg PO QD x 4 days on the PK of zanubrutinib 20 mg is shown in **Table 7**.

Table 7: Effect of Itraconazole on the PK of Zanubrutinib

Geometric Mean (%CV)	**C_{max} (ng/mL)**	**$AUC_{0\text{-}inf}$ (ng·h/mL)**
Zanubrutinib 20 mg Alone	47.5 (41.0)	183.6 (29.4)
Zanubrutinib 20 mg + Itraconazole 200 mg QD x 4 days	121.9 (28.5)	693.4 (31.3)
Geometric Mean Ratio (90% CI)	256.5 (226.2, 290.8)	377.6 (343.5, 415.0)

Source: BGB-3111-104 CSR, Table 11

The effects of other strong or moderate CYP3A4 inhibitors on the PK of zanubrutinib were assessed using PBPK modeling. The predicted impact of CYP3A4 inhibitors on zanubrutinib PK varied by drug and dose and are shown in **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%

Source: BGB-3111-104 CSR, Table 11 and Response to PBPK Information Request Dated 9/10/2019, Table 1

Based on the results shown in **Table 7** and **Table 8**, the recommended dose modification of zanubrutinib when used in combination with strong CYP3A inhibitors is 80 mg PO QD (a 75% dose reduction relative to the typical dosing regimen).

The Applicant also proposed a dose reduction of zanubrutinib to 80 mg BID (a 50% dose reduction relative to the typical dosing regimen) when used in combination with moderate CYP3A inhibitors. Based on the PBPK model predictions, this dosing strategy may result in higher zanubrutinib exposure despite the dose reduction relative to exposure at the recommended dose without concomitant CYP3A inhibitors in some scenarios. For example, administration of zanubrutinib 80 mg BID + erythromycin (a moderate CYP3A inhibitor) 500 mg four times daily, is predicted to result in a mean increase in zanubrutinib C_{max} of 113% and AUC of 133% relative to administration of zanubrutinib 160 mg BID alone. The predicted mean zanubrutinib C_{max} and AUC after accounting for the DDI would remain within the range of exposure that does not have an apparent exposure-response relationship for safety events. Additional data on the PBPK analysis are provided in **Section 19.5.2.**

Given the variability in the magnitude of the changes in exposure as well as the limited clinical data, the proposed zanubrutinib dose modifications for use with concomitant moderate or strong CYP3A inhibitors may still result in higher than expected exposures for specific CYP inhibitors and further dose reductions are recommended if toxicities occur. The Applicant's proposed labeling was updated to reflect this recommendation. In addition, the Applicant will evaluate the impact of concomitant CYP3A inhibitor use on zanubrutinib PK and safety in their ongoing studies as a PMR (see Post-Marketing Requirements) to further guide dose modifications for drug interactions.

CYP3A Inducers:

The Applicant assessed the effect of multiple doses of a strong CYP3A inducer (rifampin) on the pharmacokinetics of a single dose of zanubrutinib in 20 healthy subjects in Study BGB-3111-104. Blood samples for PK analysis were collected up to 48 hours after administration and zanubrutinib PK parameters were calculated using noncompartmental methods. The effect of the co-administration of rifampin 600 mg PO QD x 7 days on zanubrutinib exposure was a decrease in C_{max} by 92% and $AUC_{0\text{-}inf}$ by 93% (see **Table 9**). Based on these results, co-administration of zanubrutinib with strong CYP3A inducers should be avoided.

Table 9: Effect of Rifampin on the PK of Zanubrutinib

Geometric Mean (%CV)	**C_{max} (ng/mL)**	**$AUC_{0\text{-}inf}$ (ng·h/mL)**
Zanubrutinib 320 mg Alone	532.1 (40.0)	3,524 (36.1)
Zanubrutinib 320 mg + Rifampin 600 mg QD x 7 days	42.1 (41.4)	260.7 (43.3)
Geometric Mean Ratio (90% CI)	7.9 (6.6, 9.5)	7.4 (6.0, 9.1)

Source: BGB-3111-104 CSR, Table 9

The effect of a moderate CYP3A4 inducer (efavirenz) on the PK of zanubrutinib was assessed using PBPK modeling. After co-administration of efavirenz 600 mg PO QD x 10 days, zanubrutinib C_{max} is predicted to decrease by 58% and AUC by 60%. There is limited data on the efficacy of zanubrutinib at lower exposures.

In Study BGB-3111-AU-003, only 5 patients with MCL received a zanubrutinib starting dose less than 320 mg per day. Decreased zanubrutinib exposure may result in decreased efficacy and therefore co-administration of zanubrutinib with moderate CYP3A inducers should be avoided. A PMC will be issued for a clinical trial to determine an appropriate dose of zanubrutinib in combination with moderate CYP3A4 inducers (see Post-Marketing Commitments). Additional data on the PBPK analysis are provided in **Section 19.5.2**.

Effect of Zanubrutinib on Other Drugs

CYP3A, CYP2C9, CYP2C19, P-gp, or BCRP Substrates:

Based on *in vitro* studies, multiple potential CYP and transporter-based interactions for zanubrutinib were identified. The Applicant conducted a cocktail DDI study (BGB-3111-108) to evaluate the impact of multiple doses of zanubrutinib on the PK of probe substrates for CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), and BCRP (rosuvastatin). The PK of each substrate was assessed in healthy volunteers alone and after administration of zanubrutinib 160 mg PO BID x 7-12 days. A summary of the effects of concomitant zanubrutinib administration on the PK of probe substrates is shown in **Table 10.**

Table 10: Effect of Zanubrutinib on the PK of Probe Substrates

Substrate Drug	Substrate Drug Exposure Geometric Mean (%CV)				Change in Exposure After Co-administration of Zanubrutinib	
	C_{max}		AUC		C_{max}	AUC
	Alone	With Zanubrutinib	Alone	With Zanubrutinib		
Midazolam (CYP3A)	10.2 (28.7)	7.1 (35.6)	28.5 (43.6)	15.0 (36.2)	↓ 29.8%	↓ 47.4%
Warfarin (CYP2C9)	699 (14.9)	666 (22.2)	19,150 (19.7)	19,220 (19.6)	↓ 4.7%	↑ 0.4%
Omeprazole (CYP2C19)	229 (63.4)	182 (78.4)	480 (78.5)	305 (45.7)	↓ 20.5%	↓ 36.5%
Digoxin (P-gp)	1,164 (33.1)	1,561 (43.2)	6,544 (19.2)	7,281 (20.1)	↑ 34.1%	↑ 11.3%
Rosuvastatin (BCRP)	3.47 (62.5)	3.75 (47.6)	39.9 (42.7)	35.6 (36.8)	↑ 8.0%	↓ 10.7%

Source: BGB-3111-108 CSR, Table 14.2.3-1

Based on the cocktail DDI study, zanubrutinib is a weak inducer of CYP3A and CYP2C19 (AUC decrease ≥20 to <50%) and an inhibitor of P-gp. Repeated doses of zanubrutinib at the therapeutic dose had no clinically meaningful impact on the PK of sensitive substrates of CYP2C9 or BCRP.

CYP2B6 Substrates:

Zanubrutinib induces CYP2B6 *in vitro*. Cryopreserved human hepatocytes from 3 donors were cultured in the presence of zanubrutinib at 0.3, 3, and 30 µM or positive control (phenobarbital 1000 µM). Enzyme activity was assessed by incubating a probe substrate (bupropion 50 µM) with the cultured hepatocytes and mRNA was evaluated by fluorescence quantitative PCR after RNA extraction from the hepatocytes. Mean CYP2B6 activity was increased by 1.53-, 3.67-, and 1.93-fold at 0.3, 3, and 30 µM zanubrutinib, respectively, compared to 9.57-fold for positive control. The mean CYP2B6 mRNA fold-change was 1.64-, 3.55-, and 2.62-fold at 0.3, 3, and 30 µM zanubrutinib, respectively, compared to 6.39-fold for positive control. The Applicant's PBPK model to evaluate the impact of zanubrutinib on the PK of a CYP2B6 substrate (bupropion) has limitations that make it unsuitable to support labeling recommendations (see **Section 19.5.2**). Based on the limited and variable results of the *in vitro* studies and lack of clinical data, there is insufficient data to characterize the magnitude of induction of CYP2B6 by zanubrutinib. However, the anticipated clinical impact of CYP2B6 induction is low given the weak induction observed for CYP3A and CYP2C19, lack of significant induction of CYP2C9, and limited number of sensitive CYP2B6 substrates used clinically. The Applicant's proposed labeling was updated to reflect that zanubrutinib induces CYP2B6 *in vitro*.

Effect of Zanubrutinib on CYP Enzymes and Transporters in vitro

Inhibition of CYP Enzymes: In human liver microsomes, the zanubrutinib IC_{50} for reversible inhibition was >10 µM for CYP3A4 and CYP2D6 and >100 µM for CYP1A2 and CYP2B6. Zanubrutinib did not exhibit time-dependent inhibition for any CYP tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A).

Substrate of Transporters:

In a Caco-2 monolayer model, zanubrutinib was highly permeable (>$10x10^{-6}$ cm/s). The efflux ratios for zanubrutinib were 3.5, 2.4, and 0.2 at 0.5, 2, and 10 µM, respectively. The efflux ratio decreased when zanubrutinib was co-administered with P-gp inhibitors (0.9 with elacridar and 1.5 with LY335979). Together, these results suggest that zanubrutinib may be a substrate of P-gp with potential for efflux at low concentrations. Given the high permeability of zanubrutinib, the impact of P-gp inhibition on the PK of zanubrutinib is unlikely to be clinically significant.

In vesicles expressing human BCRP or HEK293 cells expressing other human transporters (OATP1B1, OATP1B3, OAT1, OAT3, and OCT2), the uptake ratios for zanubrutinib incubated at 0.1 to 5 µM were all <2-fold, indicating that zanubrutinib is not a substrate for these transporters.

Inhibition of Transporters:

In vesicles expressing human BCRP or HEK293 cells expressing other human transporters (OATP1B1, OATP1B3, OAT1, OAT3, and OCT2), the uptake activities of probe substrates for BCRP, OATP1B1, OATP1B3, OAT1, and OAT3 were not significantly changed after incubation with zanubrutinib at 0.1 to 5 µM. OCT2 uptake activity was inhibited by 51.6% in the presence of 5 µM zanubrutinib but not inhibited at lower concentrations. The observed zanubrutinib C_{max} in patients was 543 ng/mL after administration of 320 mg QD. Assuming 6% unbound zanubrutinib, the unbound C_{max} (~0.07 µM) is significantly lower than the concentration that may inhibit OCT2 and therefore inhibition of OCT2 by zanubrutinib is unlikely at clinically relevant doses.

X

Lauren Price, PhD
Primary Reviewer

X

Olanrewaju Okusanya, Pharm D
Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submitted data from 5 clinical studies of zanubrutinib monotherapy in B-cell malignancies. Two of the studies BGB-3111-206 and BGB-3111-AU-003 were included data to support efficacy in patients with relapsed and refractory MCL. The additional three studies BGB-3111-205, BGB-3111-210, and BGB-3111-1002 evaluated zanubrutinib monotherapy in patients with CLL/SLL, Waldenström macroglobulinemia (WM), and NHL, were included to support safety. The table below lists the efficacy and safety studies emphasized in this review.

Data Sources

Original Submission

Study BGB-3111-206: \\CDSESUB1\evsprod\NDA213217\0001\m5\datasets\bgb-3111-206
Study BGB-3111-AU-003: \\CDSESUB1\evsprod\NDA213217\0001\m5\datasets\bgb-3111-au003\

Post-Adjudication

The Applicant has agreed with FDA adjudication of response and submitted updated datasets.

Study BGB-3111-206

- Time-to-Event: \\CDSESUB1\evsprod\NDA213217\0025\m5\datasets\bgb-3111-206\
- Response: \\CDSESUB1\evsprod\NDA213217\0027\m5\datasets\bgb-3111-206\

Study BGB-3111-AU-003

- Time-to-Event: \\CDSESUB1\evsprod\NDA213217\0027\m5\datasets\bgb-3111-au003\
- Response: \\CDSESUB1\evsprod\NDA213217\0027\m5\datasets\bgb-3111-au003\

To derive the final efficacy outcome adjudication, please note the use of subsetting variable for patients whose response has changed or has not changed due to adjudication.

Duration of Response Example:

1. Set 1: Subset patients whose efficacy outcome has been changed due to adjudication with PARAM = "Duration of Response (PR or better) by IRC PET-CT Adj. (days)"
2. Set 2: Subset patients whose efficacy outcome has not been changed by adjudication with PARAM = "Duration of Response (PR or better) by IRC PET-CT (days) and exclude patients in Set 1.
3. Merge Set 1 and Set 2.

Table 11: Listing of Clinical Studies Relevant to this NDA

Study Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Pivotal Study							
BGB-3111-206	Phase 2, multicenter, single arm, open label study	160mg PO twice daily until disease progression or unacceptable toxicity	Overall Response Rate (ORR) as defined by IRC assessed Lugano (2014) criteria	Until PD, relapse or unacceptable toxicity	86	Patients with MCL who had received between 1 and 4 prior therapies	13 sites China
BGB-3111-AU-003	Phase 1 dose escalation with dose expansion phase	40-320mg PO daily	Overall Response Rate (ORR) as defined by IRC assessed Lugano (2014) criteria	Until PD, relapse or unacceptable toxicity	37 with R/R MCL 376 total patients	Patients with B cell malignancies	25 sites Australia Italy New Zealand South Korea UK US
Additional Studies to Support Safety							
BGB-3111-205	Phase 2, single arm multicenter, study	160 mg PO BID	IRC assessed ORR	Until PD, death, or unacceptable toxicity	91	Patients with previously treated CLL/SLL	13 centers China
BGB-3111-210	Phase 2, single arm, multi-center study	160 mg PO BID	Major Response Rate	Until PD, death or unacceptable toxicity	44	Waldenström' s macroglobulinemia with at least one prior line of therapy	11 centers China
BGB-3111-1002	Phase 1, multicenter, open-label study	Part 1320mg PO daily or 160 PO BID Part 2: 160mg PO BID	DLTs ORRs	Until PD, relapse or unacceptable toxicity	44	Part 1: Patients with B cell malignancies Part 2: R/R FL or MZL	4 centers China

7.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study reports, case report forms, and responses to the review team's IRs.
- Relevant published literature
- Relevant information in the public domain

The clinical review of efficacy was primarily based on an analysis of Study BGB-3111-206 and supported by patients with relapsed refractory mantle cell lymphoma who received zanubrutinib at 160mg twice daily or 320mg once daily on study BGB-3111-AU-003. The review of safety is primarily based on data from patients with R/R MCL who received from studies 206 and 003 and the pooled data from three additional studies in Table 11 which include a total of 641 patients who with B cell malignancies who received continuous daily zanubrutinib therapy. The review emphasis was placed on patients who received either 160mg twice daily or 320mg once daily. A 90-day safety update increased the total safety population by an additional 9 patients from study 003.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using R and SAS/JMP 13.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.8 (Enterprise Performance and Lifecycle System Design).

Adjudication of Efficacy

The reviewer adjudicated the key efficacy analyses per IRC (ORR, BOR, DOR, and PFS) by reviewing efficacy narratives, source datasets, supplemented by pathology reports and the electronic case report forms (eCRFs). To evaluate the accuracy of the reported efficacy outcomes, multiple IRs were required and included:

- Clarifications regarding the algorithms used for assessing bone marrow response with discordant PET histologic bone marrow results
- Clarifications regarding discrepancies between ADLB bone marrow results and results from response datasets
- Reasons for patients being NE for efficacy, which had not been captured.
- Review of datasets that provided tumor measurements per IRC; the response determinations of all IRC reviewers (radiologist 1, radiologist 2, adjudicating radiologist if needed, and the medical oncologist's final overall response designation); Deauville scores; and waterfall and swimmer's plots.

There were multiple discordances between the Applicant assessed BOR and FDA adjudicated BOR. Discrepancies were mainly due to discordant bone marrow and PET bone marrow results in patients who had bone marrow involvement at diagnosis and at follow

up, and whether clinical (non-radiographic) progressive disease (PD) per INV was considered in the overall assessment of disease status per IRC. The table below summarizes the key differences between FDA's and the Applicant's approach.

Table 12: Difference between FDA and Applicant Analysis of Efficacy per IRC

Setting	Difference in approach	Comment
Non-radiographic PD	FDA counts documentation of clinical progression events per INV as DOR/PFS failure, rather than discounting such events.	The IRC assessments, which per the charter were to consider both radiographic and clinical data, did not count the date of some clinical (non-radiographic) progression events as the date of loss of response. The Applicant instead classified patients with progression at the time of radiographic progression rather than the time of clear clinical progression. The Agency adjudicated the date of clinical progression as the time of loss of response.
Complete Response	FDA views subjects with histologic bone marrow disease at screening with a discordant PET (PET negative bone marrow at screening) to require documentation of bone marrow negative status by histology (regardless of PET bone marrow assessment) in order to be considered as having a complete response consistent with CR or PR.	Although the study protocols stated that patients with bone marrow or GI disease at diagnosis must have documentation of clearance by histology or complete response, this was late protocol amendment and therefore several patients with extranodal (bone marrow or GI) disease were assessed as complete responders based solely on PET bone marrow or GI status at response assessment, even with multiple positive histologic evaluations. The Applicant accepted the FDA's adjudication of these as partial responses.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study BGB-3111-206

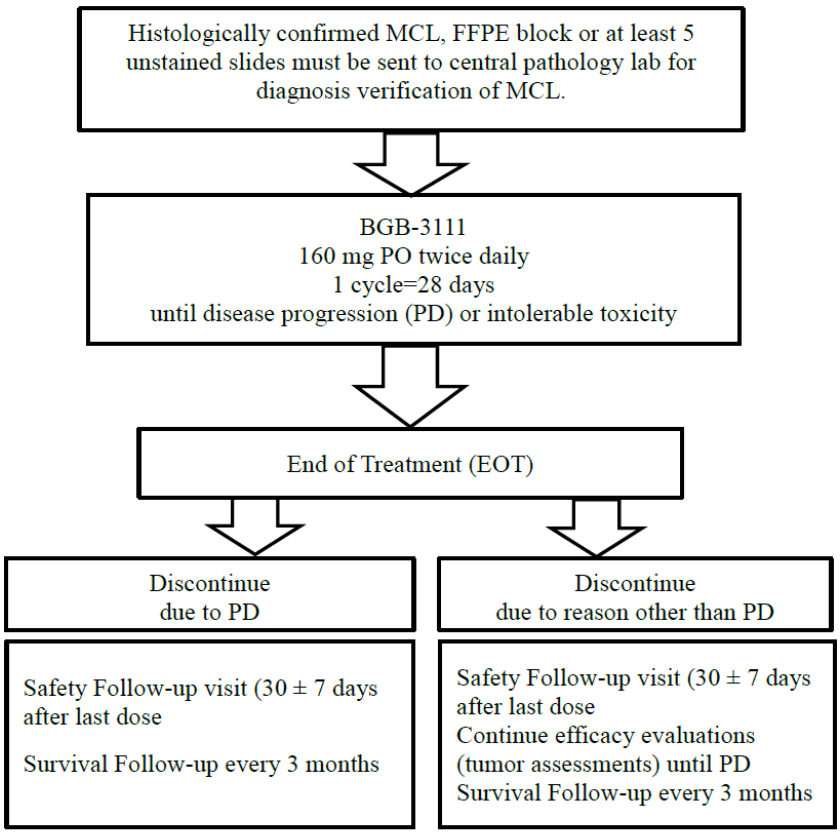
Study Title: A Single Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, A Bruton's Tyrosine Kinase Inhibitor, In Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)

ClinicalTrials.gov identifier: NCT 03206970
First Patient Treated: March 2, 2017
Clinical cut-off dates for this submission:
February 15, 2019 (Efficacy)
February 15, 2019 (Primary safety data)
May 8, 2019 (Safety update)

Trial Design

BGB-3111-206 is an ongoing single-arm, open-label, multicenter Phase 2 study in patients with the diagnosis of MCL confirmed by central pathologic review, who had no response or relapsed after ≥ 1 but < 5 prior treatment regimen(s) for MCL. The study was composed of an initial screening phase (up to 28 days), a single-arm treatment phase, and a follow-up phase. The schema for this study is shown in Figure 7.

Figure 7. Study BGB-3111-206 Schema



Abbreviations: EOT, end of treatment; FFPE, formalin-fixed, paraffin-embedded (tumor tissue); MCL, mangle cell lymphoma; PD, progressive disease

[Source: Study BGB-3111-206 Protocol v4.0]

Primary Objective

To evaluate the efficacy of BGB-3111 at a dose of 160 mg orally (PO) twice daily (BID) in subjects with centrally confirmed relapsed or refractory mantle cell lymphoma (MCL) as measured by overall response rate (ORR) assessed by an Independent Review Committee (IRC) in accordance with the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria.

Treatment Administration

All patients received zanubrutinib 160 mg (two 80-mg capsules) orally twice daily in repeated 28-day cycles. Treatment with zanubrutinib was continued for up to 3 years until progressive disease (PD), unacceptable toxicity, death, withdrawal of consent, or until the study is terminated by the sponsor for the final analysis.

Tumor Assessment

Tumor response was evaluated by an independent review committee according to the Lugano classification. Tumor assessments performed during screening included a computed tomography (CT) scan with contrast (or magnetic resonance imaging [MRI]) of the neck, chest, abdomen and pelvis, fluorodeoxyglucose (FDG)-positron-emission tomography (PET) scan, bone marrow biopsy and endoscopic gastrointestinal biopsy (for patients with suspected gastrointestinal involvement). For patients with FDG-avid disease at screening, PET and CT or MRI were to be repeated every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until PD or end of study. The PET and contrast CT were required for confirmation of CR for all subjects. Endoscopy was mandatory to confirm CR for any subject with a documented history of gastrointestinal involvement. Bone marrow biopsy were required for confirmation of CR in subjects with bone marrow tumor involvement prior to study drug. Prior to protocol amendment 4, response was assessed radiographically every 12 weeks for the first 48 weeks and then every 24 weeks until disease progression or the end of study.

Study Population (Key Eligibility Criteria)

- Age 18-75y
- ECOG 0-2
- Pathologic diagnosis of MCL to include evidence for morphologic and Cycle D1 and B cell markers and CD5 co-expression or t (11; 14). Tumor tissue or unstained slides must have been sent for central laboratory for confirmation of MCL.
- Measurable disease by CT/MRI
- Received at least one but less than five prior regimens for MCL
- Documented failure to achieve any response or documented progressive disease after response to the most recent treatment
- Organ and Marrow Function:
    - Creatinine Clearance of ≥ 30mL/min (as estimated by Cockcroft-Gault equation or estimated glomerular filtration rate from the Modification of Diet in Renal Disease)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.5X upper limit of normal (ULN)
    - Total bilirubin ≤ 2 X upper limit of normal (ULN)
    - Neutrophils ≥ 1 x 10^9/L independent of growth factor support within 7 days of study entry
    - Platelets ≥ 75 x 10^9/L independent of growth factor support or transfusion within 7 days of study entry
- Excluded subjects with central nervous system (CNS) lymphoma
- Excluded subjects with prior BTK inhibitor therapy
- Excluded subjects requiring corticosteroids in excess of prednisone 10mg/day or equivalent
- Excluded subjects requiring ongoing treatment with medications that are strong cytochrome P450, family 3 subfamily a (CYP3A) inhibitors or inducers
- Excluded subjects who had received allogeneic stem cell transplant

Study Endpoints

The primary endpoint is the objective response rate (ORR), defined as the achievement of either a partial response (PR) or complete response (CR) as assessed by the IRC according to the 2014 modification of the International Working Group on Non-Hodgkin's lymphoma (NHL) Criteria at any time on study drug. Additional outcome is duration of response (DOR) per IRC, defined as the time between the date of the earliest qualifying response (PR or CR, whichever occurs earlier) and the date of progressive disease (PD) or death from any cause, whichever occurred earlier.

Statistical Analysis Plan

Analysis Population

A total of 86 patients were enrolled into the study. All received at least one dose of study drug.

Sample Size Determination

Approximately 80 subjects were planned to be enrolled. The sample size calculation was mainly based on the level of precision of the estimated ORR. With a sample size of 80 patients, for an observed ORR of 70% (60/86), the 95% exact confidence interval (CI) is (59%, 79%).

Analysis of the Efficacy Endpoints

A binomial exact test will be performed for hypothesis testing H_0: ORR=40% vs. H_a: ORR ≥ 40%. Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the point estimate of ORR. Kaplan-Meier (KM) method will be used to estimate duration of response.

Protocol Amendments

The study was amended 4 times:

Original Protocol: October 1, 2016
Amendment 1: January 5, 2017
Amendment 3: October 25, 2017
Amendment 4: September 6, 2018

The table below provides the details of the major protocol amendments.

Table 13. Study BGB-3111-206 Major Protocol Changes

Protocol Version (Date)	Major Changes
4.0 (6 September 2018)	• Revised text to clarify that, for patients with avid PET diseases at screening, PET and contrast CT should be repeated every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until disease progression (PD) or end of study, whichever comes first. • For subjects with non-avid PET diseases at screening, only contrast CT should be performed every 12 weeks for the first 96 weeks, and every 24 weeks thereafter until PD or end of study, whichever comes first.
3.0 (25 October 2017)	• Clarified that primary efficacy endpoint will be assessed by an Independent Review Committee (IRC) • Clarified that for patients who did not discontinue due to AE, the collection of adverse events (AEs) is to take place through 30 days after the last dose regardless of when anti-tumor therapy is started. • Clarified timing of positron emission tomography (PET) scans for efficacy. • Revised text to clarify that if a patient discontinues due to an AE, they are still followed for disease progression, regardless of if new anticancer therapy is started. • Clarified inclusion and exclusion criteria • Added a list of concomitant treatment allowed during the study. • Clarified that patients with GI tumors prior to study drug should have complete response (CR) confirmed with endoscopy. • Clarified cytology and immunohistochemistry (IHC) must be performed for bone marrow aspirate/biopsy • Primary Efficacy Analysis: Corrected the Ha to ORR ≥ 40% • Prohibited Medications: Removed moderate CYP3A inhibitors from the table of prohibited medications to match changes made in Section 6.6.3.
2.0 (5 January 2017)	• Previous protocol: Treatment duration of three years. After revision: Treatment duration up to three years. • Previous protocol: Measurable disease is defined as at least one lymph node ≥ 1.5 cm in longest diameter. After revision: Measurable disease is defined as at least one lymph node >1.5 cm in longest diameter. • In previous protocol there is no clear definition for progression-free survival (PFS), time to response (TTR), duration of response (DOR) and overall survival (OS). After revision: The definitions are clarified. • Previous protocol: Only contrast CT is used for tumor assessment. After revision: PET and contrast CT will be performed for tumor assessment at screening, week 12, week 24 in treatment period, and complete remission. Contrast CT will be performed at week 36, 48, and every 24 weeks thereafter. If PET scan is negative at screening, then only contrast CT is used for subsequent tumor assessment. • Previous protocol: Tumor assessment is conducted by investigator. After revision: Tumor assessment is conducted by independent review committee.

Study Results

Compliance with Good Clinical Practices

The protocol, protocol amendments, and patient informed consent forms for Study BGB-3111-206 were reviewed and approved by the Institutional Review Boards or Independent Ethics Committees of the participating study centers.

Study BGB-3111-206 was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the U.S. Code of Federal Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representatives voluntarily consented prior to trial enrollment.

Financial Disclosure

The Applicant submitted financial disclosure information from 69 principal investigators and 485 sub-investigators from five studies including the 15 principal investigators and 72 sub-investigators from study 206 indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 19.3.

Data Quality and Integrity

Data from the study BGB-3111-206 were provided electronically with standard formats. The data and analysis quality of the submission was acceptable to perform the review.

Patient Disposition

A total of 112 patients were screened, of which 86 patients were enrolled and received study treatment. Twenty-six of the 112 patients were either screen failures (24), withdrew consent prior to starting therapy (3), or died prior to starting therapy (1). As of the cutoff date of February 15, 2019, 60% of patients were continuing on treatment.

Table 14 shows disposition of patients who were enrolled on study 206.

Table 14. Study BGB-3111-206 Disposition in Patients with R/R MCL

	n (%)
N	86 (100)
Study	
Ongoing	60 (70)
Discontinued	26 (30)
Lost to Follow-Up	3 (3)
Withdrawal by Subject	9 (10)
Death	14 (16)
Adverse Event	7 (8)
Other Reason	1 (1)
Progressive Disease	6 (7)
Treatment	
Ongoing	52 (60)
Discontinued	34 (40)
Adverse Event	8 (9)
Investigator's Discretion	1 (1)
Progressive Disease	24 (28)
Withdrawal by Subject	1 (1)

Source: Reviewer's analysis

Protocol Violations/Deviations

Eight (9.3%) of subjects had at least one major protocol deviation. The majority of protocol deviations were related to the subject receiving prohibited medications (5). An additional patient had an inadvertent overdose, and one patient had a drug reduction and did not resume per protocol and one deviation was considered GCP non-compliance due to source documentation not adequately maintained.

Table 15 summarizes study BGB-3111-206 major protocol deviations and violations.

Table 15. Study BGB-3111-206 Major Protocol Deviations and Violations

Deviation/Violation Group Code	n (%)
Investigational Product Administration/Study Treatment	2 (2)
Disallowed Medications	5 (6)
Other[1]	1 (1)

[1] GCP non-compliance: source documentation not adequately maintained.
[Source: Reviewer's analysis, adapted from study BGB-3111-206 CSR Listing 16.2.2.1]

The prohibited medications resulting in protocol violations included azithromycin (1), moxifloxin (3), droperidone (1), were all prohibited due to the potential for QTc elevation and would not have been expected to have any impact on tumor response on any efficacy evaluations.

The patient overdose included one patient who received 8 (640 mg) vs 4 (320 mg) capsules on one day due to forgetting the doses has already been taken that day. This one time (one day) increased dose for a continually administered treatment therapy would not be expected to substantially impact tumor response or efficacy assessments.

The GCP non-compliance violation was related to a failure to produce documents documenting study drug administration and accounting. Per the investigator, the patient was not willing to return additional study drug or drug diary despite repeated requests. This patient discontinued study drug due to an AE on study day 9 and therefore did not have response assessment. This violation does not significantly impact study conclusions.

Reviewer's Comment: *The small number and the nature of the violations/deviations, as described above, are unlikely to have a substantial impact on the final efficacy results of the Study BGB-3111-206.*

Table of Demographic and Baseline Characteristics

The table below summarizes the demographics and disease characteristics of patients in the 206 study. The median age of 61 years, 78% percent were male and 100% of the patients were

of Asian race. Forty-two percent of patients had stage 4 disease, and 36% had either intermediate risk (29%) or high risk (13%) disease. The median number of prior therapy regimens was 2 (range 1-4). Fifty-two percent of patients had refractory disease as determined by the investigator defined as stable or progressive disease on current therapy.

Table 16. Study BGB-3111-206 Demographics and Disease Characteristics in Patients with R/R MCL

Characteristic	n (%)
N	86 (100)
Age, Median (Range)	60.5 (34.0, 75.0)
< 65 Years	64 (74)
≥ 65 Years	22 (26)
Sex	
Female	19 (22)
Male	67 (78)
Race: Asian	86 (100)
Blastoid Histology	
No	68 (79)
Yes	12 (14)
Unknown	6 (7)
Revised Ann Arbor Stage	
Stage I	1 (1)
Stage II	7 (8)
Stage III	14 (16)
Stage IV	64 (74)
MIPI Risk Group	
High Risk	11 (13)
Intermediate Risk	25 (29)
Low Risk	50 (58)
Bulky Disease	
Largest Diameter ≤ 10 cm	79 (92)
Largest Diameter > 10 cm	7 (8)
Extranodal Disease	
No	25 (29)
Yes Bone Marrow Gastrointestinal	61 (71) 39 (45) 15 (17)
ECOG	
0	60 (70)
1	22 (26)

Characteristic	n (%)
2	4 (5)
Prior Lines of Therapy	
1	25 (29)
2	32 (37)
3	19 (22)
4	10 (12)
Disease Status	
Relapsed disease	41 (48)
Refractory disease	45 (52)

MIPI = MCL International Prognostic Index,
ECOG = Eastern Cooperative Oncology Group Performance Status
[Source: Reviewer's Analysis]

Prior Therapies

The median number of prior therapies for patients on BGB-3111-206 was 2 (range 1-4). Almost all (95.2%) of patients had received rituximab as a single agent or as part of a regimen. A breakdown of prior therapies is provided in the table below.

Table 17: Summary of Prior Therapy for Subjects Treated on BGB-3111-206

	All Subjects N = 86 n (%)
Number of prior therapies for MCL	
Mean (SD)	2.2 (0.98)
Median	2
Min, Max	1,4
1	25 (29)
2	32 (37)
3	19 (22)
4	10 (12)
Prior Therapies	
CHOP based regimen (R-CHOP, R-CHOPE, R-CHOP-like) Cyclophosphamide,/doxorubicin/vincristine/prednisone	78 (91)
Rituximab as single agent or part of a regimen	64 (74)
DHAP (Dexamethasone, High Dose cytarabine, Cisplatin)	20 (23)
Hyper-CVAD (Cyclophosphamide, Vincristine, Adriamycin Dexamethasone)	13 (15)
DICE/ICE (Dexamethasone, Ifosfamide, Cisplatin, Etoposide)	
Lenalidamide	12 (14)
Gemcitabine, Dexamethasone, Cisplatin	8 (9)

Bortezomib	7 (8)
GMOX (Gemcitabine, Oxaliplatin)	6 (7)
ESHAP (Etoposide, Solumedrol, High-Dose Cytarabine, Cisplatin)	4 (5)
Bendamustine	2 (2)
Autologous Stem Cell Transplant	3 (4)

Source: Applicant CSR, page 57, Applicant Data Sets ADCM, ADBASE

Reviewer comment: The population studied in BGB-3111-206 was comparable to the characteristics of the demographics expected for patients with relapsed and refractory mantle cell lymphoma. This population represented a heavily pretreated population of patients who received standard accepted chemotherapy regimens. The majority of patients had disseminated disease which is characteristic of mantle cell lymphoma. Results from this study would be expected to be experienced by patients with relapsed and refractory lymphoma in the post marketing setting.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most subjects (87%) received concomitant medications after study entry. Unspecified herbal and traditional medicine were reported in 48% of patients. Other therapeutic classes of concomitant medications received by ≥10% of subjects included antibacterials for systemic use included antibacterials (44%), antivirals (29%), immunostimulants (24), blood products (24%) and analgesics (20%).

Reviewer comment: The types of concomitant medications used in this trial would not have been expected to affect efficacy as they would have no activity against mantle cell lymphoma. The use of Chinese herbal therapies was common. Analysis of this subgroup in confounded by the limited specific data available regarding the composition of products. Chinese herbal medications were not permitted at study entry and were not permitted to be used for anti-cancer effect. In most cases, Chinese herbal medications were used for symptoms relief and for short duration.

Based on the reported relative dose intensity of 99%, compliance was not a significant concern or identified on review of exposure.

Efficacy Results – Primary Endpoint

Overall response rate is 84% (95% CI: 74, 91) – the null hypothesis is rejected.

Efficacy Results – Secondary and other relevant endpoints

Response Rates

Table 18 shows response rates. Complete response rate is 59% (95% CI: 48, 70).

Table 18. Study BGB-3111-206 FDA-adjudicated Response Rates

Response	n (%)
CR	51 (59)
PR	21 (24)
PD	6 (7)
SD	1 (1)
DS[1]	6 (7)
NED	1 (1)

CR = complete response, PR – partial response, PD – progressive disease, SD – stable disease, DS – discontinued prior to first assessment, NED – no evidence of disease.

The following subjects who were initially assessed as having a complete response by the Applicant were adjudicated to partial response based on inadequate confirmation of bone marrow or gastrointestinal disease response.

Table 19: Patients with discordant Applicant and Agency assessed BOR

USUBJID	Applicant BOR	FDA BOR	Rationale for Discrepancy
BGB-3111-206-(b) (6)	Complete Response	Partial Response	Bone marrow positive at screening, PET bone marrow negative (discordance). No documentation of bone marrow negativity at assessment of CR.
BGB-3111-206-(b) (6)	Complete Response	Partial Response	Bone marrow positive at screening, PET bone marrow negative (discordance). No documentation of bone marrow negativity at assessment of CR.
BGB-3111-206-(b) (6)	Complete Response	Partial Response	Gastrointestinal disease documented by endoscopy at screening. No documentation of negative endoscopy at assessment of CR.

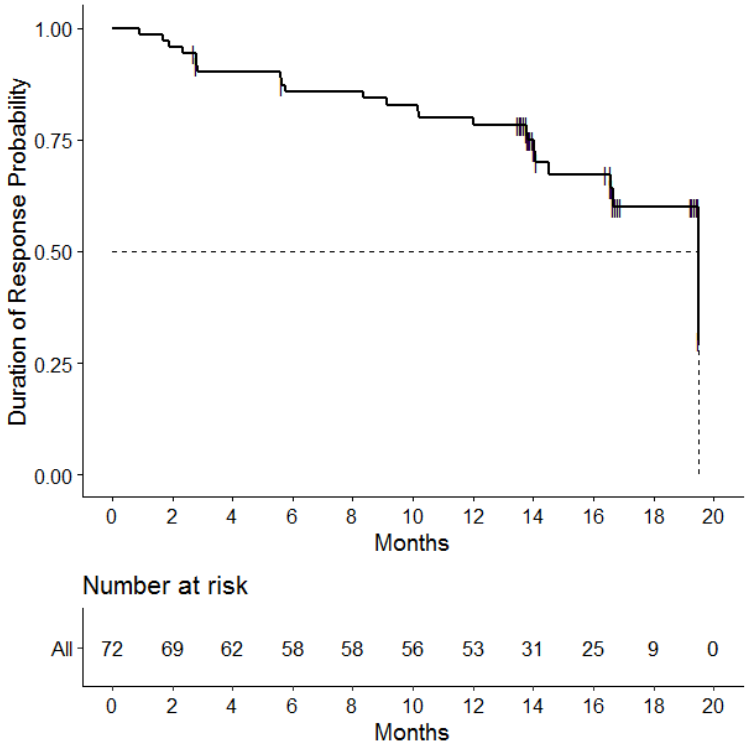
USUBJID	Applicant BOR	FDA BOR	Rationale for Discrepancy
BGB-3111-206-(b) (6)	Complete Response	Partial Response	Bone marrow positive at screening, PET bone marrow negative (discordance). No documentation of bone marrow negativity at assessment of CR.
BGB-3111-206-(b) (6)	Complete Response	Partial Response	Bone marrow positive at screening, PET bone marrow negative (discordance). No documentation of bone marrow negativity at assessment of CR.
BGB-3111-206-(b) (6)	Complete Response	Partial Response	Bone marrow positive at screening, PET bone marrow negative (discordance). No documentation of bone marrow negativity at assessment of CR.
BGB-3111-206-(b) (6)	Complete Response	Partial Response	Gastrointestinal disease documented by endoscopy at screening. No documentation of negative endoscopy at assessment of CR.
BGB-3111-206-(b) (6)	Complete Reponses	Partial Response	Bone marrow positive at screening, PET bone marrow negative (discordance). No documentation of bone marrow negativity at assessment of CR.

Source: Reviewer Analysis, CRF, Applicant Datasets ADRSIRC, XR, XS

Duration of Response

Figure 8 shows a Kaplan-Meier curve for patients with PR or CR (n=72). Percentage of patients with duration of response exceeding 12 months is 74% (53/72). Estimated median duration of response is 19.5 months (Range: 0.9, 19.5; 95% CI: 16.6, NA; number of events = 23). Duration of response results are supportive of the primary efficacy endpoint.

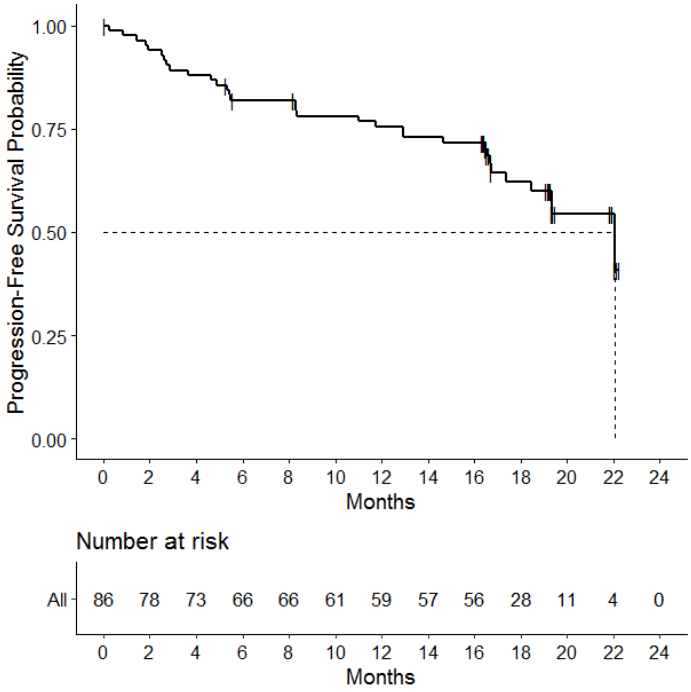
Figure 8. Study BGB-3111-206 FDA-adjudicated Duration of Response



FDA-adjudicated Progression-Free Survival

Figure 9 shows a Kaplan-Meier curve of progression-free survival (n=86). Percentage of patients with duration of response exceeding 12 months is 69% (59/86). Estimated median of progression-free survival is 22.1 months (Range: 0, 22.3; 95% CI: 17.4, NA; number of events = 32). No definitive conclusions can be drawn based on these data.

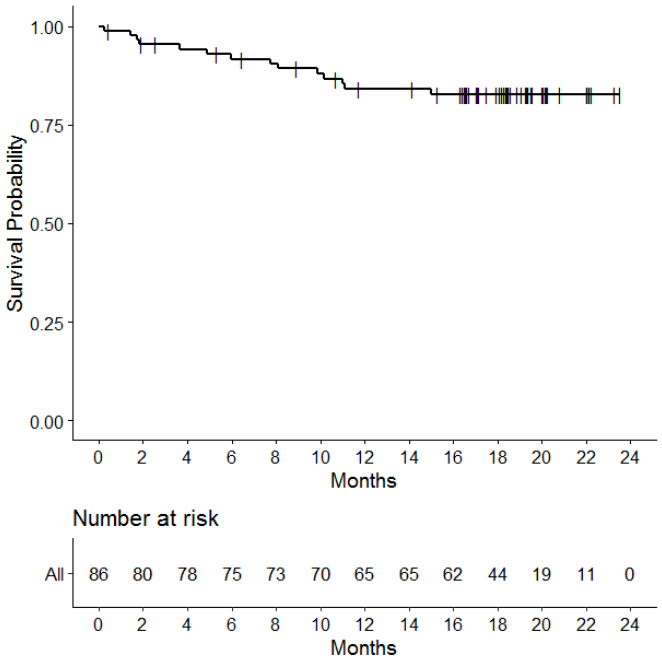
Figure 9. Study BGB-3111-206 FDA-adjudicated Progression-Free Survival



Overall Survival

Figure 10 shows Kaplan-Meier curve of overall survival (n=86). Overall survival estimation based on 14 events is unreliable due to high uncertainty. Median is not estimable, range is 0 to 24 months, and 76% of patients are alive at 12 months. No definitive conclusions can be drawn based on these data.

Figure 10. Study BGB-3111-206 Overall Survival



Dose/Dose Response

See Clinical Pharmacology review section.

Durability of Response

See *Efficacy Results – Secondary and other relevant endpoints* section.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses

Table 20 shows primary efficacy endpoint results by age and sex. Race and region are not reported because the study BGB-3111-206 was conducted in China and all patients were Asian. The subgroups analyses generally support the efficacy of zanubrutinib. No outlier subgroups are observed. Study BGB-3111-206 does not contain sufficient information to determine if subgroup response rates differ.

Table 20. Study BGB-3111-206 Subgroup Analysis of the Primary Efficacy Endpoint

Group	ORR, r/n, % (95% CI)	CR, r/n, % (95% CI)
N (%)	86 (100)	86 (100)
Age		
< 65	59/64, 92 (83, 97)	41/64, 64 (51, 76)
≥ 65	13/22, 59 (36, 79)	10/22, 45 (24, 68)

Sex		
Female	15/19, 79 (54, 94)	8/19, 42 (20, 67)
Male	57/67, 85 (74, 93)	43/67, 64 (52, 76)

r – Responders, n – Number of patients in a subgroup
CI – Confidence interval

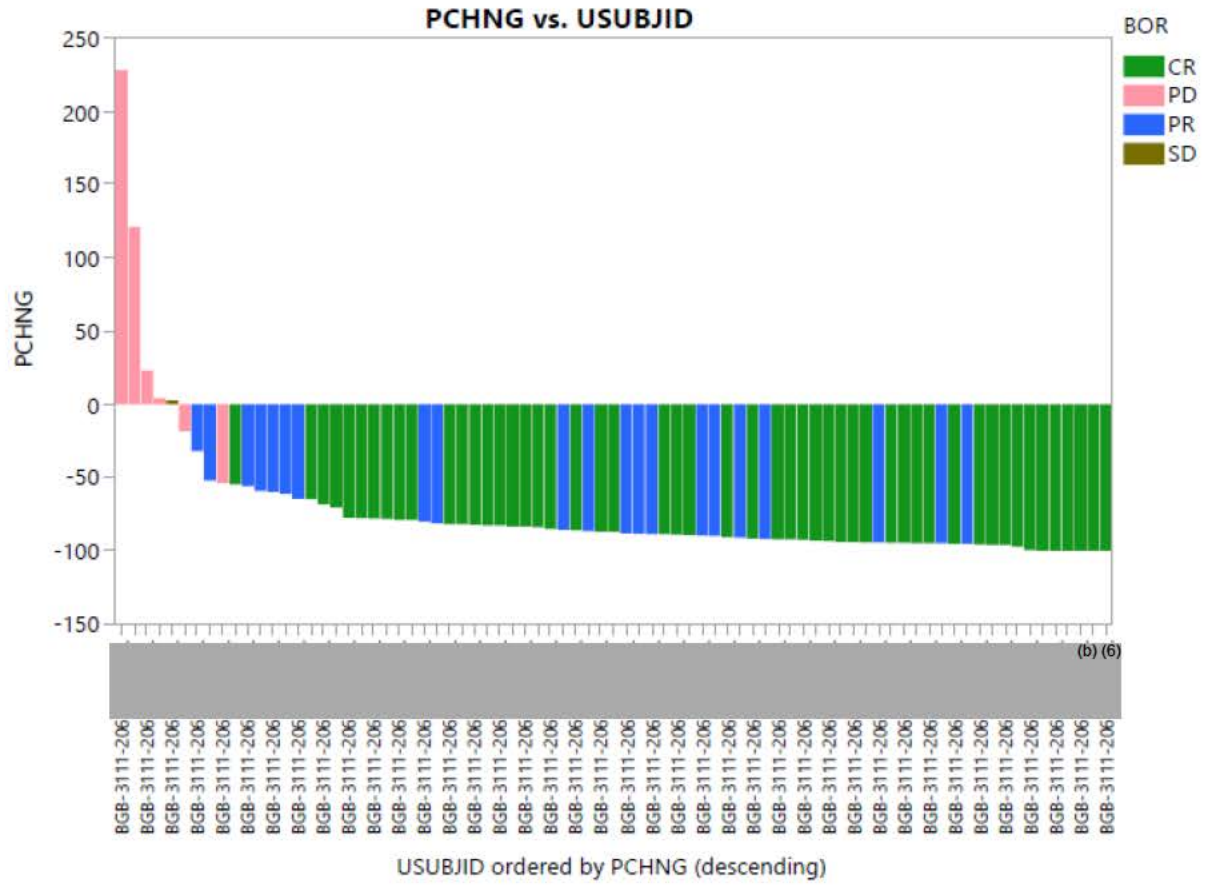
Tumor Shrinkage

A reduction in tumor size as assessed radiographically was demonstrated in 94% of the patients who had response assessments. The majority of responses were > 50% tumor shrinkage.

Reviewer Comment: This further supports clinical benefit since in general patients who experience a reduction in tumor size in mantle cell lymphoma would likely experience clinical benefit due to symptom reduction due to mass effect.

The waterfall plot below demonstrates tumor shrinkage in patients on BGB-3111-206.

Figure 11: Waterfall plot of Percent Change of Tumor Volume and Best Overall Response for Individual Patients on BGB-3111-206



Source: Clinical Reviewer Analysis from Applicant ADRSIRC and TR dataset

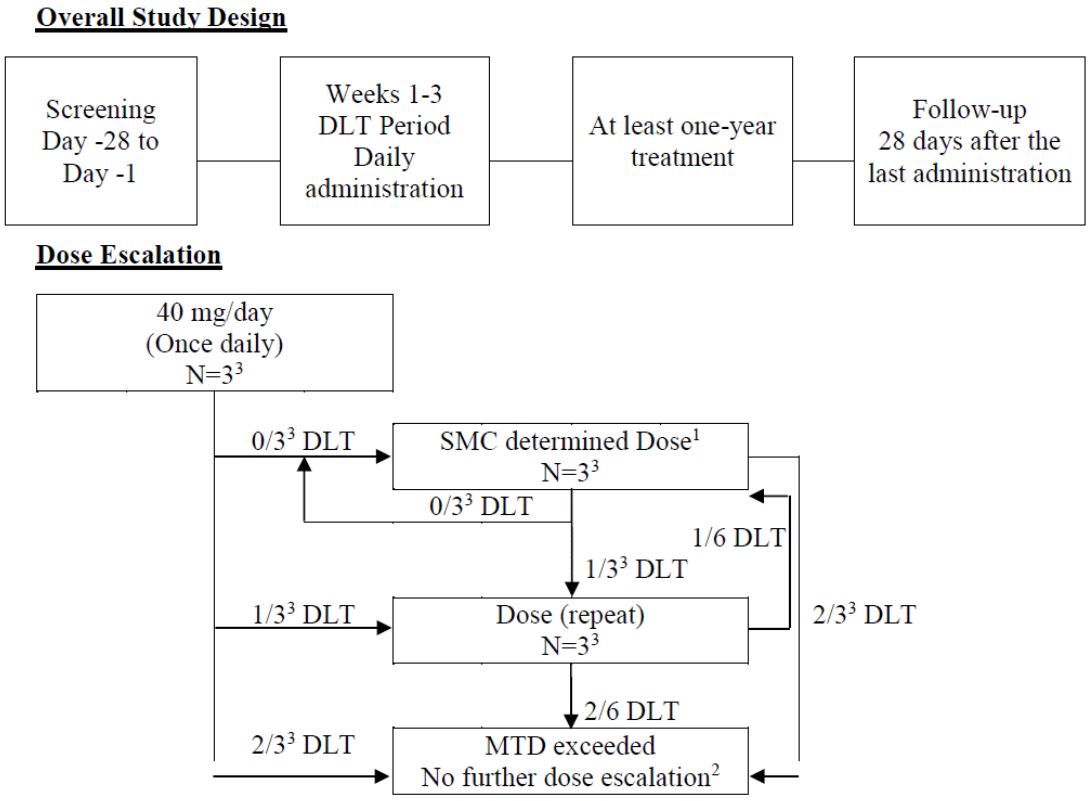
8.1.2. Study BGB-3111-AU-003

Study Title: A Phase I/II, 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
ClinicalTrials.gov identifier: NCT02343120
First Patient Treated: August 25, 2014
Clinical cut-off dates for this submission:
December 13, 2018 (Efficacy)
December 13, 2019 (Primary safety data)
May 8, 2019 (Safety update)

Trial Design

BGB-3111-AU-003 is an ongoing multicenter, Phase 1/2, open-label, multiple-dose, dose-escalation, and first-in-human study of zanubrutinib in patients with different types of B-cell lymphoid malignancies. The study included 2 parts: a dose-escalation part and a study expansion part. The schema for this study is shown in Figure 12.

Figure 12. Study BGB-3111-AU-003 Schema



[Source: Study BGB-3111-AU-003 Protocol v8.0]
1. If 0 of the patients in the cohort experience a DLT by the end of Cycle 1, the dose to be administered in the next cohort will be increased by up to 100%, as determined by the Safety Monitoring Committee (SMC). If a DLT occurs

in 1 of the patients, additional patients will be treated at that dose level, up to a maximum of 6 patients in total. If 1 out of 6 patients experience a DLT during DLT assessment period, the dose to be administered in the next cohort will be increased by up to 100%, as determined by the SMC.
2. No additional patients will be treated at a given dose level if 2 or more out of 3 or 6 patients develop a DLT during DLT assessment period. In this instance, the MTD is considered to have been exceeded.
3. Additional patient(s), up to a maximum of 6 patients in total, will be enrolled if more than 3 patients have been screened and are eligible for the cohort. The DLT assessment and dose-escalation scheme will follow the same principle as stipulated for the standard 3+3 design. For example, 3 additional patients will be enrolled if a DLT is observed in 1 of 3 patients; 2 additional patients will be enrolled if a DLT is observed in 1 of 4 patients; and 1 additional patient will be enrolled if a DLT is observed in 1 of 5 patients. No additional patients are required if a DLT is observed in 1 of 6 patients.
4. If the MTD is exceeded, the next lower dose level is planned to be taken forward into Expansion part. Depending on the decision of the SMC and on review of available data, an additional intermediate dose level, between the MTD exceeding dose level and the next lower dose level, may be explored prior to a final decision on the Expansion dose.
5. In the event that a MTD is not identified due to paucity of DLTs, the Expansion schedule will be based on PK, pharmacodynamic studies of BTK inhibition in PBMCs, safety, tolerability, and preliminary efficacy.

Primary Objective

Part 1. Dose Escalation

- To determine the safety and tolerability of zanubrutinib (also known as BGB-3111) in patients with B-cell malignancies.
- To determine the recommended Phase 2 dose (RP2D) and regimen of zanubrutinib when given continuously orally.

Part 2. Expansion
To further assess the safety and tolerability of zanubrutinib, administered orally either once a day (QD) or twice a day (BID), in patients with specific B-cell malignancies.

Treatment Administration

Patients following a once daily regimen took a single dose of zanubrutinib in the morning. Patients following a twice daily regimen took a single administration of zanubrutinib (half of the total daily dose) in the morning of Day 1, followed by administration of study drug twice daily (once in the morning and once in the evening with 12 ± 2 hours between doses), starting from Day 2. Patients continued to receive study drug until disease progression, intolerance or death, withdrawal of consent, or loss to follow-up.

Tumor Assessment

For MCL, the Lugano Classification (also known as the International Working Group Guidelines) response criteria were used. Each imaging timepoint for a subject was assessed by two independent reviewers who determined radiology (CT/MRI and/or PET) based overall tumor assessment at each post-baseline timepoint and then globally. Adjudication was required if the independent reviewers' endpoint determinations for a global radiology review were in

disagreement for any of the following: Best Overall Response, Timepoint of Best Overall Response, Timepoint of Progression, or Timepoint of First Response. During radiology adjudication review, an independent reviewer who did not participate in the timepoint by timepoint or global radiology review for the subject chose the CT/MRI and/or PET based global radiology endpoint determination(s) he/she agreed with most as the final assessment(s). Following radiology review, one independent oncologist reviewed the final radiology review assessments and available clinical data and provided final CT/MRI-based and FDG-PET-based tumor response assessments per timepoint.

For periodic tumor assessment, computed tomography (CT) with contrast was performed at baseline, every 12 weeks during treatment, and at disease progression. Prior to Protocol Amendment 5 (Version 6), CT scans were performed only as clinically indicated after 1 year. Starting with Protocol V6, CT scans were performed every 6 months after 52 weeks of treatment with zanubrutinib, except for patients with hairy cell leukemia; the frequency of CT scans for patients with hairy cell leukemia followed institutional standard after Week 52.

For patients who discontinued, a CT scan was performed at the early termination visit if the previous scan was performed more than 3 months ago. If patients had no assessable disease by CT at baseline (eg, Waldenström macroglobulinemia without nodal enlargement), repeat scans were not required. Patients with MCL underwent contrast-enhanced CT or MRI scan of the neck, chest, abdomen, and pelvis, as well as other anatomic areas of disease involvement at Screening. Thereafter, scans were repeated every 12 weeks until Week 48. The CT scans were performed every 6 months at 76 weeks of study, or when a significant change in response was suspected. For patients who discontinued study drug for a reason other than PD, a CT imaging was performed at the study termination visit if the previous scan was performed more than 3 months earlier.

An MRI scan may have been used in place of a CT scan at the investigator's discretion in clinical scenarios where anatomical location of an evaluable lesion precluded accurate measurement by CT. At baseline, a whole body fluorodeoxyglucose (FDG) PET or an integrated PET/CT could be performed at investigator discretion. Complete response was to be confirmed by PET scan or an integrated PET/CT for subjects who had FDG-avid disease during screening. Assessment of metabolic activity by PET scan was not required for tumor assessment.

Of the 32 patients in the efficacy population for study 003, 24 (75%) had tumor assessment by CT only, 21 had no PET assessments at any time, and three only had PET at screening. For these patients, response assessment was based on radiographic tumor shrinkage. Of the remaining 8 patients 3 had PET assessments at baseline and at follow up and 5 had PET assessed only at follow up. For these patients PET results were considered in the response assessment.

A bone marrow examination was performed at screening for all patients and within 7 days of the end of Week 12 for patients with baseline marrow involvement. For patients who achieved a possible CR via physical examination or CT scan and who had evidence of bone marrow

disease at the time of enrollment, a bone marrow aspirate and biopsy were obtained to confirm the CR. Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessment(s) for minimal residual disease were performed at least 3 months after the last dose of study drug if there was evidence of CR in both response parameters (i.e., hematology and CT scan). Patients who had disease relapse at any time were asked to undergo re-biopsy of representative tumor sites to obtain samples for studying mechanisms of resistance. These studies could have included phosphoprotein analysis of relevant pathways, whole exome or genome sequencing, and assessments of RNA expression.

Study Endpoints

For the purposes of this review, CR rate and ORR, along with duration or response are considered.

Primary Endpoint (Dose Escalation)

- The safety of zanubrutinib will be assessed throughout the study by monitoring adverse events (AEs), serious adverse events (SAEs), per the NCI-CTCAE Version 4.03, physical examination, and laboratory measurements.
- The RP2D and regimen of zanubrutinib will be determined based on PK, BTK inhibition in PBMCs, safety and tolerability and preliminary efficacy.

Primary Endpoint (Dose Expansion)
The safety and tolerability of zanubrutinib will be further evaluated as described.

Statistical Analysis Plan

Analysis Population

Patients R/R MCL who received either 160 BID (n=14) or 320 QD (n=18) were considered in this review (n=32).

Sample Size Determination

Part 1. Dose Escalation.
The number of dose levels examined and the emerging zanubrutinib toxicities determined the sample size. Initially, it was estimated that approximately 12 subjects would be required to establish the dose and regimen of zanubrutinib to be administered as a single agent in Part 1, but the number was expanded to allow for an anticipated total of up to approximately 25 patients in Part 1.

Part 2. Dose Expansion.
Approximately 380 patients were planned for enrollment in the expansion cohorts in Part 2. In general, the sample size for individual disease cohorts was based on obtaining rigorous

descriptions of the safety profile and estimates of the response rates for zanubrutinib in specific B-cell malignancies that have sufficient precision.

Analysis of the Efficacy Endpoints
Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the point estimate of ORR. Kaplan-Meier (KM) method will be used to estimate duration of response.

Protocol Amendments

Table 21 shows major protocol amendments.

Table 21. Study BGB-3111-AU-003 Major Protocol Changes

Protocol Version (Date)	Major Changes
8 (25 September 2018)[1]	• Clarified process of response evaluation by independent review for Waldenström macroglobulinemia and MCL and added other clarifications for response criteria; for patients with MCL, after Week 52, appropriate imaging for response assessment should be conducted every 12 weeks stating form Week 64 (end of Weeks 64, 76, 88, and 100) and every 24 weeks thereafter from Week 100 or when a significant change in response is suspected (PD or upgrade of response) • Increased frequency of scans for patients with MCL (Year 1: every 12 weeks; Year 2: every 12 weeks beginning with Week 64 through Week 100 then every 24 weeks thereafter for patients with MCL (as stated above); every 24 weeks for other cohorts)
7 (02 October 2017)	• Extended study treatment option beyond 1 year, allowing for patients to receive zanubrutinib until disease progression • Added response assessments following Week 52 (i.e., every 6 months instead of only as clinically indicated) • Added a survival follow up assessment
6 (09 September 2016)	• Reduced the frequency of clinical visits and PK sample collection • Removed the collection of pharmacodynamic samples • Added assessment schedule for CT scans after 1 year
5 (11 January 2016)	• Added Part 2g (20 patients with relapsed or refractory MCL)
4 (24 June 2015)	• Changed inclusion criterion #2 to restrict enrollment in Part 1 to patients with relapsed or refractory disease following at least 1 line of therapy, with no therapy of higher priority available • Extended the schedule of assessments to include timepoints after Week 52 • Added follow-up assessment for progression and survival
3 (02 December 2014)	• Limited biopsy of lymph node only in Part 2
2 (5 January 2017)	• Modified the 3+3 dose escalation scheme in Part 1 to allow more than 3 patients (up to a maximum of 6) to enroll before assessments of DLTs. • Modified the DLT definition for non-hematologic Grade 3 events to exclude asymptomatic laboratory abnormalities

[1] No patients have been enrolled under Version 8 of the protocol as of the data cutoff date (13 December 2018).

Study Results

Compliance with Good Clinical Practices

The protocol, protocol amendments, and patient informed consent forms for Study BGB-3111-003 were reviewed and approved by the Institutional Review Boards or Independent Ethics Committees of the participating study centers.

During the course of the study, both site and independent audits of one site (003) revealed deviations from GCP. Enrollment of the site was suspended at the time of an internal audit in August 2015. A total of 12 patients were enrolled at this site including one patient with R/R MCL. These subjects were excluded from all analyses of safety, efficacy, PK, and PD.

For the remainder of the study sites Study BGB-3111-003 was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the U.S. Code of Federal Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representatives voluntarily consented prior to trial enrollment.

Financial Disclosure

The Applicant submitted financial disclosure information from 69 principal investigators and 485 sub-investigators from five studies including the 28 principal investigators and 295 sub-investigators from study 003 indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 19.3.

Data Quality and Integrity

Data from the study BGB-3111-AU-003 were provided electronically with standard formats. The data and analysis quality of the submission was acceptable to perform the review.

Patient Disposition

Table 22 shows disposition of patients.

Table 22. Study BGB-3111-AU-003 Disposition in Patients with R/R MCL

	n (%)
N	32 (100)
Study	
Ongoing	17 (53)
Discontinued	15 (47)
New Therapy	1 (3)
Progressive Disease	1 (3)
Adverse Event	3 (9)
Death	10 (31)
Adverse Event	2 (6)
Progressive Disease	6 (19)
Septic Shock	1 (3)
Unknown	1 (3)
Treatment	
Ongoing	14 (44)
Discontinued	18 (56)
Adverse Event	8 (25)
Progressive Disease	10 (31)

Protocol Violations/Deviations

No patients with relapsed/refractory MCL in study BGB-3111-AU-003 had any major protocol deviations.

Table of Demographic and Baseline Characteristics

Table 23 shows demographic and baseline characteristics.

Table 23. Study BGB-3111-AU-003 Demographics and Disease Characteristics in Patients with R/R MCL

	n (%)
N	32 (100)
Age, Median (Range)	70.5 (42.0, 86.0)
< 65 Years	8 (25)
>= 65 Years	24 (75)
Sex	
Female	10 (31)
Male	22 (69)
Race	
Asian	3 (9)
Black or African American	1 (3)
Other	3 (9)
White	25 (78)
Blastoid Histology	
No	28 (93)
Yes	2 (7)
Stage	
Stage I	2 (6)
Stage II	1 (3)
Stage III	1 (3)
Stage IV	28 (88)
MIPI Risk Group	
High Risk	10 (31)
Intermediate Risk	13 (41)
Low Risk	9 (28)

	n (%)
Bulky Disease	
Longest Diameter ≤ 10 cm	29 (91)
Longest Diameter > 10 cm	3 (9)
Extranodal Disease	
No	22 (69)
Yes	10 (31)
Bone Marrow	18 (56)
ECOG	
0	15 (47)
1	14 (44)
2	3 (9)
Prior Lines of Therapy	
1	19 (59)
2	4 (12)
3	7 (22)
4	2 (6)

MIPI = MCL International Prognostic Index,
ECOG = Eastern Cooperative Oncology Group Performance Status

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All 32 subjects received concomitant medications after study entry. The most common therapeutic class of concomitant medications was antibacterials (73%), analgesics (62%), and drugs for acid-related disorders (57%).

Reviewer comment: The types of concomitant medications used in this trial would not have been expected to affect efficacy as they would have no activity against mantle cell lymphoma.

Based on the reported relative dose intensity of 99%, compliance was not a significant concern or identified on review of exposure.

Efficacy Results – Primary Endpoint

Overall response rate is 84% (27/32; 95% CI: 67, 95).

Efficacy Results – Secondary and other relevant endpoints

Response Rates

Table 18 shows response rates. Complete response rate is 22% (7/32, 95% CI: 9, 40).

Table 24. Study BGB-3111-AU-003 FDA-adjudicated Response Rates

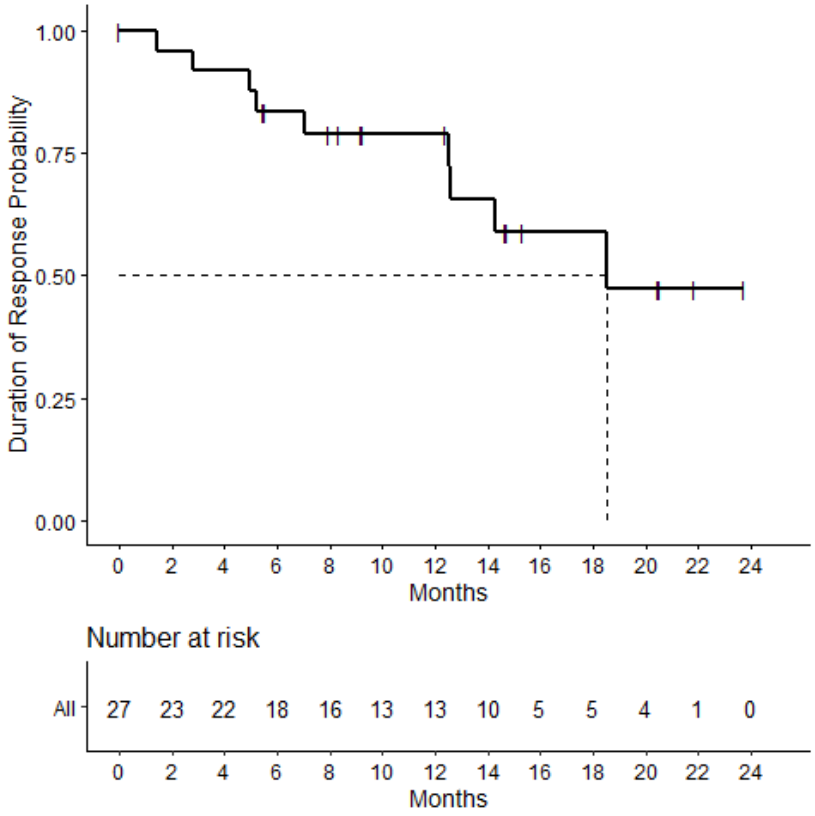
Response	n (%)
CR	7 (22)
PR	20 (62)
PD	2 (6)
SD	2 (6)
Unknown	1 (3)

Reviewer's Comment: *Rounding half to even per International Organization for Standardization rule (e.g 62.50 => 62, 63.50 => 64).*

Duration of Response

Figure 8 shows a Kaplan-Meier curve for patients with PR or CR (n=27). Percentage of patients with duration of response exceeding 12 months is 48% (13/27). Estimated median duration of response is 18.5 months (Range: 0, 23.8), but these estimates may be unreliable due to small number of events (n=9).

Figure 13. Study BGB-3111-AU-003 FDA-adjudicated Duration of Response



Dose/Dose Response

See Clinical Pharmacology review section.

Durability of Response

See *Efficacy Results – Secondary and other relevant endpoints* section.

Additional Analyses Conducted on the Individual Trial

Table 20 shows efficacy results by age, sex, race, and region. The subgroups analyses generally support the efficacy of zanubrutinib. No outlier subgroups are observed. Study BGB-3111-AU-003 does not contain sufficient information to determine if subgroup response rates differ.

Table 25. Study BGB-3111-AU-003 Subgroup Analysis of the Primary Efficacy Endpoint

Group	ORR, r/n, % (95% CI)	CR, r/n, % (95% CI)
N (%)	32 (100)	32 (100)
Age		
< 65 years	5/8, 62 (24, 91)	2/8, 25 (3, 65)
≥ 65 years	22/24, 92 (73, 99)	5/24, 21 (7, 42)

Sex		
Female	10/10, 100 (69, 100)	3/10, 30 (7, 65)
Male	17/22, 77 (55, 92)	4/22, 18 (5, 40)
Race		
White	23/25, 92 (74, 99)	7/25, 28 (12, 49)
Asian	1/3, 33 (1, 91)	NA
Other	3/3, 100 (29, 100)	NA
Region		
Australia/New Zealand	19/20, 95 (75, 100)	3/20, 15 (3, 38)
North America	8/10, 80 (44, 97)	4/10, 40 (12, 74)

r – Reponders, n – Number of patients in a subgroup, CI – Confidence interval

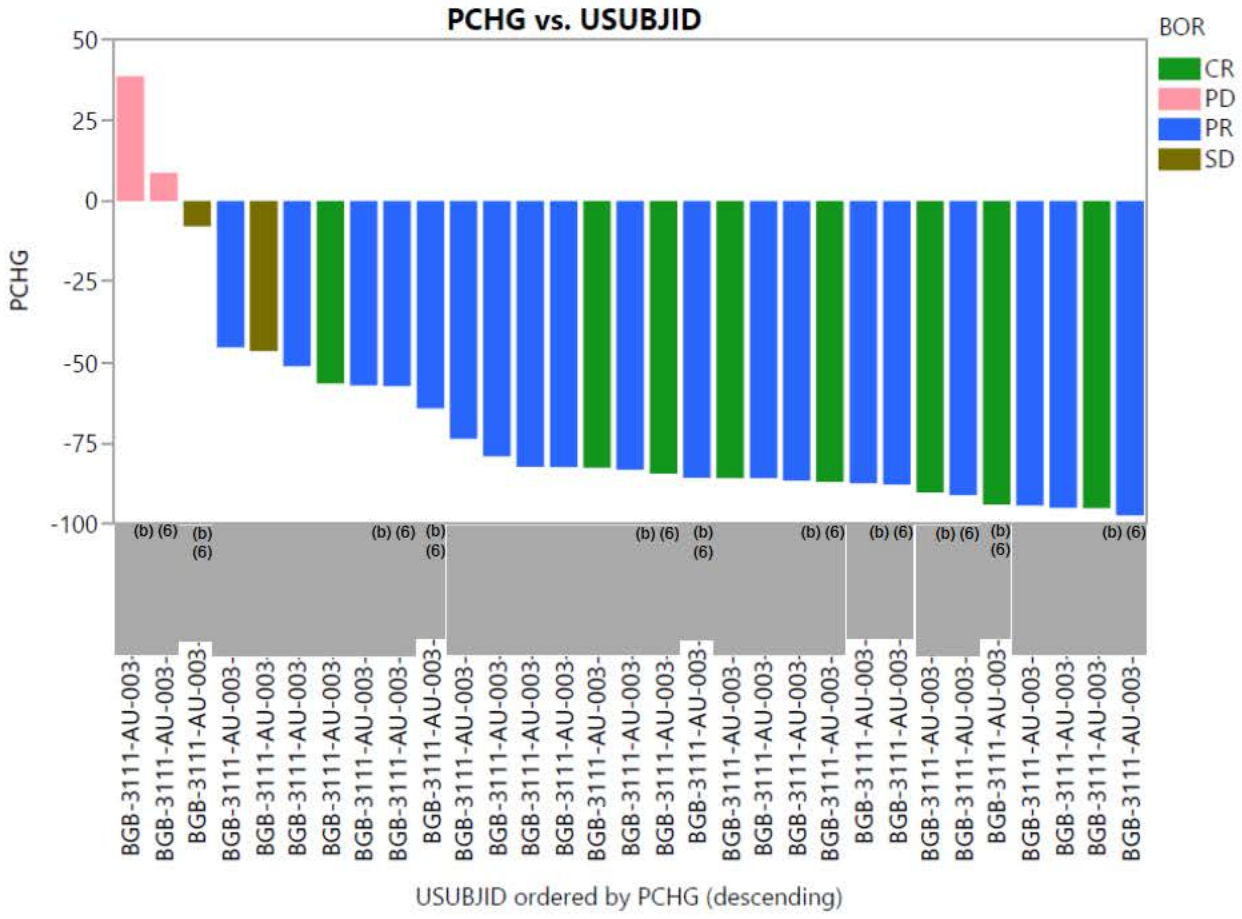
Tumor Shrinkage

A reduction in tumor size as assessed radiographically was demonstrated in 90% of the patients in the efficacy population (patients who received 160mg BID or 320mg once daily) who had response assessments. The majority of responses were > 50% tumor shrinkage.

Reviewer Comment: This further supports clinical benefit since in general patients who experience a reduction in tumor size in mantle cell lymphoma would likely experience clinical benefit due to symptom reduction due to mass effect.

The waterfall plot below demonstrates tumor shrinkage in patients on BGB-3111-AU-003.

Figure 14: Waterfall plot of tumor shrinkage and best response for individual patients on BGB-3111-AU-003



Source: Reviewer Analysis from Applicant ADRSIRC dataset

8.1.3 Integrated Assessment of Effectiveness

The efficacy of zanubrutinib for the treatment of patients with R/R MCL has been assessed based on single-arm studies BGB-3111-206 and BGB-3111-AU-003. The major issue affecting most key efficacy outcomes was response assessment. The issue has been resolved through FDA-adjudication of IRC response assessment and correspondence with the Applicant (see Section 7.2). A total of 118 were included in the overall assessment of efficacy. The efficacy of zanubrutinib was demonstrated by a high overall response rate (84%) per IRC in both studies. Duration of response was also demonstrated and similar (19.5 months in study BGB-3111-206 and 18.5 months in study BGB-3111-AU-003) in both studies Internal consistency of

zanubrutinib favorable efficacy has been demonstrated by i) overall response rate ii) supporting evidence on the complete response rate and duration of response iii) supporting efficacy evidence from the R/R MCL patient cohort from an international study BGB-3111-AU-003 (n=32). Benefit of zanubrutinib for the treatment of patients with R/R MCL has been demonstrated primarily based on study BGB-3111-206.

The use of overall response rate in mantle cell lymphoma is considered an intermediate endpoint and is clinically meaningful with supporting evidence from duration of response. Overall response rate with verified durable response as an endpoint has been the basis for accelerated approval and regular approval in past reviews. Approvals based demonstration of an improvement on ORR for mantle cell lymphoma and other non-Hodgkin lymphomas have required confirmation of benefit based on an accepted clinically meaningful endpoint such as PFS or OS in a randomized trial to support regular approval.

The 206 study was conducted solely in China. Evaluation of the baseline characteristics, prior therapies, as well as the requirement for central review of pathology diagnosis, and IRC assessment of key endpoints diagnosis allow for a conclusion that the results from the population studied in 206 may be similar to what would be expected in a U.S. population. This is supported by the similar results (ORR) reported in the 003 study which enrolled patients globally. Difference in the CR rates reported from the two studies may be related to the requirement for PET assessment in the 206 study which allows for CR in the face of residual tumor. Some uncertainty in treatment effect magnitude in the US population remains because treatment effect cannot be estimated directly in a single-group cohort and because study BGB-3111-206 has been conducted in an Asian population. This uncertainty may be alleviated if the treatment benefit is confirmed in a large international randomized trial. Treatment effect observed in the study BGB-3111-206 should be confirmed with a progression-free or overall survival outcome in an adequately designed randomized trial.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety review emphasis was placed on the safety data in patients with relapsed or refractory MCL who received zanubrutinib at either 160mg twice daily or 320mg once daily (primary safety pool). Supportive safety data included analysis from additional patients with B-cell malignancies who received zanubrutinib as monotherapy at doses of either 160mg twice daily or 320mg once daily in the total safety pool.

The clinical review of safety is based on all-causality treatment-emergent adverse events (TEAEs) in patients who received the study therapy. TEAEs were defined as adverse events that were new or worsened from baseline grade and were reported from the start of study drug to 30 days following the last dose of study drug.

The Applicant reported adverse events using single MedDRA preferred terms (PTs). For increased sensitivity, FDA used a combination of ungrouped and custom grouped PTs, as defined in Appendix 19.7. Additionally, adverse events that involve more than one body system were consolidated and reported under the most commonly involved or most appropriate body system. Unless noted, all presented analyses use the FDA grouped preferred terms (PTs).

Case report forms were provided and reviewed for all patient in the 206 study and all patients who died or discontinued study therapy, serious AEs, and deaths that occurred in the primary within 30 days of taking zanubrutinib. Particular attention was placed on the treatment emergent adverse events (TEAE) of hemorrhage and cardiac arrhythmia, potential class effect TEAEs. The reviewer performed additional analyses for cardiac events, hemorrhage, infections, and second primary malignancies.

The clinical review of safety was based upon:

- CSR for studies 206 and 003
- Protocol and Statistical Analysis Plan for studies 206 and 003
- Integrated data sets for the populations described above
- Summary of Clinical Safety
- Integrated Summary of Safety

- Proposed labeling for zanubrutinib

8.2.2. Review of the Safety Database

The safety analysis provided by the Applicant was reviewed for 641 enrolled and treated with zanubrutinib on studies BGB-3111-206, BGB-3111-AU-003, BGB-3111-205, BGB-3111-210, BGB-3111-1002. Studies will be identified hereafter in the safety review is studies 206, 003, 205, 210 and 1002, respectively. The safety data provided by the Applicant were derived from five open-label safety and efficacy studies in patients with mantle cell lymphoma, chronic lymphocytic leukemia (CLL), CLL with Richter's transformation, Waldenström's Macroglobulinemia (WM), Diffuse Large B-cell Lymphoma (DLBL), Hairy Cell Leukemia, and Follicular Lymphoma (FL). The data included 123 patients with relapsed and refractory mantle cell lymphoma population from studies 206 and 003.

The primary focus of the safety review was the patient population with R/R MCL who received a total daily dose of 320mg, either 160mg twice daily or 320mg once daily (N = 118). The Applicant provided safety summaries and datasets from patients with R/R MCL treated on the 206 study (N=86) and the total safety pool which consisted of 641 patients who had received zanubrutinib as monotherapy for hematologic malignancies. Of the 641 patients, 629 received either 160mg twice daily or 320 mg once daily, and were considered the total safety population.

Safety analysis was conducted on the complete dataset provided by the Applicant for study 206

with a cut-off date of February 19, 2019. Safety cutoff dates for the four additional studies were December 13, 2018 for study 003, December 14, 2018 for study 205 and 1002, and December 2, 2018 for Study 210. In addition, the Applicant submitted a 90-day safety update for the total safety population with a safety cut-off date of May 8, 2019 for all studies. The 90-day safety updated included 8 additional patients to study AU-003.

Overall Exposure

A total of 641 patients in the applicant sponsored studies received at least one dose of zanubrutinib. Of the 641 patients in the total safety pool, all but 12 received a starting dose of, either 160mg BID (N=524) or 320mg once daily (105). This safety review focuses on the 629 patients in the total safety pool and the 118 patients with relapsed or refractory MCL who received 160mg twice daily or 320mg once daily. A summary of the safety populations and dose received is summarized in the table below.

Table 26: Safety Populations and Zanubrutinib Dosing

Population	Studies	Zanubrutinib Starting Dose monotherapy	Total Number	Number who received 160mg BID or 320mg once daily
Total Safety Population	003, 206, 205, 210, 1002	160mg BID (N=524) 320mg QD (N=105) 40mg QD (N=3) 80mg QD (N=4) 160mg QD (N=5)	641	629
Relapsed and Refractory Mantle Cell Lymphoma	003, 206	160mg BID (105) 320mg QD (13) 40mg QD (1) 80mg QD (2) 160mg QD (2)	123	118
Primary Efficacy Population	BGB-3111-206	160mg BID	86	86

Source: FDA summary of Applicant's EX and ADEX dataset and SCS Module 2

A summary of exposure to zanubrutinib by patient group is summarized in the table below. Exposure was similar in the all doses populations compared to those who received the indicated dose (160mg BID or 320 mg QD) in both the B cell malignancies and the R/R MCL pool. The median duration of exposure for patients who received 160mg BID or 320mg QD was longer in patients with r/r MCL (17.5 months) compared to the B cell malignancy pool (13.9 months). The median actual dose intensity of zanubrutinib (mg) in patients with r/r MCL who received 160mg BID or 320mg QD was 319 (range 147, 342) with a median relative dose intensity of 99.8 (range 46,107).

Table 27: Exposure to Zanubrutinib monotherapy

Parameter		All R/R MCL (206 + 003) N = 123			Total Safety Pool N = 641	
		206 N = 86	All doses N = 123	160mg BID or 320mg once daily N = 118	All doses N = 641	160mg BID or 320mg once daily N =629
Exposure duration, months	Median	17.7	17.5	17.5	13.9	13.9
	Range	0.2, 24	0.2, 34	0.2,34	0.1, 50	0.1, 46
Relative dose intensity	Mean (SD)	99.8 (7.2)	99.9 (46.4)	99.8 (9)	99.7 (34)	97.1 (9.2)
% of Patients on Treatment by month	≥3 months	86%	86%	86%	87%	87%
	≥6 months	79%	78%	79%	79%	79%
	≥12 months	71%	67%	68%	61%	61%
	≥18 months	47%	44%	44%	28%	28%
	≥24 months	0	3%	3%	19%	18%
	≥ 36 months	0	0	0	5%	4%

Source: FDA analysis of ADEX, ADSL datasets

Relevant characteristics of the safety population:

Demographic information for the r-r MCL patients enrolled in Study 206, 003 and the B cell malignancies pool treated at the doses included in the indication is summarized in the table below. The demographics of the pooled safety database are generally similar to the efficacy populations in Study 206 with the exception that study 206 was conducted solely in China and 100% of the population was Asian. Study 003 was a global study with 50% of the population Asian, 44% White and the remainder, other.

Table 28: Demographics and Disease Characteristics for Safety Populations

	Study 206 N=86	Pooled R/R MCL Population N= 118	B Cell Malignancies N=629
Age(years) Median (range)	61 (34,75)	62 (34,86)	63 (20,90)

	Study 206 N=86	Pooled R/R MCL Population N= 118	B Cell Malignancies N=629
Sex (%)			
Male	78	75	68
Female	22	25	32
Race (%)			
White	0	21	44
Black or African American	0	0.8	0.6
Asian	100	75	50
Other	0	3	6
ECOG Status (%)			
0	70	64	48
1	26	31	46
2	5	6	6
Prior Therapies (%)			
1	29	37	37
2	37	31	27
3 and beyond	34	32	29

Source: FDA Analysis ADSL, ADECOG, ADBASE datasets

Adequacy of the safety database:

The safety review was conducted using the integrated datasets provided by the Applicant from clinical studies listed in Table 11. A data pool including patients with relapsed and refractory B cell malignancies who received zanubrutinib monotherapy was used to develop the safety profile in patients treated at the indicated dose. This data pool provided 629 patients with hematologic malignancies, treated with either 160mg twice daily (N = 524) or 320mg (N = 105) which is an adequate number for a review of safety at both doses. The median duration of exposure in the r/r MCL and total population of 17.5 months and 13.9 months respectively is an adequate duration of exposure to assess safety for a continuously administered agent over an extended period of time.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

The data submitted to this NDA was of adequate quality to perform the safety review. Overall, there were no concerns regarding the integrity of the NDA submission.

Issues Regarding Data Integrity and Submission Quality

The data submitted to this NDA was of adequate quality to perform the safety review. Overall,

there were no concerns regarding the integrity of the NDA submission.

Adequate narratives were provided for all deaths to include those due to progressive disease, serious adverse events, adverse events leading to discontinuation from study treatment, and for the AEs of special interest of atrial fibrillation, major hemorrhage, and second primary malignancy. A subset of the safety data was traced back to the primary source (individual case report forms) and no discrepancies were identified.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 and reported down to the investigator's verbatim term. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03). Treatment emergent adverse events were defined as those events that occurred or worsened on or after the first dose of study treatment through 30 days following the last dose of study treatment

Routine Clinical Tests

Laboratory assessments were carried out as specified in the protocols (BGB-3111-206 and BGB-3111-AU-003). For study 206 complete blood count (CBC) and serum chemistry assessments assessed on day one of each cycle for cycles 1 through 13 (weeks 1 through 52) and then every 8 weeks for subsequent cycles. For study 003, CBC and serum chemistry assessments were collected on week 1 and 2 and 5 of treatment, then once every 4 weeks until week 52 and then once every 12 weeks for the remainder of treatment. In addition to datasets with laboratory findings for scheduled and unscheduled assessments with toxicity grading per CTCAE and iwCLL for patients with CLL, the Applicant provided a summary of laboratory changes from baseline. Laboratory abnormalities to be reported as AEs were defined in the protocol as any unfavorable and unintended sign temporally associated with the use of a study drug, whether considered related to study drug or not. Additional laboratory assessments were obtained for each protocol as clinically indicated.

8.2.4. Safety Results

Deaths

The Applicant assessed all deaths in the R/R mantle cell lymphoma and the pooled safety population, to include the follow-up period, deaths within 30 days after last dose, and Grade 5 TEAEs.

On FDA analysis, in the R/R MCL population who received either 160mg BID or 320mg BID, a total of 13 patients died in the absence of progressive disease. Ten deaths were considered due to adverse events by the applicant, 2 were considered due to "other" and one was considered unknown. An analysis demonstrated that infection, primarily including sepsis and pneumonia, was the most common cause of non-relapse death. Other causes included road traffic accident

cerebral hemorrhage, cerebral infarction, and congestive heart failure. The table below summarizes the death categorizations.

Table 29: Summary of Deaths in Subjects Receiving Zanubrutinib

	206 N =86 n(%)	003 N = 32 n (%)	R/R MCL N = 118 n (%)	B-cell malignancies N = 629 n(%)
All Deaths	14 (16)	11 (37)	25 (22)	87 (14)
Disease Progression	6 (7)	6 (19)	12 (10)	49 (8)
Adverse Event	7 (8)	3 (9)	10 (8)	25 (4)
Other	1 (1.2)	1 (3)	2 (3)	6 (1)
Unknown	0	1 (3)	1 (1)	7 (1)
Within 30 days of Last Dose	7 (8)	5 (16)	12 (10)	39 (6)
Disease Progression	1 (1.2)	1 (3)	2 (2)	15 (2)
Adverse Event	6 (7)	3 (9)	9 (8)	21 (3)
Other	0	0	0	0
Unknown	0	0	0	2 (0.3)

Source: FDA analysis of Applicant Data Sets ADSL, DD, ADAE, and study narratives

A review of death narratives was conducted. The Applicant's and FDA's analysis of the cause of death and related to study therapy are detailed in the table below. In general, there was agreement between the Applicant and FDA analysis. Several cases were confounded by death's attributed to AEs occurring outside of hospital settings in the setting of discontinuation of study therapy or in the setting of progressive disease.

Table 30: Summary of Deaths < 30 days form last zanubrutinib dose due to an AE or death due to "other" or "unknown" in patients with R/R MCL on study BGB-3111-206 or AU-003.

USUBJID	Study Day of Death	Days from last dose Zanubrutinib	Applicant provided cause of death and relatedness	Agency assessed cause of death and relatedness
Deaths due to AEs on Study 206 occurring within 30 days of last dose of zanubrutinib				
(b) (6)	149	1	Road Traffic Accident Not related	Road Traffic Accident Unlikely related
(b) (6)	56	2	Unknown	Unknown Likely Infection possibly related
(b) (6)	53	24	Unknown	Unknown Likely Progressive Disease
(b) (6)	8	1	Cerebral Hemorrhage Related	Cerebral Hemorrhage Related
(b) (6)	47	23	Pneumonia	Pneumonia

USUBJID	Study Day of Death	Days from last dose Zanubrutinib	Applicant provided cause of death and relatedness	Agency assessed cause of death and relatedness
			Related	Related, progressive disease likely contributing
(b) (6)	61	20	Death Unknown Possibly Related	Unknown, possibly related to zanubrutinib, confounded by progressive disease
Deaths due to AEs on Study 206 occurring > 30 days after of last dose of zanubrutinib				
(b) (4), (b) (6) *	235	66	Fungal pneumonia	Fungal Pneumonia Likely related
(b) (6) *	456	350	Other unknown Unrelated	Unknown, Pt has discontinued zanubrutinib therapy due to PD and started subsequent anticancer therapy Unrelated
Deaths due to AE or "Other" on Study 003 occurring within 30 days after the last dose of zanubrutinib				
AU-003-(b) (4)	639	3	Cerebral infarction Not related	Cerebral infarction Possibly related
AU-003-(b) (4)	295	2	Pneumonia and PD Not related	Pneumonia and PD Possibly related
AU-003-(b) (4)	59	3	CHF Not related	CHF Not related
Deaths due to AE, "Other" or unknown on Study 003 occurring > 30 days after the last dose of zanubrutinib				
AU-003-(b) (6) *	556	87	unknown	No information available on cause of death, subject. had discontinued therapy due to PD
BGB-3111-AU-003-(b) (6) *	281		Other	

*death occurred > 30 days after discontinuation of study therapy
Source: FDA analysis of Applicant datasets, ADSL, DT, ADAE, individual patient narratives, and CRFs

Narratives of individual deaths
Study 206

- **Patient** (b) (6) was a 54-year-old male who died on SD 149 after being involved in the road traffic accident. The study narrative indicated that the patient was involved in a motor vehicle incident and was taken to a hospital where resuscitative efforts failed. The most recent dose of zanubrutinib was taken on the same day. The investigator assessed that the death was unrelated to study therapy. There was no information provided to indicate that the cause of the accident was related to study therapy. The patient has one other AE reported, grade 1 abdominal pain on study day 6 that resolved after three days. No modification of study therapy occurred.

  Reviewer comment: There was no information provided to indicate that the cause of death was related to study therapy. This reviewer agrees with the Applicant's assessment based on the information provided and the timing of the death.

- **Patient** (b) (6) was a 66-year-old female who died on SD 56 after zanubrutinib had been held due to infection on SD 54. The patient had been previously treated on SD 34-40 for a UTI and was discharged from the hospital on day 40 after receiving antibiotics. On SD 54, the patient developed a fever and generalized weakness and was noted to have elevated WBC. Per the narrative, the patient was advised to go to the local hospital for evaluation but refused. The patient died at home two days later due to unknown causes although infection was suspected. No autopsy was performed.

  Reviewer comment: Per information provided in the narrative, the patient may have died due to an incompletely treated or new infection. Since there was no autopsy performed or disease assessment prior to death, it is unclear if progressive disease contributed to death. This reviewer agrees with the Applicant's assessment of "unknown" based on the information provided and the timing of death, although infection seems likely.

- **Patient** (b) (6) was a 64-year-old female who died on SD 53 after zanubrutinib had been withdrawn on SD 33 due to investigator decision due to abdominal distension attributed to bulky abdominal disease with poor disease control. The patient was discharged from the hospital on SD 35 and died on SD 53 due to unknown cause. No additional information was provided, and it was not reported if an autopsy was performed. The investigator assessed the cause of death as unknown and not related zanubrutinib. Progressive disease was suspected.

  Reviewer comment: Per information provided in the narrative, the patient likely died of progressive disease given that there was poor disease control as assessed by the investigator at the time may have died due to an incompletely treated or new infection. Since there was no autopsy performed or disease assessment prior to death, it is unclear if progressive disease contributed to death. This reviewer agrees with the Applicant's

assessment of "unknown" based on the information provided and the timing of death, although progressive disease seems a likely significant factor.

- **Patient** (b) (6) was a 70-year-old male who died on SD 8 after the patient had developed a headache and was reported to have mental status changes on SD 7. The most recent dose of zanubrutinib was taken on SD 6, one day prior to the onset of symptoms. The patient was not reported to have a history of fall or hypertension and was not taking concomitant medications. Cerebral hemorrhage was confirmed by computed tomography (CT) and the patient died on SD 8 after medical interventions to include decompression failed to improve clinical symptoms. No autopsy was performed. The investigator assessed the cause of death as cerebral hemorrhage and related zanubrutinib.

  Reviewer comment: Per information provided in the narrative, the patient died of complications from cerebral hemorrhage experienced 7 days after starting zanubrutinib therapy. The patient had no prior history of CNS or bleeding disorder and there were no other confounding factors, making it likely that zanubrutinib likely contributed to the patient's events of cerebral hemorrhage and death. This reviewer agrees with the Applicant's assessment based on the information provided and the timing of death. Bleeding, to include fatal bleeding events, have been reported with BTK inhibitors.

- **Patient** (b) (6) was a 47-year-old male who had received three prior therapies for MCL. The patient was initially hospitalized for pneumonia on study day 86 and was diagnosed with disease progression on SD 88. Zanubrutinib was permanently withdrawn at that time due to progressive disease. On SD 111 the condition of pneumonia was reported to have worsened, and the patient died on SD 111. No autopsy was performed. The investigator assessed the event of pneumonia as related to zanubrutinib.

  Reviewer comment: Per information provided in the narrative, the patient died of complications from pneumonia on SD 111 after discontinuing therapy due to progressive disease diagnosed by imaging on SD 88. The patient had a prior AE of skin rash resulting in dose reduction on SD day 4 and was receiving zanubrutinib 80mg BID at the time of the diagnosis of pneumonia. Infections are a known AE associated with BTK inhibitors. The patient was heavily pre-treated with may have contributed to the development of infection. This reviewer agrees with the Applicant's assessment based on the information provided and the timing of death. Progressive disease likely also contributed to the patient's death.

- **Patient** (b) (6) was a 61-year-old female who had received two prior therapies for MCL. On study day 280 the patient was noted to be pancytopenic and zanubrutinib was withheld. The patient developed a lung infection on SD 283. Over the next week the patient remained pancytopenic and received several transfusions as well as antibiotic therapy for lung infection. The patient was discharged home on SD 300 and died on SD

300, 20 days after zanubrutinib was discontinued. No autopsy was performed and no specific cause of death was given. The investigator assessed the AEs of death to be possibly related to zanubrutinib.

Reviewer comment: Per information provided in the narrative, the patient died of complications from pancytopenia and pneumonia possibly related to zanubrutinib or progressive disease. Of note, the patient's bone marrow evaluation in March of 2018 was reported to be negative for bone marrow involvement, but was positive in May of 2018, approximately 6 weeks prior to death. This finding is consistent with progressive disease and may have contributed to pancytopenia and death. This reviewer agrees with the Applicant's assessment of death due to unknown reason possibly related to zanubrutinib based on the information provided and the timing of death. Progressive disease likely also contributed to the patient's death.

- **Patient** (b) (6) was a 74-year-old male who had received three prior therapies for MCL. On study day 164, zanubrutinib was withdrawn due to interstitial lung disease which initially improved after zanubrutinib discontinuation. The patient was diagnosed and hospitalized for fungal pneumonia on SD 198 and died of fungal pneumonia on SD 236, 66 after the last dose of zanubrutinib. No autopsy was performed. The investigator assessed the AE of fungal pneumonia as unlikely related to zanubrutinib.

  Reviewer comment: Per information provided in the narrative, the patient died of complications from fungal pneumonia. Infections, to include opportunistic infections are a known AE associated with BTK inhibitors. Since the patient's pulmonary symptoms began while the patient was receiving zanubrutinib without additional anti-cancer therapy, this reviewer considers the AE of fungal pneumonia as possibly relate dot zanubrutinib. Confounding factors include corticosteroid therapy administered for interstitial lung disease. pancytopenia and pneumonia possibly related to zanubrutinib or progressive disease. This reviewer disagrees with the Applicant's assessment of death as unrelated to zanubrutinib based on the information provided and the timing of death.

- **Patient** (b) (6) was a 74-year-old male who had received three prior therapies for MCL. On study day 164, zanubrutinib was withdrawn due to interstitial lung disease which initially improved after zanubrutinib discontinuation. The patient was diagnosed and hospitalized for fungal pneumonia on SD 198 and died of fungal pneumonia on SD 236, 66 after the last dose of zanubrutinib. No autopsy was performed. The investigator assessed the AE of fungal pneumonia as unlikely related to zanubrutinib.

  Reviewer comment: Per information provided in the narrative, the patient died of complications from fungal pneumonia. Infections, to include opportunistic infections are a known AE associated with BTK inhibitors. Since the patient's pulmonary symptoms began while the patient was receiving zanubrutinib without additional anti-cancer therapy, this reviewer considers the AE of fungal pneumonia as possibly relate dot zanubrutinib. Confounding factors include corticosteroid therapy administered for

interstitial lung disease. pancytopenia and pneumonia possibly related to zanubrutinib or progressive disease. This reviewer disagrees with the Applicant's assessment of death as unrelated to zanubrutinib based on the information provided and the timing of death.

- **Patient** (b) (6) was a 62-year-old male who died 350 days after the last dose of zanubrutinib which had been discontinued due to progressive disease. The patient had received subsequent anti-lymphoma therapy and the cause of death was unknown. The investigator assessed the cause of death as unlikely related to zanubrutinib.

  Reviewer comment: Per information provided in the narrative, given the length of time from zanubrutinib therapy (350 days) as well as subsequent anti-lymphoma therapy, this reviewer agrees with the Applicant's assessment of death as unrelated to zanubrutinib based on the information provided and the timing of death.

Study 003

- **Patient AU-003-** (b) (6) was an 85-year-old female who died on study day 641 after being hospitalized on study day 639 due to cerebral infarction. The last dose of zanubrutinib prior to the event was the same day. The patient had previously been diagnosed with atrial flutter on SD 622 which resolved with medical management and the patient had continued zanubrutinib therapy. Cerebral infarction was diagnosed by imaging on SD 636 after the patient presented with focal neurologic findings. Zanubrutinib therapy was discontinued at that time. The patient was transitioned to comfort care and died SD 641 due to complications from cerebral infarction. The investigator assessed the cause of death as not related to zanubrutinib.

  Reviewer comment: The patient's history of atrial flutter, a known AE associated with BTK inhibitors, may have contributed to the event of cerebral infarction leading to the patient's death. Therefore, this reviewer considers the event of cerebral infarction as possibly related to zanubrutinib therapy.

- **Patient AU-003-** (b) (6) was a 78-year-old male who died on SD 295, 2 days after the last dose of zanubrutinib due to pneumonia. The patient had previously been diagnosed with bronchopulmonary aspergillus (bronchoscopy positive) on SD 261 and had been treated with voriconazole. The patient had also received corticosteroid treatment for lower respiratory tract infection on SD 209. The patient developed worsening respiratory symptoms and AKI and died on SD 295 after transitioning to palliative care. The which had been discontinued due to progressive disease. The investigator assessed the cause of death as unlikely related to zanubrutinib.

  Reviewer comment: Per information provided in the narrative, given the time from initial diagnosis of bronchopulmonary aspergillus, which is an opportunistic infection and is associated with BTK inhibitor therapy. This reviewer disagrees with the Applicant's assessment of death as unrelated to zanubrutinib based on the information provided

and the timing of death. The death is considered possibly related to zanubrutinib therapy.

- **Patient AU-003-** (b) (6) was a 77-year-old male who had received one prior therapy for MCL who died on study day 59, 3 days after the last dose of zanubrutinib which had been discontinued due to congestive heart failure. The patient had a significant medical history of acute myocardial infarction and myocardial ischemia, and congestive heart failure. The patient developed symptoms related to CHF on SD 45 which worsened on da 51. The patient was noted to have pleural effusion and edema as well as symptoms of dyspnea and edema consistent with CHF. No arrhythmia was reported. The patient was reported to have died on SD 59 due to CHF. The investigator assessed the cause of death as unlikely related to zanubrutinib.

  Reviewer comment: Per information provided in the narrative, given the patient's prior history of cardiac disease, this reviewer agrees with the Applicant's assessment of death as unrelated to zanubrutinib based on the information provided. The possibility of anemia related zanubrutinib therapy or underlying disease exacerbating the patients CHF symptoms cannot be ruled out.

- **Patient AU-003-** (b) (6) was a 58-year-old male who had received four prior systemic therapies for MCL who died on study day 219, 162 days after the last dose of zanubrutinib which had been discontinued 119, due to myelodysplastic syndrome. The patient was noted to have pancytopenia starting on SD 93. MDS was diagnosed on SD 100 and therapy was discontinued on SD 118 due to this event. MDS was ongoing at the time of the patient's death, due to septic shock, on SD 219. The investigator assessed the cause of death as unlikely related to zanubrutinib.

  Reviewer comment: Per information provided in the narrative, given the time of 162 days from the last dose of zanubrutinib, the cause of death, septic shock was unlikely related to be directly related to zanubrutinib. However, the adverse event of MDS should be considered as possibly related.

Reviewer Comment: Overall, the causes of death due to AEs were due to the known AEs associated with BTK inhibitors, to include infection, hemorrhage, and cardiac AEs or occurred in the setting of co-morbidities expected to occur in patients in the study population age demographics. The USPI provides adequate warnings for the fatal AEs reported on the study.

Serious Adverse Events

Serious adverse events were defined as any untoward medical occurrence that at any dose results in death, is life -threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect.
SAEs were reported in 24% of the patients in the primary efficacy population, 31% of patients in the R/R MCL population and 37% of the subjects in the B-cell malignancy pool. The most

common SOC category for SAEs was Infections and Infestations and the most common SAE by preferred term was pneumonia (6%) and hemorrhage (5%). SAE rates were similar to those reported in the pooled safety populations and are provided in the table below.

Table 31: Serious Adverse Events by System Organ Class and Preferred Term Occurring in ≥ 2% of patients in the R/R MCL population

System Organ Class Preferred Term	206 N=86 n(%)	R/R MCL N=118 n (%)	B Cell Malignancy N=629 n (%)
Any SAE	**21 (24)**	**36 (31)**	**231 (37)**
Infections and infestations	**11 (13)**	**15 (13)**	**115 (18)**
Pneumonia	10 (12)	14 (12)	53 (8)
Sepsis	0	0	10 (2)
Gastrointestinal Disorders	**2 (2)**	**4 (3)**	**29 (5)**
Gastrointestinal hemorrhage	2 (2)	3 (3)	5 (0.7)
General Disorders and administration site conditions	**2 (2)**	**3 (3)**	**22 (3)**
Death (NOS)	2 (2)	2 (2)	3 (0.5)
Pyrexia	0	0	10 (2)
Blood and Lymphatic System Disorders	**1 (1)**	**4 (3)**	**21 (3)**
Anemia*	1 (1.2)	2 (1.7)	7 (1.1)
Platelet Count Decreased*	2 (2.3)	2 (1.7)	5 (0.8)
Neutrophil Count Decreased*	1 (1.2)	2 (1.7)	18 (3)
Cardiac Disorders	**0**	**3 (3)**	**15 (2)**
Atrial fibrillation or flutter	0	1 (1)	3 (0.5)
Neoplasms benign, malignant and unspecified	**0**	**2 (2)**	**20 (3)**
Squamous Cell Carcinoma of the Head and Neck	1 (0.8)	1 (0.2)	2 (0.3)
Squamous Cell Carcinoma of the Auricular cartilage	1 (0.8)	1 (0.2)	2 (0.3)
Breast Cancer	0	0	2 (0.3)
Respiratory, thoracic and mediastinal disorders	**1 (1)**	**2 (2)**	**19 (3)**
Interstitial lung disease	1 (1)	1 (1)	1 (0.2)
Pleural Effusion	0	1 (1)	8 (1)
Metabolism and nutrition disorders	**0**	**2 (2)**	**7 (1)**
Fluid Overload	0	1 (1)	2 (0.3)
Tumor lysis syndrome	0	1 (1)	1 (0.2)

* includes laboratory investigations reported as AEs

Reviewer comment: The incidence and types of serious adverse events are consistent with the known safety signals reported with oral BTK inhibitors. Labeling should include appropriate warnings and recommendations for monitoring for infections, cytopenias, bleeding and cardiac arrhythmias to include atrial fibrillation and flutter.

Dropouts and/or Discontinuations Due to Adverse Effects

The table below provides a summary of discontinuations, dose reduction, and dose interruption due to treatment-emergent adverse events (TEAEs) with zanubrutinib. Rates and reasons for discontinuation due to AEs were similar in the R/R MCL population and the B-cell malignancy pool.

Table 32: Adverse Events leading to Zanubrutinib discontinuation, reduction or interruption

Outcome	R/R MCL 160mg BID or 320mg QD N = 118 n (%)	B-Cell Malignancies 160mg BID or 320mg QD N=629 n(%)
Discontinuation due to AE	10 (8)	63 (10)
Dose reduction due to AE	3 (3)	29 (5)
Dose interruption due to AE	33 (28)	182 (29)

The most common AEs leading to treatment discontinuation in more than 1 patient in the R/R MCL were pneumonia/lung infection (4%).

Reviewer comment: The rates and types of AEs leading to study drug discontinuation, reduction and interruption were similar in the R/R MCL and the B-cell pool and similar to what have been reported in similar in class agents. There are no new safety signals based on these results. Infectious and bleeding are leading causes of SAEs and AEs leading to death and treatment discontinuation. These are included in the warnings and precautions section of the USPI and may be mitigated by monitoring and early intervention. The TEAE profile is acceptable in this patient population.

Significant Adverse Events

Adverse events of special interest (ESI) were identified by the Applicant based on non-clinical findings and emerging data from published reports of BTK inhibitors (Tang, 2017, Yun, 2016). An analysis was provided by the Applicant on the following events of clinical interest: infections to include the subcategory opportunistic infections, cytopenias, cardiac events including a subcategory of atrial fibrillation, hemorrhage including the subcategory major hemorrhage, hypertension, infections, second primary malignancies, and tumor lysis syndrome. Definitions of ECIs were provided in the ISS SAP and were acceptable. For the subcategory of atrial fibrillation, preferred terms of atrial fibrillation and atrial flutter were used. Major hemorrhage was defined and any hemorrhagic event that is serious or ≥ grade 3 in severity or that is a central nervous hemorrhage of any grade.

Reviewer comment: The Applicant's classification of ECIs was acceptable to capture appropriate events for each category.

The table below displays the events of clinical interest in the R/R MCL population and the B-cell Malignancy Pool.

Table 33: Summary of Adverse Events of Clinical Interest

	R/R MCL N = 118		B-Cell Malignancy N = 629	
	Any grade n (%)	≥ Grade 3 n (%)	Any grade n (%)	≥ Grade 3 n (%)
Infections	75 (64)	21 (18)	440 (69)	145 (23)
Opportunistic Infections	3 (3)	2 (1.6)	15 (2)	7 (1.1)
Cardiac Events	10 (8)	4 (3)	62 (10)	13 (2)
Atrial Fibrillation	2 (1.6)	1 (0.8)	12 (2)	3 (0.5)
Cytopenias*				
Neutropenia	47 (40)	21 (18)	218 (35)	139 (22)
Thrombocytopenia	33 (28)	7 (5)	120 (19)	44 (7)
Anemia	17 (14)	9 (8)	100 (16)	49 (8)
Hemorrhage (including bruising)	40 (34)	4 (3)	315 (50)	58 (9)
Major Hemorrhage	6 (5)	4 (3)	14 (2)	17 (3)
Hypertension	15 (13)	4 (3)	56 (9)	21 (3)
Second primary malignancies**	7 (6)	1 (0.8)	58 (9)	24 (4)
Second primary malignancies, non-skin	2 (1.6)	1 (0.8)	29 (5)	18 (3)
Tumor Lysis Syndrome	2 (1.6)	2 (1.6)	2 (0.3)	2 (0.3)

* Include AEs reported as laboratory investigations
** Includes myelodysplastic syndrome

The most common ECI reported were infections, of which 18% were greater than grade 3 in the R/R MCL. Opportunistic infections were rare, reported in 3% (all grades) of R/R MCL population. Rates of infections and opportunistic infections were similar in the B-cell malignancy pool. The incidence of major hemorrhage was 5% in the R/R MCL population and 2% in the B-Cell Malignancy population, including one fatal intracranial hemorrhage. Population.

Each adverse event of special interest is further reviewed in section 8.2.5.1

Treatment Emergent Adverse Events and Adverse Reactions

Treatment Emergent Adverse Events and Adverse Reactions were defined as AEs that occurred or worsened after the first dose of zanubrutinib through the safety follow up visit which occurred 30 days after the last dose of zanubrutinib.

The sponsor provided data from a total of 641 patients with B-Cell malignancies who received zanubrutinib at any dose in the studies described in section 7.1. Rates of AEs were analyzed for

patients in the 206 study, and the R/R MCL patients from the 003 study. In general rates were similar between the two groups. The FDA analysis included only patients who received the indicated dose of 160mg twice daily or 320mg once daily which were 629 of the 641 patients in the B-cell malignancy pool and 118 of the 123 patients with R/R MCL from the 206 and 003 study.

Table 34: Treatment Emergent Adverse Event reported in greater than 10% of the safety population

Preferred Term	R/R MCL N = 118		B-Cell Malignancies N = 629	
	All Grades n (%)	Grades ≥3 n (%)	All Grades n (%)	Grades ≥3 n (%)
Any AE	114 (97)	55 (47)	361 (57)	616 (98%)
Infections and Infestations	75 (64)	18 (15)	440 (70)	145 (23)
Upper respiratory Tract Infection*	46 (39)	0	239 (38)	22 (3)
Pneumonia*	18 (15)	12 (10)	110 (17)	59 (9)
Urinary Tract Infection	13 (11)	1 (0.8)	81 (13)	20 (3)
Blood and lymphatic system disorders**				
Neutropenia and neutrophil count decreased	47 (40)	21 (18)	218 (35)	139 (22)
Thrombocytopenia and platelet count decreased	33 (28)	7 (5)	120 (19)	44 (7)
Anemia and hemoglobin decreased	17 (14)	9 (8)	100 (16)	49 (8)
Skin and subcutaneous tissue disorders	43 (36)	0(0)	160 (25)	2 (0.3)
Rash	17 (14)	0 (0)	146 (23)	0(0)
Bruising				
Gastrointestinal Disorders	27 (23)	4 (0.8)	125 (20)	6 (1)
Diarrhea*	15 (13)	0 (0)	68 (11)	1 (0.2)
Constipation				
Vascular Disorders				
Hypertension	15 (13)	4 (3)	56 (9)	21 (3)
Hemorrhage*	13 (11)	4 (3)	72 (11)	9 (2)
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain	16 (14)	4(3.4)	118 (19)	10 (1.6)
Renal				
Hematuria	8 (7)	0 (0)	76 (12)	2 (0.3)
Metabolism and nutritional disorders				
Hypokalemia	16 (14)	2 (2)	60 (9)	12 (2)
General				
Fatigue	9 (8)	1 (0.8)	82 (13)	6 (1)

* includes grouped terms as detailed in appendix 19.7
** includes laboratory investigations

Laboratory Findings

The table below summarizes common (>10% of patients) treatment emergent hematologic laboratory abnormalities in patients in the primary efficacy population (R/R MCL on study 206 and on study 003 and from the total safety population who received either 160mg BID or 320mg once daily.

Table 35: New or Worsening Laboratory Abnormalities (≥20% of Patients)

Hematology Laboratory Abnormality*	R/R MCL N=118			Total Safety Population N = 629		
	All Grades n (%)	Grade 3-4 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3-4 n (%)	Grade 4 n (%)
Neutropenia	53 (45)	23 (19)	(9)	329 (52)	168 (27)	72 (11)
Thrombocytopenia	47 (39)	8 (7)	(4)	246 (39)	65 (10)	20 (3)
Anemia	31 (27)	7 (6)	0	178 (28)	50 (8)	0
Lymphocytosis	44 (37)	18 (15)	-	168 (27)	92 (15)	-
Lymphopenia	27 (23)	12 (10)	3 (3)	127 (20)	62 (10)	13 (2)
Leukopenia	38 (32)	12 (10)	1 (0.8)	173 (28)	42 (7)	6 (1)

Source FDA analysis of ADLB dataset
*represents new or worsening abnormalities

Cytopenias of all grades were common during treatment, with the most common cytopenia neutropenia reported in 45% (all grades) and 19% (greater than grade 3). Cytopenias as assessed laboratory data were higher than those reported as AEs (blood and lymphatics + investigations).

Lymphocytosis was reported in 37% of patients with mantle cell lymphoma.

Table 36: Treatment Emergent Biochemical Laboratory Abnormalities

Biochemical Laboratory Abnormality	r/r MCL N = 118			Total Safety Population N = 629		
	All Grades n (%)	Grade 3-4 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3-4 n (%)	Grade 4 n (%)
Hyperglycemia	48 (41)	8 (7)	1 (<1)	299 (48)	28 (4)	1 (<1)
ALT increase	31 (26)	1 (<1)	0	143 (23)	3 (<1)	1 (<1)
AST increase	20 (17)	0	0	84 (13)	4 (<1)	1 (<1)
Hyperbilirubinemia	28 (24)	1 (<1)	0	127 (20)	4 (<1)	1 (<1)
Hyperuricemia	35 (30)	3 (3)	3 (3)	123 (20)	16 (3)	16 (3)
Hypokalemia	22 (19)	1 (<1)	0	117 (19)	16 (3)	3 (<1)
Creatinine increase	21 (18)	1 (<1)	1 (<1)	110 (17)	3 (<1)	1 (<1)

The most common chemistry abnormalities by analysis of laboratory values were hyperglycemia with 7% greater than or equal to grade 3. There were less than 1% grade 3 or higher elevations of AST/ALT or bilirubin.

Hyperuricemia by laboratory analysis occurred in 30% of patients (all grades), and 3% were grade 4. A comparison of the analysis of the AE of hyperuricemia in the total safety pool was 7% (all grades) 2% greater than grade 3 and 1% grade 4. For the R/R MCL patients 9% had an AE of uricemia reported, 4% were greater than grade 3 and 3% were grade 4. There were no fatal events of hyperuricemia or tumor lysis reported.

Reviewer comment: Laboratory chemistry abnormalities were generally low grade and occurred commonly. Although there was no specific laboratory chemistry pattern indicative of a specific toxicity, since chemistry abnormalities may be related to infectious or tumor related complications, elevated ALT, bilirubin and uric acid should be included in the USPI to adequately inform providers and routine laboratory monitoring is recommended.

Vital Signs

The Applicant provided a record of the vital signs and a description of the changes in vital signs during treatment with zanubrutinib. The applicant did not identify any unexpected trends or clinically meaningful post-baseline findings in vital sign parameters.

Hypertension

Hypertension is a reported TEAE with other BTK inhibitors. Hypertension TEAEs were reported for 12% (all grades) and 3% (≥ grade 3) of the R/R MCL patients which was similar than the B-Cell malignancy pool 9% (all grades) 3% (≥ grade 3). There were no treatment discontinuations due to hypertension.

The FDA noted that potentially clinically significant post-baseline diastolic blood pressure elevations, defined as a value ≥ 90mmHg and greater than 5 mmHg higher than baseline on more than one occasion were observed in 25% of subjects in the R-R MCL population and 21% of subjects in the B-cell Malignancy Pool, detailed in the table below. For potentially clinically significant blood pressure elevations defined as a systolic blood pressure value ≥ 160mm Hg and greater than 5 mmHg higher than baseline on more than one occasion was observed in 105 of patients in the R/R MCL population and 12% in the larger, B-cell Malignancy pool. A review of weight, heart rate, and temperature did not reveal any significant safety signals.

Table 37: Elevations in Blood Pressure from Baseline

	R-R MCL Pool (N=118) n (%)	B-Cell Malignancy Pool (N=629) n (%)
SBP ≥ 160 mm Hg	12(10%)	75 (12%)
DBP ≥ 90 mm Hg	30 (25%)	133 (21%)

Source: FDA analysis of Applicant ADVS data set

Reviewer comment: The hypertension observed in patients on zanubrutinib was higher when assessed by vital sign analysis than was reported as AEs. Overall the incidence AEs that were ≥ grade 3 hypertension were low in both study populations and no events of grade 4 hypertension or hypertension leading to dose discontinuation or reduction were reported. Hypertension is included in section 6.1 of the USPI and can be adequately monitored and managed by standard of care practices.

Electrocardiograms (ECGs)

Electrocardiograms were obtained at screening, on day 1 of cycle 1 and 2, at the end of treatment and as clinically indicated on study 206 and at screening, week 1, 2, 5 at the end of treatment an as clinically indicated on study 003. TEAEs related to ECG changes were reviewed along with all cardiac events.

ECG related TEAEs in the SOC cardiac disorders included atrial fibrillation or flutter in 12 (2%) of the B-cell malignancy pool and in 2 (2%) of the R/R MCL pool, including one grade 3 event in an 85-year-old. None of the events in atrial fibrillation or flutter occurred in patients less than 65 years old.

QT

The Applicant conducted an analysis of ECG intervals in all subjects in B-Cell Malignancy Pool who received zanubrutinib at any dose (N = 641). The results of the applicant's analysis are shown in the table below. The applicant's conclusion was that zanubrutinib had no clinically relevant effect on ECG parameters.

Table 38: QTcF Increase in patients with both baseline and at least 1 post baseline QTcF measure

QTcF (msec)	R/R MCL 160mg BID or 320 mg daily (N=81)	B-cell Malignancies 40mg, 80mg or 160mg daily 160mg BID or 320 mg daily (N=560)
QTcF increased from baseline		
≤ 30 msec	50 (61%)	364 (65%)
> 30 to ≤ 60 msec	6 (7%)	72 (13%)
> 60 msec	2 (3%)	24 (4%)

A thorough QT/QTc study, BGB-3111-106 "A 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" was conducted in 8 (Part A) and 26 (Part B) healthy adult subjects and reviewed by the QT Interdisciplinary Team. In Part A, subjects received a single dose of zanubrutinib 480mg (N=6) or placebo (N = 2). Part B of the study was a randomized, placebo and positive-controlled four-way crossover, single dose thorough QT (TQT) study. Subjects received either single dose zanubrutinib 160mg, single dose zanubrutinib 480mg, placebo to match zanubrutinib, or moxifloxin 400mg (open label).

No significant QTc prolongation effect of zanubrutinib was detected in the thorough QT study. The largest upper bounds of the 2-sided 90% confidence interval for the main differences between zanubrutinib and placebo were below 10ms, the threshold for regulatory concern as described in ICH E-14 guidelines.

The QT-IRT recommend the following language for Section 12.2 of the USPI: At the therapeutic dose of 160 mg BID or 320 mg QD, there were no clinically relevant effects on the QTc interval. Drug effect on the QTc interval above the therapeutic exposure has not been evaluated.

Reviewer comment: I agree with the IRT reviewer that there is no evidence to suggest that zanubrutinib is associated with significant QTc prolongation.

Immunogenicity

There is no immunogenicity data about zanubrutinib in this application.

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Hemorrhage

The incidence of any hemorrhage to include bruising was 50% in the B cell malignancy population, which was higher than the 34% reported in the R/R MCL pool. One explanation may be underreporting of minor bleeding in the 206 study, conducted solely in China. Events of major hemorrhage were low and occurred at similar rates in the MCL and B-cell malignancy patients. Events included one fatal cerebral hemorrhage. In R/R MCL patients, the median time to onset of the first hemorrhage events was 47 days. A similar trend was reported in the B-cell malignancy pool with the majority of patients who experienced hemorrhage, had the event reported within the first three months of zanubrutinib exposure. hemorrhage events were 120 days (range 3-1259 days). The median time to onset for major hemorrhage was 149 days (range 7-526 days.

The Applicant conducted an analysis of the correlation between hemorrhagic events and the use of antithrombotic agents. The rates of any grade hemorrhage and greater than grade three hemorrhage in patients with and without antithrombotic or anti-platelet agents is displayed in the table below.

Table 39: Incidence of Hemorrhage with and without anticoagulant therapy in the B-Cell Malignancy Pool.

	No antithrombotic Agent	**Anti-thrombotic Agent**	**No Anti-Platelet Agent**	**Anti-platelet Agent**
Hemorrhage (all grade)	53.2%	41.8%	52%	42%
≥ Grade 3	1.4%	3.5%	2.1%	2.4%

In patients with R/R MCL, major hemorrhagic events occurred in 6 patients. One event was a fatal cerebral hemorrhage. Other events included upper gastrointestinal hemorrhage (2), renal hematoma (1), tumor hemorrhage (1). A similar pattern of major hemorrhage was noted in the B-Cell malignancy pool with gastrointestinal hemorrhage occurring in 3/17 patients with major hemorrhage.

Reviewer comment: The 50% incidence of bleeding of any type (mostly grade 1 or 2) is

consistent with known class effect of BTK inhibitors and thought to be related to platelet dysfunction. Patients who receive zanubrutinib are at risk for major hemorrhage, which occurs at a low rate with or without concomitant anticoagulant medications. The risk of bleeding and caution against concomitant anticoagulant use is warranted in the UPSI.

Atrial Fibrillation and Atrial Flutter

In the combined database of 629 patients 2% of patients experienced atrial fibrillation or atrial flutter of any grade. Grade 3 atrial fibrillation or flutter occurred in 0.5% of these patients.

Reviewer comment: Atrial fibrillation and flutter occur at low rates in patients receiving zanubrutinib. The current USPI adequately conveys this risk and recommendations for monitoring.

Infections:

Infections defined as any TEAE with a PT in MedDRA SOC Infections and Infestations occurred in 70% (all grades) and 18% (≥ grade 3) of the patients in the R/R MCL population. Rates were similar in the B-Cell malignancy pool, reported in 69% (all grades) and 23% (≥ grade 3). The most frequently reported infections in the B-cell malignancy pool were upper respiratory tract infection, pneumonia, sinusitis, cellulitis, and pneumonia.

Serious infections were reported for 13% of the patients on the R/R MCL population, including the fatal infections of pneumonia in 2 patients. In the B-cell malignancy population, 11 patients were reported to have fatal infections including 6 patients with the fatal events of pneumonia, and 4 with the events of sepsis, and one with the fatal event of scedosporium infection.

Opportunistic Infections:

The Applicant conducted an analysis of opportunistic infections which were reported in three patients in the R/R MCL population and 16 (2.5%) of patients in the B-cell malignancy pool. A description of the types of opportunistic infections are described in the table below.

Table 40: Opportunistic Infections reported in patients receiving zanubrutinib therapy

	R/R MCL N = 118		B-Cell Malignancy N = 629	
	Any grade n (%)	≥ Grade 3 n (%)	Any grade n (%)	≥ Grade 3 n (%)
Opportunistic Infections	3 (2.5)	2 (1.7)	15 (2.4)	7 (0.1)
Bronchopulmonary Aspergillus	1 (0.8)	1 (0.8)	4 (0.6)	1 (0.2)
Cerebral Aspergillus	0 (0)	0 (0)	1 0.2)	1 (0.2)
Herpes Simplex	3 (2.5)	1 (0.8)	5 (0.8)	1 (0.2)

Scedosporium infection	0 (0)	0 (0)	1 (0.2)	1 (0.2)
Cryptococcal meningitis	0 (0)	0 (0)	2 (0.3)	2 (0.3)
Listeria Sepsis	0 (0)	0 (0)	1 (0.2)	1 (0.2)
Candidal esophagitis and oral thrush	1 (0.8)	0 (0)	5 (0.8)	0 (0)

Reviewer comment: Opportunistic infections involving both fungal viral and bacterial were rare, generally occurring in less than 1% of patients. However, fatal events were reported. Opportunistic infections were reported in both the R/R population as well as the B-cell malignancy pool. Given the need for unique monitoring and treatment as well as the potential for prophylaxis, the risk of opportunistic infections should be included in the USPI.

Tumor Lysis Syndrome

In the R/R MCL population, two subjects had a tumor lysis event. Both events were reported as grade 3, resolved and occurred later in therapy (study days 412 and 570) In a review of the narratives, TLS syndrome occurred in the setting of progressive disease and is potential confounder.

Elevated uric acid was identified by laboratory analysis

Reviewer Comment: Patients who developed tumor lysis on this study had progressive disease at the time of diagnosis of TLS. Tumor lysis syndrome was not noted in any patient in the first two weeks of therapy. Tumor lysis syndrome does not seem to be associated with zanubrutinib therapy although the relatively high (29%) incidence of elevated uric acid levels to include 2.6% of grade 3 or higher in patients on this study raises the possibility of sub-clinical tumor lysis syndrome. Patients receiving zanubrutinib therapy are expected to be managed by hematologist-oncologists who have training and experience in the identification and management of tumor lysis syndrome.

Second Primary Malignancies (SPM)

Fifty-eight (9%) of patients in the B-cell malignancy pool and 7 (6%) of patients with R/R MCL developed a second primary malignancy while receiving zanubrutinib therapy. The majority of the second primary malignancies were skin malignancies, with 1.6% and 5% non-skin malignancies in the R/R MCL population and B-cell malignancy pool respectively.

Table 41: Second Primary Malignancies Occurring in Patients with R/R MCL treated with Zanubrutinib

Type of Second Primary Malignancy	n(%)
Skin Cancer (Squamous Cell)	1 (0.8)
Basal Cell Carcinoma	3 (2.5)
Squamous Cell Carcinoma of the Head and Neck	1 (0.8)
Melanoma	1 (0.8)
Myelodysplastic Syndrome	1 (0.8)

Type of Second Primary Malignancy	n(%)
Total	7 (6)
Non-Skin	2 (1.6)

Source: FDA analysis of Applicant ADAE table, and study narratives

In the B-cell malignancy pool, combined database of 629 patients (SPMs occurred in 9% of patients, 5 percent were non-skin and included squamous cell carcinoma of the head and neck (6), prostate cancer (4), breast cancer (3), lung cancer (2), colon cancer (2), squamous cell carcinoma (2), malignant neoplasm of the auricular cartilage (2), and neuroendocrine carcinoma, gastric adenocarcinoma, Richter's syndrome, salivary gland cancer, myelodysplastic syndrome, AML, B-cell lymphoma, renal cell carcinoma, laryngeal cancer (1 each).

Reviewer Comment: *There was no clear pattern for non-skin or skin SPMs and the incidence in this relatively small population does not appear to be significantly increased over what would be expected in patients with mantle cell lymphoma. The incidence of SPM in patients with MCL has been reported to be 8.2% in a published report of 3149 patients with median latency time of 47 months from diagnosis to development of SPM. In the population-based study, the most common SPM categories with the highest observed/expected ratios were CLL, AML, NHL, anal and rectal, skin, and thyroid (Shah, 2015). Since immune suppression can be associated with malignancies and many patients treated with zanubrutinib may be exposed for long-term therapy, inclusion in the warnings and precautions is warranted.*

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

There were no additional COA data included in the application.

8.2.7 Safety Analyses by Demographic Subgroups

The single arm study data from the r-r MCL population (N = 118) and the B-cell malignancy pool (N = 629) was not adequately powered to reach conclusions regarding the safety among the demographic subgroups (sex, age and race).

Age
TEAEs were analyzed for age groups <65 and ≥ 65 in the r-r MCL population and the B cell malignancy pool.

Table 42: Adverse Events by Age Groups in the B-Cell Malignancy and R/R MCL Populations

	B – Cell Malignancies N = 629			R/R MCL N = 118		
	< 65y N = 324	≥ 65y - ≤ 75y N = 210	> 75y N = 95	< 65y N = 72	≥ 65y -≤ 75y N = 32	> 75y N = 14
Any TEAE	318 (98%)	205 (98%)	93 (98%)	72(100%)	30 (94%)	14 (100%)
≥ Grade 3	182 (56%)	125 (60%)	54 (57%)	27 (38%)	14 (44%)	10 (71%)
SAE	93 (29%)	93 (44%)	47 (49%)	18 (25%)	10 (31%)	9 (64%)
Leading to death	10 (3%)	11 (5%)	10 (11%)	3 (4%)	2 (6%)	3 (21%)
Leading to treatment discontinuation	17 (5%)	21 (10%)	12 (13%)	4 (6%)	3 (9%)	4 (31%)
Leading to dose reduction	12 (4%)	4 (2%)	2 (2%)	3 (4%)	0	0

Adverse events that were reported higher in patients ≥ 65 years old age group in patients with R/R MCL by > 5% were contusion, urinary tract infection, lower respiratory tract fatigue, constipation, peripheral edema, cellulitis, and fall. Rates of specific AEs are summarized in the table below.

Table 43: AEs with rate difference > 5% between patients < 65 years and greater than 65 years in the B-Cell Malignancies Population

SOC Preferred Term	Subjects < 65y N = 324	Subjects ≥ 65y N = 305
Infections and Infestations		
Upper Respiratory Tract Infection, all grades	51%	35%
≥ Grade 3	8.3%	1.3%
Cellulitis	1.9%	6.6%
≥ Grade 3	0	3.3%
Blood and Lymphatic		
Neutropenia	35%	17%
≥ Grade 3	21%	10%
Thrombocytopenia	17%	11%
≥ Grade 3	6%	4%
Gastrointestinal		
Constipation	6%	16%
≥ Grade 3	0	0.3%

SOC Preferred Term	Subjects < 65y N = 324	Subjects ≥ 65y N = 305
Skin and Subcutaneous		
Rash	28%	21%
≥ Grade 3	<1%	<1%
Musculoskeletal		
Back Pain	6.8%	11.8%
≥ Grade 3	0.6%	0.3%
Injury Poisoning and Procedural complications		
Fall	1.5%	6.6%
≥ Grade 3	0.3%	0.7%

Gender

There were no differences greater than 5% in the percentage of AEs, SAEs, AEs leading to death or treatment discontinuation between males and females receiving study therapy.

Race

The Applicant performed an analysis of AEs in the Asian vs non-Asian patients. Overall patients of Asian race made up 50% of the B-cell malignancy pool and 75% of R/R MCL patients. Overall rates of SAEs. AEs leading to death, and AEs leading to discontinuation were reported at slightly decreased rates in patients of Asian race vs non-Asian patients. Rates of AEs of any grade were similar, 97% (Asian) vs. 98% (non-Asian), ≥ grade 3 AEs were 59% in Asian patients vs. 56% in White patients. Serious AEs were reported in 30% (Asian) vs 42% (non-Asian) and AEs leading to death were 3.5% (Asian) vs. 5.4% (non-Asian). Adverse events leading to treatment discontinuation were reported in 9% of Asian subjects and 11% of non-Asian subjects.

Reviewer Comment: Overall, there was no concerning safety signals with regards to differences in Asian patients vs. non-Asian patients. Limited conclusions can be drawn given that no formal statistical analysis was performed. Small differences in the rates of AEs may be related to the relatively small numbers of non-Asian populations.

8.2.8 Specific Safety Studies/Clinical Trials

There were no special safety studies or clinical trials in this application

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

An evaluation of second primary malignancies was conducted. See the section 8.2.4.

Human Reproduction and Pregnancy

Refer to section 5.5.4 of this review.

Pediatrics and Assessment of Effects on Growth

There were no children enrolled in any of the studies submitted with this application. The safety of zanubrutinib in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no experience of overdose reported in the clinical studies of zanubrutinib . Zanubrutinib is intended to be prescribed by specialists in hematology and oncology. There is no evidence that zanubrutinib produces physical or psychological dependence in patients with hematologic malignancies.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Zanubrutinib is not marketed in any country. No postmarketing safety data is available.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application. Although, since it is expected that some patients may take zanubrutinib for an indefinite period of time, safety with long-term use of zanubrutinib should be followed the median duration of treatment was 19.5 months at the time cut off of the 90-day safety update.

8.2.11 Integrated Assessment of Safety

The safety of zanubrutinib as monotherapy as doses of either 160mg BID or 320mg once daily was evaluated in 118 patients with relapsed or refractory mantle cell lymphoma. The median duration of exposure was 17.5 months at the primary analysis and 19.5 months at the time of the 90-day safety update. The population of patients for the pivotal study was representative of the expected demographic population for mantle cell lymphoma with a median of 2 prior therapies variety of prior chemotherapy and immunotherapies. Safety data from an additional 411 patients with hematologic malignancies who received zanubrutinib monotherapy at either 160mg BID or 320mg once daily at any dose supported the safety conclusions from the primary safety population.

The most common non-hematological adverse reactions of any grade were upper respiratory infection (39%), rash (27%), diarrhea (20%), and contusion (20%). None of these common events led to drug discontinuation. The most common hematological adverse events (hematologic TEAEs and laboratory abnormalities) were neutropenia (45%), thrombocytopenia (40%), and anemia (27%).

Treatment discontinuation occurred due to any adverse reaction was reported in 14% of patients with R/R MCL and in 10% of the B cell malignancy pool. No one adverse reaction was predominant in leading to treatment discontinuation.

Serious adverse events were reported in 31% of patients. The most frequent SAEs were pneumonia (11%) and hemorrhage (5%).

The following adverse events of special interest were also identified:

Cytopenias: Cytopenias as adverse reactions (including investigations) including neutropenia (38%), anemia (14%), and thrombocytopenia (27%), were reported in patients receiving zanubrutinib therapy. Hematologic laboratory abnormalities occurred in > 20% of the population for ANC decreased (45%), Hemoglobin decreased (27%), and Platelets decreased (40) and these were more frequently reported than the related AEs. The incidence of hematologic laboratory abnormalities is clinically relevant and should be included in the USPI. Mean ANC and hemoglobin values decreased after initiating therapy but improved for patient remaining on therapy. Mean platelet counts decreased initially and generally did not return to baseline but remained greater than 100 X 10^9/L for those patients remaining on therapy. CBCs should be monitored monthly on therapy.

Atrial fibrillation and atrial flutter: Atrial fibrillation and flutter are a known class effect of BTK inhibitors. In the R-R MCL there were no cases reported, however in the B-Cell malignancy pool, atrial fibrillation or flutter was reported in 2% (all grades) and 0.6% (greater than grade 3) of the patients. Atrial fibrillation and flutter are an AE associated with the BTK inhibitor class and should be included in warnings and precautions.

Hemorrhage: Reports of major hemorrhage in the R/R MCL population was 4%, with serious hemorrhagic events including fatal cerebral. Mild hemorrhage (ecchymosis and bleeding) was relatively common in the pivotal study, reported in 30% of patients on the pivotal study. The mechanism of bleeding is not well understood but thought to be related to platelet dysfunction, supported by in vitro evidence of thrombin generation inhibition in patients receiving zanubrutinib and in healthy volunteers. This warrants inclusion in warnings and precautions and supports recommendations for withholding zanubrutinib prior to major surgery.

Infections: Serious infections to include bacterial, viral and fungal infections occurred in the combined safety data base of patients. In the larger database of patients, grade 3 or higher infections occurred in 18% of patients with the most common grade 3 or 4 infection of pneumonia. Opportunistic infections are an important AE associated with BTK therapy and were noted to occur at low rates in the safety populations. Since opportunistic infections require an additional level of clinical suspicion and may prevented with prophylaxis, the risk

opportunistic infections the recommendations to consider prophylaxis should be included in the USPI.

Second Malignant Neoplasm: Patients with MCL have an increased risk for second malignancies. In this small study with relatively short follow up the rate of second malignancies appears to be similar to what would be expected in this population. Since early detection of some of this SPM may benefit patients, it is appropriate to include this in warnings and precautions.

In addition, lymphocytosis occurred in the first weeks of treatment however the lymphocytosis was not associated with AEs and resolved within the first several weeks of treatment, Lymphocytosis occurred in 41% of patients on study, typically within the first month.

Reviewer comment: A comprehensive review of the safety data demonstrates that zanubrutinib demonstrated a favorable safety profile and was well tolerated in both the primary trial establishing efficacy (206) as well as the supportive trial (003) and in the B cell malignancy population with a manageable adverse event profile and a low rate of drug discontinuation due to AEs.

8.3 Statistical Issues

The major issue affecting most key efficacy outcomes was response assessment. Multiple discrepancies between Applicant and FDA assessment in best overall response and duration of response have been identifed, including best overall response status and date, first response status, loss of response reason and date, censoring/event status. The issue has been resolved through FDA-adjudication of IRC response assessment and correspondence with the Applicant (see Adjudication of Efficacy in Section 7.2).

8.4 Conclusions and Recommendations

Relapsed and refractory mantle cell lymphoma is a serious and life-threatening condition for which zanubrutinib monotherapy demonstrated clinical activity. In two separate trials, BGB-3111-206 and BGB-3111-AU-003 the ORR was 84% (95% CI: 74, 91) and 84% (95% CI 67, 95) based on independent review committee assessed response per the Lugano 2014 classification. The median DOR was 19.5mo (16.6, NE) and 18.5 (12.6, NE) respectively. In addition, the CR rate was 59% and 22% respectively. The efficacy results from this trial indicated that zanubrutinib has clinical activity in patients with relapsed and refractory MCL.

Overall, zanubrutinib was well tolerated with the most frequently reported grade 3 or 4 AEs of neutropenia (18%), pneumonia (10%) anemia (8%), and thrombocytopenia (5%)). The overall incidence of SAEs was 31% in patients with relapsed and refractory mantle cell lymphoma and 37% in the B-Cell Malignancy population. Most of the deaths in patients with R/R MCL were due to progressive disease and few patients discontinued study drug due to adverse events (8%).

The clinical and statistical review teams recommends Accelerated Approval for zanubrutinib . Section 21 CFR 314.50 addresses approval based on a clinical endpoint other than survival or irreversible mortality. Accelerated approval is subject to the requirement that the Applicant study the drug further, to verify and describe the clinical benefit.

Because multiple therapies are now approved for mantle cell lymphoma, a comprehensive characterization of the efficacy of anti-neoplastic agents, disease course and determination of adequacy of long-term follow up is important. Important questions remain regarding the treatment of mantle cell lymphoma such as optimal use of combination treatments, characterization of disease course (nodal, extranodal sites, BM involvement), and evaluation of treatment effect on time-to-event endpoints including progression free survival and overall survival.

The rationale for the recommendation of accelerated approval for zanubrutinib is founded upon the following considerations:

- Uncertainty as to the relationship of ORR and DOR to ultimate outcome of overall survival. Althoughthe ORR was 84% in both studies per independent review committee, in the combined R/R mantle cell lymphoma population, 29% of patients discontinued treatment due to progressive disease and 10% of patients died due to progressive disease.
- The most optimal use of zanubrutinib for the treatment of mantle cell lymphoma is not known. The Applicant's ongoing randomized controlled trial of zanubrutinib + and rituximab versus bendamustine + rituximab in patients with mantle cell lymphoma (Subpart H postmarketing requirement) would allow for adequate evaluation of time-to-event endpoints and the role of zanubrutinib in combination regimens.

In conclusion, the benefit-risk assessment is favorable for the use of zanubrutinib as monotherapy for patients with mantle cell lymphoma who have received at least one prior therapy.

X

Alexei Ionan, PhD
Primary Statistical Reviewer

X

Jingjing Ye, PhD
Statistical Team Leader

X

Margret Merino, MD
Primary Clinical Reviewer

X

R. Angelo de Claro, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncologic Drug Advisory Committee or other external consultants because zanubrutinib is not first-in-class, and the application did not raise new efficacy or safety issues for the recommended indications.

10 Pediatrics

Patients less than 18 years of age were excluded from Applicant-sponsored clinical studies of zanubrutinib. The efficacy and safety of zanubrutinib in pediatric patients has not been studied.

11 Labeling Recommendations

Prescription Drug Labeling

The table below summarizes the revisions that FDA made to the submitted labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights and FPI-Dosage and Administration	Recommended dose: 160 mg (b) (4) orally twice daily, (b) (4) swallow whole with water and with or without food	Recommended dose: 160 mg orally twice daily *or 320 mg orally once daily*; swallow whole with water and with or without food
Highlights-Adverse Reactions	--	Revised List of most common ARs based upon review of AE data.
Highlights-Drug Interactions	(b) (4)	Revised to avoid concomitant admin with (b) (4) moderate and strong CYP3A inducers.
Warnings and Precautions	--	Revised to remove mention of (b) (4) Added to 6.1 a summary of the population used to calculate the Warnings and Precautions.
Adverse Reactions	--	Revised Common AR Table to reflect current approach of populating AR table using only AE datasets and adding lab table using lab datasets. Grouped similar terms into single terms, to avoid splitting, and defined terms beneath table.
Clinical Pharmacology	--	Revised QT Cardiac Electrophysiology information to reflect inclusion of 320 mg daily dosing. Added Table 4 to describe varying magnitude of interaction with different CY3A inhibitors.
Clinical Studies	--	Revised to reflect the main efficacy population of study BGB-3111-206.

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team and Division of Risk Management (DRISK) agree that REMS is not necessary for the safe use of zanubrutinb. There are no additional risk management strategies needed beyond recommended labeling.

13 Postmarketing Requirements and Commitment

The following postmarketing requirements are recommended:

1. Accelerated Approval PMR Description:
   To verify the clinical benefit of zanubrutinib, complete and submit the final results of Trial BGB-3111-306 - the ongoing randomized, Phase 3 clinical trial of BRUKINSA in combination with rituximab versus bendamustine and rituximab in patients with previously untreated mantle cell lymphoma. The primary endpoint is progression free survival as assessed by Independent Review Committee (IRC). Overall survival is a key secondary endpoint. The statistical plan should include a plan for a superiority evaluation of the primary endpoint. Enrollment of approximately 500 patients is expected.

2. Determine the effect of a broad range of concentrations of BRUKINSA on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects of zanubrutinib on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

   LABORATORY STUDIES: Assess the effect of zanubrutinib on platelet function. Assessment methods should evaluate for effects of zanubrutinib on platelet aggregation, including GPIb mediated aggregation. Evaluation should include patients with concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction).

3. Conduct an analysis evaluating the pharmacokinetics and safety of zanubrutinib when administered with concomitant CYP3A4 inhibitors (including ciprofloxacin, diltiazem, erythromycin, fluconazole, posaconazole, voriconazole, and clarithromycin) utilizing data from ongoing studies (including but not limited to Studies BGB-3111-AU-003, BGB-3111-214, BGB-3111-215, BGB-3111-302, and BGB-3111-306). Evaluate the effect of each inhibitor on both the Cmax and AUC of zanubrutinib and assess the safety (including adverse events, dose modifications, dose interruptions, and dose discontinuations) of the recommended dose modifications before, during, and after the concomitant dosing period. Submit a final report including PK and safety data and analyses from Studies BGB-3111-AU-003, BGB-3111-214, BGB-3111-215, BGB-3111-302, and BGB-3111-306.

The following postmarketing commitment is recommended:

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

Refer to action letter for final wording of postmarketing requirements and commitments.

14 Division Director (DHOT)

X

Haleh Saber, PhD

15 Division Director (OCP)

X

Brian Booth, PhD

16 Division Director (OB) Comments

X

Thomas Gwise, PhD

17 Division Director (Clinical) Comments

[This section was based in part on the reviews of the CDTL (Dr. Angelo de Claro) and the clinical reviewer (Dr. Margret Merino.)]

Background: On June 23, 2019, BeiGene, USA submitted NDA 213217 in which BeiGene requested approval of zanubrutinib (Brukinsa) for the following indication: the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This request relied on two single arm studies: BGB-3111-206 (206), a phase 2 trial which entered 86 patients with MCL entirely from China, and BGB-3111-AU-003 (003), a phase 1/2 global study of B cell malignancies 36 of whom had MCL. The primary endpoint in 206 was overall response rate (ORR) by PET scan (IRC) and was ORR in 003, as determined mainly by CT/MRI scans (IRC).
Efficacy Results: In study 206, the ORR was 84% (95% CI: 74, 91) and the complete response (CR) rate was 59% (95% CI: 48, 70). In study 003, the ORR was 84% (95% CI: 67, 95) and the CR was 22% (95% CI: 9, 40). The difference in the CR rate in 206 vs 003 was likely due to the

requirement for PET scans to define the response rate in 206 and the use of MRI/CT for this purpose in 003.
The duration of response (DOR) in study 206 was 19.5 months (95% CI: 16.6, NE) with a median follow up of 18.4 months, and 18.5 month (12.6, NE) with a median follow up of 18.8 months in study in 003.
Safety Results: This is a single arm trial in which 22% of patients were discontinued from therapy due to progressive disease. In the safety population of 629 patients, 4 of the 8 on study deaths were possibly related to zanubrutinib (one due to infection, one due to intracerebral hemorrhage and two unknown cause of death). Serious adverse events (31%) were comprised most commonly of pneumonia (12%), and hemorrhage (5%). Grade 3 or higher adverse reactions occurred in 47% of patients. The most common hematopoietic adverse reaction was neutropenia (15%); the most common non-hematopoietic was pneumonia (10%).
Benefit Risk Discussion: The Supervisory Associate Division Director for Clinical (Albert Deisseroth) agrees with the review divisions recommendation for approval because the benefit risk ratio was favorable.
Recommended Regulatory Action: Accelerated Approval is recommended rather than regular approval because of questions about how well the ORR endpoint in these studies can be used to predict the effect of zanubrutinib on OS and progression free survival.

X

Albert Deisseroth, MD, PhD

18 Office Director (or designated signatory authority) Comments

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

Marc Theoret, MD

19 Appendices

19.1 References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017

2. Swerdlow, S. H. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood, 127*(20), 2375-2390.

3. Vose, J. M. (2017). "Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management." Am J Hematol **92**(8): 806-813.

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6. Cheah, C. Y., Seymour, J. F., & Wang, M. L. (2016). Mantle Cell Lymphoma. *J Clin Oncol, 34*(11), 1256-1269.

7. Fakhri, B., & Kahl, B. (2017). Current and emerging treatment options for mantle cell lymphoma. *Ther Adv Hematol, 8*(8), 223-234.

8. Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., et. Al. United Kingdom National Cancer Research, I. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol, 32*(27), 3059-3068.

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10. Shah, B. K., & Khanal, A. (2015). Second Primary Malignancies in Mantle Cell Lymphoma: A US Population-based Study. *Anticancer Res, 35*(6), 3437-3440.

19.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): BGB-3111-206

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 87, 15 Principal investigators and 72 sub-investigators		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): BGB-3111-AU-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 322, 28 Principal investigators and 294 sub-investigators _____		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3 Nonclinical Pharmacology/Toxicology

No additional data.

19.4 Additional Clinical Outcome Assessment Analyses

No additional data.

19.5 OCP Appendices (Technical documents supporting OCP recommendations)

19.5.1 Pharmacometric Review

19.5.1.1 Results of Sponsor's Analysis

19.5.1.1.1 Population PK Analysis

The final PopPK model was developed from a dataset of 5333 observed plasma concentrations from 600 subjects enrolled in nine 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 7.3.0 (ICON, Maryland) was used for the PopPK analysis.

Table 44. Summary of studies included in the population PK analysis

Region	Study No.	Title	Phase	Oral Dose Regimen	Clinical Pharmacology Analyses*
Global	BGB-3111-AU-003	A Phase 1, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Patients with B-Cell Lymphoid Malignancies	1	40 mg, 80 mg, 160 mg, and 320 mg QD 160 mg BID	PK and PD Ongoing study 16 September-2018 datacut
China	BGB-3111-1002	A Phase 1 clinical study to investigate the safety, tolerability and pharmacokinetics/ pharmacodynamics of the BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma	1	320 mg QD 160 mg BID	PK and PD 14 Dec 2017 datacut
China	BGB-3111-205	A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)	2	160 mg BID	Sparse PK 15 Jun 2018 datacut
China	BGB-3111-206	A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate the Efficacy and Safety of BGB-3111, a BTK Inhibitor, in Patients with Relapsed or Refractory MCL	2	160 mg BID	Sparse PK 27 Mar 2018 datacut
Australia	BGB-3111-103	A Single-Center, Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of a Single Dose of 320 mg BGB-3111 Given Orally to Healthy Adult Subjects	1	320 mg QD	PK and food effects
USA	BGB-3111-104	A Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of BGB-3111 in Healthy Subjects	1	320 mg (Part A) 20 mg (Part B)	PK and DDI
USA	BGB-3111-105	A Phase 1 Study to investigate the absorption, metabolism, and excretion of [^{14}C]-BGB-3111 following a single oral administration in healthy male subjects	1	320 mg	PK and ADME
USA	BGB-3111-106	A 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	1	160 mg 480 mg	PK and QTc
Global	BGB-3111-302	A Study Comparing BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)	3	160 mg BID	Sparse PK Ongoing study

(Source: Applicant's Population PK Report, Table 2)

Table 45. Summary of data exclusions in the Population PK Datasets

Study	Original Dataset		Data Exclusions						Model Development Dataset	
	No. of subjects	No. of samples	C0	C1	C2	C3	C4	|CWRES|>5	No. of subjects	No. of samples
BGB-3111-AU-003	365	2337	52	20	7	-	13	3	295	2242
BGB-3111-1002	44	728	-	1	-	-	-	-	44	727
BGB-3111-205	13	62	-	-	-	-	-	-	13	62
BGB-3111-206	20	98	-	-	-	-	-	-	20	98
BGB-3111-103	18	395	-	-	-	-	-	4	18	391
BGB-3111-104	38	386	-	-	-	-	-	-	38	386
BGB-3111-105	6	61	-	1	-	-	-	-	6	60
BGB-3111-106	37	774	-	-	-	-	-	-	37	774
BGB-3111-302	129	596	-	-	1	2	-	-	129	593
Total	670	5817	52	22	8	2	13	7	600	5333

C0=measurement concentrations after week 9
C1=negative sampling time or missing sampling time
C2=missing dosing time
C3=measurable concentration before the 1st treatment
C4=duplicate samples at the same time

(Source: Applicant's Population PK Report, Table 3)

Table 46. Baseline Continuous Covariates [Mean (SD)] in the Population PK Development Dataset

Study	Number of patients	ALB (g/L)	ALT (IU/L)	AST (IU/L)	BIL (μmol/L)	CRCL (mL/min)	Creatine (μmol/L)	Weight (kg)	Age (Year)
BGB-3111-1002	44	43.3 (5.05)	15.6 (9.13)	24.6 (8.30)	13.1 (4.18)	103 (25.9)	70.3 (16.6)	68.1 (13.6)	50.1 (11.2)
BGB-3111-103	18	40.7 (3.08)	20.5 (6.64)	19.9 (4.46)	10.0 (5.79)	117 (26.6)	72.7 (11.9)	75.2 (11.7)	45.2 (13.8)
BGB-3111-104	38	44.6 (2.80)	25.8 (12.5)	23.0 (5.49)	10.6 (4.15)	154 (45.4)	64.4 (18.1)	78.8 (13.0)	40.2 (10.1)
BGB-3111-105	6	44.2 (1.94)	23.3 (11.4)	20.3 (5.68)	9.98 (9.52)	123 (21.2)	86.9 (10.3)	78.3 (11.1)	29.8 (4.79)
BGB-3111-106	37	46.1 (2.31)	22.6 (8.52)	19.8 (4.51)	8.32 (3.65)	118 (26.2)	88.3 (9.97)	85.3 (13.0)	41.2 (9.5)
BGB-3111-206	13	44.7 (5.24)	15.5 (4.79)	23.7 (4.20)	15.9 (6.51)	80.1 (18.4)	71.1 (13.6)	61.3 (9.71)	61.5 (8.3)
BGB-3111-206	20	42.7 (4.52)	16.5 (12.5)	24.1 (8.08)	11.7 (3.30)	92.1 (30.3)	76.9 (20.0)	71.1 (12.1)	61.4 (7.21)
BGB-3111-302	129	35.1 (5.75)	18.0 (12.3)	20.8 (10.4)	9.96 (5.20)	85.8 (31.7)	81.9 (28.2)	74.6 (16.9)	69.3 (11.0)
BGB-3111-AU-003	295	38.4 (5.18)	26.8 (20.9)	27.2 (18.7)	11.7 (7.95)	86.0 (33.3)	84.7 (27.4)	77.3 (17.8)	65.9 (11.1)
Total	600	39.4 (5.95)	23 (17.2)	24.5 (14.7)	11.2 (6.69)	95 (37.2)	81.1 (25.4)	76.1 (16.7)	61.1 (14.8)
Total [median (range)]	600	40 (19-53)	19 (3-197)	22 (5-190)	10 (3-101)	89.3 (13.5-240)	78 (35.4-278)	74.2 (36-140)	63 (19-90)

(Source: Applicant's Population PK Report, Table 4)

Table 47. Baseline Categorical Covariates in the Population PK Model Development Dataset

Study	Sex (M/F)	Race (Missing/W/A/O/B)	TUMTP (HV/CLL-SLL/MCL/WM/Other)	COMED (Other/PPI/H2RA)
BGB-3111-1002	24/20	0/0/44/0/0	0/9/2/2/31	41/3/0
BGB-3111-103	13/5	1/17/0/0/0	18/0/0/0/0	18/0/0
BGB-3111-104	29/9	0/16/16/1/5	38/0/0/0/0	38/0/0
BGB-3111-105	6/0	0/2/2/0/2	6/0/0/0/0	6/0/0
BGB-3111-106	36/1	0/15/0/0/22	37/0/0/0/0	37/0/0
BGB-3111-205	8/5	0/0/13/0/0	0/13/0/0/0	10/3/0
BGB-3111-206	16/4	0/0/20/0/0	0/0/20/0/0	17/2/1
BGB-3111-302	82/47	11/114/4/0/0	0/0/0/129/0	89/32/8
BGB-3111-AU-003	207/88	1/235/45/13/1	0/98/39/62/96	176/82/37
Total	421/179	13/399/144/14/30	99/120/61/193/127	432/122/46

* W=White, A=Asian, O=Other, B=Black

(Source: Applicant's Population PK Report, Table 5)

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'smacroglobulinemia [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). The following PK parameter-covariate relationships (Table 46) were significant at $p<0.01$ and were thus carried forward to the forward addition and backward elimination covariate search on CL and V_c: ALT and PAT.

Table 48. Impact of covariates on the Bayesian posthoc PK parameters from the final base model

	etaCL	etaVc	N
ALT	3e-04	0.001	596
AST	0.4773	0.4174	591
BIL	0.8252	0.9109	592
CRCL	0.0236	0.1547	586
WT	0.1286	0.4667	598
AGE	0.1393	0.5599	600
PAT	0	7e-04	600
COMED	0.3503	0.4201	501
TUMTP	0.0223	0.0242	501
SEX	0.4915	0.7652	501
RACE	0.2326	0.4078	501

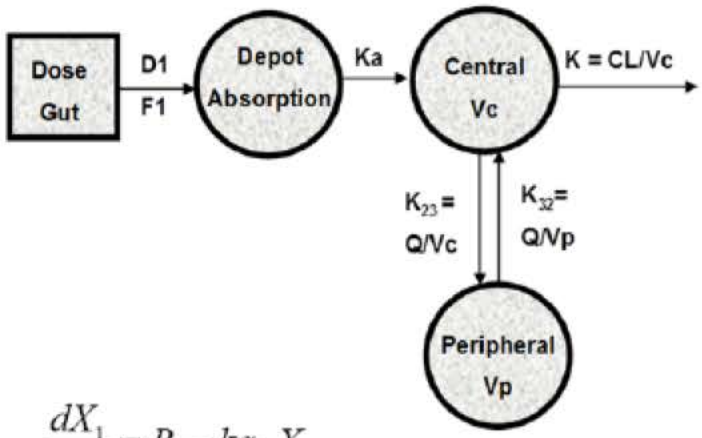
	etaCL	etaVc	N
ALT	9e-04	0.0021	497
AST	0.2818	0.3157	492
BIL	0.9939	0.9623	493
CRCL	0.5878	0.5274	487
WT	0.098	0.2638	499
AGE	0.0693	0.0994	501
COMED	0.9871	0.902	501
TUMTP	0.0223	0.0242	501
SEX	0.4419	0.4967	501
RACE	0.0339	0.0844	501

(Source: Applicant's Population PK Report, Table 6)

The PK of zanubrutinib in the dose range (20 mg - 480 mg) tested was best described by a two-compartment model with sequential zero-order (D1) then first-order (ka) absorption as well as first-order elimination from the central compartment and redistribution from the peripheral compartment, as illustrated in Figure 15. The PopPK 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), the duration (D1), and a lag time (ALAG1).

Figure 15. Population PK model schematic



$$\frac{dX_1}{dt} = R_1 - ka \cdot X_1$$

$$\frac{dX_2}{dt} = ka \cdot X_1 - (k + k_{23}) \cdot X_2 + k_{32} \cdot X_3$$

$$\frac{dX_3}{dt} = k_{23} \cdot X_2 - k_{32} \cdot X_3$$

t = 0 if time ≤ ALAG1
t = time -ALAG1 if time > ALAG1

(Source: Applicant's Population PK Report, Figure 1)

The final PopPK 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:

$$CL_i(\text{L/hr}) = exp\left(5.21 - 0.151 \times log\left(\frac{ALT}{19}\right) - 0.349 \times HV + \eta_{CL,i}\right)$$

$$Vc_i(\text{L}) = exp\left(6.15 + 0.231 \times HV + \eta_{Vc,i}\right)$$

Baseline ALT and health status were identified as significant covariates on CL/F. Health status was identified as a significant covariate on Vc/F. For a typical patient with ALT of 19 U/L, the estimated CL/F was 183 L/hr, Vc/F was 468 L, Q/F was 21.1 L/hr, Vp/F was 568 L, ka was 1.58 hr-1, D1 was 0.495 hr, and lag time was 0.202 hr Interindividual variability on CL/F, Vc/F, Vp/F, Q/F, ka and D1 were 36.9%, 39.2%, 98.0%, 42.3%, 44.1%, and 108%, respectively. A summary of key pop PK parameters and covariate effects is presented in Table 42. The geometric mean elimination half-life was 2.92 hours with a CV of 49.7%.

Table 49. Key PK parameters and covariate effects for representative subjects

PK Parameters and Baseline Covariates		Estimate	Change from Typical
Typical CL/F (L/hr, ALT=19 U/L, patient)		183	—
ALT (U/L)	**10th percentile (10 U/L)**	202	10.2%
	90th percentile (39 U/L)	164	-10.3%
Health status	**HV**	129	-29.5%
Typical V_c/F (L, patient)		468	—
Health status	**HV**	590	26.0%
Typical Q/F (L/hr)		21.1	—
Typical V_p/F (L)		568	—
Typical k_a (hr^{-1})		1.58	—
Typical D_1 (hr)		0.495	—
Lag time (hr)		0.202	—
Proportional residual error (%)		57.8	—

*African American, native Hawaiian or other pacific islander, and others

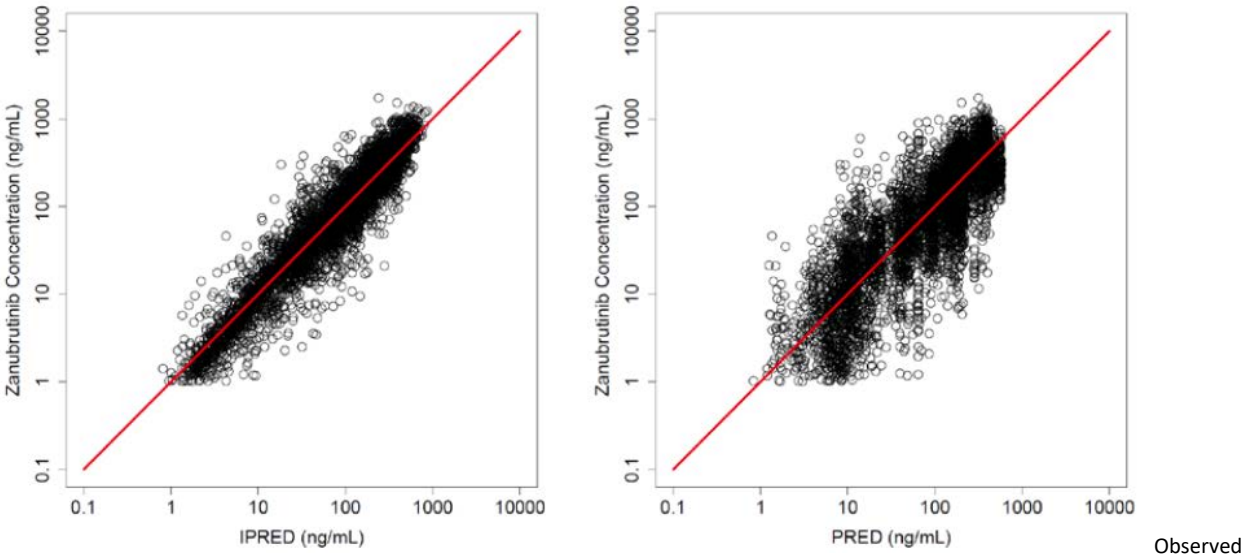
(Source: Applicant's Population PK Report, Table 1)

Table 50. Summary of final population PK parameters

Parameter	Parameter Description	Population Estimate (%SE)	Inter-Individual Variability (%SE)	Inter-occasion variability (%SE)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	183 (2.32%)	36.9 (11.7%)	25.3 (16%)
θ_8	Influence of ALT on CL	-0.151 (18.4%)	-	-
θ_9	Influence of PAT on CL	-0.349 (15.5%)	-	-
$exp(\theta_2)$	Apparent central volume, V_c/F (L)	468 (3.37%)	39.2 (16.6%)	19.9 (51.4%)
θ_{10}	Influence of PAT on V_c/F	0.231 (27%)	-	-
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)	21.1 (7.46%)	98 (15.7%)	-
$exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)	568 (12.4%)	42.3 (82.3%)	-
$exp(\theta_5)$	Absorption rate constant, k_a (hr^{-1})	1.58 (6.21%)	44.1 (31.6%)	-
$exp(\theta_6)$	Duration, D_1 (hr)	0.495 (7.41%)	108 (11.9%)	-
$exp(\theta_7)$	Lag time (hr)	0.202 (5.61%)	-	-
$\omega^2_{Cl,Vc}$	Covariance (CL,V_c)	0.141 (11.4%)	-	-
σ	Residual error (%)	57.8 (2.5%)	-	-

(Source: Applicant's Population PK Report, Table 7)

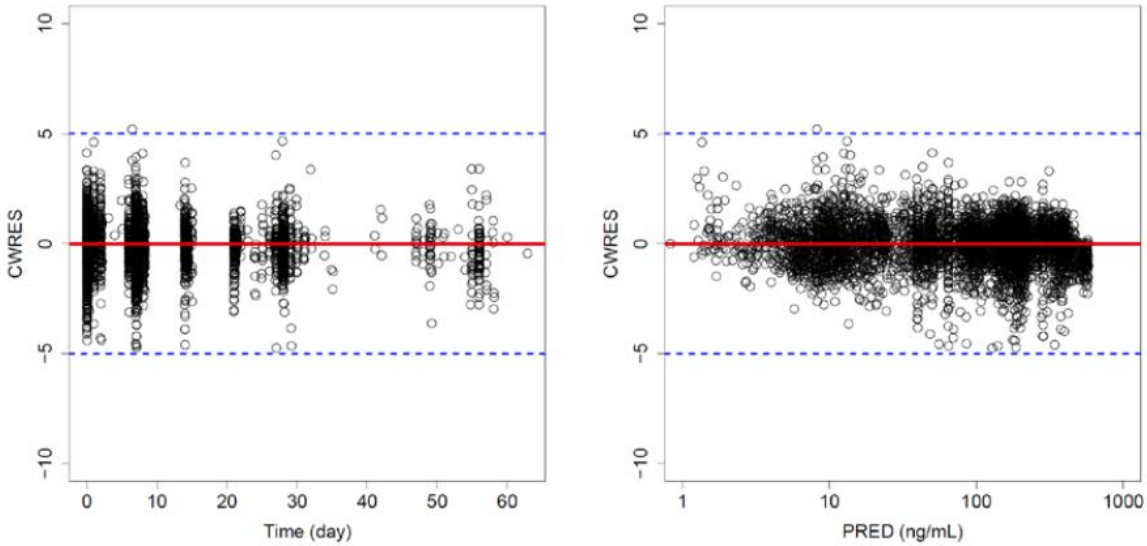
Figure 16. Predicted versus observed concentration diagnostic plots for the final Population PK model



Observed versus individual predicted concentrations (left) and observed versus population predicted concentrations (right) for the final PopPK model. Points are individual data and red lines represent the line of unity .

(Source: Applicant's Population PK Report, Figure 4)

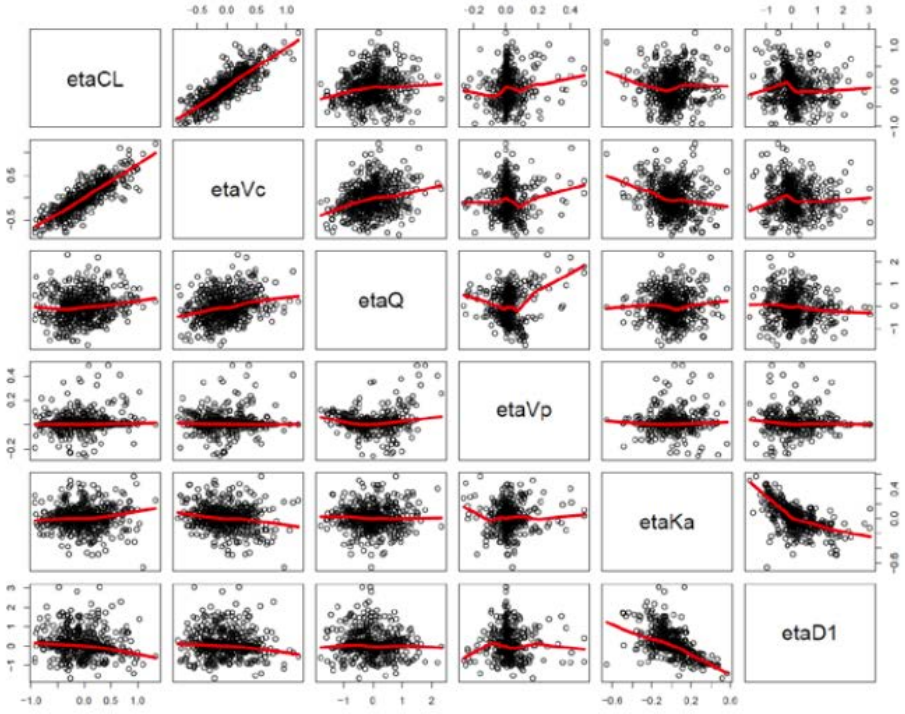
Figure 17. Residual diagnostic plots for the final population PK model



Conditional weighted residuals (CWRES) versus time (left) and PRED (right). Points are individual data. Red solid lines represent the unit line at zero. Blue dashed lines represent |CWRES| of 5.

(Source: Applicant's Population PK Report, Figure 5)

Figure 18. Pairwise correlation plots of the individual ETA estimates from the final population PK model.



Points are the post-hoc estimates from NONMEM. Red lines are smooth curves (lowess) showing the relationship between two variables.

(Source: Applicant's Population PK Report, Figure 7)

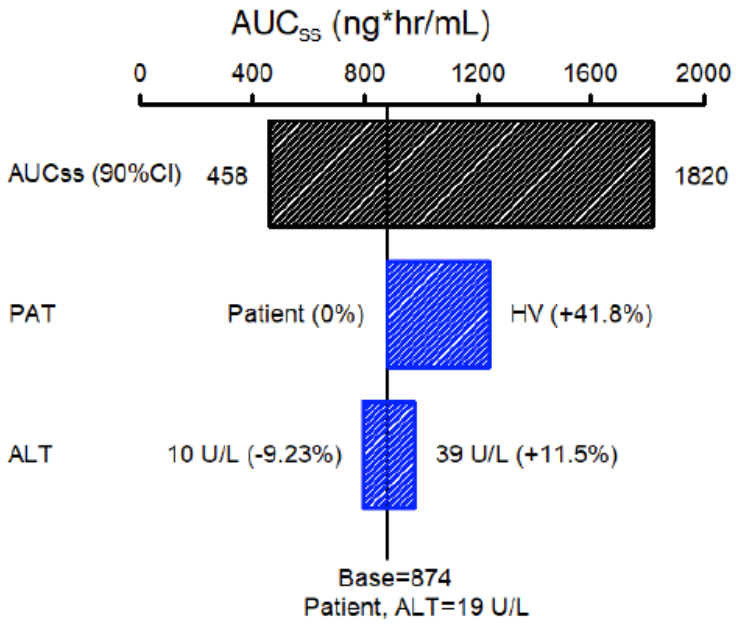
Shrinkage of the final model parameters is presented in Table 49. The magnitude of shrinkage of the final PopPK model was considered small enough for CL/F and Vc/F (<30%). This suggests that the final PopPK model generated reliable Bayesian estimations for CL/F and Vc/F and was considered robust enough to describe the relationship between CL/F, Vc/F and the related covariates. Vp/F and ka had greater η-shrinkage of >50% in the final model, suggesting that PK data might be insufficient to adequately characterize IIV of those parameters in the final model.

Table 51. Shrinkage of the final model parameters

Parameters	Shrinkage (%)
ETA1 (inter-individual variability in CL/F)	24.5
ETA2 (inter-individual variability in V_c/F)	25.4
ETA3 (inter-occasion variability in Q/F)	38.5
ETA4 (inter-occasion variability in V_p/F)	82.5
ETA5 (inter-individual variability in k_a)	65.6
ETA6 (inter-individual variability in D_1)	42.1
EPS (residual error)	13.3

(Source: Applicant's Population PK Report, Table 10)

Figure 19. Sensitivity analysis plot comparing the effect of covariates on zanubrutinib steady-state exposure (AUC_{SS})



Base, as represented by the black vertical line and values, refers to the predicted exposure (AUC_{ss}) of zanubrutinib in a typical male patient after repeated 10 doses of 160 mg BID. AUCss indicates AUC over the 12-hour dosing interval at steady-state. The black shaded bar with value at each end shows the 5th to 95th percentile exposure range across the entire population. Each blue shaded bar represents the influence of covariates on the exposure. The label at left end of the bar represents the covariate being evaluated. The upper and lower values for each covariate capture 80% of the plausible range in the population. The length of each bar describes the potential impact of the covariates on zanubrutinib exposure, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The most influential covariates are at the top of the plot for each exposure parameter.

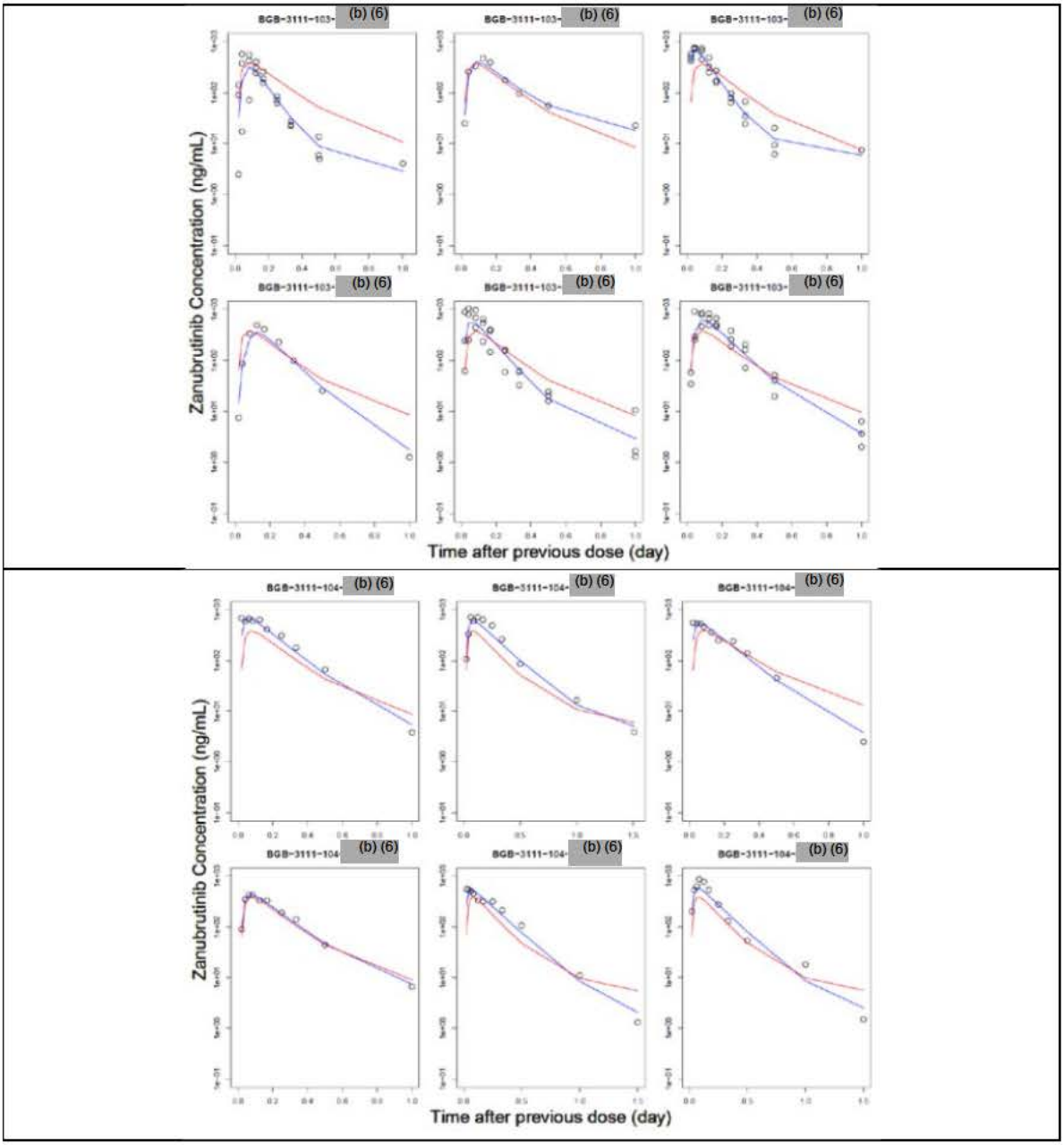
(Source: Applicant's Population PK Report, Figure 2)

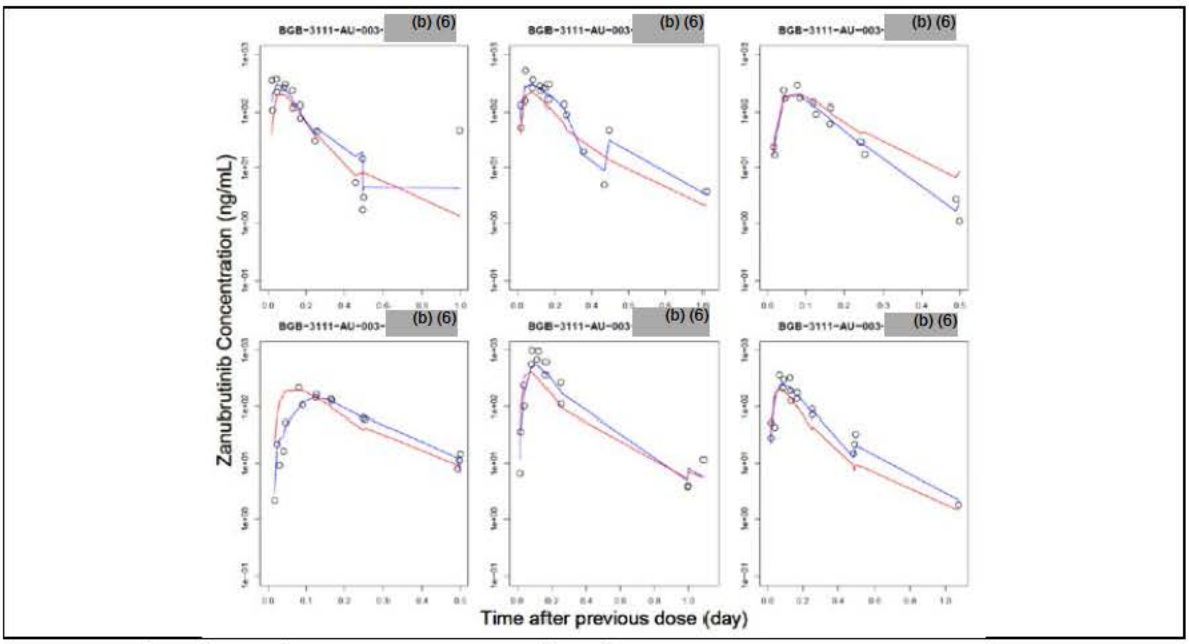
The sensitivity analysis (Figure 19) showed that predicted steady-state Cmax (Cmax,ss) and AUC over the 12-hour dosing interval (AUCss) after repeat dose administration were 216 ng/mL and 874 ng·hr/mL in a typical patient. This corresponds to a total daily AUC of 1748 ng·hr/mL. This analysis also indicated that health status was the most influential covariate on PK of zanubrutinib. The impact of health status on zanubrutinib CL and Vc resulted in 41.8% higher AUCss, and 0.344% lower Cmax,ss in healthy volunteers compared to patients with B-cell malignancies. This result is consistent with observed clinical data in healthy subjects.

Race was not found to be a statistically significant covariate in the PopPK analysis. The model predicted steady state zanubrutinib exposures were similar among Asian, Caucasian, and Other (p value >0.2, ANOVA), as well as between Asian and Caucasian (p-values are 0.078, 0.286, and 0.409 for AUCss, Cmax,ss and Cmin,ss, respectively by ttest).

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.

Figure 20. Individual model fitting goodness of fit plots for the final population PK model for the first 6 individuals in three studies with rich PK sampling: 103 (top panel), 104 (middle panel), and 003 (bottom panel)





(Source: Applicant's Population PK Report, Appendix 8.6)

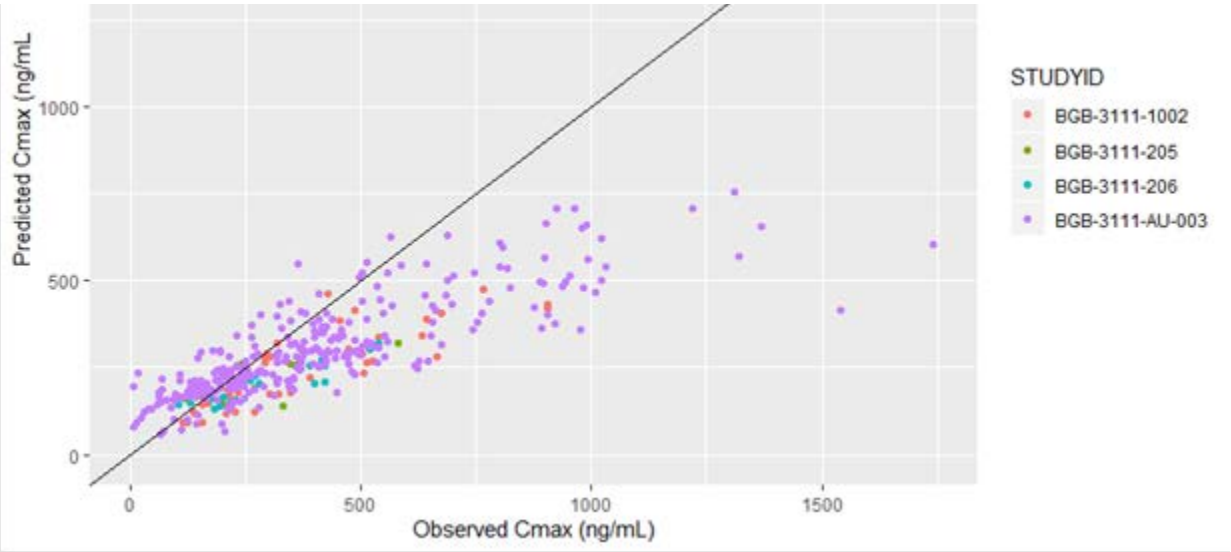
The applicant's final zanubrutinib PopPK model was used to obtain empirical Bayes estimates of individual PK parameters of all zanubrutinib treated patients from studies BGB-3111-AU-003, BGB-3111-205, BGB-3111-206, and BGB-3111-1002. Zanubrutinib time-course PK profile at steady state was simulated using the Bayesian posthoc PK parameters following a 10-dose administration for QD or 20-dose administration for BID of zanubrutinib of actual dose regimen (40 mg, 80 mg, 160 mg 320 mg QD or 160 mg BID) for each patient in all 4 studies. The model-predicted exposure metrics at steady state (AUC0-24,ss, Cmax,ss and Cmin,ss) were computed and merged into the efficacy and safety datasets for E-R analysis.

Reviewer's Comments for applicant's population PK analysis

The applicant used the population PK model-predicted Cmax values for exposure-safety analyses. Additionally, Cmax values were simulated for patients without PK data in the exposure-safety dataset. This analysis may be inappropriate as indicated by the goodness of fit plots, the applicant's final PK model appears to underestimate Cmax for many cases.

The reviewer's analysis also confirmed that there is a discrepancy between the population PK estimates of C_{max} at steady-state and the observed C_{max} values in study BGB-3111-AU-003. Accordingly, the reviewer performed sensitivity analysis using the observed Cmax to evaluate the exposure-safety relationship (Figure 21). This scatter plot indicates that the population PK model underpredicts the measured C_{max} up to ~ 3-fold at the higher end of concentrations. Thus, predicted C_{max} from the population PK model is not reliable as an exposure metric.

Figure 21. Comparison of the applicant's predicted steady-state Cmax and the patient's observed Cmax values for those with PK in the safety analysis dataset.



19.5.1.1.2 Exposure-Response Analysis for Efficacy

The applicant's efficacy endpoints included ORR based on investigator assessment and ORR based on IRC assessment. Responders included complete response (CR) or partial response (PR), and non-responders included stable disease (SD), and progressive disease (PD). The applicant's E-R analysis for efficacy evaluated data obtained from study BGB-3111-AU-003 and pooled data from studies BGB-311-AU-003 and BGB-3111-206.

A dose response is also presented for study BGB-AU-003 in Table 50. Patients receiving a dose of ≤160 mg QD were not in sufficient number for a reasonable comparison of the efficacy rate, whereas the response rate observed between the patients 160 mg BID or 320 mg QD appeared numerically similar.

Table 52. ORR (IRC) by dose for relapsed refractory patients in Study 003

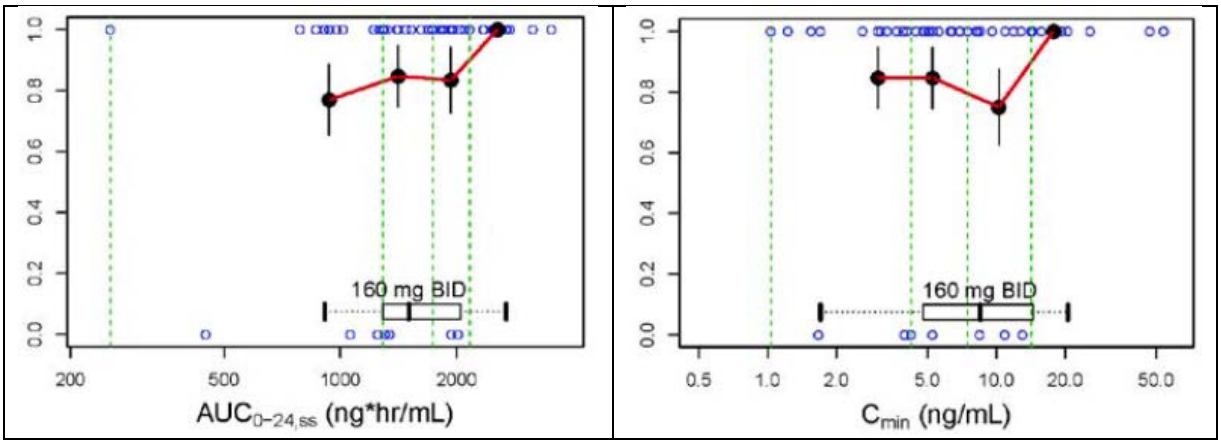
	≤160mg QD					
Response Category	40 mg QD (N=1)	80 mg QD (N=2)	160 mg QD (N=2)	Total (N=5)	160 mg BID (N=14)	320 mg QD (N=18)
Overall Response Rate, n (%)	1 (100.0)	1 (50.0)	1 (50.0)	3 (60.0)	12 (85.7)	15 (83.3)
95% CI [b]	(2.5, 100.0)	(1.3, 98.7)	(1.3, 98.7)	(14.7, 94.7)	(57.2, 98.2)	(58.6, 96.4)

(Source: Applicant's CSR for Study 003, Table 14.2.1.2.1.1.)

Study 206 and 003 Data Combined

The applicant explored graphical relationships for E-R for ORR with $AUC_{0\text{-}24}$, $C_{min,SS}$, and $C_{max,SS}$. The plots for $C_{max,SS}$ are not being presented because of the disconnect between predicted $C_{max,SS}$ and Observed $C_{max,SS}$ in study 003 (see the reviewer's analysis). Graphical presentation of the ORR rates by exposure quartile for $AUC_{0\text{-}24}$ and $C_{min,SS}$ are shown in Figure 22 and Figure 23.

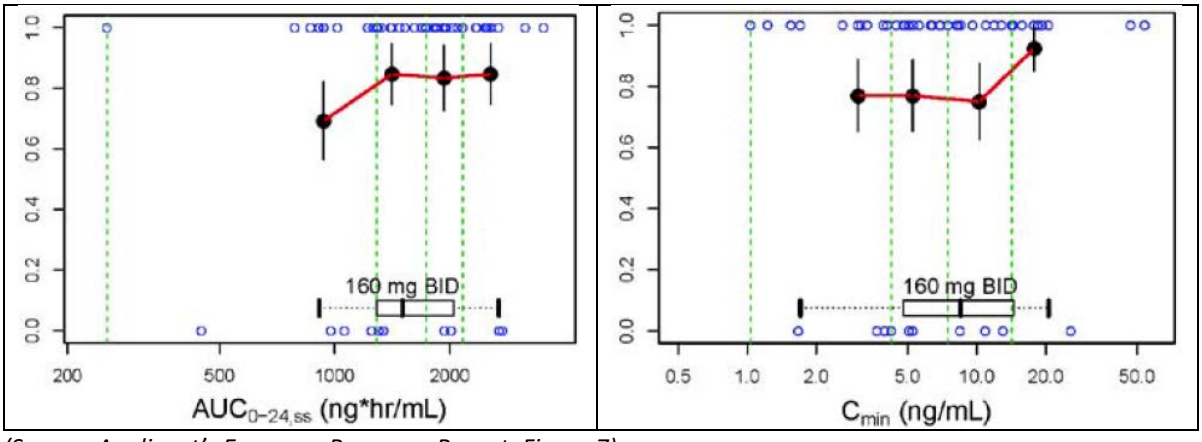
Figure 22. Probability of ORR (Investigator) versus exposure for MCL patients in studies BGB-3111-AU-003 and BGB-3111-206.



(Source: Applicant's Exposure-Response Report, Figure 2)

The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/7) the percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between two variables.

Figure 23. Probability of ORR (IRC) versus exposure for MCL patients in studies BGB-3111-AU-003 and BGB-3111-206.



(Source: Applicant's Exposure-Response Report, Figure 7)

The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/7) the percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between two variables.

Additionally, the applicant performed logistic regression for both Investigator ORR and IRC ORR against AUC (Table 51/Figure 24 and Table 52/Figure 25). Although a numerical trend is present,

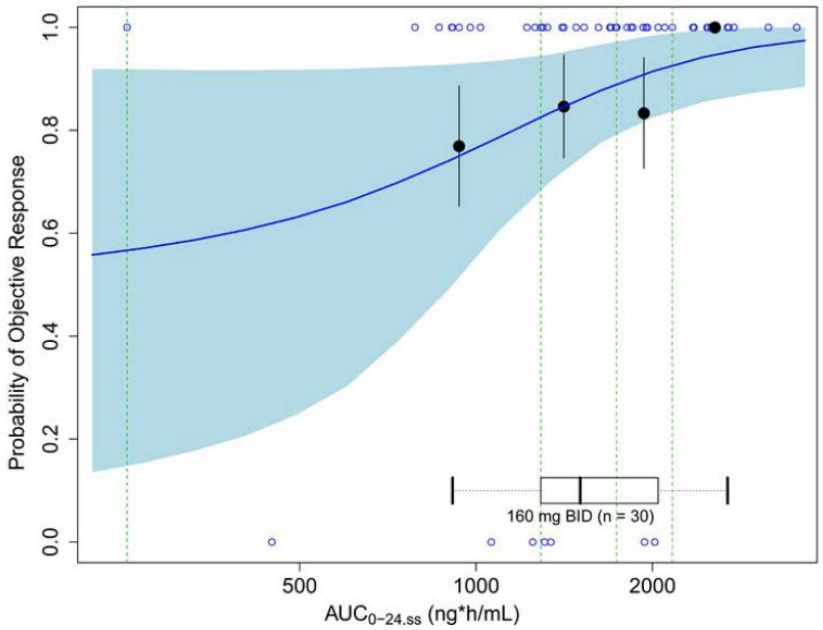
no statistically significant relationship was identified for E-R for efficacy by logistic regression across the dose range of exposures tested.

Table 53. Summary of model parameters from the final ORR model with $AUC_{0\text{-}24,SS}$ for patients with MCL

Parameter	Estimate	Std. Error	p value
Intercept	-5.9949	5.4702	0.2731
$Log(AUC_{0\text{-}24,ss})$	1.0772	0.7584	0.1555

(Source: Applicant's Exposure-Response Report, Table 8)

Figure 24. Diagnostic plot for the final ORR model with $AUC_{0\text{-}24,SS}$



The open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at $100x(1/q)_{th}$ percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue line is the model predicted probability. The light blue shaded area is the 95% prediction interval based on 1000 bootstrap samples.

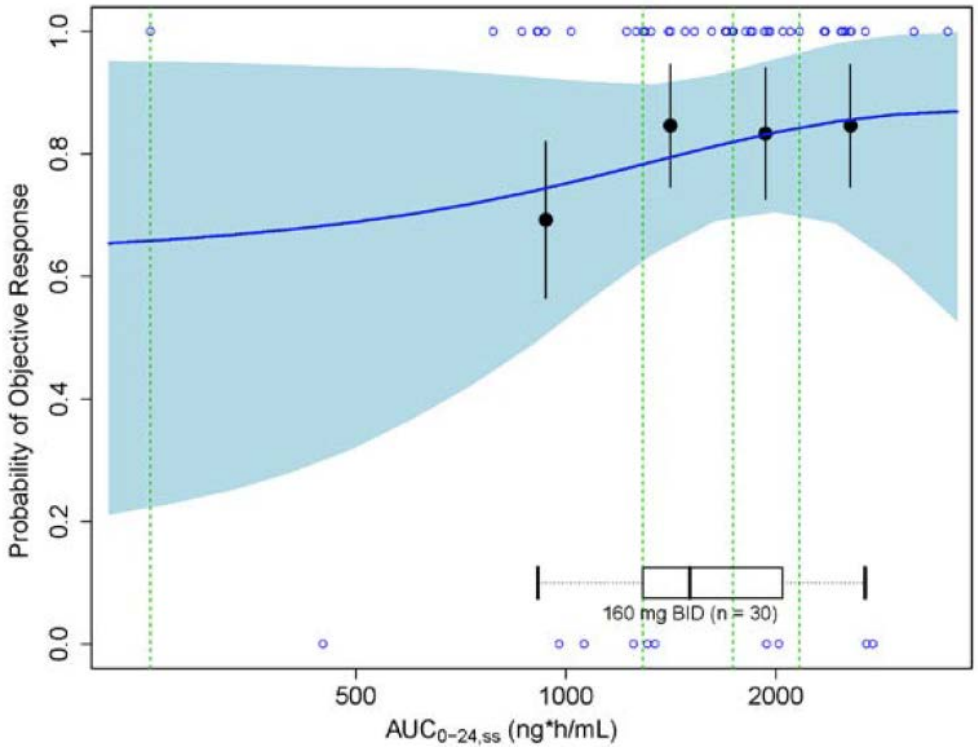
(Source: Applicant's Exposure-Response Report, Figure 27)

Table 54. Summary of model parameters from the final ORR model with $AUC_{0\text{-}24,SS}$

Parameter	Estimate	Std. Error	p value
Intercept	-2.7613	5.0338	0.5833
$Log(AUC_{0\text{-}24,ss})$	0.5698	0.6892	0.4084

(Source: Applicant's Exposure-Response Report, Table 14)

Figure 25. Diagnostic plot for the final ORR model with $AUC_{0\text{-}24,SS}$

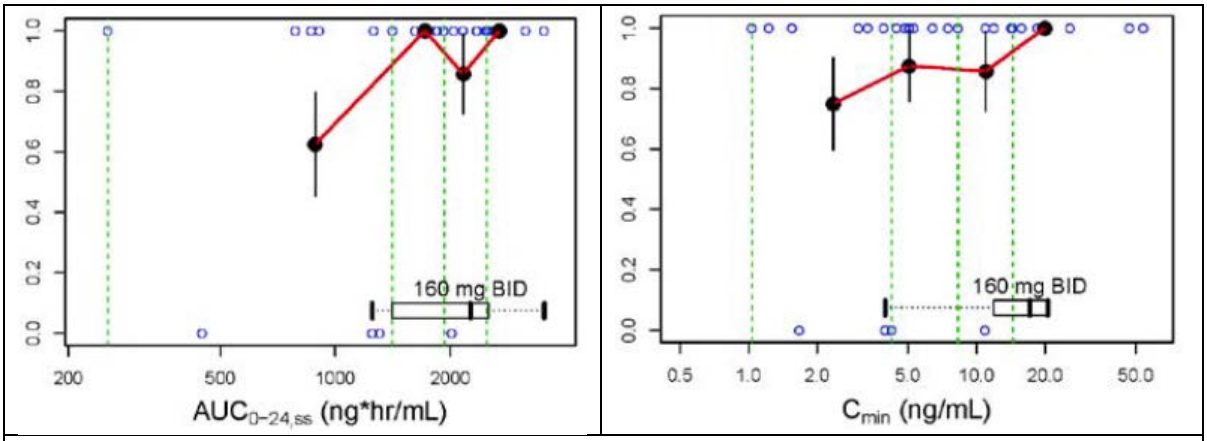


The open blue circles reflect the observed events. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/q)th percentiles, vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue line is the model predicted probability. The light blue shaded area is the 95% prediction interval based on 1000 bootstrap samples.
(Source: Applicant's Exposure-Response Report, Figure 30)

Exposure-Response for Efficacy, Study 003 Only

Graphical exploration of the exposure-response data was also performed for study BGB-3111-AU-003. Results are shown in Figure 26 and Figure 27 and are consistent with results from both study data pooled.

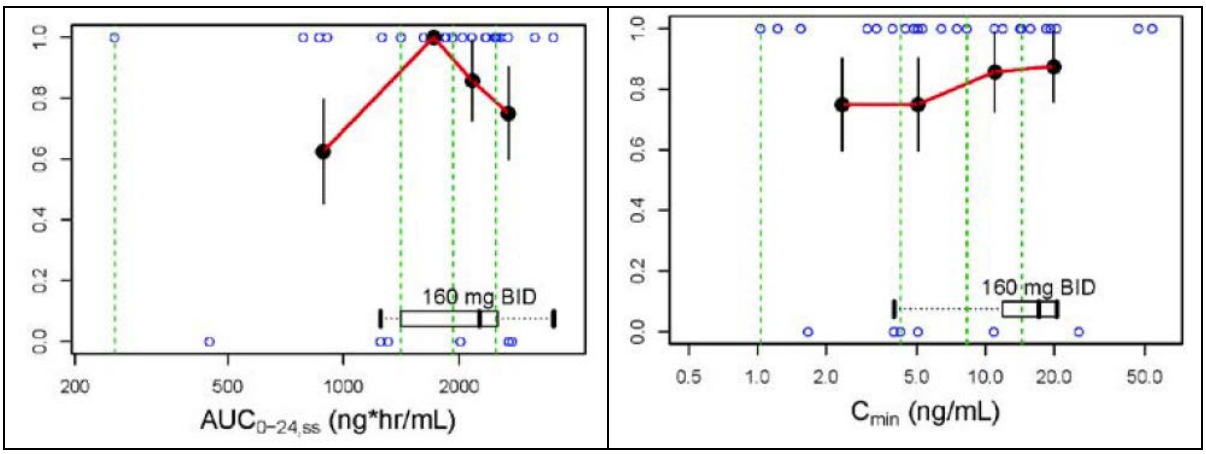
Figure 26. Probability of ORR (Investigator) versus exposure for MCL patients in study BGB-3111-AU-003.



The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/7)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between two variables.

(Source: Applicant's Exposure-Response Report, Figure 4)

Figure 27. Probability of ORR (IRC) versus exposure for MCL patients in study BGB-3111-AU-003.



(Source: Applicant's Exposure-Response Report, Figure 9)

The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/7)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between two variables.

Reviewer's Comments on Exposure-Response for Efficacy: While exposure-response trends appear to exhibit a mildly positive relationship, the similar AUC between the 160 mg BID and 320 mg QD groups suggest that 320 mg QD may serve as an alternate dosing regimen. The applicant did not present a similar analysis for Study 206 data alone. This is likely due to the limited number (n = 20) of subjects with PK data at only one dose level (160 mg BID) and is acceptable.

19.5.1.1.3 Exposure-Response Analysis for Safety

Safety endpoints evaluated included grade ≥ 3 neutropenia, grade ≥ 3 thrombocytopenia, grade ≥ 3 infections/infestations, grade ≥ 3 anemia, secondary primary malignancies, atrial fibrillation and flutter, major bleeding events and any bleeding events. These endpoints were characterized by incidence only, and data from studies BGB-3111- AU-003, BGB-3111-1002, BGB-3111-205, and BGB-3111-206 were used in the analysis.
Data included in the exposure-AE analysis are briefly summarized by study in Table 53.

Table 55. Summary of selected AEs in the safety analysis dataset.

Safety Endpoints	The percentage of patients having AE (Yes/No)				N of AE
	BGB-3111-1002	BGB-3111-205	BGB-3111-206	BGB-311-AU-003	
Grade≥3 neutropenia	27.3% (12/44)	46.2% (42/91)	20.9% (18/86)	22.6% (85/376)	157
Grade≥3 thrombocytopenia	9.09% (4/44)	16.5% (15/91)	4.65% (4/86)	11.4% (43/376)	66
Grade≥3 anemia	13.6% (6/44)	15.4% (14/91)	6.98% (6/86)	12.5% (47/376)	73
Grade≥3 infections/infestations	18.2% (8/44)	38.5% (35/91)	14.0% (12/86)	20.5% (77/376)	132
All events of secondary primary malignancies	0.00% (0/44)	2.20% (2/91)	0.00% (0/86)	14.9% (56/376)	58
All events of atrial fibrillation and flutter	0.00% (0/44)	0.00% (0/91)	0.00% (0/86)	3.46% (13/376)	13
Major bleeding events	0.00% (0/44)	2.20% (2/91)	3.49% (3/86)	3.46% (13/376)	15
Any bleeding events	31.8% (14/44)	62.6% (57/91)	25.6% (22/86)	55.6% (209/376)	302

(Source: Applicant's Population PK/PD Report, Table 6)

Rates of adverse events by dose were summarized for study BRB-3111-AU-003 in Table 54. Too few subjects were included in the 40, 80, and 160 mg QD dosing regimens to infer rates of AEs

for these groups. Between the 160 mg BID and 320 mg QD regimens there did not appear to be a meaningful difference.

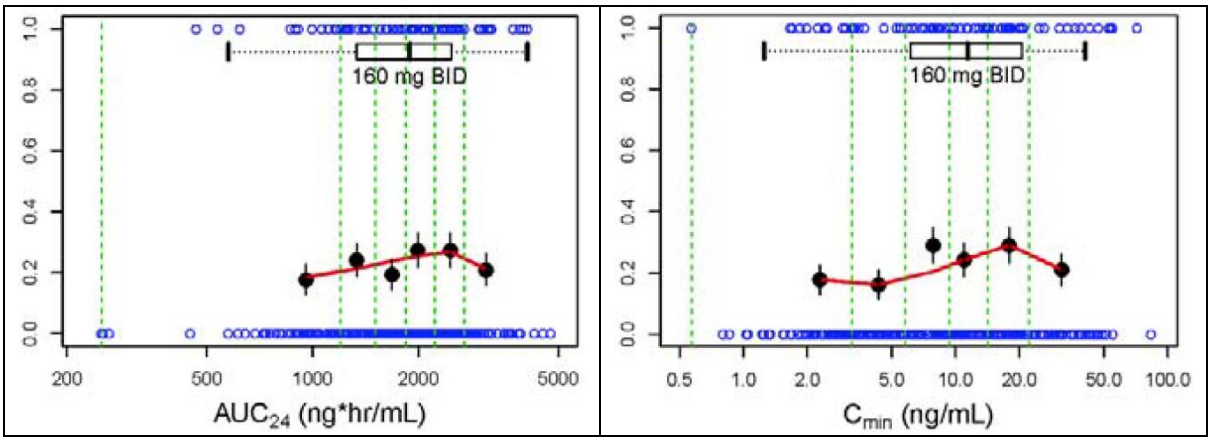
Table 56. Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set in Combined Parts 1 and 2 by Dose and Schedule)

	40 mg QD (N=3) n (%)	80 mg QD (N=4) n (%)	160 mg QD (N=5) n (%)	160 mg BID (N=269) n (%)	320 mg QD (N=95) n (%)	Overall (N=376) n (%)
Patients with at least one TEAE	2 (66.7)	4 (100.0)	5 (100.0)	262 (97.4)	94 (98.9)	367 (97.6)
Grade 3 or Higher[a]	2 (66.7)	3 (75.0)	4 (80.0)	157 (58.4)	47 (49.5)	213 (56.6)
Serious	1 (33.3)	2 (50.0)	3 (60.0)	118 (43.9)	36 (37.9)	160 (42.6)
Leading to Death	1 (33.3)	0 (0.0)	0 (0.0)	18 (6.7)	2 (2.1)	21 (5.6)
Leading to Treatment Discontinuation	1 (33.3)	0 (0.0)	0 (0.0)	30 (11.2)	10 (10.5)	41 (10.9)
Leading to Dose Reduced	0 (0.0)	0 (0.0)	0 (0.0)	17 (6.3)	2 (2.1)	19 (5.1)
Patients with at least one treatment-related TEAE[b]	2 (66.7)	4 (100.0)	4 (80.0)	182 (67.7)	70 (73.7)	262 (69.7)
Grade 3 or Higher[a]	1 (33.3)	0 (0.0)	1 (20.0)	63 (23.4)	19 (20.0)	84 (22.3)
Serious	0 (0.0)	0 (0.0)	1 (20.0)	31 (11.5)	10 (10.5)	42 (11.2)
Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.8)
Leading to Treatment Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.0)	2 (2.1)	10 (2.7)
Leading to Dose Reduced	0 (0.0)	0 (0.0)	0 (0.0)	15 (5.6)	1 (1.1)	16 (4.3)
Patients with at least one AESI	2 (66.7)	4 (100.0)	5 (100.0)	232 (86.2)	88 (92.6)	331 (88.0)
Grade 3 or Higher[a]	2 (66.7)	2 (50.0)	3 (60.0)	121 (45.0)	34 (35.8)	162 (43.1)
Serious	1 (33.3)	1 (25.0)	1 (20.0)	75 (27.9)	20 (21.1)	98 (26.1)

(Source: Applicant's CSR for BGB3111-AU-003, Table 14.3.1.2.1.2)

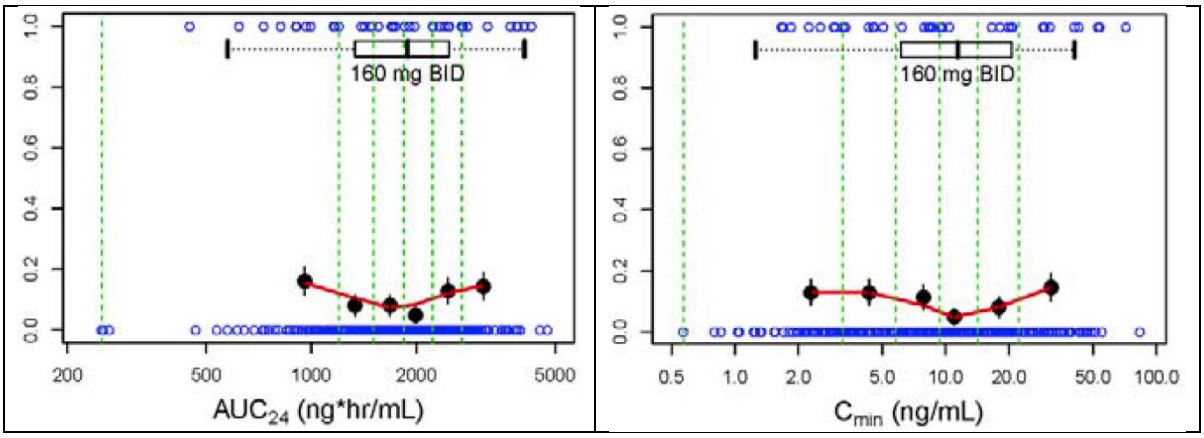
The applicant's E-R analysis for safety was a graphical exploration of adverse event incidence rate by exposure sextile. The results are shown in Figure 28 through Figure 35 for $AUC_{0\text{-}24}$ and $C_{min,SS}$ and suggest there is no apparent relationship between exposure and adverse event rates. Logistic regression was not performed for the safety events. Results are not presented for Cmax given the discrepancy between predicted Cmax and observed Cmax for study BGB-3111-AU-003. The following text is relevant for each of Figure 28 through Figure 35: The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/7)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between two variables.

Figure 28. Probability of Grade ≥3 Neutropenia versus Steady-State Exposures



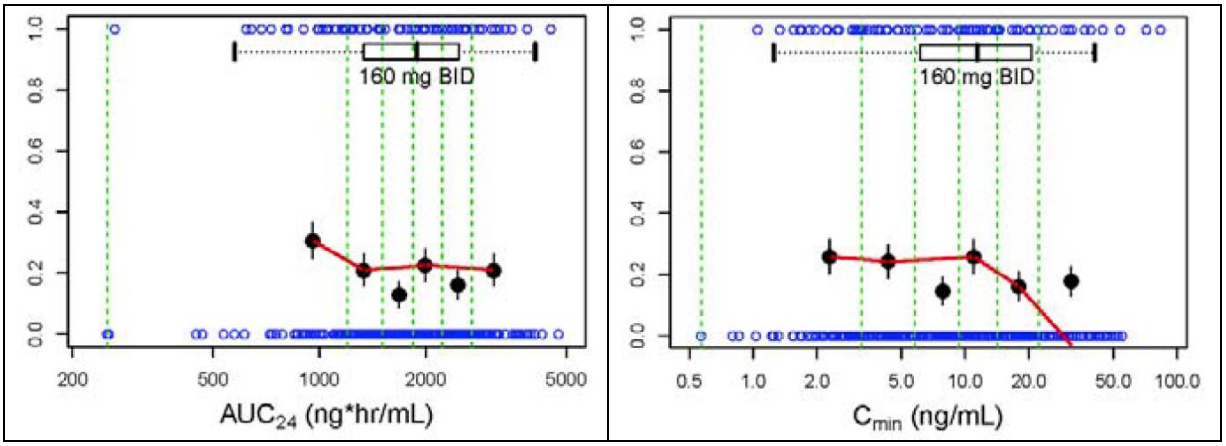
(Source: Applicant's Population PK-PD Report, Figure 12)

Figure 29. Probability of Grade ≥3 Thrombocytopenia versus Steady-State Exposures



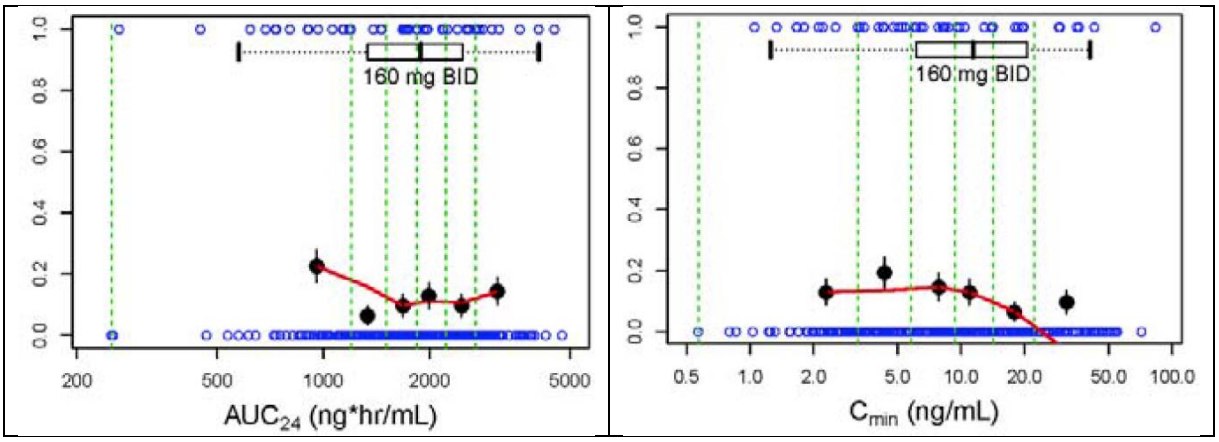
(Source: Applicant's Population PK-PD Report, Figure 14)

Figure 30. Probability of Grade ≥3 Infections/Infestations versus Steady-State Exposures



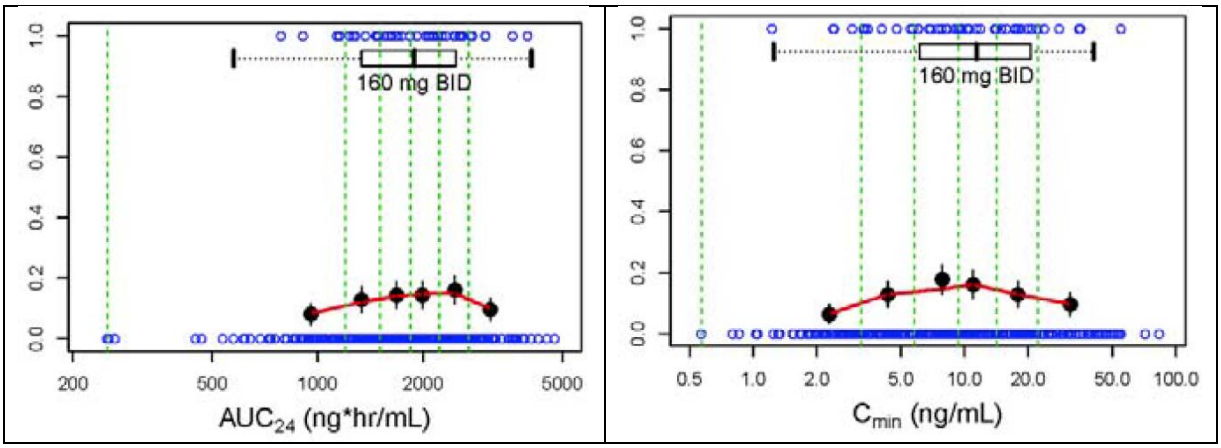
(Source: Applicant's Population PK-PD Report, Figure 16)

Figure 31. Probability of Grade ≥3 Anemia versus Steady-State Exposures



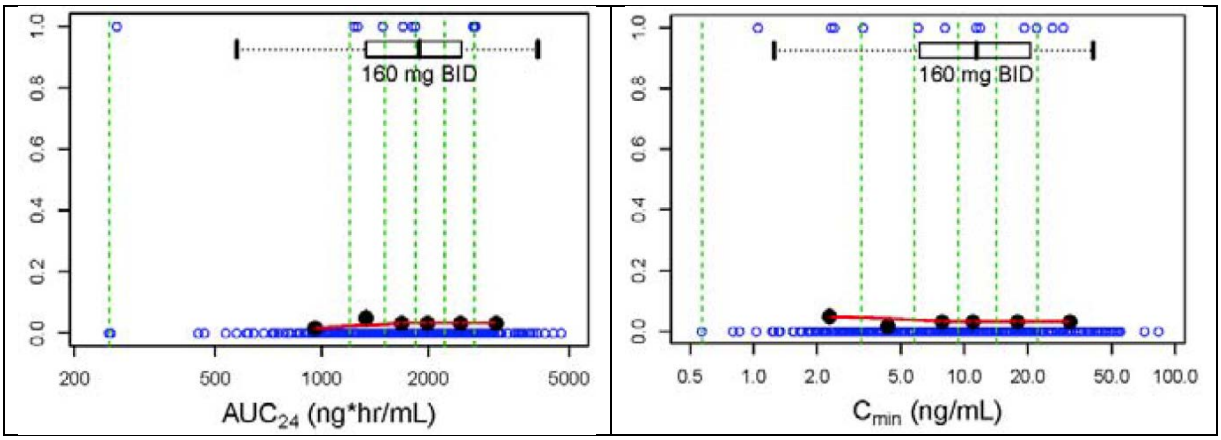
(Source: Applicant's Population PK-PD Report, Figure 18)

Figure 32. Probability of Secondary Primary Malignancies versus Steady-State Exposures



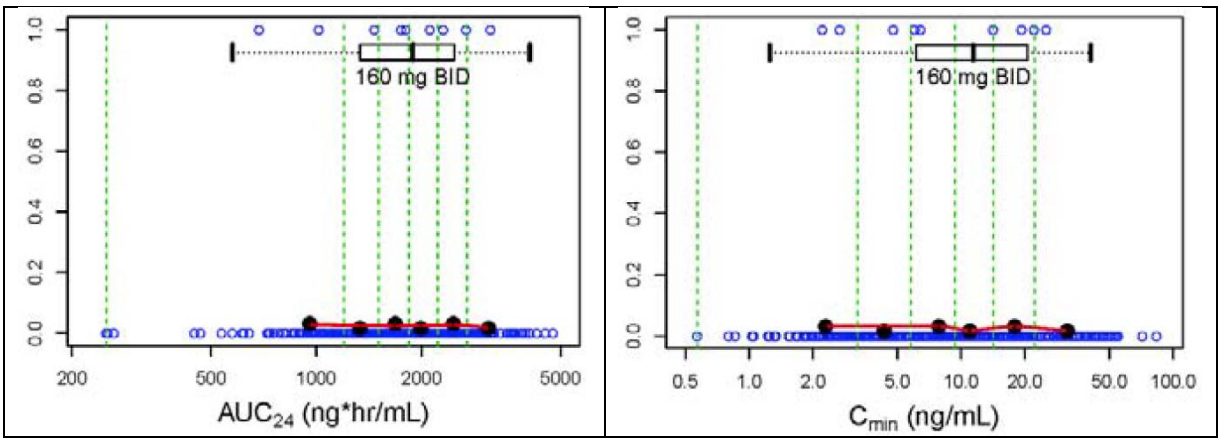
(Source: Applicant's Population PK-PD Report, Figure 20)

Figure 33. Probability of Atrial fibrillation and flutter versus Steady-State Exposures



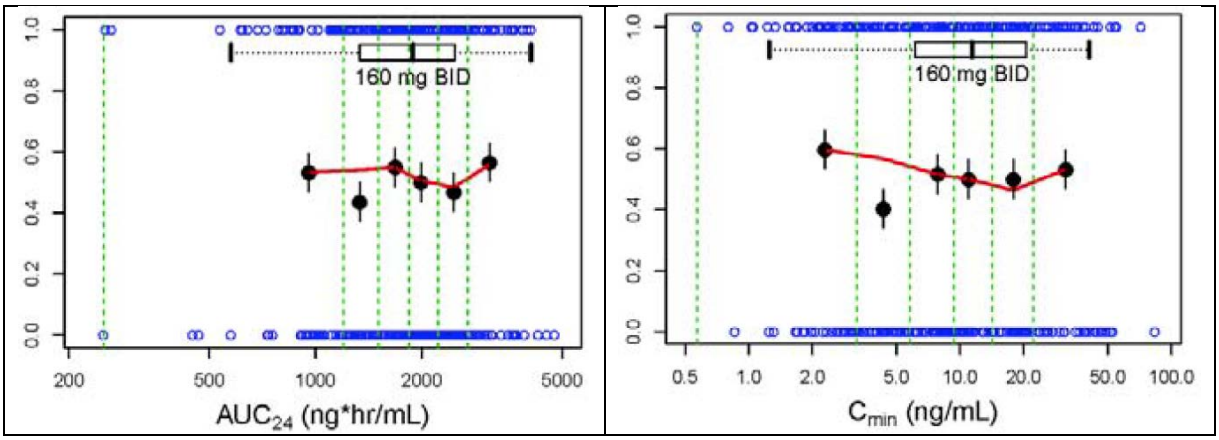
(Source: Applicant's Population PK-PD Report, Figure 22)

Figure 34. Probability of Major Bleeding Events versus Steady-State Exposures



(Source: Applicant's Population PK-PD Report, Figure 24)

Figure 35. Probability of Any Bleeding Event versus Steady-State Exposures



(Source: Applicant's Population PK-PD Report, Figure 26)

Reviewer's Comments on Exposure-Response for Safety: The applicant's exposure-safety analysis is in part limited by number of subjects across different doses. In fact, only 12 subjects in the safety dataset of 597 subjects had doses less than the total daily dose of 320 mg. Thus, the exposure-response for safety is mainly driven by one total daily dose level (160 mg BID and 320 mg QD). To add to the degree of uncertainty, not all subjects in the safety dataset had PK observations collected. Therefore, the applicant utilized the population PK model to predict their steady-state exposures. Given the degree of between subject variability (37%, relevant for AUC) and shrinkage in ETA for CL and Vd (≥24%), it is likely that this analysis is not as reliable for exposure-response as those with measured PK data for each individual. The reviewer modified the applicant's analysis to utilize observed PK as the exposure metric to determine whether this made a difference in the exposure-response assessment for safety.

19.5.1.2 Reviewer's Analysis

19.5.1.2.1 Introduction

The office of clinical pharmacology is recommending labeling 320 mg QD zanubrutinib in addition to 160 mg BID zanubrutinib. The reviewer's analysis is aimed at evaluating where the E-R analyses for efficacy and safety support the use of 320 mg QD in adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
The applicant's analysis utilized predicted Cmax as a metric for the exposure-response analysis. However, their final population PK model seems to underestimate the observed Cmax. The reviewer evaluated the discrepancy between predicted and observed Cmax, and update the E-R analysis to assess the E-R relationship in patients with observed Cmax values.

19.5.1.2.2 Objectives

Analysis objectives are:
1. Evaluate whether dose/exposure-response relationships for efficacy supports the 320 mg QD dosing regimen

2. Evaluate whether exposure-response relationships for safety support the 320 mg QD dosing regimen

19.5.1.2.3 Methods

Data Sets
Data sets used are summarized in Table 55.
Table 57. Analysis Data Sets

Study Number	Name	Link to EDR
BGB-3111-AU-003	Adsl.xpt	\\\\cdsesub1\\evsprod\\NDA213217\\0001\\m5\\datasets\\bgb-3111-au003\\analysis\\adam\\datasets\\adsl.xpt
BGB-3111-AU-003	Adbase.xpt	\\\\cdsesub1\\evsprod\\NDA213217\\0001\\m5\\datasets\\bgb-3111-au003\\analysis\\adam\\datasets\\adbase.xpt
BGB-3111-AU-003	Adexsum.xpt	\\\\cdsesub1\\evsprod\\NDA213217\\0001\\m5\\datasets\\bgb-3111-au003\\analysis\\adam\\datasets\\adexsum.xpt
BGB-3111-AU-003	Adtte.xpt	\\\\cdsesub1\\evsprod\\NDA213217\\0001\\m5\\datasets\\bgb-3111-au003\\analysis\\adam\\datasets\\adtte.xpt
Population PK	Pkinput0.xpt	\\cdsesub1\evsprod\NDA213217\0001\m5\datasets\pop-pk\analysis\legacy\datasets\pkinput0.xpt
Exposure-Response	Erpk-safety.xpt	\\cdsesub1\evsprod\NDA213217\0001\m5\datasets\e-r\analysis\legacy\datasets\erpk-safety.xpt
Exposure-Response	Erpk-efficacy.xpt	\\cdsesub1\evsprod\NDA213217\0001\m5\datasets\e-r\analysis\legacy\datasets\erpk-efficacy206003.xpt
Exposure-Response	Adex.xpt	\\cdsesub1\evsprod\NDA213217\0001\m5\datasets\e-r\analysis\legacy\datasets\adex.xpt

Software
NONMEM (version 7.3) was utilized to evaluate the applicant's final population PK model and variations of that model. The statistical software R was utilized to generate review plots and summarize potential confounders by exposure group.

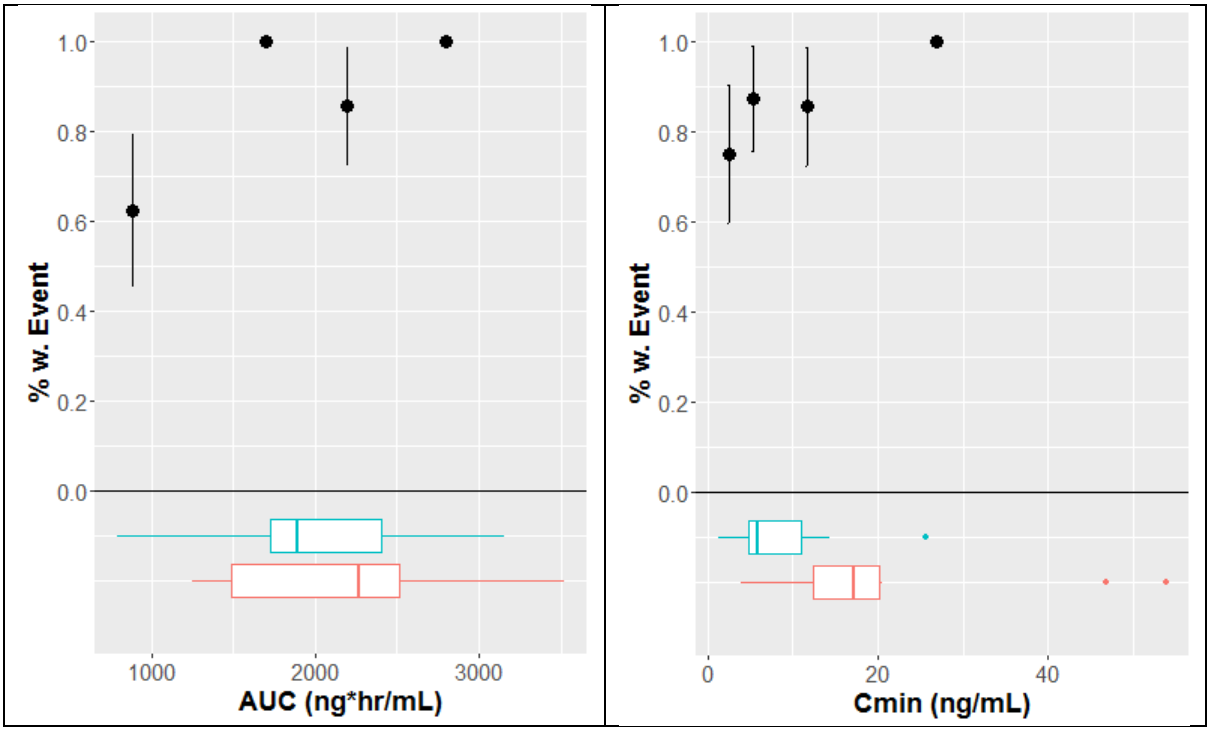
19.5.1.2.4 Results

Dose/Exposure-Response for Efficacy
The reviewer updated the applicant's E-R analysis to determine if there were advantages or disadvantages to offering 320 mg QD as an alternate dosing regimen to 160 mg BID. The applicant's graphical analysis was updated to place the exposures from the 320 mg QD regimen alongside those for the 160 mg BID regimen. The analysis suggests comparable $AUC_{0\text{-}24,SS}$ values between the regimens and comparable response rates, whereas a slightly lower response may be apparent for 320 mg QD compared to 160 mg BID at the lower end of $C_{min,SS}$ range (Figure 3 and Figure 36).

Only data from study BGB-3111-AU-003 were utilized for this analysis as this was the dose ranging study. Additionally, a comparison of exposure between these two dose levels including data from 206 could confound this comparison since in study 206 on day 1 only one dose of 160 mg was

administered to allow for determination of the full 24-hr PK profile after administration of a single dose.

Figure 36. Probability of ORR (Investigator) versus Steady-State AUC (left panel) and Cmin (right panel) in Study BGB-3111-AU-003.



Distribution of zanubrutinib exposures are shown for 160 mg BID (red) and 320 mg QD (blue) in the box plots at the bottom of each plot.

As this is an exploratory analysis within a subset of the population by AUC and Cmin quartiles, summary statistics of baseline patient demographics and disease characteristics were generated to determine if there were any imbalances across the exposure quartiles in study 003. Of note is that there were at most 8 subjects per quartile of exposure in 003. The patient factors are shown in Table 56 for AUC quartile and Table 57 for Cmin quartile. There are potential imbalances with ECOG score, duration since diagnosis, number of prior therapies, and LDH at baseline. This suggests that the exposure-response analysis could possibly be confounded by these factors.

Table 58. Summary of baseline patient and disease characteristics by AUC quartile in the exposure-efficacy dataset

	AUC Quartile			
Parameter	**Q1**	**Q2**	**Q3**	**Q4**
N	8	8	7	8
Age (years)	71.6	74.8	70.7	66.1
M/F	6/2	5/3	4/3	7/1
ECOG at Baseline	0.5	0.375	0.714	0.875
Duration Since Diagnosis (months)	39.3	52.8	77.6	62.5
Number of Prior Therapies	1.5	2.4	2.1	1.6
MIPI Baseline	6.38	6.17	5.91	5.97
LDH Baseline (g/dL)	291	392	264	260

Mean values are reported for all parameters except N and Sex.

Table 59. Summary of baseline patient and disease characteristics by Cmin quartile in the exposure-efficacy dataset

	Cmin Quartile			
Parameter	**Q1**	**Q2**	**Q3**	**Q4**
N	8	8	7	8
Age (years)	72.8	71.3	66.7	72.1
M/F	6/2	5/3	4/3	7/1
ECOG at Baseline	0.375	0.625	0.714	0.75
Duration Since Diagnosis (months)	48.2	59.6	76.7	47.6
Number of Prior Therapies	1.5	2.1	2.7	1.4
MIPI Baseline	6.33	6.00	5.96	6.14
LDH Baseline (g/dL)	250	400	317	245

An exploratory analysis of the time to response and duration of response by dose level was also performed to help determine if there are differences in response between the 160 mg BID and 320 mg QD dosing regimen (Table 58 and Table 59). No apparent trends were observed for median time to response (PR or better). Duration of response appeared to be longer for patients on 320 mg QD compared to 160 mg BID, however this may be limited by sample size.

Table 60. Summary of time to response and duration of response for relapsed/refractory patients in study BGB-3111-AU-003 (investigator adjudicated)

Dose	Median Time in Days to PR or Better	Duration of Response (PR or Better)	N
40 mg	78	858	1
80 mg QD	80	469	1
160 QD	78	350	1
320 QD	83	415	16
160 BID	81	382	12

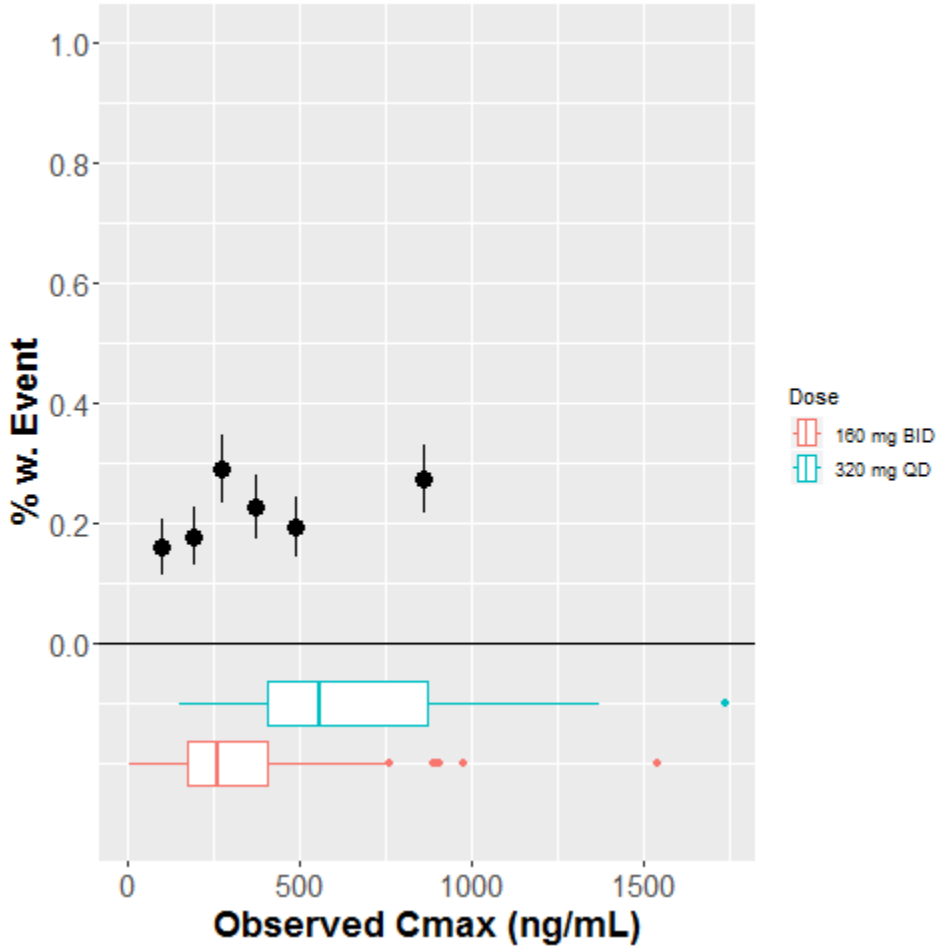
Table 61. Summary of time to response and duration of response for relapsed/refractory patients in study BGB-3111-AU-003 (IRC adjudicated)

Dose	Median Time in Days to PR or Better	Duration of Response (PR or Better)	N
40 mg	78	858	1
80 mg QD	80	469	1
160 QD	78	350	1
320 QD	79	410	14
160 BID	84	335	12

Exposure-Response for Safety

The reviewer modified the applicant's analysis to utilize observed $C_{max,SS}$ as the exposure metric to determine whether this made a difference in the exposure-response relationships for safety. Based on the results, no apparent relationship was evident for neutropenia as well as the other safety endpoints explored by the applicant (grade ≥ 3 thrombocytopenia, grade ≥ 3 infections/infestations, grade ≥ 3 anemia, secondary primary malignancies, atrial fibrillation and flutter, major bleeding events and any bleeding events), which is consistent with the applicant's E-R results using predicted Cmax. As an example, the updated E-R result for grade ≥3 neutropenia is shown in Figure 37.

Figure 37. Incidence Rate of Grade ≥3 Neutropenia vs Cmax, observed in patients with PK in the exposure-safety dataset.



Distribution of zanubrutinib exposures are shown for 160 mg BID (red) and 320 mg QD (blue) in the box plots at the bottom.

19.5.1.3 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
ZanubrutinibER.R	PK and ER analysis file	\\Reviews\PM Review Archive\2019\

19.5.1 Physiologically-Based Pharmacokinetic (PBPK) Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses report (BGB-3111-CP-001) entitled "Physiologically Based Pharmacokinetic Model for zanubrutinib Drug–Drug Interaction Prediction" to support intended

uses. The objectives of the PBPK analyses were to 1) predict the effect of CYP3A inhibitors/ inducers on zanubrutinib exposure; 2) predict the DDI potential of zanubrutinib on the exposure of CYP2B6 (bupropion) and CYP2C8 (repaglinide and rosiglitazone) substrates; 3) predict the impact of elevated gastric pH on zanubrutinib exposure; and 4) provide a dosing recommendation based on the predicted DDI potential.
The Division of Pharmacometrics has reviewed the original PBPK report, the addendum to the report, supporting modeling files, the Applicant's response to FDA request for information dated August 14, August 30, and September 27, 2019, and concluded the following:

- The PBPK model of zanubrutinib is adequate to predict the PK of zanubrutinib following single or multiple dose administration of zanubrutinib ranging from 20 mg to 360 mg daily.
- The PBPK analyses are adequate to predict the magnitude of the effect of CYP3A4 inhibitors on zanubrutinib exposure. Depending on the inhibitors and dosage, the model predicted zanubrutinib AUCtau,ss may increase from 2.83- to 8.32-fold with co-administration of a strong CYP3A4 inhibitor (such as clarithromycin, itraconazole, or ritonavir). Zanubrutinib AUCtau,ss may increase from 2.57-to 4.17-fold with co-administration of a moderate CYP3A4 inhibitor (such as diltiazem, erythromycin or fluconazole).
- The PBPK analyses are adequate to predict the magnitude of effect of a moderate CYP3A4 inducer on zanubrutinib exposure. The model predicted that a moderate CYP3A4 inducer (such as efavirenz) may decrease the steady-state AUC of zanubrutinib by 60%.
- The PBPK analyses suggest the inhibitory effect of zanubrutinib on a CYP2C8 substrate is minimal.

Background
Zanubrutinib (Brukinsa) is developed to treat mantle cell lymphoma (MCL) patients who have received at least one prior therapy. The proposed dosing of zanubrutinib is 160 mg orally twice daily or 320 mg orally once daily with or without food. Refer to Clinical Pharmacology Review (Section 6) for pharmacology and pharmacokinetic characteristics of zanubrutinib.

In summary, dose-exposure relationships in plasma for zanubrutinib were approximately linear following multiple dose in patients in the doses ranging from 20 mg to 320 mg daily. Human mass balance study (BGB-3111-105) reported that approximately 37.62% of total oral dose was excreted unchanged in feces following a single oral dose of 320 mg of zanubrutinib. Minimal unchanged drug was detected in urine (<1%). Results of the human mass balance study suggested the major clearance pathway of zanubrutinib is oxidation (approximately 80%), and to a lesser extent direct cysteine/glutathione conjugation of zanubrutinib (approximately 15% to 20%) (section3.2.3 Summary of Clinical Pharmacology Studies).

Recombinant cytochrome (rCYP) and human liver microsomal assay suggested that CYP3A mediated oxidation was the dominant clearance pathway. Zanubrutinib is a reversible inhibitor for CYP2C8 with an IC50 value of 4.03 μM. Zanubrutinib is an inducer for CYP2B6 and CYP3A in human hepatocytes (Applicant's Nonclinical Overview, Section 2.4.5). Given that CYP3A and

CYP2C are both mediated by the Pregnane-X Receptor (PXR) pathway, zanubrutinib may also have induction potential for CYP2Cs. In vitro, zanubrutinib is a substrate and inhibitor for P-glycoprotein (P-gp), and an inhibitor for BCRP. Zanubrutinib is not a substrate or perpetrator of OATP1B1/3, OATP1B3, OAT1/3, and OCT2.

The Applicant conducted clinical drug-drug interaction (DDI) studies in healthy subjects to assess DDI potential of zanubrutinib as a CYP3A substrate (BGB-311-104) and an inducer for CYP3A, CYP2C9 and CYP2C19 pathways (BGB-311-108). The inhibition potential of zanubrutinib on BCRP and P-gp substrate was also evaluated using the cocktail approach (BGB-311-108). Table 60 summarizes the ratios of the observed maximum plasma concentration (Cmax) and plasma area under the curve (AUC) of substrates in the presence and absence of a perpetrator in these studies.

Table 62. Clinical DDI effects of zanubrutinib as a CYP substrate or as a perpetrator

Target Pathway (CYPs/Transporters)	Substrate (dose)	Perpetrator (dose)	Substrate's Cmax ratio*	Substrate's AUC_{0-t} ratio*, †
CYP3A	Zanubrutinib (20 mg SD)	Itraconazole (200 mg QD)	2.57 (2.26-2.91)	3.68 (3.50, 4.26)
CYP3A	Zanubrutinib (320 mg SD)	Rifampin (600 mg QD)	0.07 (0.066-0.095)	0.07 (0.059-0.056)
CYP3A	Midazolam (2 mg SD)	Zanubrutinib (160 mg BID)	0.70 (0.63-0.78)	0.52 (0.48-0.57)
CYP2C9	Warfarin (10 mg SD)	Zanubrutinib (160 mg BID)	0.95 (0.87-1.04)	1.00 (0.97-1.02)
CYP2C19	Omeprazole (20 mg SD)	Zanubrutinib (160 mg BID)	0.80 (0.65-0.97)	0.64 (0.57-0.70)
P-gp	Digoxin (0.25 mg SD)	Zanubrutinib (160 mg BID)	1.34 (1.16-1.55)	1.11 (1.04-1.19)
OATP1B1, OATP1B3, BCRP	Rosuvastatin (10 mg SD)	Zanubrutinib (160 mg BID)	1.08 (0.92-1.27)	0.85 (0.79-1.02)

*Values as geometric mean (GM) (90% CI); † AUC_{0-48} for zanubrutinib; AUC_{0-12} for Omeprazole; AUC_{0-24} for other substrates; Source: Applicant's Summary of Clinical Pharmacology Studies Table 8, 9, 17; Figure 21. SD: single dose

The Applicant developed PBPK models to predict the effects of strong, and moderate CYP3A inhibitors, and strong and moderate CYP3A inducers on the PK of zanubrutinib, the effects of zanubrutinib on the exposure of CYP2B6 (bupropion) and CYP2C8 (repaglinide and rosiglitazone) substrates, and the effect of gastric pH on zanubrutinib exposure. Dose modification of zanubrutinib was proposed with concomitant use of CYP3A inhibitors/inducers based on the simulation results.

Methods

I. PBPK model structure and development

The PBPK model of zanubrutinib was developed based on in vitro properties, physicochemical properties, the human ADME study (study#BGB-3111-105) and clinical PK data. In summary, an Advanced Dissolution, Absorption and Metabolism (ADAM) model and a minimal PBPK model was used to describe the distribution and PK of zanubrutinib. The fraction of unbound drug in plasma (fu) was measured ex vivo in healthy human plasma using equilibrium dialysis. The average unbound fraction of zanubrutinib in plasma was 5.83% (ranging 5.03% to 6.46%), and the blood to plasma concentration ratio (B/P) was 0.804 (Study 3D_RN016124).

The effective membrane permeability (Peff) in human was estimated to be 3.035×10^{-4} cm/s for zanubrutinib. This number was later modified to $0.9\text{x}10^{-4}$ cm/s to account for the unchanged zanubrutinib (37.62%) in feces as reported in mass-balance study (study#BGB-3111-105). Zanubrutinib has pH dependent solubility of 0.247 mg/mL in pH 1.2 HCL solution, 0.073 mg/mL in pH 4.5 acetate buffer, 0.054 mg/mL in pH 6.8 phosphate buffer, and 0.052 mg/mL in pH 7.4 phosphate buffer. The solubility in water is 0.0057 mg/mL. The in vitro solubility vs. pH profile was used as the model input for simulations of potential interaction of zanubrutinib with acid reducing agents such as proton pump inhibitors (PPIs).

In vitro studies indicated that zanubrutinib metabolism is mediated predominantly by CYP3A and the in vitro intrinsic clearance is 109 µL/min/mg protein based on the in human liver microsomes study [3D_RN016107]. The initial simulation under-estimated the total zanubrutinib clearance compared to the observed PK in the clinical studies and over-estimated the DDI effect with itraconazole. The value of the intrinsic clearance of zanubrutinib was further adjusted to 120 µL/min/mg protein and additional clearance of value of 60 µL/min/mg protein was added to describe the clinical data. The contribution of CYP3A pathway to the total clearance (fmCYP3A4) of 0.82 was used in the final PBPK model. The renal clearance was set as 0.5 L/h.

Reviewer's comments: The Applicant's in vitro study suggested that zanubrutinib is predominately metabolized by the CYP3A pathway. On the other hand, the human mass balance study suggests additional pathways such as cysteine/glutathione conjugation could also contribute to the zanubrutinib metabolism to a lesser extent. Thus, it is reasonable to explore alternative clearance pathways.

Zanubrutinib is a weak CYP3A inducer. AUC and Cmax values of midazolam were approximately 47% and 30% lower, respectively, when midazolam was co-administered with zanubrutinib (Study BGB-311-108). Two sets of in vitro induction parameters, Indmax (maximum fold induction) and IndC50 (the concentration of inducer required to elicit half of Indmax), were evaluated by comparing the simulated and observed DDI effect of zanubrutinib on midazolam PK (Study BGB-311-108). One was obtained by fitting the change in mRNA with an Emax model

(Indmax of 15.9 and IndC50 of 0.89 µM). The other was obtained based on the change in CYP3A activity (Indmax of 6.27 and IndC50 of 0.47 µM). The latter set was used as the final CYP3A induction parameters for zanubrutinib due to the better agreement with clinical midazolam DDI data. In vitro induction parameters of CYP2B6 for zanubrutinib are 2.21 and 0.73 µM for Indmax and IndC50, respectively, which were used for DDI simulation of zanubrutinib co-administered with a CYP2B6 substrate. The CYP2C8 inhibition parameter (Ki) of zanubrutinib obtained from the in vitro study was 2.015 µM (IC50/2). Induction parameters of CYP2C8 of zanubrutinib were not available.

*Reviewer's comments: Given CYP3A and CYP2C are both mediated by the Pregnane-X Receptor (PXR) pathway, zanubrutinib may also have induction potential for CYP2Cs. As shown in Table 60, the clinical DDI data showed the zanubrutinib is a weak CYP2C19 inducer (*decrease omeprazole *AUC by 37%) and is not a clinically relevant inducer for CYPC9. Thus, the reviewer considered the induction potential of zanubrutinib on CYP2C8 enzyme is expected to be low.*

Simulations were performed using the default healthy volunteer population model (software's library, V16). Six perpetrators' PBPK models from SimCYP built-in library including clarithromycin, diltiazem, efavirenz (inducer), erythromycin, fluconazole, ritonavir; and three substrate models: bupropion, repaglinide and rosiglitazone were used in the PBPK simulations for the respective DDIs. In addition, the itraconazole PBPK model developed by Chen et al 2016 (PMID: 26692192) and the rifampicin PBPK model developed by Yamashita et al 2013 (PMID: 24086247) were used in the Applicant's PBPK analyses.

Reviewer's comments: The Applicant used the itraconazole (ITZ) and OH-itraconazole (OH-ITZ) models developed by Chen et al, 2016 (PMID: 26692192) which were different from the itraconazole model in Simcyp library (V16) in many parameters, such as logP, pKa, fa, Ka, Vss, CYP3A4 clearance parameters (Vmax, Km), Peff (for itraconazole), and CYP3A4 Ki (for OH-itraconazole). The Applicant stated that Chen's model (refer as Chen-Itra-2016 model) has been verified with itraconazole and OH-ITZ plasma concentration-time profiles observed following single and multiple dose administration of itraconazole and clinical ITZ DDI studies (Chen et al 2016, PMID: 26692192).

A rifampicin PBPK model developed by Yamashita et al 2013 (PMID: 24086247) were used to simulate the DDI between zanubrutinib and rifampicin. Comparing to the Simcyp' s rifampicin PBPK model, the Yamashita's model (referred as YF-rifampicin model) has higher maximal induction potential (Indmax). The Indmax in YF-rifampicin model was 37.1 compared to the value of 16 used in Simcyp's rifampicin model. The IndC50 values were 0.28 and 0.32 µM for YF-rifampicin model and simcyp's model, respectively. The Applicant stated that the high Indmax value (37.1) used YF-rifampicin model was based on 17 rifampicin-mediated DDI studies where the fmCYP3A4 values of substrates ranged from 0.18 to 1.

II. PBPK model verification

The performance of PBPK model in predicting the PK profiles of zanubrutinib after single and multiple dose administration in healthy volunteers and patients was evaluated by comparing the simulated and observed clinical PK data (Table 61). The fmcyp3A of zanubrutinib was verified against the DDI study with itraconazole and rifampicin (Study E2006-A004).

Table 63. Summary of the clinical PK and DDI sets used for model development and verification

#	Population	Zanubrutinib dose (mg)	Dose regimen	Co-med	Dose regimen	Study # (BGB-311-)	Analysis
1	HVs[1]	80	SD			107	Pred-vs-obs
2	HVs[1]	160	SD			106	Pred-vs-obs
3	HVs[1]	320	SD			104	Pred-vs-obs
4	HVs[1]	160	BID Days 1 - 7			108	Pred-vs-obs
5	Patient[1]	40	QD Days 1 - 8			AU-003	Pred-vs-obs
6	Patient[1]	80	QD Days 1 - 8			AU-003	Pred-vs-obs
7	Patient[1]	160	QD Days 1 - 8			AU-003	Pred-vs-obs
8	Patient[1]	320	QD Days 1 - 8			AU-003	Pred-vs-obs
9	Patient[1]	160	BID Days 1 - 8			AU-003	Pred-vs-obs
10	HVs[1]	320	SD on day 7	rifampicin 600 mg	QD Day 1-7	104	Pred-vs-obs
11	HVs[1]	20	SD on day 4	itraconazole 200 mg capsule	QD Day 1-5	104	Pred-vs-obs
12	HVs[2]	160	BID Days 1 - 7	midazolam 2 mg	single dose on day 7	108	Pred-vs-obs

Healthy Volunteers (HVs)[1]: simulation protocol: Health subject; age 20-63; Female ratio 0.16
Patient[1]: simulation protocol: Health subject; age 20-90; Female ratio 0.3
Healthy Volunteer[2]: simulation protocol: Health subject; age 20-50; Female ratio 0.5

III. PBPK model application

The verified PBPK model of zanubrutinib was applied to predict the following:

- the effects of strong CYP3A inhibitors (such as ritonavir and clarithromycin), moderate CYP3A inhibitors (such as erythromycin, fluconazole and diltiazem), and moderate inducers (such as efavirenz) on the PK of zanubrutinib
- the effects of zanubrutinib on the PK of CYP2B6 (such as bupropion) and CYP2C8 (such as repaglinide and rosiglitazone) substrates
- the effects of gastric pH changes on the PK of zanubrutinib

Reviewer's comments: The Applicant also used PBPK modeling to predict the changes in zanubrutinib exposure when it is co-administered with weak CYP3A inhibitors (such as cimetidine). Given that the increase in zanubrutinib exposure was less than 4-fold in the ITZ DDI study, the DDI effect between zanubrutinib and a weak CYP3A inhibitor is expected to be low. Given no clinically significant differences in zanubrutinib pharmacokinetics were observed when it was co-administered with gastric acid reducing agents (proton pump inhibitors, or H2-receptor antagonists), the Applicant's PBPK simulation of the effects of gastric pH changes on zanubrutinib PK was not reviewed

Results

I. Can PBPK analyses provide a reasonable description of the PK of zanubrutinib?

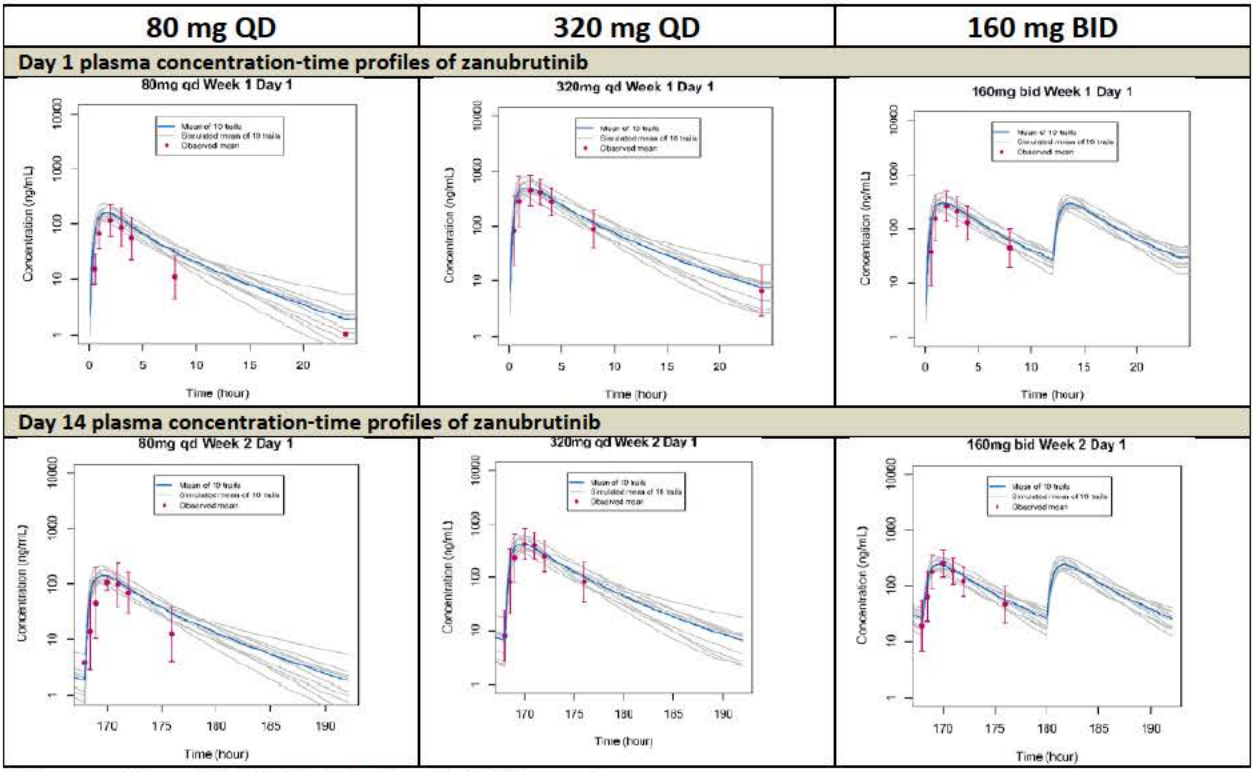
Yes. The Applicant's zanubrutinib PBPK model was able to describe zanubrutinib PK following a single and multiple dose of zanubrutinib in both healthy volunteers and patients. The comparison of the predicted and the observed PK from clinical studies are shown in Table 62 and Figure 38. Refer to Table 61 for the corresponded clinical studies and simulation designs.

Table 64. Comparison of PBPK predicted and observed mean Cmax and AUC values of zanubrutinib

	Simulated		Observed		Pred/Obs	
	Cmax (ng/mL)	AUC (ng.hr/mL)	Cmax (ng/mL)	AUC (ng.hr/mL)	Cmax	AUC
80 mg SD (HV)	138	743	163	683	0.85	1.09
160 mg SD (HV)	265	1444	216	1230	1.23	1.17
320 mg SD (HV)	444	2659	532	3431	0.83	0.77
160 mg BID (HV)	220	1132	231	1088	0.95	1.04
40 mg QD (Patient)	81.05	324.95	79	339	1.03	0.96
80 mg QD (Patient)	156	626	179	595	0.87	1.05
160 mg QD (Patient)	288	1167	390	1277	0.74	0.91
320 mg QD (Patient)	468	1939	608	2279	0.77	0.85
160 mg BID (Patient)	261	1111	344	1195	0.76	0.93

Simulated Cmax and AUC(0-t) values are expressed as geometric mean, and observed values are expressed as mean. SD: single dose; QD: repeated once-daily dose;
For AUC calculation: AUC_{0-24} for SD, $AUC_{8h, ss}$ for multiple dosing. (Source: Applicant's PBPK report Tables 11, 12, and 14)

Figure 38. Predicted vs observed plasma concentration-time profiles of zanubrutinib after single or multiple oral doses of zanubrutinib in Patients with B-cell Malignancy



Reference: Figure 10, 12, 13 of Applicant's PBPK report

II. Can PBPK analyses predict the effects CYP3A inhibitors and inducers on the PK of zanubrutinib?

Yes, PBPK analyses are adequate to predict the effects of CYP3A inhibitors and inducers on the PK of zanubrutinib.

Evaluation of the uncertainty in the estimated fmcyp3A based on itraconazole DDI data

In the itraconazole DDI study (BGB-3111-104), itraconazole 200 mg in capsule formulation was given on Days 1 to 3, and day 5, approximately 30 minutes after meal. On Day 4, both itraconazole and zanubrutinib was administrated in the fasted state (sec 9.4.1 Study BGB-3111-104). The reviewer compared the Applicant's itraconazole model and the simulated itraconazole PK profile with those in Chen et al 2016 publication. The simulated itraconazole PK profiles were similar to those simulated in fasted condition in Chen et al. An information request (IR) was sent on August 30, 2019 to request further model verifications. The Applicant's response confirmed that the analysis was simulated in the fasted conditions. Formulation-dependent food effects on the exposure of itraconazole have been reported. As shown in Table 63, the exposure of itraconazole in fed condition is higher with capsule

formulation following a single 200-mg dose of itraconazole capsule (SPORANOX® USPI label)[1]. Given that the half-life of itraconazole ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing, the simulated itraconazole PK in fasted condition may have underestimated the itraconazole exposure in the Applicant's DDI study. Since the itraconazole PK data was not reported in study BGB-3111-104, additional simulations were conducted to evaluate the potential impact of higher itraconazole exposure on the estimated fmcyp3A of zanubrutinib and subsequent DDI predictions.

Table 65. Observed PK of itraconazole and OH-ITZ following a single dose of 200 mg with or without a full meal

	Itraconazole		Hydroxyitraconazole	
	Fed	Fasted	Fed	Fasted
C_{max} (ng/mL)	239 ± 85*	140 ± 65	397 ± 103	286 ± 101
T_{max} (hours)	4.5 ± 1.1	3.9 ± 1.0	5.1 ± 1.6	4.5 ± 1.1
$AUC_{0-\infty}$ (ng·h/mL)	3423 ± 1154	2094 ± 905	7978 ± 2648	5191 ± 2489
$t_{1/2}$ (hours)	21 ± 5	21 ± 7	12 ± 3	12 ± 3

*mean ± standard deviation

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020083s040s041s044lbl.pdf

A. Comparison of the itraconazole PK simulated using different itraconazole PBPK models

The Reviewer first compared the performance of three itraconazole PBPK models: Chen-Itra-2016 for capsule in fasted (Chen-Itra-fasted) and fed (Chen-Itra-Fed) condition; and SV-Itraconazole_Fed Capsule.cmp from Simcyp' s library (V16). For Chen's models for capsules, different fa values were used to describe the absorption rate under fasting and fed conditions while the same distribution and elimination models (Chen-Itra-2016) were used. fa values were 0.5 and 0.9 for fasted and fed conditions respectively. Table 64 compared the simulated PK of itraconazole and OH-ITZ following itraconazole capsule 200 mg once daily for 14 days. PBPK DDI analyses were also conducted to evaluate the effects of three itraconazole models on the PK of midazolam. The simulated AUC ratios of midazolam were used as surrogates to compare the total inhibition potential of itraconazole and OH-ITZ on CYP3A pathway.

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020083s040s041s044lbl.pdf

Table 66. Comparison of predicted PK of itraconazole and OH-ITZ and CYP3A inhibition potential among three itraconazole models

Compound	Parameter	Simcyp capsule fed *	Chen-Itra-fed *	Chen-Itra-fasted *
Itraconazole	Cmax (ng/mL)	513.53	749.89	330.31
	AUC_{day14} (ng-hr/mL)	7582.28	10173.7	3909.75
OH-ITZ	Cmax (ng/mL)	862.05	1384.4	578.92
	AUC_{day14} (ng-hr/mL)	14704.32	25627.6	9079.40
AUC ratio of midazolam w/wo itraconazole[ł]		11.67	12.55	6.93

*Itraconazole capsule 200 mg QD for 14 day. ł AUC ratio of midazolam (5mg) with and without concomitant use of itraconazole, Source: Reviewer's analyses

As expected, the simulated itraconazole PK in fed condition is approximately two-fold of those simulated in fasted condition. While the PKs of itraconazole and OH-ITZ simulated using the Chen-Fed model were higher than those using Simcyp' s SV-Itraconazole_Fed Capsule model, the inhibition potential of both models was similar.

B. Exploration of alternative fmcyp3A values of zanubrutinib

Reviewer conducted additional simulations to explore alternative combinations of fm_{cyp3A} and $fm_{addtional}$ for zanubrutinib PBPK model. The Chen-Itra-Fed model was used in the Applicant workspace file, bgb-3111-20mg-itraconazole.wks, to simulate the DDI effects between itraconazole and zanubrutinib. Sensitivity analysis was used to fit an alternative set of intrinsic CYP3A clearance and additional clearance to describe the clinical PK and DDI data. The alternative CYP3A mediated intrinsic clearance of 109 µL/min/mg protein and additional hepatic clearance of 87.5 µL/min/mg protein was selected. The estimated fmcyp3A value in the reviewer's zanubrutinib model was 75.9% which was slightly lower than the fmcyp3A value of 81.6% in the Applicant's model. As the inhibition potential increased in the itraconazole model, a less sensitive CYP3A substrate (hence the lower fmcyp3A) was optimized to match the observed DDI effect. As shown in Table 65 and Table 66, the reviewer's zanubrutinib PBPK model reasonably described the clinical PK and DDI data.

Table 67. Summary of predicted and observed zanubrutinib PK using the Applicant's and the reviewer's zanubrutinib models

Zanubrutinib dose	PK parameter	Observed	Applicant's zanubrutinib model	Reviewer's zanubrutinib model	Pred/Obs ratio	
					Applicant's zanubrutinib model	Reviewer's zanubrutinib model
160 mg BID*	Cmax (ng/mL)	231	261	227.6	12.99%	-1.47%
	$AUC_{ss,\ 24\ hr}$ (ng.hr/mL)	2176	2222	2326.5	2.11%	6.92%
20 mg SD**	Cmax (ng/mL)	47.5	35.0	38.2	-26.3%	-19.6%
	$AUC_{0\text{-}inf}$ (ng.hr/mL)	183.6	189.2	203.8	3.1%	11.0%

* simulated based on study #108; PBPK report Table 14
** simulated based on study #104; PBPK report Table 7

Table 68. Summary of predicted and observed DDI using the Applicant's and the reviewer's zanubrutinib models

Dose regimen	PK parameter	Observed	Applicant's zanubrutinib model	Reviewer's zanubrutinib model
itraconazole + 20 mg zanubrutinib	Cmax ratio	2.57	3.2	3.03
	AUC ratio	3.86	3.47	3.58
rifampin*+ 360 mg zanubrutinib	Cmax ratio	0.079	0.062	0.062
	AUC ratio	0.071	0.06	0.06

* YF-rifampicin model was used

C. Evaluation of the predicted DDI effects using the Applicant's and reviewer's zanubrutinib model

The fmcyp 3A in the reviewer's zanubrutinib model is slightly lower than that in the Applicant's model. Therefore, the predicted DDI effect with CYP3A inhibitor and inducer was expected to be less than those predicted with the Applicant's model. The comparison of the predicted DDI effect between zanubrutinib and selected CYP3A modulators using the Applicant's model and the reviewer's model is shown in Table 67. The difference in the DDI prediction using two zanubrutinib models is about 15% for CYP3A moderate inhibitors and 5% for a moderate CYP3A inducer, and the predicted DDI using the Applicant's PBPK analyses is more conservative.

Table 69. Comparison of predicted Cmax and AUC ratio of zanubrutinib when co-administrated with various CYP3A perpetrators using the Applicant's and the reviewer's zanubrutinib models

Dose regimen	PK parameter	Applicant's zanubrutinib model	Reviewer's zanubrutinib model	% the decreased DDI compared to the Applicant's model prediction*
Erythromycin + 160 mg BID zanubrutinib	Cmax ratio	3.84	3.26	-15.1%
	AUC ratio	4.17	3.51	-15.8%
Fluconazole + 160 mg BID zanubrutinib	Cmax ratio	3.70	3.17	-14.4%
	AUC ratio	3.84	3.3	-14.0%
Efavirenz + 160 mg BID zanubrutinib	Cmax ratio	0.42	0.44	-4.8%
	AUC ratio	0.39	0.41	-5.1%

*calculate as (Reviewer-Applicant)/Applicant for inhibitor and (Applicant-Reviewer)/Applicant for inducer.

Given that the predicted DDI effects is more conservative using the Applicant's zanubrutinib model. The Applicant's model and PBPK analyses were used to simulate the DDI effects between zanubrutinib and perpetrators to support the dosing recommendation in the label.

Prediction of the DDI effects with various CYP3A inhibitors and inducers using the Applicant's zanubrutinib model

The Applicant conducted sensitivity analyses to test various intrinsic clearance and additional HLM hepatic intrinsic clearance values to fit the clinical PK and DDI data (in combination with Chen-Itra-fasted model). The final parameters (CYP3A mediate intrinsic clearance of 120 µL/min/mg, additional hepatic clearance of 60 µL/min/mg protein, and fmCYP3A4 of 81.6%) was able to fit the observed clinical PK and the DDI data with itraconazole.

CYP3A induction parameters of zanubrutinib were verified by comparing the predicted midazolam PK ratios (with/without zanubrutinib) with the observed clinical data (BGB-3111-108). In addition, the final zanubrutinib PBPK model also reasonably described the zanubrutinib PK profiles after repeated dosing ranges 40-320 mg daily (as shown in Table 62 and Figure 38). The simulated zanubrutinib Cmax and AUC at steady state were within ±25% of the observed values. Given that zanubrutinib is a sensitive CYP3A substrate (fmcyp ~0.8) and that the model was able to simultaneously capture the midazolam DDI data and multiple dose PK data, CYP3A induction parameters of zanubrutinib is considered verified. Comparison of predicted and observed clinical DDI data is shown in Table 68.

Table 70. Comparison of predicted and observed DDI effects of zanubrutinib

Substrate	CYP modulator	CmaxR of substrate			AUCR of substrate		
		Observed	Predicted	Pred/obs	Observed	Predicted	Pred/obs
zanubrutinib 20 mg SD on day 4	Itraconazole 200 mg QD capsule Day 1-4	2.57	3.2	1.25	3.86	3.47	0.90
zanubrutinib 320 mg SD on day 7	Rifampicin 600 mg QD day 1-7	0.079	0.062	0.78	0.071	0.06	0.85
MDZ 2 mg SD, on day 7	zanubrutinib 160 mg BID; Day 1-14	0.70	0.53	0.76	0.53	0.51	0.96

Reference: Table 9, 10 and 13 of Applicant's PBPK report

The model was then used to predict zanubrutinib DDI as a victim co-administered with various CYP3A inhibitors and inducers. An extensive set of inhibitors and inducers from Simcyp library was used to inform the range of DDI effects. Given that zanubrutinib is a weak CYP3A inducer, the steady state DDI effects of perpetrators which are also CYP3A substrates on zanubrutinib PK might be different than the effects simulated following a single dose of zanubrutinib for two reasons: 1. reduction of inhibitor exposure; 2) increase of fmcyp3A of zanubrutinib metabolism. An information request was sent on Aug 30, 2019 requesting the Applicant to simulate DDI effects of CYP3A perpetrators on zanubrutinib PK at steady state. The Reviewer conducted additional DDI simulations where clarithromycin and diltiazem were administrated at higher dose levels but within the labeling recommended dosing ranges. Predicted DDI effects on zanubrutinib PK (160 mg BID) and the ratios of AUC at steady state (AUCss) in the presence and absence of CYP3A4 inhibitors and inducers are presented in Table 69. The Reviewer noted that in vivo CL(s) were used in the PBPK models for some inhibitors. In this case, the clearance of the inhibitor won't be impacted by zanubrutinib CYP3A modulation even the compound is a CYP3A substrate (such as ketoconazole and erythromycin). For the perpetrator listed in Table 69, all compounds are CYP3A substrate, except fluconazole.

Table 71. AUC ratios of zanubrutinib at steady state with and without concomitant use of CYP3A perpetrators

Perpetrator	Assigned metabolism pathway for perpetratorsł	CYP3A DDI mechanism			zanubrutinib AUCss Ratio	zanubrutinib Cmax Ratio
		Competitive inhibition	Mechanistic inhibition	Induction		
Ritonavir (100 mg BID)	CYP specific CL; fmcyp3A>0.9		X	X	8.32	6.68
Ketoconazole (400 mg QD)*	Non-CYP specific in vivo CL	X			5.58	4.30
Chen-Itra-fasted (200 mg Capsule QD)	CYP specific CL; fmcyp3A>0.9	X			3.81	3.95
Chen-Itra-fed (200 mg Capsule QD)*	CYP specific CL; fmcyp3A>0.9	X			4.32	3.59
Clarithromycin (250 mg BID)	CYP specific CL; fmcyp3A~0.75	X	X		2.83	2.75
Clarithromycin (500 mg BID)*	CYP specific CL; fmcyp3A~0.75	X	X		4.26	3.47
Erythromycin (500 mg QID)	Non-CYP specific in vivo CL	X	X		4.17	3.84
Fluconazole (200 mg QD)	Non-CYP specific in vivo CL	X			2.77	2.79
Fluconazole (400 mg QD)	Non-CYP specific in vivo CL	X			3.84	3.70
Diltiazem[2] (60 mg TID)	CYP specific CL; fmcyp3A>0.9	X	X		2.57	2.51
Diltiazem (120 mg TID)*	CYP specific CL; fmcyp3A>0.9	X	X		3.47	3.20
Efavirenz (600 mg QD)	CYP specific CL; fmcyp3A~0.1			X	0.39	0.42

Note- the steady state AUC and Cmax ratio of zanubrutinib were simulated following multiple dosing of CYP3A modulator(s) (given from day 1-14) and zanubrutinib (160 mg BID given from day 7-14)
ł Non-CYP specific in vivo CL means that an in vivo CL was assigned in the model without specifying the specific CYP pathway(s).
*simulated by reviewer

[2] FDA will revise the current recommendation and classify diltiazem as a moderate CYP3A inhibitor

Table 72. Steady-state PK of zanubrutinib following the proposed dose regimen when co-administered with CYP3A perpetrators

Baseline (160 mg BID)	Cmax (ng/mL)	AUC0-24 on Day 14 (ng-hr/mL)
Simulated	199	2296
Steady-state PK of zanubrutinib following 80 mg QD when co-administered with a strong CYP3A inhibitor		
	Cmax ratio	AUC ratio
Ritonavir (100 mg BID)	2.82 [2.41-3.29]	2.22 [1.99-2.48]
Ketoconazole (400 mg QD)*	2.50 [2.14-2.94]	1.91 [1.74- 2.11]
Itraconazole (200 mg QD)	2.05 [1.73-2.43]	1.2 [1.05- 2.72]
Clarithromycin (250 mg BID)	1.47 [1.22-1.76]	0.9 [0.77-1.06]
Clarithromycin (500 mg BID)*	1.95 [1.63-2.33]	1.30 [1.12-1.52]
Steady-state PK of zanubrutinib following 80 mg BID when co-administered with a moderate CYP3A inhibitor		
	Cmax ratio	AUC ratio
Erythromycin (500 mg QID)	2.13 [1.85-2.46]	2.33 [2.07-2.63]
Fluconazole (200 mg QD)	1.54 [1.36-1.75]	1.54 [1.41- 1.67]
Fluconazole (400 mg QD)	2.04 [1.80-2.30]	2.13 [1.96- 2.30]
Diltiazem (120mg TID)*	1.81 [1.56-2.10]	1.93 [1.69-2.20]
Diltiazem (60 mg TID)	1.43 [1.26-1.64]	1.39 [1.20-1.63]
Steady-state PK of zanubrutinib following 160 mg BID when co-administered with a moderate CYP3A inducer		
Diltiazem (60 mg TID)	0.42 [0.39-0.45]	0.39 [0.37-0.42]

Extracted from Applicant's or Reviewer's simulation outputs; Ratio was calculated as sim-DDI/sim-baseline
*simulated by reviewer. TID: three times per day, QID: four times per day

As shown in the Table 70, the AUC ratio in some of the dosing regimens (such as fluconazole 400 mg QD + zanubrutinib 80 mg BID) is greater than expected given the AUC ratio was less than 4 following repeated dosing of fluconazole 400 mg QD and zanubrutinib 160 mg BID. One reason is that auto-induction of the CYP3A pathway is more pronounced following 160 mg BID (AUCss, 24 hr: 2296.0 ng.hr/mL) than lower doses (i.e. AUCss, 24 hr following 80 mg BID was 1269.4 ng.hr/mL), hence a slightly higher AUC ratios would be computed when compared with baseline simulated with higher dose.

III. Can the proposed PBPK model be used to predict the DDIs between zanubrutinib and a CYP2B6 substrate?

No. In vitro studies show that zanubrutinib is an inducer for CYP2B6 enzyme (Indmax: 2.21 and IndC50: 0.73μM). The Applicant conducted a PBPK analysis to evaluate the induction potential of zanubrutinib on bupropion, a CYP2B6 substrate based on in vitro induction parameters. The model predicted the geometric mean ratios for Cmax and AUCinf to be 0.96 and 0.96, respectively. However, the software developer has noted there is a discrepancy between in vivo DDI dataset and emerging in vitro metabolic data and lead to uncertainty in fmcyp2B6

value in the bupropion PBPK model. Thus, the simulated DDI results with bupropion could be inconclusive.

IV. Can the proposed PBPK model be used to predict the DDIs between zanubrutinib and a CYP2C8 substrate?

Yes. In vitro studies show that zanubrutinib can inhibit CYP2C8 enzyme (Ki = 2.03 μM). The PBPK models for repaglinide (a substrate for CYP3A4 and 2C8) and rosiglitazone (CYP2C8 substrate) from Simcyp library were used directly by the Applicant. The ability of these models to be used as a substrate model for a target CYP-mediated pathway was verified by comparing the predicted DDI effects with observed data. For example, repaglinide as a substrate for CYP3A4 and 2C8 pathway was verified using the results of clinical DDI studies where repaglinide was co-administrated with clarithromycin (a CYP3A inhibitor), itraconazole (a CYP3A inhibitor), trimethoprim (a CYP2C8 inhibitor), and gemfibrozil (a CYP2C8 inhibitor). The values of fmcyp3A and fmcyp2C8 of repaglinide are 0.6 and 0.4, respectively. The fmcyp2C8 value for rosiglitazone is 0.5.

The Applicant's PBPK model predicted a 24% decrease of repaglinide AUC following a single oral dose of 0.25 mg repaglinide with zanubrutinib 160 mg BID for 10 days. The decrease in repaglinide exposure is due to the induction effect of zanubrutinib on CYP3A. The Applicant conducted a PBPK simulation by considering the inhibitory potential of zanubrutinib on CYP2C8 activity only (turn-off the CYP3A induction). The simulation results suggested no changes on the predicted Cmax and AUC ratio. Reviewer also conducted a PBPK simulation by applying a tenfold lower Ki for CYP2C8 (1/10 of 2.03 μM); and found no changes in the predicted Cmax and AUC ratio. The PBPK simulation also showed no DDI effect between zanubrutinib and rosiglitazone. The inhibition effect of zanubrutinib on a CYP2C8 substrate is predicted to be minimal. Zanubrutinib is a weak inducer of CYP3A and CYP2C19. The induction effect of zanubrutinib on CYP2C8 has not been evaluated. Therefore, the model is limited to the evaluation of inhibition effects on CYP2C8.

Conclusion

In summary, PBPK modeling is adequate to predict the PK of zanubrutinib following single- and multiple-dose administration.

PBPK analyses are adequate to predict the effect of CYP3A4 modulators on zanubrutinib exposure. Uncertainty was evaluated for the estimated fmcyp3A value in zanubrutinib model. The difference in the predicted CmaxR and AUCR was less than 15% between the Applicant's model and the reviewer's model, and the Applicant's PBPK model was used to predict the effects CYP3A modulators on the PK of zanubrutinib.

The model predicted zanubrutinib steady-state AUCtau may increase around 4-fold (range from 2.8-to 8.3-fold) with co-administration of a strong CYP3A4 inhibitor. A moderate CYP3A4

inhibitor may increase zanubrutinib AUCtau around 3.3-fold (range from 2.6-to 4.17-fold). The model predicted that a moderate CYP3A4 inducer (such as efavirenz) may decrease the steady-state AUCtau of zanubrutinib by 60%.

PBPK analyses suggest the inhibitory effect of zanubrutinib on a CYP2C8 substrate is minimal.

19.6 Grouped Preferred Terms

FDA Grouped PT	Included
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain, Abdominal discomfort, Epigastric discomfort
Anemia	Anemia, Hemoglobin decreased,
Arrhythmia	Arrhythmia, Arrhythmia supraventricular, Atrial fibrillation, Atrial flutter, Bradycardia, Sinus bradycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Extrasystoles,
Bruising	Administration site bruise, aponeurosis contusion, application site bruise, catheter site bruise, contusion, eye contusion, eyelid contusion, contusion of specific site (i.e genital contusion, implant site bruising) increased tendency to bruise, muscle contusion, oral contusion, ecchymosis
Cardiac failure	Cardiac failure, Cardiac failure chronic, Cardiac failure congestive
Chest pain	Chest discomfort, Chest pain, Noncardiac chest pain, Angina pectoris
Diarrhea	Diarrhea, Diarrhea hemorrhagic
Fatigue	Fatigue, asthenia
Gastrointestinal hemorrhage	Gastric hemorrhage, Hematochezia, Upper gastrointestinal hemorrhage, Gastrointestinal hemorrhage, Melena, Rectal hemorrhage, Anal hemorrhage, hemorrhoidal hemorrhage
Headache	Headache, sinus headache
Hemorrhage	PT including "haemorrhage", or hematoma
Hemorrhage intracranial	Hemorrhage intracranial, subdural hematoma, subdural hemorrhage, [Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage]
Herpes virus infection	Oral herpes, Herpes zoster, Herpes simplex, Herpes simplex meningoencephalitis, Nasal herpes, Genital herpes, Herpes dermatitis, Herpes zoster disseminated, Ophthalmic herpes zoster,
Hypertension	Hypertension, Blood pressure increased
Hypokalemia [a]	Hypokalemia, blood potassium decreased
Leukopenia	Leukopenia, White blood cell count decrease

FDA Grouped PT	Included
Lower respiratory tract infection	Bronchitis, specific types of bronchitis (Bronchitis bacterial/viral), Bronchiolitis, Lower respiratory tract infection viral, Lung infection
Lymphopenia	Lymphopenia, lymphocyte count decreased
Mucositis	Stomatitis, Mouth ulceration, Tongue ulceration, Tongue discomfort, Swollen Tongue, Oral pain, Oral mucosal blistering, Oral mucosal blistering, Oropharyngeal pain or discomfort, Gingival pain, Gingival swelling, Non-infective gingivitis
Musculoskeletal pain	Back pain, Musculoskeletal pain, Musculoskeletal discomfort, Myalgia, Arthralgia
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina pectoris, Acute coronary syndrome, Myocardial ischemia, Coronary artery stenosis
Neutropenia	Neutropenia, Neutrophil count decreased, Worsening Neutropenia
Pneumonia	Pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection viral, lower respiratory tract infection bacterial, lung infection, specific types of pneumonia (e.g. pneumonia bacterial/cryptococcal/mycoplasmal/streptococcal/atypical), Bronchopneumonia, Bronchopulmonary aspergillosis
Pneumonitis	Pneumonitis, Interstitial lung disease
Rash	Dermatitis, Drug eruption, Erythema, Erythema multiforme, Exfoliative rash, Rash, Rash generalized, Rash erythematous/follicular/macular/maculo-papular/papular/pruritic/pustular, Toxic epidermal necrolysis
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection)
Sepsis	Sepsis, Abdominal sepsis, Bacterial Sepsis, Viral Sepis, Biliary sepsis, Bacteremia, Sepsis, Septic shock, Sepsis syndrome, specific types of sepsis or bacteremia, Neutropenic sepsis, postpartum sepsis, Pelvic sepsis, Umbilical sepsis, Thrombophlebitic septic, Septic vasculitis, Septic embolus, Myocarditic septic, Wound Sepsis
Sinusitis	Acute sinusitis, Chronic sinusitis, Sinusitis, Sinusitis aspergillus, Sinusitis bacterial, Sinusitis fungal, Viral Sinusitis
Thrombocytopenia	Thrombocytopenia, Platelet count decreased, worsening thrombocytopenia
Upper respiratory tract infection	Upper respiratory tract infection, [Upper respiratory tract infection bacterial], Viral upper respiratory tract infection,
Urinary tract infection	Cystitis, Urinary tract infection + specific types (e.g. Escherichia UTI), [Pyelonephritis, Kidney infection]
Wound infection	Wound infection, specific types of wound infection (e.g. Wound infection staphylococcal)

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Simon Williams, PhD	OOD/DHOT	5 Sections:	Select one: ☑ Authored ☐ Approved
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Nonclinical Team Leader	Haleh Saber, PhD	OOD/DHOT	5, 14 Sections:	Select one: ☑ Authored ☑ Approved
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Clinical Pharmacology Reviewer	Lauren Price, PharmD	OCP/DCPV	6 Sections:	Select one: ☑ Authored ☐ Approved
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Clinical Pharmacology Team Leader	Olanrewaju Okusanya, PharmD, MS	OCP/DCPV	6 Sections:	Select one: ☑ Authored ☑ Approved
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Pharmacometrics Reviewer	Justin Earp, PhD	OCP/DPM	19.5 Sections:	Select one: ☑ Authored ☐ Approved
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PBPK Reviewer	Yuching Yang, PhD	OCP/DPM	Sections: 19.5	Select one: ☑ Authored ☐ Approved
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PBPK Team Leader	Xinyuan Zhang, PhD	OCP/DPM	Sections: 19.5	Select one: ☑ Authored ☑ Approved
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Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPV	Sections: 6	Select one: ☐ Authored ☑ Approved
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Clinical Team Leader	R. Angelo de Claro, MD	OOD/DHM1	Sections: 1,2,3,4,7,8, 9,10,11,12, 13	Select one: ☑ Authored ☑ Approved
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Statistical Reviewer	Alexei Ionan, PhD	OB/DBIX	Sections: 7,8	Select one: ☑ Authored ☐ Approved
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Statistical Team Leader	Jingjing Ye, PhD	OB/DBIX	Sections: 7,8	Select one: ☑ Authored ☑ Approved
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Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 7,8	Select one: ☑ Authored ☑ Approved
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Cross-Disciplinary Team Leader (CDTL)	R. Angelo de Claro, MD	OOD/DHM1	all sections	Select one: ☑ Authored ☑ Approved
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Deputy Division Director (Clinical)	Albert Deisseroth, MD, PhD	ODE1/DHP	Sections: all sections	Select one: ☑ Authored ☑ Approved
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