15 September 2022
EMA/CHMP/232661/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Brukinsa

International non-proprietary name: zanubrutinib

Procedure No. EMEA/H/C/004978/II/0002

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BTK	Bruton tyrosine kinase
COVID-19	SARS-CoV-2
CR	complete response
CT	computed tomography
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EQ-5D-5L	5-level EQ-5D version
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ITK	interleukin-2-inducible T cell kinase
MALT	extranodal MZL of mucosa-associated lymphoid tissue
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NMPA	China National Medical Products Administration

PCR	polymerase chain reaction
PET	positron-emission tomography
PFS	progression-free survival
PI3K	phosphoinositide 3-kinases
PK	pharmacokinetic
PR	partial response
SOC	system organ class
SPD	sum of product diameters
TEC	tyrosine kinase expressed in hepatocellular carcinoma
ULN	upper limit of normal
US	United States
VAS	visual analogue scale

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BeiGene Ireland Ltd submitted to the European Medicines Agency on 30 December 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti-CD20-based therapy, based on data from 88 patients with R/R MZL from 2 ongoing pivotal studies; Study BGB-3111-214: A Phase 2, open-label, single-arm study designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL, and Study BGB-3111-AU-003: A first-in-human, Phase 1/2, dose-escalation and selection, PK/pharmacodynamic, safety, and efficacy study in adult patients with R/R or treatment-naive B-cell malignancies. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated, and the Package Leaflet is updated in accordance.
Version 1.1 of the RMP has also been submitted.
In addition, the MAH is requesting one additional year of market protection.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

At the time of submission of the application, the PIP (P/0398/2019) not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP (P/0398/2019) on 15 October 2021

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogation(s) of market exclusivity

Not applicable.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	23 Jan 2022	23 Jan 2022	☐
☐	CHMP Rapporteur Assessment Report	18 Mar 2022	17 Mar 2022	☐
☐	PRAC Rapporteur Assessment Report	25 Mar 2022	25 Mar 2022	☐
☐	CHMP Co-Rapporteur Critique	30 Mar 2022	30 Mar 2022	☐
☐	PRAC members comments	30 Mar 2022	30 Mar 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	31 Mar 2022	31 Mar 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	07 Apr 2022	07 Apr 2022	☐
☐	CHMP members comments	11 Apr 2022	11 Apr 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 Apr 2022	13 Apr 2022	☐
☐	Request for supplementary Information	22 Apr 2022	22 Apr 2022	☐
☐	Submission deadline	15 Jul 2022	15 Jul 2022	☐
☐	Start date	18 Jul 2022	18 Jul 2022	☐
☐	CHMP and PRAC Rapporteurs AR	22 Aug 2022	22 Aug 2022	☐
☐	Comments from CHMP	05 Sep 2022	05 Sep 2022	☐
☐	Updated CHMP Rapporteur AR	n/a	n/a	☐
☒	Opinion	15 Sep 2022	15 Sep 2022	☐

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The purpose of this submission is to support a type II variation application for zanubrutinib capsules as an oral therapy for the treatment of adult patients with marginal zone lymphoma (MZL) who have received ≥ 1 prior anti-CD20-based therapy.

Disease or condition

BRUKINSA as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti-CD20-based therapy.

Epidemiology

The median age at diagnosis varies between MZL subtypes, ranging from 50 to 69 years; overall, there is a higher incidence reported in men than in women (Sriskandarajah and Dearden 2017). MZLs comprise about 5% to 17% of all NHLs in adults, with MALT lymphoma as the most common subtype (50% to 70% of MZLs), followed by the splenic (20% of all MZLs) and nodal (10% of all MZLs) subtypes.

Biologic features Aetiology and pathogenesis

MZL is an indolent non-Hodgkin lymphoma (NHL) that originates from memory B lymphocytes normally present in the marginal zone of secondary lymphoid follicles within the spleen, lymph nodes, and mucosal lymphoid tissues (Kahl and Yang 2008). MZL is categorized by the World Health Organization into 3 distinct subtypes: extranodal MZL of mucosa-associated lymphoid tissue (MALT) or MALT lymphoma, nodal MZL, and splenic MZL.

Extranodal MZL can occur at any site, with the stomach being the most common. Additional extranodal sites may include, but are not limited to, ocular adnexa, lung, skin, thyroid, and salivary glands. Extranodal MZLs are frequently associated with chronic inflammation and infectious agents that can give rise to chronic infections, such as *Helicobacter pylori* in gastric extranodal MZL, *Chlamydophila psittaci* in ocular adnexa extranodal MZL, *Campylobacter jejuni* in immunoproliferative small intestinal disease, and *Borrelia burgdorferi* in cutaneous extranodal MZL. Hepatitis C infection is associated with the occurrence of splenic MZL. Autoimmune conditions that may be associated with the development of MZLs include Sjögren syndrome, lymphoepithelial sialadenitis, and Hashimoto thyroiditis (Schreuder et al 2017).

Clinical presentation, diagnosis and stage/prognosis

See section above

Management

There are no chemotherapy or immunotherapy products specifically approved for MZL in the European Union (EU) for patients with treatment-naive or relapsed/refractory (R/R) disease. Historically, very few prospective clinical trials have been conducted specifically in this patient population, and even fewer comparative, randomized trials have been carried out. Patients with MZL have been enroled and treated in clinical trials designed for patients with indolent NHL where the majority were patients with FL.

Figure 1

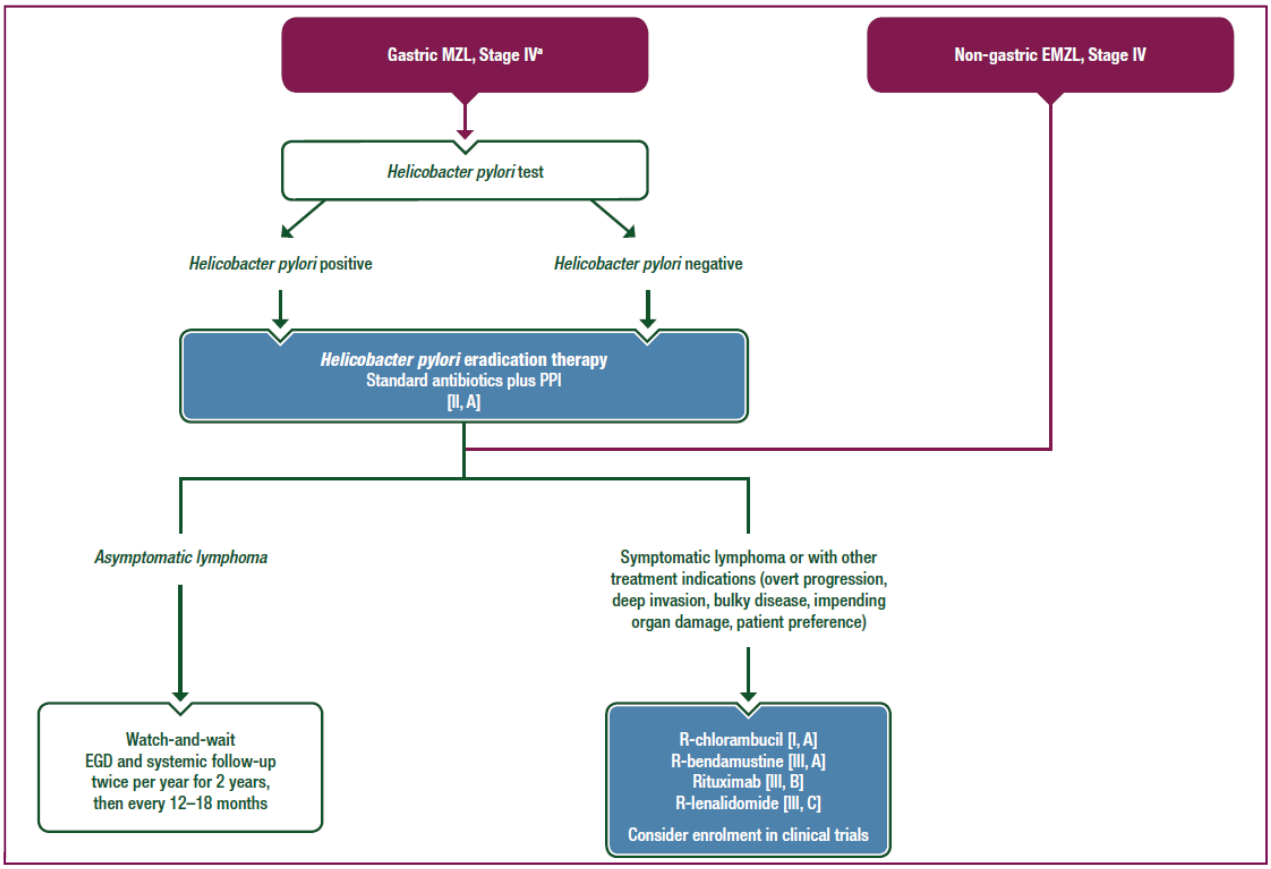


Figure 2. Treatment algorithms for advanced gastric MZL and non-gastric EMZL.
EGD, oesophagogastroduodenoscopy; EMZL, extranodal marginal zone B-cell lymphoma; MZL, marginal zone B-cell lymphoma; PPI, proton-pump inhibitor; R, rituximab.
[a] Stage is defined according to the Lugano staging system described in Table 2.

Source: Zucca et al., 2020.

As is evident from the ESMO guideline recommendations, the primary treatment options depend on the subtype of MZL:

Table 6. Summary of recommendations

Staging and risk assessment

- Initial staging for all MZL subtypes should include history and physical examination, full blood and differential counts, biochemistry including renal and liver function tests, protein electrophoresis, LDH and B2M, serum and urine immunofixation, serology for HBV, HCV and HIV and cryoglobulins and cryocrit if HCV-positive
- IHC panel including at least CD20, CD10, CD5, CD23, cyclin D1 and IgD with diagnostic evaluation by an expert haematopathologist [IV, B]
- Clinical and biological prognosticators (HPLL, MALT-IPI) should be applied in clinical routine to estimate the clinical behaviour [III—IV, C]

Treatment

EMZL

- *Helicobacter pylori* eradication therapy should be given to all patients with gastric MZL [II, A]
- ISRT is the preferred option for treatment of localised EMZL (moderate dose, which may vary according to the site) [II—IV, A—B]
- Anti-HCV therapy is recommended in patients with HCV-associated lymphoma [IV, B]
- Other treatments including ChT, immunotherapy or combination chemoimmunotherapy are indicated in patients with symptomatic disseminated disease, contraindications to RT, failure after antibiotics or after local therapy or clinical suspicion of histological transformation: R-chlorambucil [I, A], R-bendamustine [III, A], rituximab monotherapy [III, B], R-lenalidomide [III, C] and R-CHOP for (clinically suspected or biopsy-proven) histological transformation

SMZL

- Rituximab alone is the preferred initial therapy in patients with SMZL [III, A]
- Chemoimmunotherapy is indicated when rituximab alone is ineffective or in the presence of disseminated symptomatic disease and/or signs of high-grade transformation [III, B]
- Anti-HCV therapy should be considered in patients with HCV-associated lymphoma [IV, B]
- Splenectomy may be considered in selected cases, when rituximab is not indicated or ineffective [IV, B]

NMZL

- Treatment should follow the principles of therapy for follicular lymphoma [IV, B]
- Anti-HCV therapy should be considered in patients with HCV-associated lymphoma [IV, B]
- Chemoimmunotherapy is recommended in patients with NMZL (e.g. R-bendamustine, R-CHOP, R-CVP) [IV, B]

Response evaluation and follow-up

- Asymptomatic patients with disseminated MZL (SMZL and NMZL) being managed by watch-and-wait should be monitored by physical examination, imaging as clinically required, blood counts and biochemistry every 6 months
- Patients with EMZL at non-gastric sites can be re-evaluated with clinical examination, laboratory work-up and imaging/biopsy of residual lesions if indicated every 3 months for the first 2 years, and every 6 months thereafter

Gastric MZL

- Sequential evaluation of gastric biopsies remains an essential follow-up procedure for gastric MZL, particularly in patients with persistent *Helicobacter pylori* infection

SMZL

- Specific criteria for response assessment are recommended for SMZL and achievement of CR is defined by normal spleen size, normal blood counts, negative flow cytometry on blood and negative IHC on bone marrow biopsy

B2M, β2 microglobulin; ChT, chemotherapy; CR, complete remission; EMZL, extranodal marginal zone B-cell lymphoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPLL, prognostic model based on haemoglobin concentration, platelet count, LDH level and extrahilar lymphadenopathy; IgD, immunoglobulin D; IHC, immunohistochemistry; ISRT, involved-site radiotherapy; LDH, lactate dehydrogenase; MALT-IPI, mucosa-associated lymphoid tissue-International Prognostic Index; MZL, marginal zone B-cell lymphoma; NMZL, nodal splenic marginal zone B-cell lymphoma; R, rituximab; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; R-CVP, rituximab/cyclophosphamide/vincristine/prednisone; RT, radiotherapy; SMZL, splenic marginal zone B-cell lymphoma.

Source: Zucca et al., 2020.

The preferred therapy at relapse or progression, especially for nodal MZL, is not clearly defined and commonly approached with regimens used for other indolent NHLs such as follicular lymphoma (FL) (Zinzani 2012).

For patients with recurrent disease and in need of systemic treatment, immunochemotherapy may be repeated if the first remission lasted at least 24 months. However, immunochemotherapy is associated with significant toxicity in these patients, especially in elderly patients and those with comorbidities. Moreover, data that suggest efficacy of these regimens are often based on a small subset of patients and/or retrospectively evaluated (Cheah et al 2019).

Rituximab, although widely used for patients with R/R MZL (as monotherapy or in combination with chemotherapy), is only approved for patients with FL and diffuse large B-cell lymphoma.

Bendamustine is approved for indolent R/R NHLs, including MZL, as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.

Disease progression remains the cause of death for the majority of patients suffering from MZL (Olszewski et al 2013). There is an unmet medical need for effective and safe therapies to improve long-term outcomes.

2.1.2. About the product

Zanubrutinib (BRUKINSA; also known as BGB-3111) is a small molecule inhibitor of Bruton tyrosine kinase (BTK), which forms an irreversible covalent bond at Cys481 within the adenosine triphosphate binding pocket of the BTK protein. Zanubrutinib is highly potent against BTK; however, as opposed to ibrutinib, zanubrutinib has significantly less epithelial growth factor receptor, Janus kinase 3, tyrosine kinase expressed in hepatocellular carcinoma, and interleukin- 2-inducible T-cell kinase inhibitory activity, thus potentially reducing the side effects seen with ibrutinib and allowing increased exposure, which may translate into improved efficacy.

Zanubrutinib capsules (80 mg/capsule), 160 mg orally twice a day.

For the treatment of adult patients with Waldenström's macroglobulinaemia (WM), who have received at least one prior therapy, or as a first-line treatment for patients unsuitable for chemoimmunotherapy, the marketing authorisation application (MAA) for BRUKINSA obtained a positive opinion from the CHMP on 16 September 2021 and received approval from the European Commission on 22 November 2021.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No advice was sought or given for this indication.

2.1.4. General comments on compliance with GCP

Statement from the Applicant regarding pivotal study BGB-3111-214: *This study was conducted according to the principles of Good Clinical Practice as described in the International Council for Harmonisation guidelines, including the archiving of essential documents.*

2.2. Non-clinical aspects

No new non-clinical data except environmental risk assessment (ERA) studies have been submitted in this application, which is considered acceptable.

2.2.1. Introduction

In relation to the initial MAA, a Phase 1 environmental risk assessment was performed:

The logK_{OW} value of zanubrutinib is below 4.5 (i.e., 3.2 at pH 5, 3.6 at pH 7 and 3.7 at pH 9). Since, Log K_{OW} > 3, bioconcentration factor (BCF) in fish study (OECD 305) is triggered.

The Phase I $PEC_{SURFACEWATER}$ of zanubrutinib (0.022 µg/L) was above the action limit of 0.01 µg/L using an F_{pen} of 0.00014, which was based on prevalence of Waldenström's macroglobulinemia of 1.4 per 1000 as stated in the orphan designation application. Furthermore, as there are no indications that zanubrutinib affects reproduction of vertebrate organisms at low exposure levels, the applicant committed to perform a standard Phase II environmental fate and effects assessment.

Some of these studies were submitted with this variation.

2.2.2. Ecotoxicity/environmental risk assessment

Summary of ongoing Environment Risk Assessment program for MZL

This summary is written to support the type II variation application of zanubrutinib for the treatment of adult patients with relapsed/refractory marginal zone lymphoma (MZL).

An environmental risk assessment (ERA) in the course of the initial MAA for treatment of Waldenström macroglobulinemia (WM) is ongoing, and BeiGene committed to provide the final ERA report by December 2022.

The Phase I and Phase II Tier A assessments except for the fish early life stage toxicity test (OECD 210) were completed, which triggered Phase II Tier B assessment for sediment and bioaccumulation, which has been initiated.

All studies were conducted at) in accordance with organization for economic cooperation (OECD) guidelines and in compliance with the OECD principles of Good Laboratory Practice (GLP). The main study results are summarized in Table 1 below.

Table 1 ***Summary of main study results***

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 and OECD123	Log K_{OW} = 3.2 (pH 5) Log K_{OW} = 3.6 (pH 7) Log K_{OW} = 3.7 (pH 9)	Log K_{OW} < 4.5, no need to conduct definitive PBT assessment. Log K_{OW} > 3, bioconcentration factor (BCF) in fish study (OECD 305) is triggered.
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	<4.5	not B
	BCF	Awaits final report (OECD 305)	B/not B
Persistence	DT50 or ready biodegradability	Not biodegradable, see below (OECD 301B)	P
Toxicity	NOEC or CMR	Awaiting conclusions on OECD 210 and 218	T/not T
PBT-statement:	Zanubrutinib is persistent (P), however whether it is B or T awaits reporting on ongoing studies and final conclusions on the environmental risk assessment		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.022 for Waldenströms macroglobulinemia	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**

Adsorption-Desorption	OECD 106	<table><tr><th>Test system</th><th>$K_{F,oc}^{ads}$ (mL/g)</th><th>$K_{F,oc}^{des}$ (mL/g)</th></tr><tr><td>Speyer 2.2</td><td>1602</td><td>2119</td></tr><tr><td>Speyer 2.3</td><td>1835</td><td>2825</td></tr><tr><td>Speyer 6S</td><td>2845</td><td>3257</td></tr><tr><td>Tilburg</td><td>516</td><td>525</td></tr><tr><td>Aa & Maas</td><td>635</td><td>640</td></tr></table>			KOC < 10,000 mL/g, the terrestrial assessment is not triggered.
Ready Biodegradability Test	OECD 301B	3% and 6% based on ThCO2 in an aerobic aqueous medi-um with microbial activity introduced by inoculation with activated sludge.			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	<table><tr><th>Compartment</th><th>DT_{50} (days)</th><th>DT_{90} (days)</th></tr><tr><td>SW total system</td><td>15</td><td>51</td></tr><tr><td>SW water</td><td>5.8</td><td>19</td></tr><tr><td>SW sediment</td><td>18</td><td>58</td></tr><tr><td>EV total system</td><td>35</td><td>117</td></tr><tr><td>EV water</td><td>4.6</td><td>24</td></tr><tr><td>EV sediment</td><td>26</td><td>85</td></tr></table> % shifting to sediment = missing			Phase II Tier B assessment for sediment is triggered. Stated as new report, but the report is missing in dossier
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.37	mg/L	*Raphidocelis subcapitata* Risk Quotient (RQ) < 1
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.71	mg/L	Risk Quotient (RQ) < 1
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	<0.017 for larval growth	mg/L	*Pimephales promelas* Another study is planned and will be completed by December 2022.
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	NOEC = 32 mg/L; EC50 > 1000 mg/L	mg/L	No effects on microbial communities.
Phase IIb Studies					
Bioaccumulation	OECD 305-I	BCF	BCF_L at low concentration (1.6 µg/L) = 23 ± 3.1 L/kg;	L/kg	%lipids: 2.7 in fish in study Not considered to be bioaccumulative in fish as BCF<2000. However, although BCF was low, it increased slowly during the study of 28 days. Hence steady state was not reached.

			BCF_L at high concentration (16 µg/L) = 32 ± 5.3 L/kg		Reported BCF is normalised to 5% lipid. Depuration was not determined due to low uptake.
Sediment dwelling organism	OECD 218	NOEC for emergence	89 mg/kg d.w.	mg/kg	Triggered Development was not deemed affected even at the highest concentration of 289 mg/kg d.w, although only 5% of larvae emerged as midges at this concentration.

2.2.3. Discussion on non-clinical aspects

The environmental risk assessment for Brukinsa is ongoing. All finalised studies were conducted at) in accordance with organization for economic cooperation (OECD) guidelines and in compliance with the OECD principles of Good Laboratory Practice (GLP).

At this time, the following was concluded:

1. Log K_{OW} > 3, hence a bioconcentration factor (BCF) in fish study (OECD 305) was triggered. Brukinsa was not considered to be bioaccumulative in fish.
2. Brukinsa is not readily biodegradable (OECD 301B).
3. A study based on Technical Guidance OECD 308 was referred to concluding that a Phase II Tier B assessment for sediment is triggered, but no report was submitted.
4. Brukinsa is not a risk to microbial communities (OECD 209), algae (OECD 201) or daphnia (OECD 211), however a Fish early life cycle test did not provide a NOEC for larval growth of the fathead minnow (NOEC<0.017 mg/L, OECD 210). A new study is planned to be completed December 2022.
5. In support of a Phase II Tier B assessment, a sediment-water Chironomid toxicity test (OECD 218). At 289 mg/kg d.w. sediment emergence of midges was 5% of control. NOEC was 89 mg/kg d.w.

A final environmental risk assessment should include the ongoing studies and an updated $PEC_{SURFACEWATER}$ with the new indication and will be submitted following a CHMP recommendation.

2.2.4. Conclusion on the non-clinical aspects

The environmental risk assessment is still ongoing.

In view of the ongoing development of the product the CHMP recommended that the final report, including studies to support Phase II tier B assessment and updated $PEC_{SURFACEWATER}$ with the new indication, to be submitted by Q4 2022/ Q1 2023.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

Introduction

Specific to clinical development in MZL, efficacy data from patients with MZL are available from 2 studies to support claims of efficacy of zanubrutinib in the intended indication: a Phase 2, open-label study of zanubrutinib in patients with relapsed or refractory MZL (Study BGB-3111-214) and a Phase 1/2 study (BGB-3111-AU-003).

The updated clinical pharmacology results include:

• Non-compartmental analysis based on intensive PK data from Study BGB-3111-214 (N=11).

• External model validation based on the observed PK data of patients with MZL (N=68) in Study BGB-3111-214 indicated that the PK characteristics of zanubrutinib in patients with MZL are consistent with the data from the established population PK model (N=632) in patients with B-cell malignancies.

• Exposure-efficacy analysis using pooled data from 2 studies (BGB-3111-AU-003 and BGB-3111-214) to understand the relationship between exposure and efficacy endpoints in patients with MZL.

• Exposure-safety analysis using pooled data from 6 studies (BGB-3111-214, BGB-3111-AU-003, BGB-3111-302, -206, -1002, and -205) to understand the relationship between exposure and safety endpoints in patients with B-cell lymphoma.

• Results from Study BGB-3111-112, a Phase 1, open-label, fixed-sequence study to investigate the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib in healthy male subjects.

Study BGB-3111-214

Title of Study

A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma.

Methods

Study drug administration

All patients received zanubrutinib at 160 mg orally twice daily (two 80-mg capsules orally twice daily), to be continued until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination.

Bioanalytical methods

All bioanalytical methods for zanubrutinib PK analyses were based on high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS). These methods were fully validated to ensure accuracy, precision, selectivity, sensitivity, reproducibility, and stability. A description of the method used to quantify zanubrutinib in human plasma and urine samples is described in Module 2.7.1 of the initial (WM) MAA. The lower limit of quantitation of zanubrutinib is 1.0 ng/mL.

Table 2 Summary Method Performance of a Bioanalytical Method Validated to Measure Zanubrutinib (BGB-3111) in Human Plasma from Study BGB-3111-214

Method Performance in Study BGB-3111-214 Analytical Report for "A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma" (Report 402599-192056-PSA)		
Assay passing rate	10/10 (100%) runs passed	Table 1 of Report 402599-192056-PSA
Standard curve performance	Cumulative bias range: -5.0% to 6.5% Cumulative precision: ≤ 4.9% CV	Table 6 of Report 402599-192056-PSA
QC performance	Cumulative bias range: -8.5% to 4.8% Cumulative precision: ≤ 7.2% CV	Table 7 of Report 402599-192056-PSA
Method reproducibility	Incurred sample reanalysis was performed in 12.3% of study samples, and 100% of samples met the prespecified criteria.	Table 10 of Report 402599-192056-PSA
Study sample analysis/stability	A total of 374 human plasma samples were analyzed in this BA report. All those 374 samples were analyzed within the established stability timeframe of 729 days in a freezer set to - 70°C.	

Abbreviations: BA, bioanalytical; CV coefficient of variation; QC, quality control sample(s)

The method validated by was modified by changing the model of the mass spectrometer from API 4000 to API 6500 to measure zanubrutinib (BGB-3111) in human plasma from Study BGB-3111-214. The partial validation and cross-validation of this method (Interim Report No. 402599-202526-PMV) is summarized below.

Table 3 Summary of Method (Report No. 16BAS0181) Modification and Cross-Validation Results

Bioanalytical method validation report name and hyperlink	Partial Method Validation and Cross-Validation of an LC-MS/MS Assay for the Determination of BGB-3111 in Human Plasma With an Anticoagulation of K_2EDTA (Interim Report No. 402599-202526-PMV)		
Changes in method	Changed the MS/MS platform from API 4000 to API 6500		
New validated assay range if any	Not applicable		
Validation parameters	**Partial Method Validation and Cross-validation performance**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-7.4 to 12.4%	Table 7 (Run 1) of Interim Report 402599-202526-PMV
	Cumulative precision (%CV) from LLOQ to ULOQ	Not applicable	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs 1.00 ng/mL (LLOQ), 3.00 ng/mL (LQC), 50.0 ng/mL (GMQC), 300 ng/mL (MQC), 750 ng/mL (HQC)	-4.7 to 2.2%	Table 13 of Interim Report 402599-202526-PMV
	Intra-batch %CV	≤ 3.6%	Table 13 of Interim Report 402599-202526-PMV
	Percent total error (TE)	Not applicable	Not applicable
Cross-validation	21 incurred samples analyzed and result (%bias)	-12.0 to 1.3%	Table 23 of Interim Report 402599-202526-PMV
List other parameters	Not applicable	Not applicable	Not applicable

Abbreviations: CV, coefficient of variation; GMQC, geometric quality control sample; HQC, high level quality control sample; K2EDTA, dipotassium ethylenediaminetetraacetic acid; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low level quality control sample; MQC, middle level quality control sample; MS/MS, tandem mass spectrometry; QC, quality control sample(s); ULOQ, upper limit of quantitation.

Sampling

The PK profile of zanubrutinib was characterized following single and multiple doses of 160 mg twice daily.

Intensive PK Profiling: Blood samples were collected from up to 15 patients at selected study sites in China on

• Cycle 1 Day 1: predose (within 30 minutes prior to dose) and at 0.5, 1, 2, 3, 4, and 6 hours (± 15 minutes) postdose

• Cycle 1 Day 28: predose (within 30 minutes prior to dose) and at 2 hours (± 15 minutes) postdose

Sparse PK profiling: Blood samples were collected from all patients at all other study sites on

• Cycle 1 Day 1: predose (within 30 minutes prior to dose), at 2 hours (± 15 minutes) postdose, and between 4 to 6 hours (before the patient was discharged from the clinic) postdose

• Cycle 1 Day 28: predose (within 30 minutes prior to dose) and at 2 hours (± 15 minutes) postdose

Pharmacokinetic analysis

Actual collection times were used for the calculation of PK parameters. For intensive PK profiling, PK parameters such as C_{max}, $AUC_{0-\infty}$, AUC_{0-t}, and half-life and other appropriate PK parameters after single and multiple doses were derived using the standard noncompartmental method and were computed in WinNonlin® Enterprise Version 5.2 or higher. Estimates for these parameters were summarized (eg, n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation).

For intensive PK data, individual and mean plasma zanubrutinib concentration-time data were summarized and displayed in both tabular and graphical form.

The following PK parameter estimates were planned.

$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the plasma concentration-time curve from zero to t
AUC_{0-last}	area under the plasma concentration-time curve to the last measurable timepoint
C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
$t_{1/2}$	elimination half-life
CL/F	apparent plasma clearance
Vd/F	apparent volume of distribution

Results

Table 4 Demographics and other baseline characteristics

	N = 68
Age (years)	
Mean (standard deviation)	67.9 (11.41)
Median	70.0
Minimum, maximum	37, 95
Age group, n (%)	
< 65 years	27 (39.7)
≥ 65 and < 75 years	22 (32.4)
≥ 75 years	19 (27.9)
Sex, n (%)	
Male	36 (52.9)
Female	32 (47.1)
Race, n (%)	
White	41 (60.3)
Asian	13 (19.1)
Not reported	10 (14.7)
Multiple	2 (2.9)
Other	1 (1.5)
Unknown[a]	1 (1.5)
Ethnicity, n (%)	
Not Hispanic or Latino	59 (86.8)
Not reported[a]	8 (11.8)
Unknown[a]	1 (1.5)
Country, n (%)	
Australia	14 (20.6)
China	11 (16.2)
Italy	11 (16.2)
United Kingdom	11 (16.2)
New Zealand	7 (10.3)
United States	7 (10.3)
France	5 (7.4)
Czech Republic	1 (1.5)
South Korea	1 (1.5)
ECOG Performance Status	
0	39 (57.4)
1	24 (35.3)
2	5 (7.4)

Source: Table 14.1.2.1
Abbreviations: ECOG, Eastern Cooperative Oncology Group.
[a] Race/ethnicity not disclosed due to local privacy requirements.

Summary Statistics of PK-Exposure

Eleven patients had intensive PK on Cycle 1 Day 1 following a single dose of zanubrutinib at 160 mg.

Zanubrutinib was rapidly absorbed after oral administration and reached geometric mean C_{max} at 294.7 ng/mL, with a median tmax of 2 hours. Zanubrutinib was rapidly eliminated and the geometric mean of $AUC_{0\text{-}6h}$ was estimated as 819.9 ng•h/mL.

As observed in other zanubrutinib PK studies in patients, zanubrutinib exposure was highly variable. Interpatient variability as shown by %GCV after single-dose administration was 40.8% for C_{max} and 45.8% for $AUC_{0\text{-}6h}$.

Figure 2

Arithmetic Mean (± Standard Deviation) Plasma Concentration of Zanubrutinib Versus Time Profiles Following a Single Oral Dose on Cycle 1 Day 1 (Top = Linear Scale; Bottom = Semi-Log Scale)

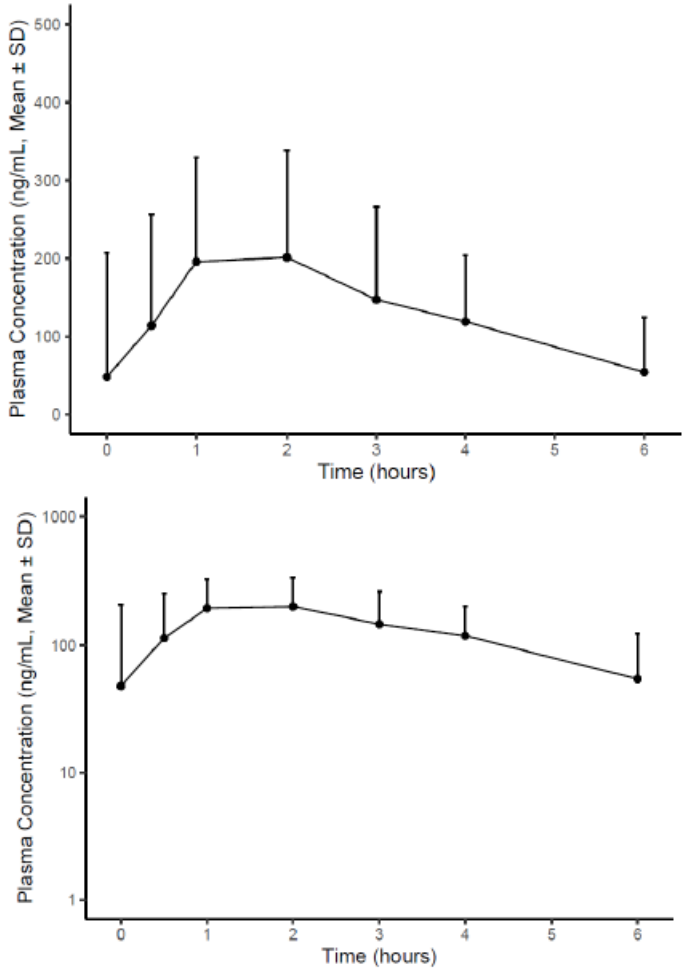


Table 5 Summary of PK parameters of zanubrutinib following a single dose of 160 mg

Summary	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-6h}}$ (ng•h/mL)	$AUC_{0\text{-}\infty}$ (ng•h/mL)	C_{max} (ng/mL)	t_{max} (hour)
N	11	9	8	11	11
GM	767.9	819.9	832.4	294.7	NR
%GCV	43.7	45.8	49.0	40.8	NR
AM ± SD [a]	826.1 ± 308.5	882.1 ± 315.0	904.5 ± 353.4	315.5 ± 120.2	2.0 (0 - 6.0)
%ACV	37.3	35.7	39.1	38.1	NR

For a patient whose the plasma concentrations at predose and 0.5 hours postdose were 529 ng/mL and below the limit of quantitation, the bioanalysis of primary and backup tubes showed similar results; thus, the cause of this finding may have been because of an inadvertent switching of the 2 blood collection tubes at predose and 0.5 hours postdose. The $AUC_{0\text{-}6h}$ was recalculated as 868.0 ± 304.3 hour*ng/mL after switching the plasma concentrations at predose and 0.5 hours postdose; switching of the concentrations had a minimal impact on the descriptive statistics of PK parameters.

Dose justification

The proposed dose regimen in patients with MZL is a 320 mg total daily dose (administered as 160 mg twice daily or 320 mg once daily). This is based on the totality of safety, efficacy, PK, and pharmacodynamic (BTK occupancy data) data from Study BGB 3111-AU-003, Study BGB 3111-1002, and Study BGB-3111-214.

In Study BGB-3111-AU-003, at dosing regimens of 40, 80, 160, and 320 mg once daily and 160 mg twice daily, the maximum tolerated dose was not reached, and no dose-limiting toxicities were observed during the dose-escalation part of the study. Moreover, nearly full occupancy of BTK in peripheral blood mononuclear cells (PBMCs) was achieved in patients at all administered doses. The BTK occupancy in lymph node tissue was assessed at 160 mg BID and 320 mg once daily. At the 160 mg twice daily dose, median BTK occupancy of 100% was observed at steady-state trough and 94% in the 320 mg once daily group. To maximize the inhibition in target tissues, the 160 mg twice daily dose has been used in Study BGB-3111-214 as well as in other ongoing Phase 2/3 clinical studies. The results of pivotal Phase 2 Study BGB-3111-214 provided the primary evidence of effectiveness in patients with MZL and supported the proposed zanubrutinib dose of 160 mg twice daily.

In Study BGB-3111-AU-003, ORR was 100% (N=3/3) for the 320 mg once daily dose compared to 76.5% (N=13/17) for the 160 mg twice daily dose. The CR rate was 33.3 % (N=1/3) for the 320 mg once daily dose compared to 17.6 % (N=3/17) for the 160 mg twice daily dose. Although the number of MZL patients treated at 320 mg once daily is limited relative to the number of patients at 160 mg twice daily dose, there is now extensive experience at the 160 mg twice daily and 320 mg once daily doses, with both schedules showing a high level of activity in patients with B-cell malignancies. Objective responses have been observed in patients with various B-cell malignancies (including CLL, MCL, WM, and FL) at all tested dose levels from 40 mg to 320 mg. Numerically comparable objective responses have been observed between once daily and twice daily regimens in patients with MCL and WM (Tam et al 2021). Furthermore, no remarkable differences were observed in adverse events between the 2 regimens in the safety population in Study BGB-3111-AU-003 (Ou et al 2021).

Additional data support a 320 mg once daily regimen as an option in addition to the 160 mg twice daily regimen for patients with MZL. At the 320 mg once daily dose, a sustained and profound BTK inhibition in PBMCs and lymph node tissue were also observed. Given the same total daily dose (320 mg) and linear PK, similar exposure/AUC were achieved between the 320 mg once daily and 160 mg BID dose. E-R analysis indicated that there was no evident E-R relationship between PK exposure ($AUC_{0\text{-}24}$, C_{max}, or C_{min}) and the safety endpoints (adverse events of interests). There were no significant relationships between zanubrutinib exposure and adverse events including cytopenias, infections, and bleeding. Higher C_{max} observed with the 320 mg once daily dose was not associated with higher adverse event rates. In addition, E-R analysis in patients with MZL (Report BGB-3111-CP-009) and other B-cell malignancies including MCL (Report BGB-3111-CP-003) and WM (Report BGB-3111-CP-007) indicated that efficacy (ORR) does not appear to be significantly impacted by C_{max} or C_{min}, and therefore the same total daily dose and corresponding AUC delivered by the 320 mg once daily dose are expected to result in similar ORR as with the 160 mg BID dose.

The totality of the data summarized here thus supports the recommended dose of a 320 mg total daily dose (as 160 mg BID or 320 mg once daily) in adult patients with MZL who had received ≥ 1 prior therapy. This is based on consistent and sustained BTK occupancy in PBMCs and target tissue, high rates of overall response in patients with relapsed or refractory MZL, and a favorable safety and tolerability profile.

Pharmacokinetic interaction studies

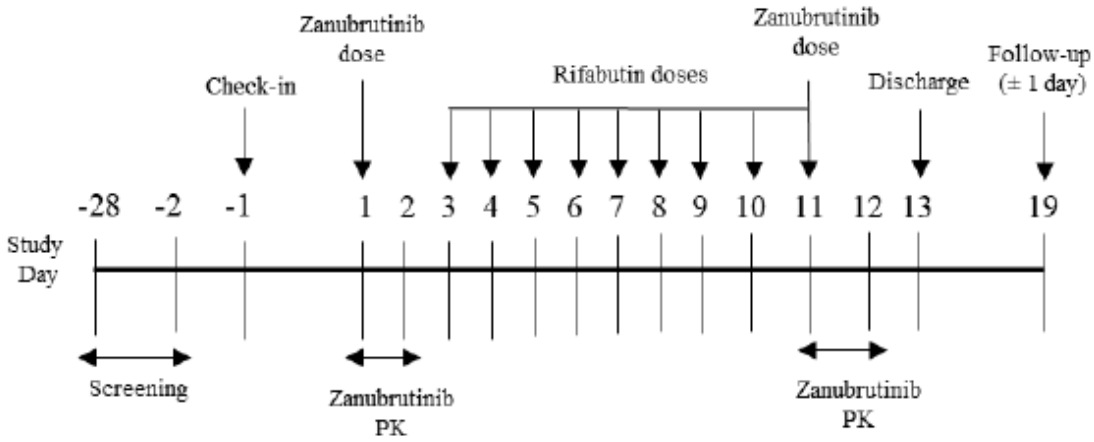
Title of Study

Study BGB-3111-112: A Phase 1, Open-label, Fixed-sequence Study to Investigate the Effect of the Moderate CYP3A Inducer Rifabutin on the Pharmacokinetics of Zanubrutinib in Healthy Male Subjects.

Methods

Study drug administration

An overview of the study design is shown in Figure 3.



Abbreviation: PK = pharmacokinetics.

All subjects received study drugs in a fixed sequence, as follows:

- Day 1: Single oral dose of 320 mg zanubrutinib after an overnight fast of 8 to 10 hours
- Days 3 to 10: Oral dose of 300 mg rifabutin once daily (QD) with food (standard meal)
- Day 11: Single oral dose of 320 mg zanubrutinib and QD dose of 300 mg rifabutin after an overnight fast of 8 to 10 hours.

Sampling

On PK sampling days (Days 1 and 11), blood samples for analysis of plasma zanubrutinib were collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours postdose. The allowed sampling windows for PK blood samples were as follows: within 15 minutes prior to dosing for the predose sample timepoint; ± 5 minutes for sampling timepoints ≤12 hours; ± 30 minutes for sampling timepoint at 24 and 36 hours.

Results

A total of 13 subjects were enrolled and were evaluable for PK analysis.

Following the administration of 320 mg zanubrutinib alone on Day 1 and the coadministration with 300 mg rifabutin on Day 11, median times of the maximum observed plasma concentration (tmax) of 1.50 and 2.00 hours post-dose were observed, respectively. Systemic exposure to zanubrutinib was lower following the coadministration of 320 mg zanubrutinib with 300 mg rifabutin compared to the administration of 320 mg zanubrutinib alone, with a geometric mean area under the plasma concentration time curve (AUC) approximately 44% lower and maximum observed plasma concentration (C_{max}) 48% lower. This represented a decreased exposure of 1.8-fold for AUC_{0-t} and $AUC_{0-\infty}$, and 1.9-fold for C_{max} when zanubrutinib was administered with a moderate CYP3A inducer.

Figure 4 Arithmetic mean (+SD) zanubrutinib plasma concentration profiles following administration of 320 mg alone and coadministration with 300mg rifabutin (linear scale)

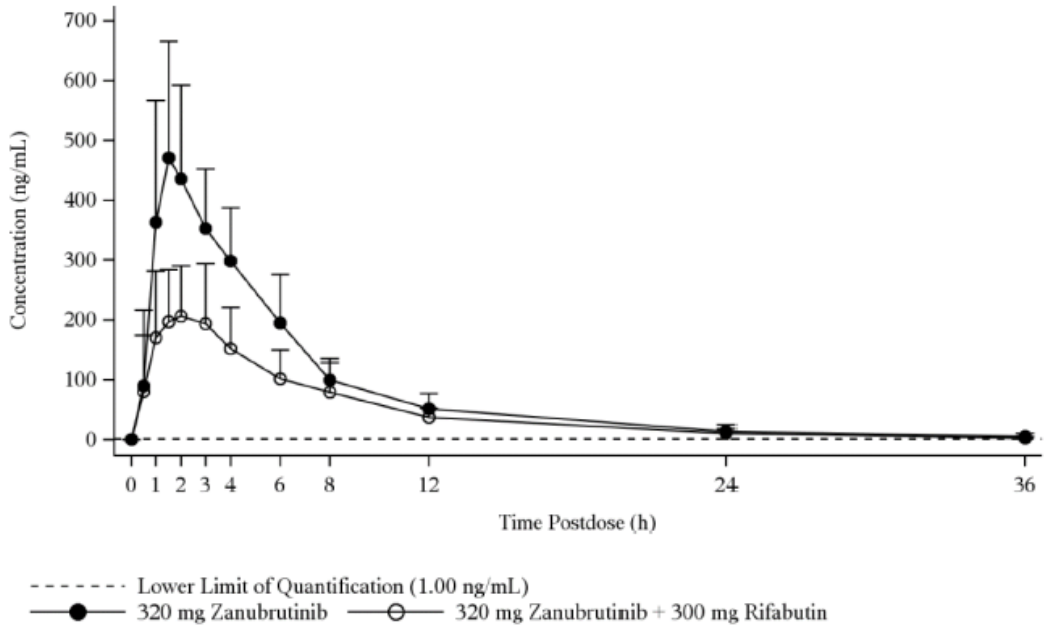


Table 6 Statistical analysis of PK parameters of zanubrutinib following administration of 320 mg zanubrutinib alone and coadministration with 300mg rifabutin

Parameter	320 mg Zanubrutinib + 300 mg Rifabutin Once a Day (Test)		320 mg Zanubrutinib (Reference)		Ratio of Geometric LS Means (%) [a]	90% CI for the Ratio [b]	$CV_{W\%}$ [d]
	n	Geometric LS Means [c]	n	Geometric LS Means [c]	(Test Reference)	(Test Reference)	
AUC_{0-t} (ng•h/mL)	13	1530	13	2700	0.566	(0.525, 0.610)	10.7
$AUC_{0-\infty}$ (ng•h/mL)	12	1560	13	2780	0.560	(0.532, 0.589)	7.0
C_{max} (ng/mL)	13	253	13	489	0.518	(0.441, 0.608)	23.2

Source: BGB-3111-112 CSR Table 6.
Abbreviations: ANOVA, analysis of variance; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV_W, within-subject coefficient of variation; LS, least squares; n, number of subjects; PK, pharmacokinetic.
Note: Subjects who did not have evaluable PK parameters on either the test or reference days were removed from the statistical analysis.
[a] Ratio of geometric LS means for natural log-transformed parameter. Natural log-transformed ratios transformed back to the linear scale (expressed as a percentage).
[b] 90% CI for the ratio of geometric LS means for natural log-transformed parameter. Natural log-transformed confidence limits transformed back to the linear scale (expressed as a percentage).
[c] Geometric LS means from ANOVA, calculated by transforming the natural-log mean back to the linear scale.
[d] $CV_W\% = [\exp(\text{mean squared error}) - 1]^{1/2} \times 100$.

There was a less than a 50% reduction of systemic exposures (AUC) of zanubrutinib following co-administration of zanubrutinib with rifabutin, a moderate CYP3A inducer, compared to the administration of zanubrutinib alone. Thus, based on the emergent data from Study BGB-3111-112, a revision to the current dose recommendation for concomitant use of moderate CYP3A inducers is proposed; it is recommended that patients use caution with concomitant use of moderate CYP3A inducers. This updated recommendation is based on the totality of data, including (1) less than 50% decrease in zanubrutinib AUC for concurrent use of a moderate CYP3A inducer, (2) an efficacy signal at doses as low as 40 and 80 mg, (3) maximal BTK inhibition (median BTK occupancy of 100%) in PBMC samples starting at doses of 40 mg once a day, and (5) no identifiable E-R relationships for efficacy or safety endpoints.

2.3.3. Pharmacodynamics

Mechanism of action

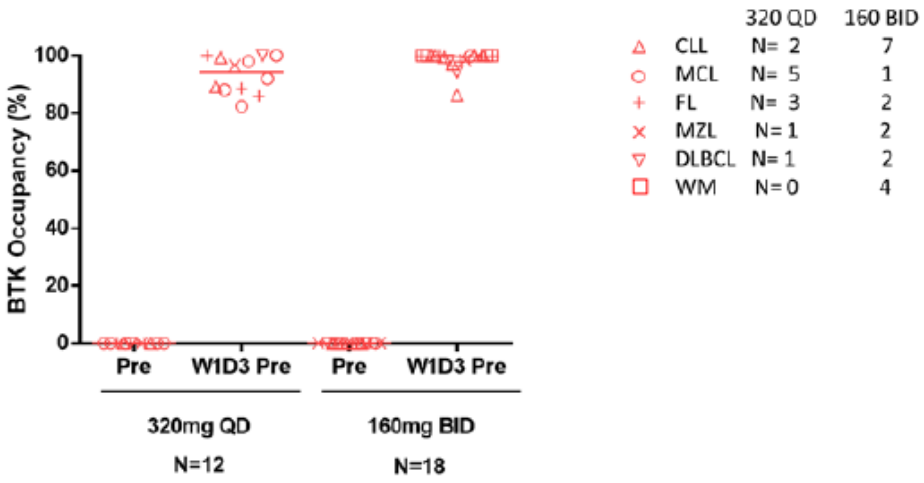
Zanubrutinib is a second-generation oral BTK inhibitor that forms an irreversible covalent bond at Cys481 within the adenosine triphosphate binding pocket of the BTK protein.

Primary pharmacology

No new pharmacodynamic analyses pertaining to BTK occupancy have been conducted since the initial WM application. For the latter, "*Pharmacodynamic (PD) analyses were performed in the Chinese phase 1 study BGB-3111-1002 and in the global phase 1/2 study BGB-3111-AU-003 based on PD data from 13 and 50 subjects, respectively. The primary PD endpoint was the BTK occupancy in peripheral blood mononuclear cells (PBMCs)*" (Brukinsa EPAR).

The number of lymph node samples included was low, 12 and 18 samples in patients with 320 mg QD and 160 mg BID dosing, respectively. As per Figure 3 below, from the Applicant's previously submitted Report BGB-3111-AU-003-PD-01, although data was very limited, there was no apparent association of lymph node BTK occupancy and tumour types, including MZL:.

Figure 5 BTK receptor occupancy in lymph nodes by different tumor types



2.3.4. PK/PD modelling

This type II variation submission contains an external validation of a previously developed population PK model, which was assessed during the MAA of Brukinsa. In this submission, the population PK model is mainly used in order to generate exposure estimates for the patients, which are then used in an exposure-response analysis. The exposure-response analysis is used as one argument to justify the dose, and as one argument to justify that no dose adjustments are necessary when zanubrutinib is coadministered with moderate CYP3A4 inducers.

External validation of a previously developed population PK model

An established population PK model using data from 632 subjects enrolled in 9 clinical studies in patients with B-cell malignancies and healthy volunteers (BGB-3111-103, BGB-3111-104, BGB-3111-105, BGB-3111-106, BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, and BGB-3111-302) (Report BGB-3111-CP-008) was submitted in the initial MAA for WM. It featured a two-compartment model with first-order elimination from the central compartment, and sequential zero-order and first-order absorption of the drug.

Baseline alanine aminotransferase (ALT) and health status were identified as significant covariates on CL/F. Health status was identified as a significant covariate on apparent volume of the central compartment (Vc/F). Race and body weight did not show a statistically significant impact on the PK of zanubrutinib. Other covariates including baseline age, aspartate aminotransferase (AST), bilirubin, creatinine clearance (CRCL), sex, tumor type, and use of acid-reducing agents also did not demonstrate a statistically significant impact on the PK of zanubrutinib.

The PK data in study BGB-3111-214 study were analyzed using the above-mentioned final zanubrutinib population PK model via an external validation approach. This study included PK data from a total of 68 subjects treated with zanubrutinib (160 mg twice daily) who had ≥1 measurable zanubrutinib PK sample post-dose.

The following data records were removed from the analysis according to data exclusion rules.

1. Missing concentrations (n=27, removed)

2. Zero concentrations before 1st dosing (n=67, removed)

3. Measurable concentration taken before first dose (n=1, EXCLFL=1)

4. Switched peak and trough concentration (n=4)

5. Measurable concentrations with missing dosing time (n=3)

6. Measurable concentrations were identified as outliers (n=5)

As a result, the final external model validation dataset was comprised of 68 subjects, defined as validation subjects, contributing a total of 289 zanubrutinib concentrations for the external model validation.

Predicted zanubrutinib plasma concentrations for the validation subjects were determined by fixing the parameters in the structural and variance model to the parameter estimates in the final population PK model using post-hoc Bayesian prediction. The predicted concentrations (PRED) were compared with the corresponding observed concentrations (DV). Prediction errors (PE) were calculated for each PRED and expressed as a percentage of DV for each data point as follows:

$$PE_{ij} = \frac{(PRED_{ij} - DV_{ij})}{DV_{ij}} \times 100\%$$

Bias (mean prediction error [MPE]) was then calculated for each subject as follows:

$$MPE_i = \frac{\sum PE_{ij}}{n_i}$$

Precision (root mean squared prediction error [RMSE]), which describes the imprecision of the population predictions relative to the observed concentrations, were calculated from the square-root of the arithmetic mean of squared Pe values as follows:

$$RMSE_i = \sqrt{\frac{\sum PE_{ij}^2}{n_i}}$$

where DV_{ij} and $PRED_{ij}$ represent the j^{th} observed and predicted concentration in normal domain, respectively, for the i^{th} subject. PE_{ij} represents the j^{th} prediction error for the i^{th} subject, and n_i denotes number of observations for subject i.

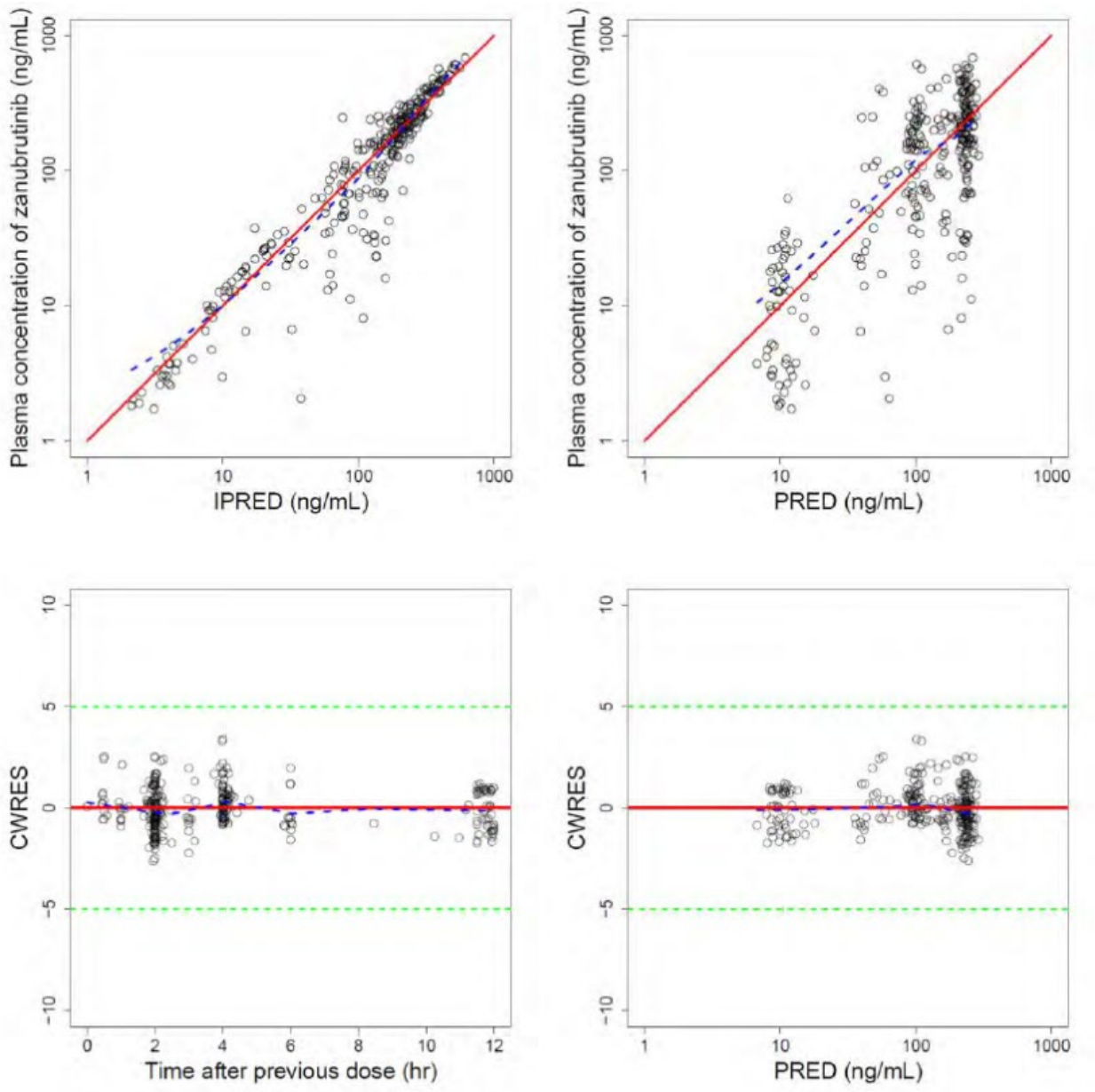
MPE and RMSE were computed for each subject, then t-test was used to check whether the MPE value across subjects was significantly different from zero at $p<0.01$ level.

The mean bias in the population predictions for validation subjects was 16.4% with 95% confidence interval (CI) of (2.96%, 29.8%), which was not significantly different from zero (p value=0.0175). The mean imprecision was 73.2% (95% CI [62.5%, 83.9%]). The results suggested that the PopPK model well predicted zanubrutinib concentrations in the validation subjects.

Goodness-of-fit analyses by standard sets of diagnostic plots, prediction-corrected visual predictive checks (pcVPCs), and numerical predictive checks (NPCs) were performed. The general goodness-of-fit plots for the zanubrutinib validation subjects are shown below. While there was a good concordance between individual predicted and observed concentrations, the population predictions well predicted the observed concentrations.

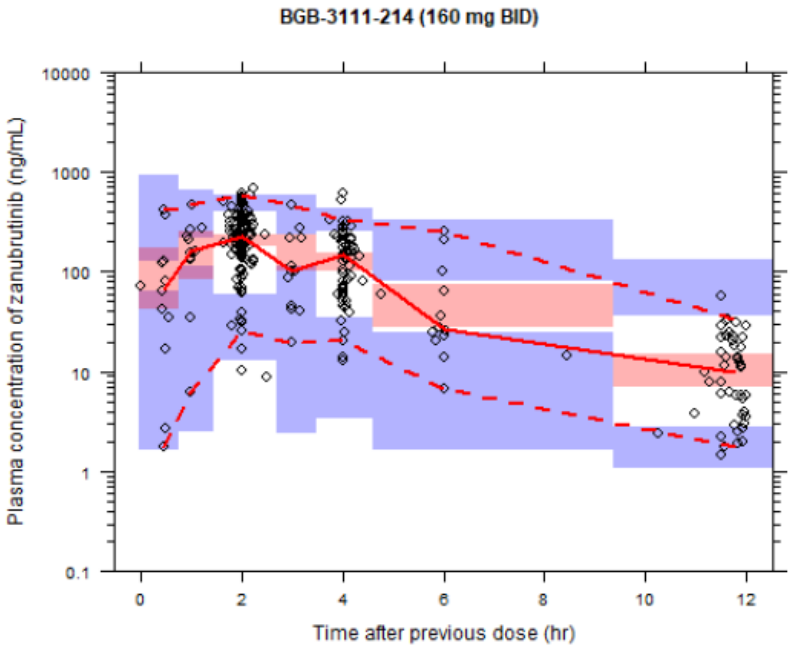
The pcVPC evaluated the ability of the model to reproduce the distribution of the PK data in validation subjects. A total of 1000 replicates of the studies were simulated using the observed covariates for each validation subject, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error. The pcVPC plot showed that the model well predicted the central tendency of the observed PK concentrations.

Figure 6 ***General goodness-of-fit plots for all zanubrutinib validation subjects***



Top: individual predicted plasma zanubrutinib concentrations (IPRED) versus observed zanubrutinib concentrations (left) and population predicted plasma zanubrutinib concentrations (PRED) versus observed plasma zanubrutinib concentrations (right). Bottom: conditional weighted residuals (CWRES) versus time (left) and PRED (right). Points are individual data. Red solid lines represent the unit diagonal (top) or line at zero (bottom). Green dashed lines represent |CWRES| of 5. Blue dashed lines represent the lowess smooth curves.

Figure 7 pcVPC of zanubrutinib concentration vs time for zanubrutinib validation subjects



Circles are observed zanubrutinib plasma concentrations, solid red lines represent the median observed value, and dashed red lines represent 2.5th percentile and 97.5th percentile of the observed values. Pink shaded areas represent the 95% CI of the predicted median concentrations, and the blue shaded areas represent the 95% CI of the 2.5th percentile and 97.5th percentile of the predicted concentrations.

Overall, the developed zanubrutinib population PK model was able to provide good predictions of zanubrutinib PK in Study BGB-3111-214. Hence, the Bayesian post-hoc individual PK parameter estimate was used to calculate the predicted PK exposures (AUCss, Cmax,ss, and Cmin,ss) for these subjects for E-R analysis.

Exposure-response analyses

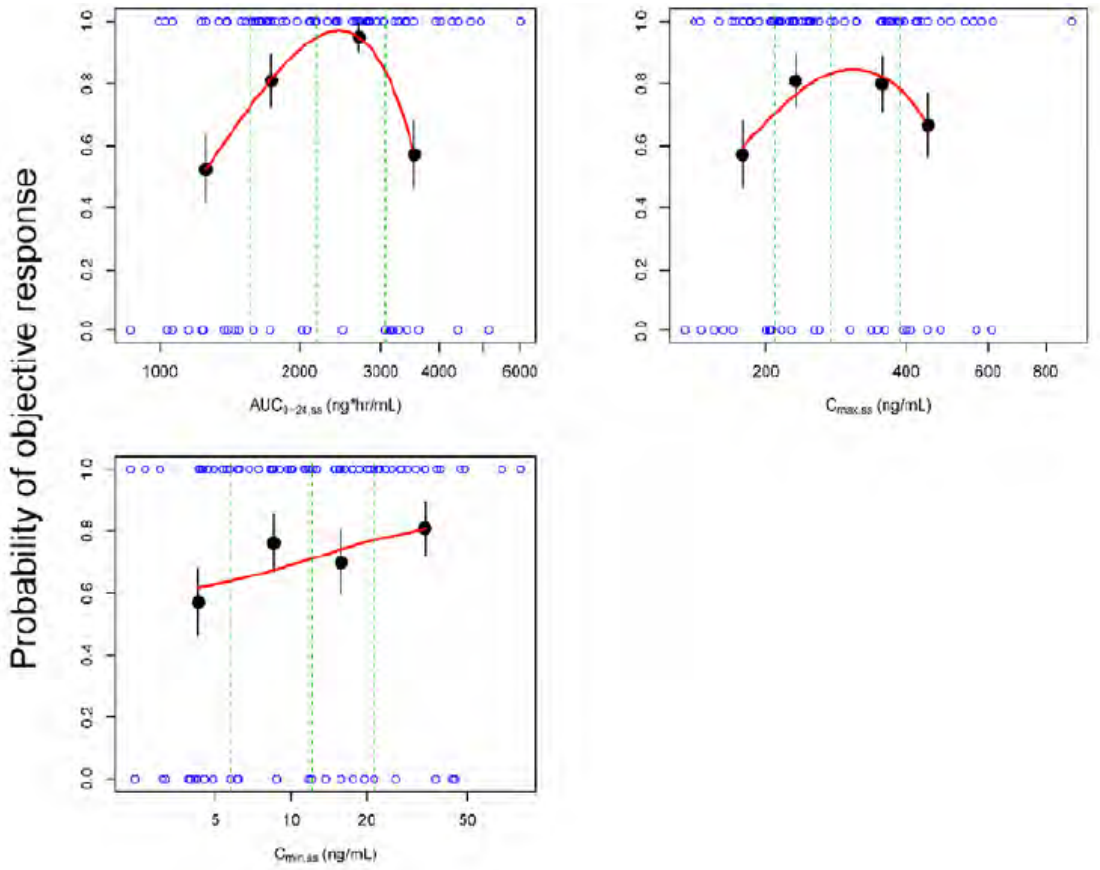
To support dose recommendations, exposure-safety and exposure-efficacy relationships were evaluated in patients with B-cell malignancies receiving zanubrutinib monotherapy in clinical studies.

The E-R relationship for efficacy endpoint of ORR with the Lugano classification was explored based on the data from studies BGB-3111-AU-003 in patients with MZL (N=17) and BGB-3111-214 (N=66). Efficacy data cutoff date was 18 January 2021 for BGB-3111-214 and 09 October 2020 for BGB 3111-AU-003. Patients with both efficacy data and PK data were included in the efficacy analysis (N=83). Out of 83 subjects, 81 subjects were treated with 160 mg BID and 2 subjects were treated with 320 mg QD. Two patients in study BGB-3111-214 were excluded from the efficacy analysis because the central pathology results showed histologic transformation to diffuse large B-cell lymphoma.

The E-R relationship was explored based on IRC-assessed objective response endpoint in patients with MZL enrolled in studies BGB-3111-AU-003 and BGB-3111-214. The median exposure values were similar between responders (N=59) and non-responders (N=24).

The probability of response plots by quantiles of zanubrutinib exposure is shown below. The results indicated that there was no apparent relationship between IRC-assessed objective response and the model predicted AUC0-24,ss or Cmax,ss. However, an apparent exposure-response trend was observed between IRC-assessed objective response and the model predicted Cmin,ss.

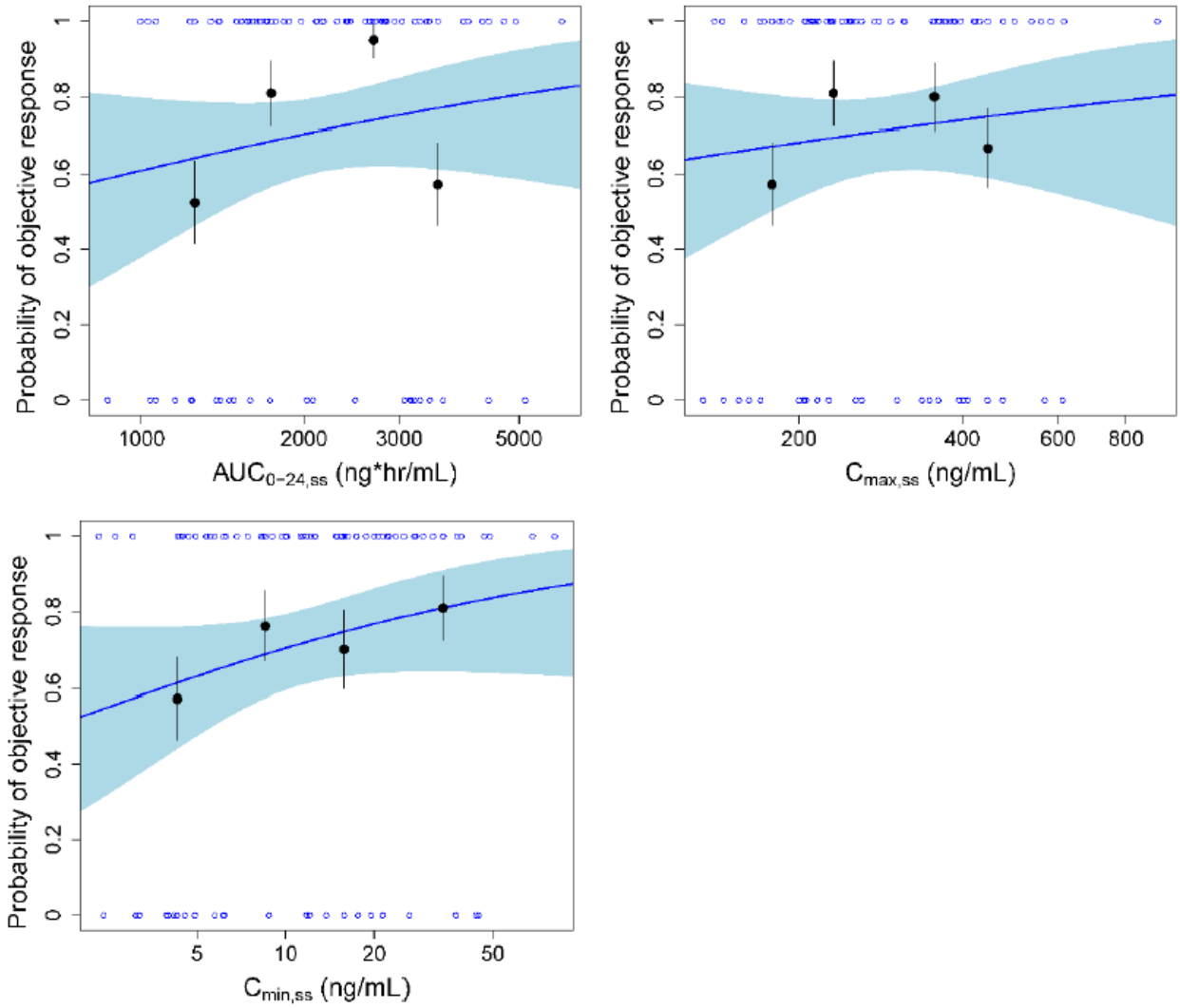
Figure 8 ***Probability of IRC-assessed objective response versus exposure***



The blue open circles reflect the observed events in zanubrutinib treated subjects. The black solid circles are the observed probability of ORs, and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of OR and N is the number of patients in each quantile bin) for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The red lines are smooth curves (loess) to show the relationship between two variables.

To investigate the E-R relationship for ORR, the E-R logistic regression model for IRC assessed objective response with Cmax,ss, Cmin,ss and AUC0-24,ss were developed based on zanubrutinib treated patients in studies BGB-3111-214 and BGB-3111-AU-003. The diagnostic plots of the logistic regression model are shown in Figure 8. The logistic regression model results suggested that Cmax,ss, Cmin,ss, and AUC0-24,ss were not associated with the probability of OR in zanubrutinib treated patients (p value > 0.01).

Figure 9 ***Logistic regression of probability of IRC-assessed objective response versus exposure***



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(1/4)th percentiles) 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.

The E-R relationship for safety endpoints was explored based on data from studies BGB- 3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-302, BGB-3111-AU-003, and BGB-3111-214. The selected safety endpoints of interest included: grade ≥3 neutropenia, grade ≥3 thrombocytopenia, grade ≥ 3 anemia, grade ≥3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, any bleeding events, and AE leading to treatment discontinuation.

No apparent E-R relationship was observed for grade ≥ 3 neutropenia; grade ≥ 3 thrombocytopenia; grade ≥ 3 anemia; grade ≥ 3 infections/infestations; all events of secondary primary malignancies; all events of atrial fibrillation and flutter; major bleeding events; any bleeding events; and AE leading to treatment discontinuation, based on zanubrutinib treated patients in studies BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111- 302, BGB-3111-AU-003 and BGB-3111-214.

The exposure-safety analyses included figures of AUC0-24h,ss Cmax,ss and Cmin,ss stratified by AEs (Grade ≥3 neutropenia, Grade ≥3 thrombocytopenia, Grade ≥3 anemia, Grade ≥3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and

flutter, major bleeding events, any bleeding events) and figures of probability of AE as a function of exposure markers. The figures are not copied to this AR for reasons of conciseness. All of the figures were highly similar to the exposure-safety analyses presented in the original MAA, since the exposure-safety dataset is a combination of previously generated safety data and the newly generated safety data, with the newly presented data being only a small fraction of the total exposure-safety dataset. As such, it is natural that no major changes can be seen in the exposure-safety profile in this updated analysis.

As a new safety endpoint, not included in the exposure-safety analyses presented in the original MAA, the relationship between AE leading to treatment discontinuation and exposure was also investigated. No exposure-safety trend was detected.

To summarize, no new exposure-safety signals have been found.

2.3.5. Discussion on clinical pharmacology

Zanubrutinib is a Bruton tyrosine kinase (BTK) inhibitor approved in the EU for treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

The present type II variation submission concerns approval of zanubrutinib as monotherapy for treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti-CD20-based therapy. The current application's clinical pharmacology package includes data from a Phase 2, open-label study of zanubrutinib in patients with relapsed or refractory MZL (Study BGB-3111-214), a Phase 1/2 study (BGB-3111-AU-003) and a clinical DDI study (BGB-3111-112). The ADME characteristics were described in the original WM marketing application and no changes have been proposed to SmPC section 5.2.

In principle, no new bioanalytical methods were applied for detection of zanubrutinib in human plasma, except that a new mass spectrometer was implemented by partial validation during the course of the BGB-3111-214 study. This study included a successful incurred sample reproducibility test (ISR). The clinical DDI study (BGB-3111-112) also included an ISR evaluation, which passed. Bioanalysis for the -214 study was conducted at and the -112 study at. The bioanalytical method underwent a full validation at both sites.

The current submission contains an external validation of a previously developed population PK model, which was assessed during the MAA of Brukinsa. In this submission, the population PK model is mainly used in order to generate exposure estimates for the patients, which are then used in an exposure-response analysis. The exposure-response analysis is used as one argument to justify the dose, and as one argument to justify that no dose adjustments are necessary when zanubrutinib is co-administered with moderate CYP3A4 inducers.

The MAH has calculated mean prediction error and root mean square error to quantify model prediction accuracy and precision. The MAH states that Bayesian post-hoc individual predictions were used. If this is true, then the value $PRED_{ij}$ is based on Empirical Bayesian predictions, given the individuals data, i.e. it corresponds to the term "IPRED" typically used in NONMEM vocabulary.

So, prediction errors are calculated on the basis of individual predictions. This is problematic for a number of reasons.

First, in the case of a high number of observations for a given individual, the individual data will predominate the population PK model in the fitting of the individual parameters; shrinkage of Empirical Bayes Estimates of random effects will be very low; the result will be an MPE_i of approximately zero for

the individual with high number of observations, even if the population PK model itself predicts badly. The diagnostic defined by the MAH will be unable to detect potential model misspecification in this scenario.

Second, in the case when there are only few observations for a given individual, a high shrinkage of Empirical Bayes Estimates of random effects will occur, and the individual PK parameters will be close to those predicted by the population PK model. In this case, a more variability in the MPE_i value will most likely result. So the variability in MPE_i will depend on the number of observations for the individual.

Third, using a t-test to check whether the MPE value across subjects was significantly different from zero at $p<0.01$ level, completely ignores the aspect that the MPE_i values may be informed by a variable number of individual PK observations, e.g. one individual may have 6 PK observations and another individual only one PK observation, yet the t-test will not take this into account in any way.

Fourth, the population PK model contains a combination of additive and proportional residual error. As such, it is expected that the relative differences between observations and individual predictions are higher at low concentrations. Thus, the concept of calculating PE_{ij} as a relative difference between observations and individual predictions is flawed.

All of these problems would have been avoided just by using appropriate residuals, such as the conditional weighted residuals (ref: https://doi.org/10.1007/s11095-007-9361-x), which do automatically take into account the uncertainty in measurement, between-occasion variability, between-subject variability, residual error model, and the number and timing of observations for each subject. A t-test of CWRES being different from zero could then have been used.

However, even though these diagnostics are not considered acceptable, The MAH has included several other diagnostics to support the external validation. It is possible to use these other diagnostics to evaluate the population PK model external validation. For this reason, no issues are raised.

No major discrepancies are seen the goodness-of-fit plots; the plots do therefore support the external validation of the previously developed population PK model.

The prediction-corrected VPC suggests no major discrepancies between the previous population PK model and the newly generated PK data, therefore supporting the external validation.

The population PK report also demonstrated that no new covariates can be identified from the newly generated PK data. Given that the original population PK model included 632 subjects with some subjects having densely sampled PK data, it is not surprising that no new covariates could be identified on the basis of 68 subjects with sparse PK sampling.

Within the exposure-response analyses, a potential exposure-response trend was detected, with Cmin,ss as a potential predictor of response probability. However, when this relationship was tested in a logistic regression model, the trend was not statistically significant. The MAH states $p>0.01$, and from the relevant results, the exact p-value for the slope being different from zero is 0.113, i.e. insignificant.

The exposure-safety analyses included figures of AUC0-24h,ss Cmax,ss and Cmin,ss stratified by AEs (Grade ≥3 neutropenia, Grade ≥3 thrombocytopenia, Grade ≥3 anemia, Grade ≥3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, any bleeding events) and figures of probability of AE as a function of exposure markers. All of the figures were highly similar to the exposure-safety analyses presented in the original MAA, since the exposure-safety dataset is a combination of previously generated safety data and the newly generated safety data, with the newly presented data being only a small fraction of

the total exposure-safety dataset. As such, it is natural that no major changes can be seen in the exposure-safety profile in this updated analysis.

As a new safety endpoint, not included in the exposure-safety analyses presented in the original MAA, the relationship between AE leading to treatment discontinuation and exposure was also investigated. No exposure-safety trend was detected.

To summarize, no new exposure-safety signals have been found.

The MAH uses the lack of observable exposure-response relationship to justify the dose. It is acknowledged that nothing in the presented data suggests that the dose should be changed, however also noting that the low number of observations and the relatively narrow range of exposures do not provide much statistical power for the analysis. As such, while the presented data do not show any signs that the dose is suboptimal, from an exposure-response perspective it is also not possible to indisputably show that the proposed dose is optimal with the current exposure-response data. Overall, based on the efficacy, safety and PK results observed, the selected dose regimen of 320 mg total daily dose, identical to the currently approved posology for WM (administered as 160 mg twice daily or 320 mg once daily) is considered acceptable.

The Applicant has submitted a clinical DDI study (BGB-3111-112) of zanubrutinib co-administered with the moderate CYP3A inducer rifabutin. Rifabutin was found to decrease average zanubrutinib exposure by nearly half, with a geometric mean AUC approximately 44% lower and C_{max} 48% lower. Based on these results, the Applicant proposes to revise the current SmPC recommendation to avoid concomitant use of moderate CYP3A inducers, suggesting that moderate CYP3A inducers may instead "*be used with caution*" during zanubrutinib treatment. However, results of Study BGB-3111-112 became available and were assessed during the initial Brukinsa EU MAA, no new clinical efficacy data has been provided by the Applicant pertaining to zanubrutinib dosing regimens below 320 mg daily, and data on BTK receptor occupancy in target tissues below the current recommended total daily dose of 320 mg are likewise lacking. The lack of observable exposure-response and exposure-safety relationships is also used as one argument to justify that no dose adjustments are needed in the presence of moderate CYP3A4 inducers. This argument cannot be wholly agreed with. While it is agreed that a 50% reduction in exposure in the median patient would not likely result in appreciable change in probability of response, no predictions can be made on the basis of the model for the effect of 50% exposure reduction in patients who are on the lower end of the exposure range after 160mg BID or 320mg QD dose. Thus, the exposure-response and exposure-safety alone are not adequate to justify that no zanubrutinib dose adjustments are needed in the presence of moderate CYP3A4 inducers, and the concern that average decreased zanubrutinib exposure in the order of 50% may result in decreased efficacy remains. Accordingly, changes to SmPC recommendations regarding co-administration of zanubrutinib with moderate CYP3A inducers with the addition of the MZL indication are not supported, the currently approved SmPC recommendations to avoid concomitant use of moderate CYP3A inducers was maintained.

2.3.6. Conclusions on clinical pharmacology

The pharmacology package included in the current application includes data from a Phase 2, open-label study of zanubrutinib in patients with relapsed or refractory MZL (Study BGB-3111-214), a Phase 1/2 study (BGB-3111-AU-003) and a clinical DDI study (BGB-3111-112). The population PK model and the exposure-response and exposure-safety analyses support the proposed dose. Based on data submitted with the initial (WM) EU MAA, the two proposed dose regimens, 160 mg twice daily and 320 mg once daily, were found to give comparable exposure (AUC), and the same posology for the MZL indication is considered acceptable based on the efficacy, safety and PK results provided with the

current application. Moreover, the exposure-response analyses provide support that zanubrutinib efficacy in the median patient is unlikely to be compromised in the presence of moderate CYP3A4 inducers. However, no reliable predictions from the exposure-response model can be made for those patients who are on the lower end of the exposure range resulting from 160 mg BID or 320 mg QD dose; the SmPC wordings recommend to avoid concomitant use of moderate CYP3A inducers.

2.4. Clinical efficacy

2.4.1. Dose response studies

See Dose justification the Pharmacokinetics section.

The proposed dose regimen in patients with MZL is a 320 mg total daily dose (administered as 160 mg twice daily or 320 mg once daily). This is based on the totality of safety, efficacy, PK and pharmacodynamics (BTK occupancy data) results from study BGB-3111-AU-003, study BGB-3111-1002, and study BGB-3111-214.

The BTK occupancy in lymph node tissue was assessed at 160 mg twice daily and 320 mg once daily. At the 160 mg twice daily dose, median BTK occupancy of 100% was observed at steady-state trough and 94% in the 320 mg once daily group (Module 2.7.2 in initial Marketing Authorisation Application for Waldenström macroglobulinemia [WM], Section 3.3). To maximize the inhibition in target tissues, the 160 mg twice daily dose has been used in study BGB-3111-214 as well as other ongoing Phase 2/3 clinical studies. The results of pivotal Phase 2 study BGB-3111-214 provided the primary evidence of effectiveness in patients with MZL and supported the proposed zanubrutinib dose of 160 mg twice daily.

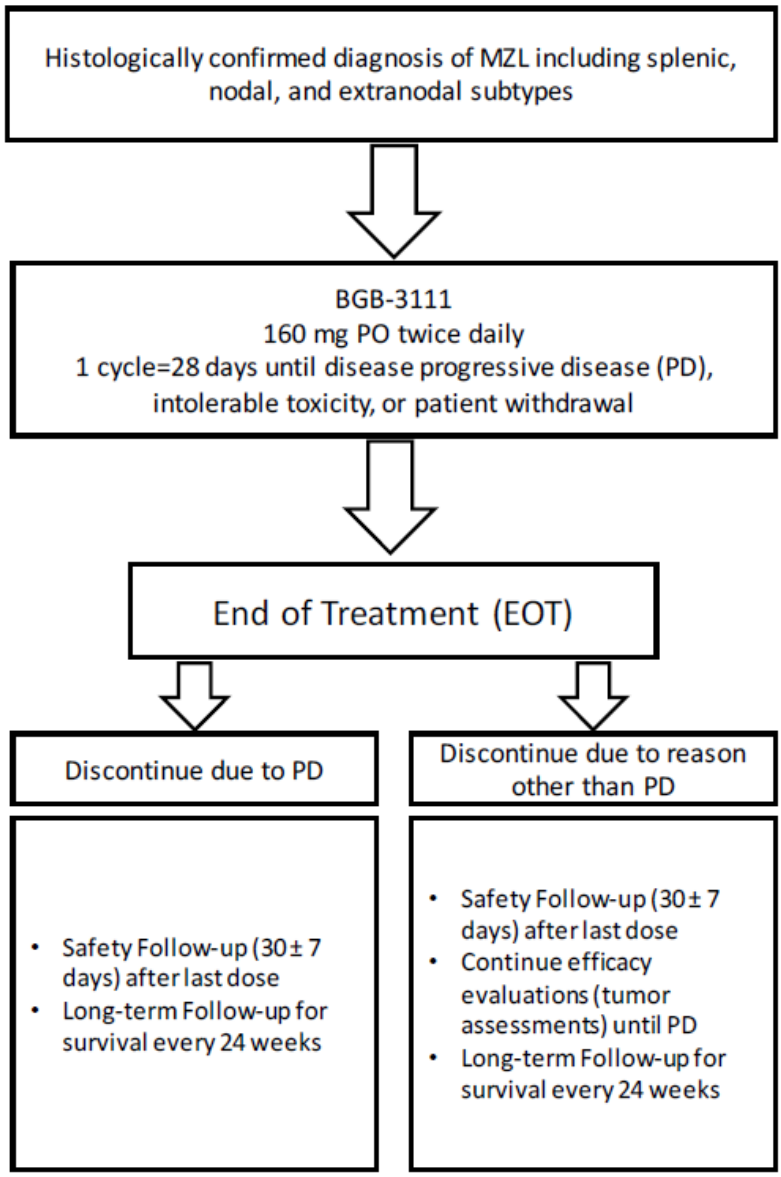
2.4.2. Main study

Study BGB-3111-214:

Study BGB-3111-214 is an ongoing Phase 2, single-arm, multicentre, open-label study designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL who have received ≥ 1 prior anti-CD20-based regimen. The study was composed of an initial screening phase (up to 35 days), a single-arm treatment phase, and a follow-up phase. Sixty-eight patients (65 planned) were enrolled in the study and received zanubrutinib 160 mg orally twice daily in repeated 28-day cycles. Treatment with zanubrutinib was continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination by BeiGene. Patients were monitored for safety until 30 days after the last dose of study drug. The data cutoff date was 18 January 2021 for inclusion of study data in the efficacy summary.

The MAH has provided updated patient disposition and efficacy results with a cutoff date of 04 May 2022 (approximately 15 months of additional follow-up efficacy data).

Figure 10 Study BGB 3111-214: design



Abbreviations: EOT, end of treatment; MZL, marginal zone lymphoma; PO, oral; PD, progressive disease.

Study BGB-3111-AU-003:

Part 1 – Dose Escalation

Patients with a WHO-defined relapsed or refractory B-cell lymphoid malignancy—with the exception of Burkitt's lymphoma/leukemia, plasma cell myeloma, acute lymphoblastic leukemia, lymphoblastic lymphoma, and plasmablastic lymphoma—were enrolled in Part 1 of the study. Part 1 followed a modified 3+3 dose-escalation scheme, and the initial planned enrollment was 20 patients. The starting dose of zanubrutinib was 40 mg once daily.

Part 2 – Expansion

Part 2 of the study had 13 disease- or patient-specific cohorts (ie, 2a through 2m) with planned enrollment of 380 patients in total. Enrollment to individual cohorts was generally conducted in parallel with the exception of Cohort 2g (relapsed or refractory MCL), which was initiated after enrollment in Cohort 2a was complete. The recommended Phase 2 dose of zanubrutinib for evaluation in Part 2 was

determined to be 320 mg administered once daily or 160 mg twice daily but was modified coincident with Protocol Version 6 (09 September 2016) to 160 mg twice daily exclusively, for all subsequent patients enrolled to Part 2. Under Version 6 (09 September 2016), patients enrolled to Cohort 2a and Cohorts 2e through 2j who were receiving zanubrutinib 320 mg once daily had the option to switch to 160 mg twice daily.

Title of Study

Study BGB-3111-214: A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma.

Supportive **Study BGB-3111-AU-003**: A Phase 1/2, 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.

Methods

Study participants

Men and women 18 years or older with histologically confirmed MZL including splenic, nodal, and extranodal subtypes and have received at least 1 or more prior lines of therapy, including at least 1 CD20-directed regimen (either as monotherapy or as chemoimmunotherapy), with documented failure to achieve at least PR or documented progressive disease after the most recent systemic treatment. Eligible patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 to 2, measurable disease, adequate organ function based on pre-defined laboratory parameters, and a life expectancy of $\geq$ 6 months.

Patients who had central nervous system involvement, prior treatment with a BTK inhibitor, clinically significant cardiovascular disease, active infections requiring systemic therapy, HIV, active hepatitis B or C infections; or major surgery within 4 weeks of the first dose of study drug were not eligible for the study.

Treatments

Patients received zanubrutinib 160 mg orally twice daily continued until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination. Patients who discontinued study drug due to reasons other than disease progression remained on study and continued with regular disease assessments including imaging studies until documented disease progression, withdrawal of consent, initiation of new anticancer therapy, death, or study closure.

Table 7 Dose reductions

Toxicity occurrence	Dose level	Zanubrutinib Dose
First	0 = starting dose	Restart at 160 mg twice daily
Second	-1 dose level	Restart at 80 mg twice a day
Third	-2 dose level	Restart at 80 mg once a day
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

Table 8 Dose modifications for haematological toxicities

Adverse event	Severity and duration	Time to restart	Zanubrutinib Dose
Neutropenia	NCI-CTCAE Grade 4 lasting > 10 days	Recover to ≤ Grade 1 or baseline	Restart at 160 mg twice daily; For second occurrence: →80 mg twice daily (Table 3)
Thrombocytopenia	NCI-CTCAE Grade 4 lasting > 10 days	Recover to ≤ Grade 1 or baseline	Restart at 160 mg twice daily; For second occurrence: →80 mg twice daily (Table 3)
Thrombocytopenia associated with significant bleeding	NCI-CTCAE Grade 3 or 4 associated with significant bleeding requiring medical intervention	Discontinuation	Not applicable
Febrile neutropenia	NCI-CTCAE Grade 3 or 4	Recover to ≤ Grade 1 or baseline	Restart at 160 mg twice daily; For second occurrence: →80 mg twice daily (Table 3)

Source: Section 6.4.1 of Protocol Amendment 3.0 in Appendix 16.1.1
Abbreviations: NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

Dose Modifications for Non-Hematologic Toxicity

For non-hematologic toxicities Grade 3 or higher suspected to be treatment related (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events), study drug was to be withheld until recovery to ≤ Grade 1 or baseline, and then restarted at the original dose level. Note that laboratory abnormalities indicative of liver or kidney dysfunction were not considered asymptomatic. In this study, asymptomatic lymphocytosis, whether related to study drug or not, was not reported as a toxicity; patients were to continue study drug without dose modification or treatment interruption as well as all study-related procedures.

If the event reoccurred at Grade 3 or higher severity, study drug was to be withheld until recovery to ≤ Grade 1 or baseline and restarted at dose level -1 (80 mg twice daily). In the event of a second, Grade 3 or higher occurrence of the event at dose level -1, drug was to be withheld until recovery to ≤ Grade 1 or baseline and restarted at level -2 (80 mg once daily). A third occurrence of the event at Grade 3 or higher after 2 dose reductions required study drug discontinuation.

For patients experiencing Grade 3 or higher atrial fibrillation that was symptomatic and/or incompletely controlled, study drug may have been restarted at either the original dose or dose level -1 per discretion of the investigator, after the atrial fibrillation was adequately controlled. Study drug was to be permanently discontinued for any intracranial hemorrhage.

Objectives & Outcomes/endpoints

The endpoints are defined as follows:

1. Overall response rate (ORR) is the proportion of patients whose best overall response was complete response (CR) or partial response (PR).
2. CR rate is the proportion of patients whose best overall response was CR.
3. Duration of response (DOR) is the time from the date of earliest response (CR or PR) to the date of first documented progressive disease or death from any cause, whichever occurred first.
4. Progression-free survival (PFS) is the time from initiation of zanubrutinib to the date of first documented progressive disease or death from any cause.
5. Time to response (TTR) is the time from initiation of zanubrutinib to the date of first documented response (CR or PR).
6. Time to treatment failure (TTF) is the time from initiation of zanubrutinib to discontinuation of study drug for any reason.
7. Time to next line of therapy is the time (months) from the first dose of zanubrutinib to the start of the first new therapy for MZL.
8. Overall survival is the time from initiation of zanubrutinib to the date of death from any cause.

Table 9 Efficacy objectives and endpoints

Study BGB-3111-214		Study BGB-3111-AU-003	
Efficacy objectives	**Efficacy endpoints [a]**	**Efficacy objectives**	**Efficacy endpoints [a, b]**
Primary			
To evaluate the efficacy of zanubrutinib in R/R MZL as measured by ORR by IRC based on Lugano Classification	ORR by IRC	To assess preliminary antitumour activity of zanubrutinib	ORR by IRC
Secondary			
To evaluate the efficacy of zanubrutinib in R/R MZL as measured by DOR, PFS, and TTR by IRC and investigator, ORR by investigator, ORR using PET in FDG-avid patients by IRC, OS, TTF and time to next line of therapy	DOR by IRC and investigator	To assess preliminary antitumour activity of zanubrutinib	CR rate by IRC and investigator
	PFS by IRC and investigator		DOR by IRC and investigator
	TTR by IRC and investigator		PFS by IRC and investigator
	ORR by investigator		TTR by IRC and investigator
	ORR using PET assessment in FDG-avid patients by IRC		
	OS		
	TTF		ORR by investigator
	Time to next line of therapy		OS
Exploratory			
To evaluate the efficacy of zanubrutinib in R/R MZL as measured by ORR by IRC using Cheson 1999 response criteria	ORR by IRC using Cheson 1999 response criteria	None	None

Source: BGB-3111-214 Clinical Study Report and Statistical Analysis Plan, Version 1 and BGB-3111-AU-003 Clinical Study Report and Statistical Analysis Plan, Version 1.
Abbreviations: CR, complete response rate; DOR, duration of response; FDG, fluorodeoxyglucose, IRC, Independent Review Committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PET, positron emission topography; PFS, progression-free survival; R/R, relapsed or refractory; TTR, time to response; TTF, Time to treatment failure.
[a] All primary and secondary efficacy endpoints were assessed according to the Lugano Classification (Cheson et al 2014).
[b] All patients with R/R MZL were enroled in Part 2.

For ORR, CR rate, DOR, PFS, and TTR, the primary analyses were performed according to the Lugano Classification (Cheson et al 2014). Patients with Independent Review Committee (IRC)-confirmed non-fluorodeoxyglucose (FDG)-avid disease were evaluated using the computed tomography (CT)-based criteria. Patients with IRC-confirmed FDG-avid disease who have both pre-treatment and postbaseline positron emission tomography (PET) scans were evaluated using the PET-based criteria. Measures were employed to ensure consistent and objective response assessment by the IRC. In patients with IRC-confirmed FDG-avid disease, target and nontarget lesions selected by the IRC must have been FDG-avid to ensure adequate and consistent evaluation of the tracked lesions. In addition, patients with histologic evidence of bone marrow and/or gastrointestinal (GI) tract involvement at baseline were required to have repeated bone marrow testing and/or endoscopy regardless of PET status to confirm CR. Response was downgraded to PR if no repeated testing was done or if retest showed persistent involvement of bone marrow and/or GI tract.

Sample size

Assuming a null hypothesized ORR of 30%, a sample size of 65 patients will provide 82% power for the alternative hypothesized ORR of 48%, at a 1-sided alpha level of 0.025 and using the exact binomial test. The alternative ORR is based on the observed IRC-assessed ORR for the ibrutinib study in R/R MZL (Noy et al 2017). For an observed ORR of 48% (31/65), the 95% exact binomial confidence interval is (35%, 60%).

Randomisation

This is a single-arm study.

Blinding (masking)

BGB-3111-214 is an ongoing open-label, single-arm, multicenter Phase 2 study of zanubrutinib in patients with MZL who were relapsed or refractory after ≥ 1 prior anti-CD20-based regimen. Efficacy outcomes were evaluated by an Independent Review Committee in accordance with the Lugano classification.

Statistical methods

Efficacy analysis sets

The Safety Analysis Set included all patients who were enrolled and received at least 1 dose of study drug. Summaries of safety, important protocol deviations, demographics and other baseline characteristics, disease history and characteristics, prior anticancer therapies, and medical history were performed using the Safety Analysis Set.

The Efficacy Analysis Set consisted of all patients in the Safety Analysis Set with a confirmed diagnosis of MZL. Efficacy analyses were performed using the Efficacy Analysis Set.

The efficacy analysis set includes all patient who were enrolled, received at least 1 dose of a study drug, and had an MZL confirmed diagnosis. According to the Intention to treat principle, all recruited patients regardless of their diagnosis and whether they received treatment should have been included in the primary efficacy population.

Primary endpoint: ORR by IRC

The point estimate and corresponding two-sided Clopper-Pearson 95% CI for ORR will be presented.

The best overall response is defined as the best response recorded from the start of zanubrutinib throughout the study. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders for the purposes of this analysis. The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no later than 12 months after the last patient received the first dose of study drug.

Secondary Efficacy Endpoints

ORR by Investigator and ORR using PET assessment in FDG-avid patients by IRC.

It will be analyzed using the same statistical methods as ORR by IRC.

PFS by IRC and PFS by Investigator

Kaplan-Meier methodology will be used to estimate the median and other quantiles of PFS. Two-sided 95% CIs of median and other quartiles, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer 1982; Klein 1997) with log-log transformation. PFS rates at selected landmark time points (e.g. 6-month) will be provided with corresponding 95% CIs calculated based on the Greenwood's formula (Kalbfleisch and Prentice 1980) with log-log transformation. The duration of the follow-up for PFS will be determined by reverse Kaplan-Meier method (Schemper 1996).

PFS will be right-censored based on rules provided. The PFS censoring rule will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018).

Table 10 Censoring rules for analysis of PFS

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline and/or post-baseline disease assessments	Date of the first dose	Censored
2	Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
3	Alive without documented disease progression at the time of data cut-off or withdrawal from study (including lost-to-follow-up without disease progression)	Date of last disease assessment	Censored
4	New anticancer treatment started before documented disease progression or death	Date of last disease assessment prior to date of new anticancer treatment	Censored
5	Death before first disease assessment	Date of death	Progressed
6	Death or progression after more than one missed scheduled disease assessment	Date of last disease assessment without documented disease progression before missed tumor assessments	Censored

OS

OS will be analyzed using the similar method as described for PFS.

Patients who remain alive before data cutoff or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the time of data cutoff or the last date the patient is known to be alive.

DOR by IRC and DOR by Investigator

The censoring rules for DOR will follow the PFS censoring rules. Kaplan-Meier methods will be used to estimate median and other quartiles and 95% CIs for DOR. Only responders will be included in this analysis.

Multiplicity Adjustment

Not applicable. A strategy for controlling the time 1 error due to multiple secondary endpoint was not implemented in the SAP. Therefore, the secondary endpoints are considered exploratory.

Interim analysis

No formal interim analyses are planned for this study. Data from the study will be reviewed by the study monitoring committee on a periodic basis. Summaries and analyses of subsets of the study data may be performed on a periodic basis for submission to professional meetings and for internal decision-making.

The MAH presented information about the efficacy analyses performed during the course of the study. The MAH performed two efficacy analyses after the last patient was recruited but before the protocol-specified primary analysis. Those analyses did not lead to changes to the study conduct.

Changes in the Planned Analyses

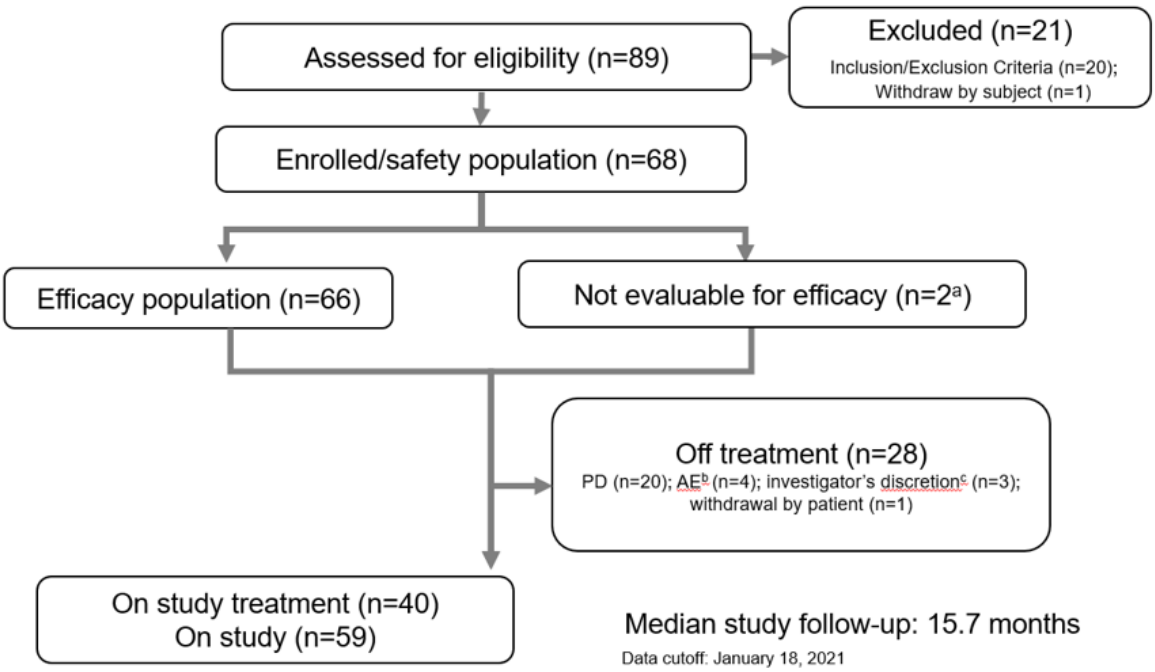
Per request from the US FDA, the definition of a treatment-emergent adverse event was updated to include any event that was associated with a current treatment-emergent adverse event and worsened to Grade 5 > 30 days after the last dose of study drug and prior to the initiation of new anticancer therapy. In addition, separate sensitivity analyses were performed for Independent Review Committee-assessed response based on CT assessments only per request from the US FDA.

The SAP dated 10 June 2020 is the only version of the SAP for this study.

Results

Participant flow

Figure 11 Participant flow



Abbreviations: AE, adverse event; MZL, marginal zone lymphoma; PD, progressive disease.

Source: Table 14.1.1.1.2

[a] Two patients were excluded due to lack of central confirmation of MZL.

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[1] Please note that the ASH abstract using data cutoff of 14 Apr 2020 before the signoff of the SAP was based on descriptive safety and efficacy data assessed by investigator, which happened before the statistical analysis on efficacy data assessed by IRC as specified in the SAP.

[b] Four patients discontinued due to AE (pyrexia later attributed to disease progression, n=1; fatal myocardial infarction in a patient with pre-existing cardiovascular disease, n=1; COVID-19 pneumonia leading to death, n=2). [c] Three patients discontinued per the investigator's discretion (requiring prohibited medications).

Recruitment

As of the data cutoff date of 18 January 2021, 68 patients from 31 clinical sites in 9 countries (Australia, China, Czech Republic, France, Italy, New Zealand, South Korea, the United Kingdom, and the United States [US]) were enroled in this ongoing study (*214*) and received at least 1 dose of study drug. The first patient was treated with zanubrutinib on 19 February 2019 and the last patient enroled received their first dose on 06 January 2020. Enrolment in the study is complete.

Study AU003:

Patients with MZL were enrolled in Part 2 of the study only. All 20 patients with MZL had relapsed/refractory disease and received at least 1 dose of study drug. As of the data cutoff date, 12 (60.0%) patients with MZL were continuing study drug treatment. Eight (40.0%) patients had

discontinued study drug, mostly due to disease progression (5 [25.0%] patients). Two (10.0%) patients withdrew consent, and 1 (5.0%) patient discontinued study drug due to adverse event.

Conduct of the study

Table 11 Major protocol amendments for study BGB 3111-214

Protocol Amendment	Approval Date	Major Changes
Amendment 1	August 2018	• For CT, PET, and disease-related constitutional symptom assessments, the first assessment was moved from Week 8 to Week 12. • Updated inclusion criteria o to ensure that patients with Waldenström macroglobulinemia were not included in this study o to ensure that all patients had either available archival tumor tissue or underwent a tumor biopsy o update definition of measurable disease to align with the Lugano classification criteria. • Updated to collect 12-lead ECG data only at screening and as clinically indicated.
Amendment 2	September 2019	• Updated inclusion criteria o list specific MZL symptoms dictating the need for systemic therapy o update contraception information for female patients of childbearing potential for consistency across BeiGene protocols and clarity. • Added to exclusion criteria: In France only, patients whose ejection fraction is < 45% should not enter the study.
Amendment 3	03 June 2020	• Extended the time window of the primary efficacy analysis to no later than 12 months (after the last patient received the first dose of study drug).

Baseline data

A comparison of patient disposition between studies BGB-3111-214 and BGB-3111-AU-003 is presented. BGB-3111-AU-003 has a longer follow-up as the study has been ongoing for approximately 6 years. The median duration of study follow-up was 35.24 months (range: 8.3, 59.2) in study BGB-3111-AU-003 versus 15.70 months (range: 1.6 to 21.9 months) in study BGB-3111-214. The percentage of patients continuing treatment was similar in both studies (study BGB-3111-214, 58.8% versus 60.0% in study BGB-3111-AU-003). More patients in study BGB-3111-214 versus study BGB-3111-AU-003 remained in the study (59 [86.8%] versus 15 [75.0%]) at the data cutoff date. Approximately 54% of patients were continuing treatment for more than 1 year in study BGB-3111-214. Approximately 60.0% of patients in study BGB-3111-AU-003 were continuing treatment for more than 2 years and 30% of patients for more than 3 years.

Table 12 Patient disposition (SAS)

Parameter	BGB-3111-214 (N = 68)	BGB-3111-AU-003 (N = 20)
Patients continuing study drug, n (%)	40 (58.8)	12 (60.0)
Patients discontinued from study drug, n (%)	28 (41.2)	8 (40.0)
Reason for discontinuation of study drug, n (%)		
Progressive disease [a]	20 (29.4)	5 (25.0)
Adverse event	4 (5.9)	1 (5.0)
Related to COVID-19	2 (2.9)	0 (0.0)
Physician discretion [b]	3 (4.4)	0 (0.0)
Withdrawal by patient	1 (1.5)	2 (10.0)
Patients discontinued from study, n (%)	9 (13.2)	5 (25.0)
Death	7 (10.3)	3 (15.0)
Related to COVID-19	2 (2.9)	0 (0.0)
Withdrawal by patient	2 (2.9)	1 (5.0)
Lost to follow-up	0 (0.0)	1 (5.0)
Patients continuing the study, n (%)	59 (86.8)	15 (75.0)
Study follow-up time (months)		
Mean (standard deviation)	15.32 (3.859)	35.19 (13.110)
Median (range)	15.70 (1.6, 21.9)	35.24 (8.3, 59.2)
Q1, Q3	13.83, 17.43	26.60, 40.23

Source: Table 2.7.3.1.1.
Note: All percentages were based on the number of patients treated. Study follow-up was defined as the time from the first dose date to the date of death or end-of-study date (whichever occurs first) for patients who either discontinued from the study or the database cutoff date for ongoing patients.
[a] Progressive disease and discontinuation of study drug as determined by the investigators.
[b] Patients requiring prohibited medications and were discontinued by the investigators.

Data-cutoff 04 May 2022

Table 13 Disposition and reasons for discontinuation:

	Zanubrutinib (N = 68)
Number of Patients Enrolled	68
Number of Patients Treated	68 (100.0)
Patients Discontinued from Treatment	68 (100.0)
Reason for Discontinuation	
Sponsor Decision to Roll Over to LTE Study	31 (45.6)
Progressive Disease	24 (35.3)
Adverse Event	5 (7.4)
Related to COVID-19	2 (2.9)
Physician Decision	4 (5.9)
Other	3 (4.4)
Study Terminated by Sponsor/Patients Not Rolling Over to LTE*	3 (4.4)
Withdrawal by Subject	1 (1.5)
Patients Remained on Treatment	0 (0.0)
Patients Discontinued from Study	68 (100.0)
Reason for Discontinuation	
Sponsor Decision to Roll Over to LTE Study	38 (55.9)
Death	13 (19.1)
Related to COVID-19	2 (2.9)
Study terminated by sponsor**	12 (17.6)
Withdrawal by Subject	3 (4.4)
Physician Decision	1 (1.5)
Other	1 (1.5)
Patient Declined to be Rolled-Over to BGB-3111-LTE1	1 (1.5)
Patients Remained in Study	0 (0.0)
Study Follow-up Time (months)	
n	68
Mean (SD)	25.463 (7.6464)
Median	28.041
Q1, Q3	24.854, 30.489
Min, Max	1.64, 32.89

Source: ADSL. Data cutoff: 04MAY2022. Data extraction: 31MAY2022.
Abbreviations: Max, maximum; Min, minimum; SD, standard deviation; LTE, long-term extension.
Study follow-up time is defined as the time from the first dose date to the death date or end of study date (whichever occurs first) for patients discontinued from the study, or the database cutoff date for ongoing patients.
All percentages are based on number of patients treated except the line of "Number of Patients Treated" with its percentage calculated based on number of patients enrolled.
* Including patients of "Study Terminated by Sponsor, Patient Not Rolling Over", "Study Terminated by Sponsor-Patient Not Rolling Over to LTE" and "Study Terminated by Sponsor-Patient Not Rolling Over".
** These patients did not roll over to BGB-3111-LTE1 study.

Table 14 Demographics and other Baseline characteristics

Parameter	BGB-3111-214 (N = 68)	BGB-3111-AU-003 (N = 20)
Sex, n (%)		
Male	36 (52.9)	10 (50.0)
Female	32 (47.1)	10 (50.0)
Race, n (%)		
White	41 (60.3)	15 (75.0)
Asian	13 (19.1)	4 (20.0)
Not reported/Unknown [a]	11 (16.2)	0 (0.0)
Multiple	2 (2.9)	0 (0.0)
Other	1 (1.5)	1 (5.0)
Geographic region, n (%)		
European Union	28 (41.2)	3 (15.0)
Oceania	21 (30.9)	12 (60.0)
Asia	12 (17.6)	4 (20.0)
North America	7 (10.3)	1 (5.0)
Age		
Mean (standard deviation)	67.9 (11.41)	69.5 (7.47)
Median	70.0	69.5
Range	37, 95	52, 85
Age Group n (%)		
< 65 years	27 (39.7)	4 (20.0)
≥ 65 to < 75 years	22 (32.4)	12 (60.0)
≥ 75 years	19 (27.9)	4 (20.0)
ECOG performance score, n (%)		
0	39 (57.4)	7 (35.0)
1	24 (35.3)	11 (55.0)
2	5 (7.4)	2 (10.0)

Source: Table 2.7.3.2.1.
Abbreviations: ECOG, Eastern Cooperative Oncology Group.
[a] Race unknown/not reported by site due to local privacy regulations.

Table 15 Baseline disease history characteristics (Safety Analysis Set)

Parameter	BGB-3111-214 (N = 68)	BGB-3111-AU-003 (N = 20)
Time from Initial Diagnosis of MZL to Study Entry (years)		
Mean (standard deviation)	6.74 (5.804)	6.44 (4.511)
Median	5.12	5.97
Range	0.2, 29.5	0.4, 17.2
Bulky Disease, n (%)		
≤ 5 cm	43 (63.2)	15 (75.0)
> 5 cm	25 (36.8)	5 (25.0)
MZL Subtype, n (%)		
Extranodal MZL of Mucosa-Associated Lymphoid Tissue (MALT)	26 (38.2)	9 (45.0)
Nodal Marginal Zone Lymphoma	26 (38.2)	5 (25.0)
Splenic Marginal Zone Lymphoma	12 (17.6)	6 (30.0)
Unknown [a]	4 (5.9)	0 (0.0)
Extranodal Disease at Study Entry, n (%) [b]	53 (77.9)	20 (100.0)
Bone Marrow Involvement, n (%) [c]	29 (42.6)	14 (70.0)
Disease Status to Last Prior Therapy, n (%) [d]		
Relapsed	44 (64.7)	15 (75.0)
Refractory	22 (32.4)	4 (20.0)
Unknown/Not Evaluable	2 (2.9)	1 (5.0)

Source: Table 2.7.3.2.2.
Abbreviations: MZL, marginal zone lymphoma.
Note: Baseline value is the last nonmissing value before first dose of zanubrutinib.
[a] Unknown subtypes in 4 patients who presented with both nodal and extranodal disease, thus the investigator was unable to classify MZL subtype.
[b] Extranodal disease was defined as patients with any target or non-target extranodal lesions at baseline or with baseline bone marrow involvement by biopsy/aspiration per investigator assessment.
[c] Derived from baseline bone marrow biopsy/aspiration per investigator assessment.
[d] Relapsed, complete or partial response to last prior anticancer regimen; refractory, stable or progressive disease to last prior anticancer regimen.

Table 16 Prior anti-cancer therapies (Safety Analysis Set)

Parameter	BGB-3111-214 (N = 68)	BGB-3111-AU-003 (N = 20)
Number of prior lines of therapy		
Mean (standard deviation)	2.0 (1.26)	1.9 (1.02)
Median (range)	2.0 (1, 6)	2.0 (1, 5)
Number of prior lines of therapy, n (%)		
1	31 (45.6)	8 (40.0)
2	18 (26.5)	8 (40.0)
3	10 (14.7)	3 (15.0)
4	6 (8.8)	0 (0.0)
5	1 (1.5)	1 (5.0)
≥ 6	2 (2.9)	0 (0.0)
Median time from end of last therapy to first study entry (months) (range)	20.62 (1.0, 176.6)	17.28 (1.9, 108.7)
Prior Radiotherapy, n (%)	15 (22.1)	1 (5.0)
Prior stem cell transplantation, n (%) [a]	4 (5.9)	0 (0.0)
Prior systemic regimens, n (%) [b]	68 (100.0)	20 (100.0)
Rituximab-based Chemotherapy	67 (98.5)	19 (95.0)
Alkylating Agents	58 (85.3)	4 (20.0)
R-CVP	25 (36.8)	13 (65.0)
BR	22 (32.4)	4 (20.0)
R-CHOP	17 (25.0)	4 (20.0)
Rituximab Mono Therapy	15 (22.1)	4 (20.0)
R-chlorambucil	5 (7.4)	0 (0.0)
CHOP	4 (5.9)	1 (5.0)
CVP	3 (4.4)	1 (5.0)
R-fludarabine-mitoxantrone	3 (4.4)	1 (5.0)
Chlorambucil	2 (2.9)	0 (0.0)
R-lenalidomide	2 (2.9)	0 (0.0)

Source: Table 2.7.3.2.3.

Abbreviations: BR, bendamustine + rituximab; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; CRF, case report form; CVP, cyclophosphamide + vincristine + prednisone; MZL, marginal zone lymphoma; R, rituximab; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisone.

Note: Prior anticancer regimens do not include radiotherapy. The number of prior anticancer regimens is considered 0 for patients without any record of prior systemic anticancer regimens.

[a] Based on medical review of prior anticancer therapies received and prior anticancer drug therapies CRF for MZL patients in BGB-3111-AU-003.

[b] Categories are not mutually exclusive, and a patient may be summarized with multiple regimens.

Numbers analysed

The number (percentage) of patients included in each analysis set is presented below. Two patients were excluded from the Efficacy Analysis Set because the central pathology results showed histologic transformation to diffuse large B-cell lymphoma. Patient enrolment was based on the local pathology results. Central pathology review was not required before enrolment.

Table 17 Analysis Sets

	N = 68 **n (%)**
Safety Analysis Set	68 (100)
Efficacy Analysis Set	66 (97.1)
Pharmacokinetic Analysis Set	68 (100)

Outcomes and estimation

Updated efficacy results of the pivotal study BGB-3111-214 with a data cutoff date of 04 May 2022. The updated data represents approximately 15.5 months of additional follow-up from the initial data cut on 18 January 2021.

Table 18 Study BGB-3111-214 Updated Efficacy results by IRC

Efficacy results	**BGB-3111-214 (DCO 4 May 2022)** Updated results	**BGB-3111-214 (DCO 18 Jan 2021)** Initial submission	**BGB-3111-AU-003 (DCO 2 Oct 2020)** Initial submission
Overall Response Rate by IRC, n (%), [95% CI]	45 (68.2) (55.56, 79.11)	45 (68.2) (55.56, 79.11)	16 (80) (56.3, 94.3)
Complete Response	17 (25.8)	17 (25.8)	4 (20.0)
Partial Response	28 (42.4)	28 (42.4)	12 (60.0)
Overall Response rate by MZL Subtype, n (%) Extranodal Nodal Splenic Unknown	 16/25 (64.0) 19/25 (76.0) 8/12 (66.7) 2/4 (50.0)	 16/25 (64.0) 19/25 (76.0) 8/12 (66.7) 2/4 (50)	 8/9 (88.9) 5/5 (100) 3/6 (50.0) -
Median Study Follow-up (range), months[1]	28.04 (1.64, 32.89)	15.7 (1.6, 21.9)	35.2 (8.3, 59.2)
Duration of Response (DOR) by IRC			
Median DOR follow-up time (range), months	23.4 (2.7, 25.8)	8.31 (0.03, 14.75)	31.4 (2.7, 55.5)
Median DOR[2] (95% CI), months	NE (25.00, NE)	Not Reached (95% CI: NE to NE)	Not Reached (95% CI: 8.4 to NE)

Efficacy results	BGB-3111-214 (DCO 4 May 2022) Updated results	BGB-3111-214 (DCO 18 Jan 2021) Initial submission	BGB-3111-AU-003 (DCO 2 Oct 2020) Initial submission
DOR Event-free rate (%) at[3]			
6 Months (95% CI)	93.3 (80.74, 97.80)	93.0 (79.8, 97.7)	87.5 (58.6, 96.7)
12 Months (95% CI)	93.3 (80.74, 97.80)	93.0 (79.8, 97.7)	71.6 (40.3, 88.4)
15 Months (95% CI)	83.5 (68.43, 91.79)	NE (NE, NE)	71.6 (40.3, 88.4)
18 Months (95% CI)	83.5 (68.43, 91.79)	NE (NE, NE)	71.6 (40.3, 88.4)
24 Months (95% CI)	72.9 (54.42, 84.90)	NE (NE, NE)	71.6 (40.3, 88.4)
30 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	71.6 (40.3, 88.4)
36 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	71.6 (40.3, 88.4)
Progression-free Survival (PFS) by IRC			
Median PFS follow-up time (range), months	27.4 (0.0, 28.7)	11.14 (0.03, 16.92)	33.8 (4.1, 58.3)
Median PFS[2] (95% CI), months	NE (27.56, NE)	NE (NE, NE)	NE (20.3, NE)
Progression/death event-free rate (%) at[3]			
6 Months (95% CI)	82.7 (70.96, 90.05)	84.4 (72.95, 91.30)	90.0 (65.6, 97.4)
12 Months (95% CI)	82.7 (70.96, 90.05)	82.5 (70.55, 89.93)	84.0 (57.9, 94.6)
15 Months (95% CI)	82.7 (70.96, 90.05)	82.5 (70.55, 89.93)	84.0 (57.9, 94.6)
18 Months (95% CI)	73.0 (59.55, 82.62)	NE (NE, NE)	78.0 (51.2, 91.2)
24 Months (95% CI)	70.9 (57.20, 80.95)	NE (NE, NE)	72.0 (45.0, 87.4)
30 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	72.0 (45.0, 87.4)
36 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	72.0 (45.0, 87.4)

Source: BGB-3111-214 CSR efficacy addendum, Table 14.1.1.1 , Table 14.2.1.2.7, Table 14.2.1.2.10 and Table 14.2.1.2.11; efficacy results provided in initial MZL submission: SCE Tables 4, 9 10, 11 for study 214 and Tables 19, 24, 25, 26 for study AU003; CI, confidence interval; NE, non-estimable.

[1] Study follow-up time was defined as the time from the first dose date to the death date or end of study date (whichever occurred first) for patients who discontinued from the study, or the database cutoff date for ongoing patients.

[2] Median was estimated by Kaplan-Meier method (95% confidence interval) estimated with Brookmeyer and Crowley method (1982).

[3] Event-free rates were estimated by Kaplan-Meier method (95% confidence interval) using Greenwood's formula.

Primary endpoint: Overall response rate (ORR)

A comparison of the IRC-assessed ORR for studies BGB-3111-214 and BGB-3111-AU-003 is presented.

BGB-3111-214 and BGB-3111-AU-003 enrolled patients with similar baseline characteristics. Patient's age, gender, ECOG status, MZL subtypes, number, and nature of prior lines of therapies were comparable between the studies. Of note, in study BGB-3111-214, 5 (7.6%) of patients with stable disease were continuing on study treatment.

ORR by IRC for study 214 was 45/66 (68.2%) with a CR of 25.8%, The ORR of 68.2% ruled out the prespecified null hypothesis of 30% with an exact 1-sided p-value <0.0001. Overall response rate was defined as the proportion of patients who achieved a best overall response of PR or CR as determined by an Independent Review Committee in accordance with the Lugano classification.

ORR by IRC was a secondary endpoint for study AU003; the results are presented here as they are considered supportive of the results from the pivotal study 214. No prespecified null hypothesis exists for this study.

Secondary endpoints:

ORR by Investigator

Table 19 Concordance of ORR by IRC and by Investigator based on Lugano classification (Cheson et al 2014) Efficacy Analysis Set

	Zanubrutinib (N = 66)		
	IRC assessment: ORR (yes/no)		
	Yes	No	Total
Investigator assessment: ORR (yes/no)			
Yes	43 (65.2)	6 (9.1)	49 (74.2)
No	2 (3.0)	15 (22.7)	17 (25.8)
Total	45 (68.2)	21 (31.8)	66 (100.0)
Concordance rate [a]			58/66 (87.9%)

Source: ADSL,ADRS,ADRSIRC. Data cutoff: 18JAN2021. Data extraction: ~~05FEB20~~21.
Abbreviations: IRC, independent review committee.
Percentages are based on N.
Overall Response Rate is defined as the proportion of patients who achieved at least a best overall response of PR or better.
[a] Concordance rate is defined as the proportion of patients with same assessments based on both methods

Duration of response (DOR)

CCOD 18 Jan 2021:

Table 20 IRC-assessed Duration of response (Efficacy Analysis set)

Parameter	BGB-3111-214 (N = 66)	BGB-3111-AU-003 (N = 20)
Duration of response (months) [a]		
Number of responders	45 (68.2)	16 (80.0)
Events, n (%)	5 (11.1)	4 (25.0)
Progressive disease	3 (6.7)	3 (18.8)
Death	2 (4.4)	1 (6.3)
Censored, n (%)	40 (88.9)	12 (75.0)
No documented disease progression or death	39 (86.7)	11 (68.8)
Progressive disease/death after non protocol anticancer therapy	1 (2.2)	0 (0.0)
No documented progressive disease/death: Withdrew consent/lost to follow-up	0 (0.0)	1 (6.3)
Follow-up (months) [b]		
Median (95% confidence interval)	8.31 (8.18, 13.50)	31.44 (5.52, 36.76)
Range	(0.03, 14.75)	(2.66, 55.52)
Duration of response (months) [c]		
Median (95% confidence interval)	NE (NE, NE)	NE (8.4, NE)
Range	(0.03+, 14.75+)	(2.66, 55.52+)
Progression/death event-free rate at [d]		
6 months (95% confidence interval)	93.0 (79.8, 97.7)	87.5 (58.6, 96.7)
9 months (95% confidence interval)	93.0 (79.8, 97.7)	79.5 (48.6, 93.0)
12 months (95% confidence interval)	93.0 (79.8, 97.7)	71.6 (40.3, 88.4)
15 months (95% confidence interval)	NE (NE, NE)	71.6 (40.3, 88.4)
18 months (95% confidence interval)	NE (NE, NE)	71.6 (40.3, 88.4)
24 months (95% confidence interval)	NE (NE, NE)	71.6 (40.3, 88.4)
30 months (95% confidence interval)	NE (NE, NE)	71.6 (40.3, 88.4)
36 months (95% confidence interval)	NE (NE, NE)	71.6 (40.3, 88.4)

Abbreviations: +, censored; IRC, Independent Review Committee; NE, not estimable.
[a] Duration of response was summarized for responders only (patients with a best overall response of partial response or above). Percentages were calculated based on the number of responders.
[b] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[c] Median was estimated by Kaplan-Meier method (95% confidence interval) estimated by Brookmeyer and Crowley method (1982).
[d] Event-free rates were estimated by Kaplan-Meier method (95% confidence interval) using Greenwood's formula.

Duration of response as assessed by the Independent Review Committee is summarized and displayed in a Kaplan-Meier plot below (CCOD 04 May 2022).

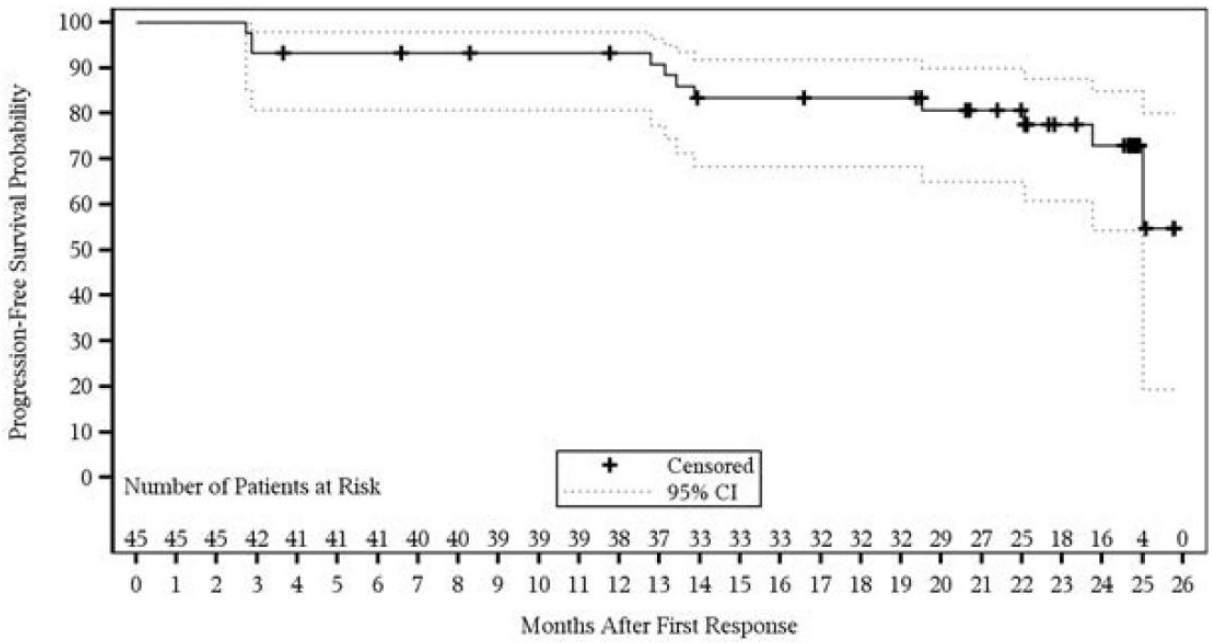
Table 21 Analysis of Duration of response by MZL subtype based on the Lugano Classification (Cheson et al 2014) – Efficacy Analysis set

	Zanubrutinib (N = 66)				
Response Category	**MALT (N = 25)**	**NMZL (N = 25)**	**SMZL (N = 12)**	**Unknown (N = 4)**	**Total (N = 66)**
Duration of Response					
Number of Responders, n (%)	16 (64.0)	19 (76.0)	8 (66.7)	2 (50.0)	45 (68.2)
Events, n (%)	3 (18.8)	4 (21.1)	3 (37.5)	1 (50.0)	11 (24.4)
Progressive disease	2 (12.5)	2 (10.5)	3 (37.5)	1 (50.0)	8 (17.8)
Death	1 (6.3)	2 (10.5)	0 (0.0)	0 (0.0)	3 (6.7)
Censored, n (%)	13 (81.3)	15 (78.9)	5 (62.5)	1 (50.0)	34 (75.6)
No documented progressive disease/death	13 (81.3)	14 (73.7)	5 (62.5)	1 (50.0)	33 (73.3)
Progressive disease/death after non-protocol anti-cancer therapy	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (2.2)

	Zanubrutinib (N = 66)				
Response Category	**MALT (N = 25)**	**NMZL (N = 25)**	**SMZL (N = 12)**	**Unknown (N = 4)**	**Total (N = 66)**
Follow-up Time (months) [a]					
Median (95% CI)	24.7 (20.60, 24.84)	22.8 (21.98, 24.71)	19.5 (16.59, 22.11)	25.8 (NE, NE)	23.4 (22.08, 24.71)
(Min, Max)	(6.6, 25.1)	(2.9, 25.8)	(2.7, 22.1)	(25.0, 25.8)	(2.7, 25.8)
DOR (months) [b]					
Median (95% CI)	NE (22.08, NE)	NE (NE, NE)	NE (2.73, NE)	NE (25.00, NE)	NE (25.00, NE)
Q1 (95% CI)	23.8 (19.52, NE)	NE (2.86, NE)	8.0 (2.73, NE)	25.0 (25.00, NE)	23.8 (13.14, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (13.14, NE)	NE (25.00, NE)	NE (25.00, NE)
Range	(6.6+, 25.1+)	(2.9, 25.8+)	(2.7, 22.1+)	(25.0, 25.8+)	(2.7, 25.8+)
Event-free Rate at, % (95% CI) [c]					
3 Months	100.0 (NE, NE)	94.7 (68.12, 99.24)	75.0 (31.48, 93.09)	100.0 (NE, NE)	93.3 (80.74, 97.80)
6 Months	100.0 (NE, NE)	94.7 (68.12, 99.24)	75.0 (31.48, 93.09)	100.0 (NE, NE)	93.3 (80.74, 97.80)
9 Months	100.0 (NE, NE)	94.7 (68.12, 99.24)	75.0 (31.48, 93.09)	100.0 (NE, NE)	93.3 (80.74, 97.80)
12 Months	100.0 (NE, NE)	94.7 (68.12, 99.24)	75.0 (31.48, 93.09)	100.0 (NE, NE)	93.3 (80.74, 97.80)
15 Months	100.0 (NE, NE)	78.0 (51.48, 91.14)	62.5 (22.93, 86.07)	100.0 (NE, NE)	83.5 (68.43, 91.79)
18 Months	100.0 (NE, NE)	78.0 (51.48, 91.14)	62.5 (22.93, 86.07)	100.0 (NE, NE)	83.5 (68.43, 91.79)
24 Months	74.6 (39.76, 91.10)	78.0 (51.48, 91.14)	NE (NE, NE)	100.0 (NE, NE)	72.9 (54.42, 84.90)
30 Months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Source: ADSL,ADRSIRC,ADTTEIRC. Data cutoff: 04MAY2022. Data extraction: 31MAY2022.
Abbreviations: CI, confidence interval; DOR, duration of response; IRC, Independent Review Committee; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; Max, maximum; Min, minimum; MZL, marginal zone lymphoma; NE, not estimable; NMZL, nodal marginal zone lymphoma; Q1, first quartile; Q3, third quartile. SMZL, splenic marginal zone lymphoma.
Percentages are based on patients with best overall response of at least PR for each MZL subtype or total except for Number of responders.
DOR for responders (CR or PR) is defined as the time from the date of the earliest qualifying response (PR or better) to the date of PD or death for any cause, whichever occurs earlier.
[a] Median follow-up time is estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Figure 12 Kaplan-Meier plot of DOR by IRC based on Lugano classification (Efficacy Analysis Set)



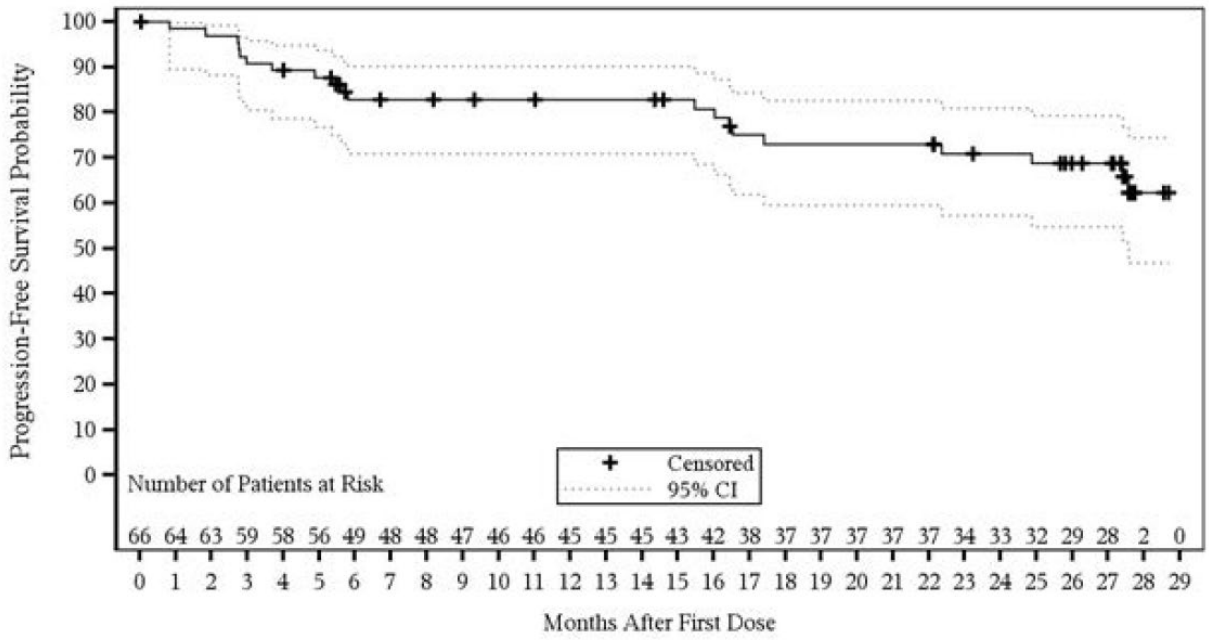
Source: ADSL,ADTTEIRC. Data cutoff: 04MAY2022. Data extraction: 31MAY2022.
Abbreviation: CI, confidence interval; IRC, Independent Review Committee.
Note: Confidence intervals were calculated using a generalized Brookmeyer and Crowley method.
Only patients with either PR or CR are included.

Progression-free survival (PFS)

After a median follow-up time for PFS of 27.4 months (range: 0.0 to 28.7 months; CCOD 04 May 2022) for study BGB-3111-214 and 33.77 months (range: 4.11 to 58.28 months) for study BGB-3111-AU-003, the median PFS was not reached in either study.

Updated progression-free survival (PFS) as assessed by the Independent Review Committee is summarized and displayed in a Kaplan-Meier plot below (CCOD 04 May 2022).

Figure 13 Kaplan-Meier plot of PFS by IRC based on Lugano classification (Efficacy Analysis Set)



Source: ADSL,ADTTEIRC. Data cutoff: 04MAY2022. Data extraction: 31MAY2022.
Abbreviation: CI, confidence interval; IRC, Independent Review Committee.
Note: Confidence intervals were calculated using a generalized Brookmeyer and Crowley method.

Time-to-response (TTR)

Table 22 Study BGB-3111-214: IRC – assessed Time to response (Efficacy Analysis Set)

	N = 66
Time to response (months)	
N	45
Mean (standard deviation)	3.47 (1.606)
Median	2.79
Range	1.7, 11.1
Time to complete response (months)	
N	17
Mean (standard deviation)	4.57 (3.592)
Median	2.86
Q1, Q3	2.79, 5.32
Range	2.6, 16.9

Source: BGB-3111-214 clinical study report Table 14.2.1.2.7.
Abbreviations: IRC, Independent Review Committee
Note: Time to response was summarized for responders only (patients with a best overall response of partial response or above).

Table 23 Study BGB-3111-AU-003: IRC -assessed time to response

	N = 20
Time to response (months)	
N	16
Mean (standard deviation)	6.3 (6.81)
Median	2.8
Range	2.6, 23.1

Source: BGB-3111-AU-003 clinical study report Table 14.2.1.1.1.
Abbreviations: IRC, Independent Review Committee.
Note: Time to response was summarized for responders (patients with a best overall response of partial response or above).

Overall survival (OS)

Table 24 Summary of Overall Survival (Efficacy Analysis set)

Parameter	**BGB-3111-214 (N = 66)**	**BGB-3111-AU-003 (N = 20)**
Overall Survival		
Deaths, (n %)	6 (9.1)	3 (15.0)
Alive, n (%)	60 (90.9)	17 (85.0)
Follow-up time (months) [a]		
Median (95% confidence interval)	14.06 (13.83, 15.44)	35.48 (32.13, 39.39)
Range	(1.6, 21.0)	(8.3, 58.3)
Overall Survival (months) [b]		
Median (95% confidence interval)	NE (NE, NE)	NE (NE, NE)
Range	1.6^{+}, 21.0^{+}	(8.3^{+}, 58.3^{+})
Event-free rate [c]		
6 months (95% confidence interval)	96.9 (88.3, 99.2)	100.0 (NE, NE)
9 months (95% confidence interval)	96.9 (88.3, 99.2)	100.0 (NE, NE)
12 months (95% confidence interval)	95.3 (86.0, 98.4)	100.0 (NE, NE)
15 months (95% confidence interval)	92.9 (81.9, 97.3)	100.0 (NE, NE)
18 months (95% confidence interval)	84.8 (67.1, 93.5)	100.0 (NE, NE)
24 months (95% confidence interval)	NE (NE, NE)	83.9 (57.9, 94.5)
30 months (95% confidence interval)	NE (NE, NE)	83.9 (57.9, 94.5)
36 months (95% confidence interval)	NE (NE, NE)	83.9 (57.9, 94.5)

Source: Table 2.7.3.3.5.1.
Abbreviations: +, censored; NE, not estimable.
Note: Percentages are based on N.
[a] Median follow-up time was estimated by reverse Kaplan-Meier method.
[b] Median was estimated by Kaplan-Meier method with 95% confidence interval using the Brookmeyer and Crowley method (1982).
[c] Event-free rates were estimated by Kaplan-Meier method with 95% confidence interval using the Greenwood formula.

Updated overall survival for study 214 including MZL subtypes is summarized:

Table 25 Analysis of Overall Survival by MZL subtype (Efficacy Analysis Set)

	Zanubrutinib (N = 66)				
	MALT (N = 25)	**NMZL (N = 25)**	**SMZL (N = 12)**	**Unknown (N = 4)**	**Total (N = 66)**
Overall Survival					
Events, n (%)	5 (20.0)	5 (20.0)	1 (8.3)	1 (25.0)	12 (18.2)
Death	5 (20.0)	5 (20.0)	1 (8.3)	1 (25.0)	12 (18.2)
Censored, n (%)	20 (80.0)	20 (80.0)	11 (91.7)	3 (75.0)	54 (81.8)
Alive	20 (80.0)	20 (80.0)	11 (91.7)	3 (75.0)	54 (81.8)
Follow-up Time (months) [a]					
Median (95% CI)	30.6 (27.63, 30.82)	28.6 (27.43, 29.80)	27.6 (24.41, 29.11)	28.6 (10.22, 30.59)	28.7 (27.79, 30.36)
(Min, Max)	(1.6, 32.9)	(10.3, 32.2)	(13.8, 32.1)	(3.6, 30.6)	(1.6, 32.9)
OS (months) [b]					
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (3.58, NE)	NE (NE, NE)
Q1 (95% CI)	NE (2.79, NE)	NE (10.28, NE)	NE (13.83, NE)	NE (3.58, NE)	NE (19.58, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (3.58, NE)	NE (NE, NE)
Range	(1.6+ ,32.9+)	(10.3 ,32.2+)	(13.8 ,32.1+)	(3.6 ,30.6+)	(1.6+ ,32.9+)

	Zanubrutinib (N = 66)				
	MALT (N = 25)	**NMZL (N = 25)**	**SMZL (N = 12)**	**Unknown (N = 4)**	**Total (N = 66)**
Event-free Rate at, % (95% CI) [c]					
3 Months	95.8 (73.92, 99.40)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	98.5 (89.58, 99.78)
6 Months	95.8 (73.92, 99.40)	100.0 (NE, NE)	100.0 (NE, NE)	75.0 (12.79, 96.05)	96.9 (88.25, 99.22)
9 Months	95.8 (73.92, 99.40)	100.0 (NE, NE)	100.0 (NE, NE)	75.0 (12.79, 96.05)	96.9 (88.25, 99.22)
12 Months	95.8 (73.92, 99.40)	96.0 (74.84, 99.43)	100.0 (NE, NE)	75.0 (12.79, 96.05)	95.4 (86.30, 98.48)
15 Months	95.8 (73.92, 99.40)	96.0 (74.84, 99.43)	91.7 (53.90, 98.78)	75.0 (12.79, 96.05)	93.8 (84.31, 97.63)
18 Months	91.7 (70.61, 97.85)	84.0 (62.81, 93.67)	91.7 (53.90, 98.78)	75.0 (12.79, 96.05)	87.5 (76.58, 93.55)
24 Months	91.7 (70.61, 97.85)	80.0 (58.44, 91.15)	91.7 (53.90, 98.78)	75.0 (12.79, 96.05)	85.9 (74.69, 92.42)
30 Months	77.9 (54.73, 90.19)	80.0 (58.44, 91.15)	91.7 (53.90, 98.78)	75.0 (12.79, 96.05)	80.6 (68.26, 88.50)

Source: ADSL,ADTTE. Data cutoff: 04MAY2022. Data extraction: 31MAY2022.
Abbreviations: CI, confidence interval; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; Max, maximum; Min, minimum; MZL, marginal zone lymphoma; NE, Not Estimable; OS, overall survival; Q1, first quartile; Q3, third quartile; NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma.
Percentages are based on N for each MZL subtype or total.
OS is defined as the time from study treatment start to death due to any cause.
[a] Median follow-up time is estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

As a strategy for controlling the time 1 error due to multiple secondary endpoint was not implemented, the secondary endpoints are considered exploratory.

The MAH has provided updated results from the pivotal study BGB-3111-214 supporting the extension of indication to R/R MZL. While the observed CR rate of 25.8% is not particularly high, an ORR of 68.2% in an indolent disease such as MZL with a median follow-up time for DOR of almost 2 years and median DOR not reached (72.9% at 24 months) could be regarded as promising taking into account the single arm design of the study. Thus, results from the ongoing phase 3 study should provide additional data on time-to-event endpoints to further confirm the observed efficacy results from the pivotal study BGB-3111-214.

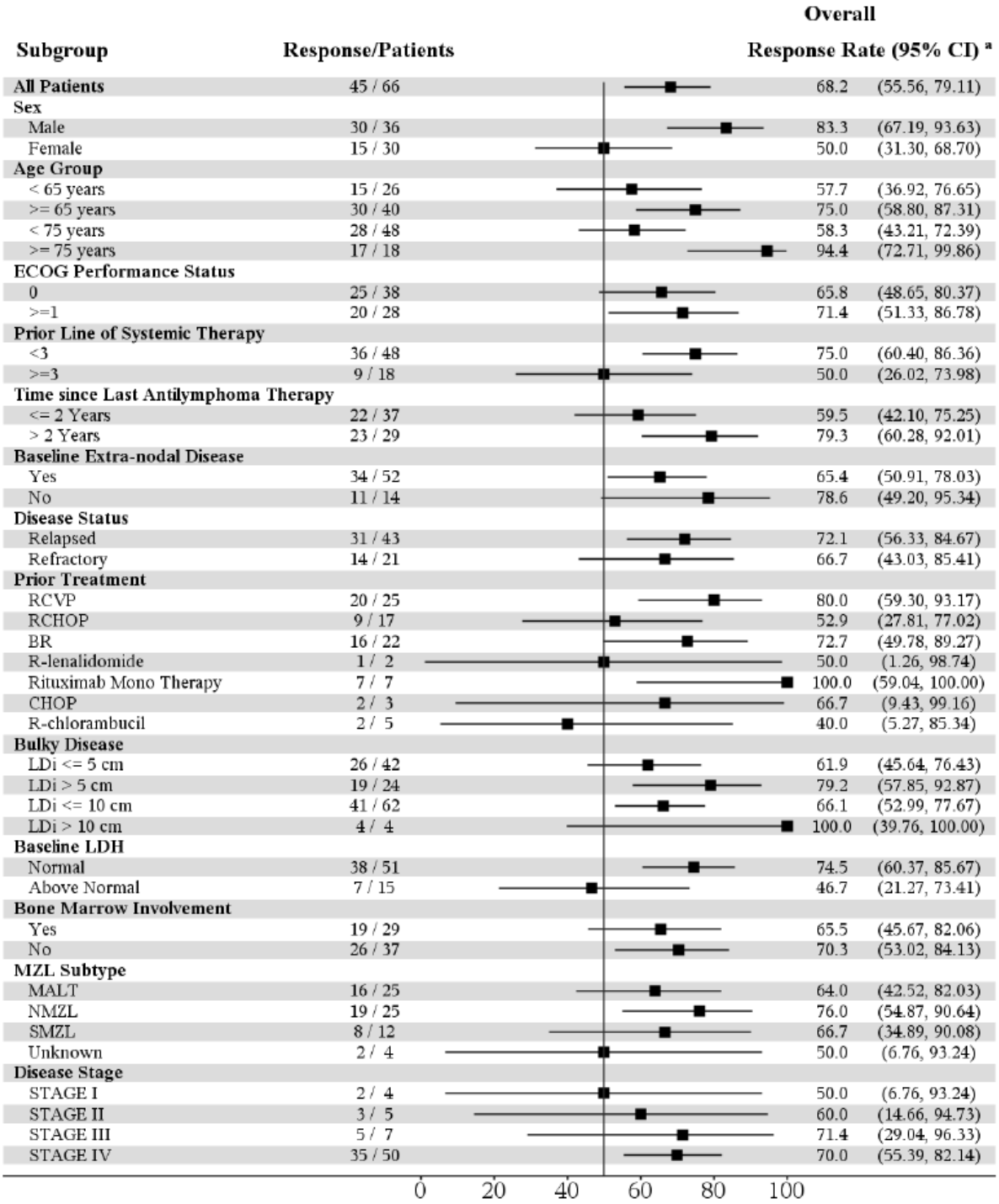
Response was rapid in both studies with a similar median TTR (2.79 versus 2.8 months) in study 214 and study AU003, respectively.

Ancillary analyses

Primary and selected secondary endpoints were summarized descriptively for baseline demographic and disease characteristic subgroups listed in the Statistical Analysis Plan when there was a sufficient number of patients, otherwise relevant subgroups could have been combined. These included: sex, age group (< 65 versus ≥ 65 years), ECOG performance status (0 versus ≥ 1), prior line of therapy for MZL (< 3 versus ≥ 3), and MZL subtypes. Within-group summary statistics (eg. overall response rate and medians for PFS, duration of response and their 95% CIs) were presented in forest plots. The subgroup variables and/or the cutoff values were subject to change if warranted to better represent the data.

A forest plot for IRC-assessed ORR by subgroup is presented below.

Figure 14 Forest plot for IRC-assessed ORR– based on Lugano classification (Efficacy Analysis Set)



Source: ADSL, ADBASE, ADRSIRC. Data cutoff: 04MAY2022. Data extraction: 31MAY2022.Abbreviations: BR, bendamustine + rituximab; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; LDH, lactate dehydrogenase; LDi, longest transverse diameter; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; R, rituximab; RCHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; RCVP, rituximab + cyclophosphamide + vincristine + prednisone; SMZL, splenic marginal zone lymphoma.
[a]2-sided Clopper-Pearson 95% confidence intervals for Overall Response Rate.

High ORR was observed in both studies for the extranodal, nodal and splenic subtypes (study BGB-3111-214: 64%, 76%, and 66.7% versus study BGB-3111-AU-003: 88.9%, 100.0% and 50.0%, respectively).

Table 26 Analysis of disease response by IRC and by MZL subtype (Efficacy Analysis set)

	BGB-3111-214 (N = 66)				BGB-3111-AU-003 (N = 20)		
	Extranodal (MALT) (N = 25)	NMZL (N = 25)	SMZL (N = 12)	Unknown [e] (N = 4)	Extranodal (MALT) (N = 9)	NMZL (N = 5)	SMZL (N = 6)
Best Overall Response, n (%)							
Complete Response	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	1 (11.1) [a]	3 (60.0) [a]	0 (0.0)
Partial Response	6 (24.0)	14 (56.0)	7 (58.3)	1 (25.0)	7 (77.8)	2 (40.0)	3 (50.0)
Stable Disease	4 (16.0)	5 (20.0)	3 (25.0)	1 (25.0)	1 (11.1)	0 (0.0)	1 (16.7)
Progressive Disease	3 (12.0)	1 (4.0)	1 (8.3)	1 (25.0)	0 (0.0)	0 (0.0)	1 (16.7)
Non-Evaluable [b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Non-Progressive Disease [c]	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued Before First Assessment	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Overall Response Rate, n (%)	16 (64.0)	19 (76.0)	8 (66.7)	2 (50.0)	8 (88.9)	5 (100.0)	3 (50.0)
(95% confidence interval) [d]	(42.52, 82.03)	(54.87, 90.64)	(34.89, 90.08)	(6.76, 93.24)	(51.75, 99.72)	(47.82, 100.00)	(11.81, 88.19)
Complete Response Rate, n (%)	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	1 (11.1)	3 (60.0)	0 (0.0)
(95% confidence interval) [d]	(21.13, 61.33)	(6.83, 40.70)	(0.21, 38.48)	(0.63, 80.59)	(0.28, 48.25)	(14.66, 94.73)	(0.00, 45.93)

Source: BGB-3111-214 clinical study report, Table 14.2.1.2.7 and BGB-3111-AU-003 clinical study report, Table 14.2.1.1.1.
Abbreviations, CT, computed tomography; FDG, fluorodeoxyglucose; IRC, Independent Review Committee; MALT, Mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; PET, positron emission tomography; SMZL, splenic MZL

[a] Only CT scans were mandated, and PET scans (n = 4) were performed only at the investigator's discretion.
[b] For Patient S4208-2-308, the IRC reported no measurable disease, and only splenomegaly was present. Per the IRC charter, if there was no measurable disease, then an assessment of not evaluable was reported.
[c] One patient with FDG-avid disease missed the PET scan at Cycle 3 and was assessed as having non-progressive disease by independent review due to missing PET scan. CT scan results showed stable disease at Cycle 3.
[d] Two-sided Clopper-Pearson 95% confidence interval.
[e] Unknown subtypes in 4 patients who presented with both nodal and extranodal disease, thus the investigator was unable to classify MZL subtype.

Table 27 Study BGB 3111-214 IRC-Assessed responses based on Lugano classification in patients with 1 or 2 prior therapies (Efficacy Analysis set)

Response category	1 Prior Therapy (N = 30)[a]	2 Prior Therapies (N = 18)	1 or 2 Prior Therapies (N = 48)	Total (N = 66)
Best overall response, n (%)				
Complete response	9 (30.0)	6 (33.3)	15 (31.3)	17 (25.8)
Partial response	15 (50.0)	6 (33.3)	21 (43.8)	28 (42.4)
Stable disease	4 (13.3)	2 (11.1)	6 (12.5)	13 (9.7)
Progressive disease	2 (6.7)	3 (16.7)	5 (10.4)	6 (9.1)
Non-Progressive disease	0 (0.0)	1 (5.6)	1 (2.1)	1 (1.5)
Discontinued study before first assessment	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)
Overall response rate, n (%)	24 (80.0)	12 (66.7)	36 (75.0)	45 (68.2)
95% CI [b]	(61.43, 92.29)	(40.99, 86.66)	(60.40, 86.36)	(55.56, 79.11)

Source: Table 14.2.1.2.1.1 Data cutoff: 18JAN2021. Data extraction: 05FEB2021.

Abbreviations: IRC, independent review committee; CI, confidence interval; Percentages are based on N.

Overall Response Rate is defined as the proportion of patients who achieved at least a best overall response of PR or better. Only responders are included in the analysis.

a In the Efficacy Analysis Set (N=66), 30 patients had 1 prior therapy, while in the Safety Analysis Set (N=68) 31 patients had 1 prior therapy;

b 2-sided Clopper-Pearson 95% CI.

Updated efficacy results of the pivotal study BGB-3111-214

The updated data with a data cutoff date of 04 May 2022 represents approximately 15.5 months of additional follow-up from the initial data cut on 18 January 2021.

Table 28 ***Study BGB-3111-214: Update Efficacy Results Assessed by IRC (Efficacy Analysis Set)***

Efficacy results	BGB-3111-214 (DCO 4 May 2022) Updated results	BGB-3111-214 (DCO 18 Jan 2021) Initial submission	BGB-3111-AU-003 (DCO 2 Oct 2020) Initial submission
Overall Response Rate by IRC, n (%), [95% CI]	45 (68.2) (55.56, 79.11)	45 (68.2) (55.56, 79.11)	16 (80) (56.3, 94.3)
Complete Response	17 (25.8)	17 (25.8)	4 (20.0)
Partial Response	28 (42.4)	28 (42.4)	12 (60.0)
Overall Response rate by MZL Subtype, n (%) Extranodal Nodal Splenic Unknown	 16/25 (64.0) 19/25 (76.0) 8/12 (66.7) 2/4 (50.0)	 16/25 (64.0) 19/25 (76.0) 8/12 (66.7) 2/4 (50)	 8/9 (88.9) 5/5 (100) 3/6 (50.0) -
Median Study Follow-up (range), months[1]	28.04 (1.64, 32.89)	15.7 (1.6, 21.9)	35.2 (8.3, 59.2)
Duration of Response (DOR) by IRC			

Median DOR follow-up time (range), months	23.4 (2.7, 25.8)	8.31 (0.03, 14.75)	31.4 (2.7, 55.5)
Median DOR[2] (95% CI), months	NE (25.00, NE)	Not Reached (95% CI: NE to NE)	Not Reached (95% CI: 8.4 to NE)
DOR Event-free rate (%) at[3]			
6 Months (95% CI)	93.3 (80.74, 97.80)	93.0 (79.8, 97.7)	87.5 (58.6, 96.7)
12 Months (95% CI)	93.3 (80.74, 97.80)	93.0 (79.8, 97.7)	71.6 (40.3, 88.4)
15 Months (95% CI)	83.5 (68.43, 91.79)	NE (NE, NE)	71.6 (40.3, 88.4)
18 Months (95% CI)	83.5 (68.43, 91.79)	NE (NE, NE)	71.6 (40.3, 88.4)
24 Months (95% CI)	72.9 (54.42, 84.90)	NE (NE, NE)	71.6 (40.3, 88.4)
30 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	71.6 (40.3, 88.4)
36 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	71.6 (40.3, 88.4)
Progression-free Survival (PFS) by IRC			
Median PFS follow-up time (range), months	27.4 (0.0, 28.7)	11.14 (0.03, 16.92)	33.8 (4.1, 58.3)
Median PFS[2] (95% CI), months	NE (27.56, NE)	NE (NE, NE)	NE (20.3, NE)
Progression/death event-free rate (%) at[3]			
6 Months (95% CI)	82.7 (70.96, 90.05)	84.4 (72.95, 91.30)	90.0 (65.6, 97.4)
12 Months (95% CI)	82.7 (70.96, 90.05)	82.5 (70.55, 89.93)	84.0 (57.9, 94.6)
15 Months (95% CI)	82.7 (70.96, 90.05)	82.5 (70.55, 89.93)	84.0 (57.9, 94.6)
18 Months (95% CI)	73.0 (59.55, 82.62)	NE (NE, NE)	78.0 (51.2, 91.2)
24 Months (95% CI)	70.9 (57.20, 80.95)	NE (NE, NE)	72.0 (45.0, 87.4)
30 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	72.0 (45.0, 87.4)
36 Months (95% CI)	NE (NE, NE)	NE (NE, NE)	72.0 (45.0, 87.4)

Summary of studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

*Table 29. **Summary of Study BGB-3111-214***

Title: Study BGB-3111-214 is a Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma (MZL)	
Study identifier	MAGNOLIA (protocol number BGB-3111-214), EudraCT 2018-001284-24

Design	Study BGB-3111-214 is a Phase 2, multicentre, single-arm, open-label study of zanubrutinib (BGB-3111) in patients with relapsed or refractory marginal zone lymphoma who have received at least 1 prior anti-CD20-based therapy.		
	Duration of main phase:		First patient was enrolled on 19 February 2019 and the last patient was enrolled on 06 January 2020. Study data was based on the data cutoff date of 18 January 2021.
Hypothesis	For Study BGB-3111-214**,** the primary efficacy endpoint is ORR according to the Lugano Classification (Cheson et al 2014) as assessed by an Independent Review Committee (IRC). A two-sided Clopper-Pearson 95% confidence interval (CI) for ORR will be calculated. Assuming 48% ORR of zanubrutinib, a sample size of 65 patients will provide 82% power to rule out an ORR of 30%, at a 1-sided alpha level of 0.025 and using the exact binomial test.		
Treatments group for Study BGB-3111-214	Zanubrutinib		Zanubrutinib, 160 mg BID, until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination, 68 patients enrolled.
Endpoints and definitions	Primary endpoint	ORR by IRC	Overall response rate (ORR) (CR + partial response [PR]) in accordance with the Lugano Classification (Cheson et al 2014) determined by the Independent Review Committee (IRC)
	Secondary endpoints	ORR by INV	Overall response rate (ORR) determined by investigator assessment (INV)
		ORR by PET-CT in Patients with FDG-avid disease by IRC	ORR (as assessed by the IRC) for the subset of patients determined by the IRC to have FDG-avid disease at baseline
		PFS by IRC and by INV	PFS, defined as the time from the date of the first dose of study drug until progressive disease or death from any cause, whichever occurred first, determined by Independent Review Committee and by investigator
		OS	Overall survival (OS), defined as the time from the date of the first dose of study drug to death due to any cause
		DOR by IRC and by INV	Duration of response (DOR), defined as the time from the date of the earliest qualifying response (CR or PR) to the date of progressive disease or death from any cause (whichever occurred earlier), determined by Independent Review Committee and by investigator
		TTR by IRC and by INV	Time to response (TTR), defined as the time from the first dose of study drug to the date of the earliest qualifying response (PR or CR), determined by Independent Review Committee and by investigator
		TTF	Time to treatment failure (TTF), defined as the time from the first dose of study drug to the date of discontinuation of study drug due to any reason.

		TTNT	Time to next line of therapy (TTNT) for MZL defined as the time from the first dose of study drug to the start of the first new therapy for MZL.
		PRO	To evaluate patient-reported outcomes (PRO)
		Safety	To determine the safety of zanubrutinib
		PK	To determine pharmacokinetic (PK) parameters of zanubrutinib
Database lock	Study period: Date first patient dosed: 19 February 2019 Date last patient enrolled: 06 January 2020 Study was ongoing as of the data cutoff date (18 January 2021)		

Table 02. Summary of Study BGB-3111-AU-003

Title: Study BGB-3111-AU-003 is a Phase 1/2, 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; 20 patients with Relapsed or Refractory Marginal Zone Lymphoma received zanubrutinib treatment at the recommended dose for Phase 2.			
Study identifier	protocol number BGB-3111-AU-003, EudraCT 2016-003364-39		
Design	Study BGB-3111-AU-003 is a Phase 1/2, multicentre, 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		
	Duration of main phase:		Study BGB-3111-AU-003 started on 25 August 2014 and MZL patients were enrolled in **Part 2** expansion phase. The study was ongoing as of the data cutoff date 02 October 2020 for MZL.
Hypothesis	Not applicable		
Treatments group for Study BGB-3111-AU-003	Zanubrutinib		Zanubrutinib, 160 mg BID or 320 mg QD, until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination, 20 patients with relapsed/refractory MZL enrolled in Study BGB-3111-AU-003.
Endpoints and definitions [Primary Endpoints: AEs, SAEs per the NCI-CTCAE Version 4.03 (or higher), physical	Secondary endpoints:	ORR by IRC (Primary efficacy endpoint)	Overall response rate (ORR) in accordance with the Lugano Classification (Cheson et al 2014) determined by the Independent Review Committee (IRC)
		CR by IRC and ORR	Complete response rate (CR) determined by IRC and by investigator assessment (INV) according to the Lugano classification.

examination, and laboratory measurements]		PFS by IRC and by INV	PFS, defined as the time from the date of the first dose of study drug until progressive disease or death from any cause, whichever occurred first, determined by Independent Review Committee and by investigator
		OS	Overall survival (OS), defined as the time from the date of the first dose of study drug to death due to any cause
		DOR by IRC and by INV	Duration of response (DOR), defined as the time from the date of the earliest qualifying response (CR or PR) to the date of progressive disease or death from any cause (whichever occurred earlier), determined by Independent Review Committee and by investigator
		TTR by IRC and by INV	Time to response (TTR), defined as the time from the first dose of study drug to the date of the earliest qualifying response (PR or CR), determined by Independent Review Committee and by investigator
		Safety	To determine the safety of zanubrutinib in patients with B-cell malignancies
		PK	To further characterize pharmacokinetic (PK) profile of zanubrutinib
Database lock	Study period: Date first patient dosed: 25 August 2014 Study was ongoing as of the data cutoff date (02 Oct 2020)		

*Table 30**. Summary of efficacy for Study BGB-3111-214 and Study BGB-3111-AU-003***

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Study BGB-3111-214:** efficacy analysis set, including 66 patients with centrally-confirmed diagnosis of MZL (2 patients were excluded due to transformation to diffuse large B-cell lymphoma) **Data cutoff date** 18 January 2021/ 04 May 2022 **Study BGB-3111-AU-003:** 20 patients with relapsed/refractory MZL enrolled and treated at the RP2D dose. **Data cutoff date** 20 October 2020		
Descriptive statistics and estimate variability	Study	BGB-3111-214	BGB-3111-AU-003
	Number of subjects	66	20
	ORR by IRC, n (%)	45 (68.2)	16 (80)
	95% CI	55.56, 79.11	56.3, 94.3
	CR (Complete Response), n (%)	17 (25.8)	4 (20.0)
	PR (Partial Response), n (%)	28 (42.4)	12 (60.0)

	Median time to response, months (range)	2.8 (1.7-11.1)	2.8 (2.6-23.1)
	Median study follow-up, months (range)	15.7 (1.64-21.88) 28.04 (1.64, 32.89)	35.24 (8.3-59.2)
	Overall Response rate by MZL Subtype, n (%) Extranodal Nodal Splenic Unknown	 16/25 (64.0) 19/25 (76.0) 8/12 (66.7) 2/4 (50)	 8/9 (88.9) 5/5 (100) 3/6 (50.0) -
	Duration of Response (DOR)		
	Median DOR follow-up time (range), months	8.31 (0.03, 14.75) 23.4 (2.7, 25.8)	31.4 (2.7, 55.5)
	Median DOR (95% CI), months	Not Reached (95% CI: NE/25.00 to NE)	Not Reached (95% CI: 8.4 to NE)
	Estimated DOR rate (%) at[1],		
	6 Months (95% CI)	93.0 (79.8, 97.7)	87.5 (58.6, 96.7)
	12 Months (95%CI)	93.0 (79.8, 97.7)	71.6 (40.3, 88.4)
	24 Months (95% CI)	NE/72.9 (54.42, 84.90)	71.6 (40.3, 88.4)
	36 Months (95% CI)	NE	71.6 (40.3, 88.4)
	Progression-free Survival (PFS)		
	Median PFS follow-up time (range), months	11.14 (0.02, 16.92) 27.4 (0.0, 28.7)	33.8 (4.1, 58.3)
	Median PFS (95% CI), months	Not Reached (95% CI: NE/27.6 to NE)	Not reached (20.3, NE)
	Progression/death event-free rate (%) at[1],		
	6 Months (95% CI)	84.4 (72.95, 91.30)	90.0 (65.6, 97.4)
	12 Months (95% CI)	82.5 (70.55, 89.93)	84.0 (57.9, 94.6)
	15 Months (95% CI)	82.5 (70.55, 89.93)	84.0 (57.9, 94.6)
	18 Months (95% CI)	NE/73.0 (59.55, 82.62)	78.0 (51.2, 91.2)
	24 Months (95% CI)	NE/70.9 (57.20, 80.95)	72.0 (45.0, 87.4)
	30 Months (95% CI)	NE	72.0 (45.0, 87.4)
	36 Months (95% CI)	NE	72.0 (45.0, 87.4)
Notes	Updated data in red.		

NE, non-estimable

1 Event-free rates were estimated by Kaplan-Meier method (95% confidence interval) using Greenwood's formula.

Analysis performed across trials (pooled analyses and meta-analysis)

Studies 214 and AU003 have been presented side by side in this AR. No further analyses in MZL patients are available.

Clinical studies in special populations

No specific clinical studies were submitted

Supportive study

Study AU003 is considered supportive and has been presented side-by-side with the pivotal study 214 in the main study section.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant has presented two single-arm trials conducted in patients with MZL (all three subtypes included). The pivotal study BGB-3111-214 (214) included 66 patients (efficacy analysis). The primary endpoint was ORR (the proportion of patients who achieved a best overall response of PR or CR) as determined by an Independent Review Committee (IRC) in accordance with the Lugano classification, which is considered acceptable in a SAT in an indolent disease such as MZL. The MAH aimed to show that the ORR was larger than 30 % based on the observed IRC-assessed ORR for the ibrutinib study in R/R MZL (ORR 48 %, Noy et al 2017). However, there are no available data from RCTs supporting the assumption that achieving PR, or even CR with continuous, long term treatment with Bruton kinase inhibitors in R/R MZL with at least moderate prognosis, translate into PFS or OS benefit.

Supportive evidence is presented from study BGB-3111-AU-003 (AU003); a phase 1/2 study with safety and PK as the primary endpoint (N=20 for MZL).

The MAH has started a phase 3 randomised, open-label study of zanubrutinib plus rituximab versus lenalidomide plus rituximab in patients with R/R MZL, with a targeted sample size of ~374 patients. The primary objective is PFS; the secondary objectives are EFS, ORR, CR, DoR and OS. While there are uncertainties of the PFS benefit if treating R/R MZL patients with lenalidomide plus rituximab, this comparator seems to be acceptable and will also provide additional data from other chemotherapy free option, lenalidomide. According to MAH, the estimated primary completion date will be in May 2028.

The MAH has agreed to the proposal to provide additional efficacy data post-authorisation. As such, the abovementioned phase 3 trial is proposed as a PAES. The MAH has agreed to provide the results of the RCT as a PAES in order to support the results of the single-arm trial 214.

Efficacy data and additional analyses

Zanubrutinib demonstrated high response rates; ORR by IRC was documented in 45/66 (68.2%) patients in the pivotal study 214, with a CR of 17/66 (25.8%). Demonstration of efficacy relies on a small single arm study with few patients (N=66) and initially very limited median follow-up time. The updated analysis of Study BGB-3111-214 provides meaningful additional follow-up data for the evaluation of duration of response and PFS: median duration of response follow-up time is 23.4

months compared to 8.31 months in the primary analysis; the median PFS follow follow-up time is 27.4 months compared to 11.14 months in the primary analysis.

Given the small study populations (N=66 for 214 and N=20 for AU003) no conclusion with regards to special populations can be made. With regards to race, there were 11/66 patients from China in study 214, and 4/20 Asian patients in study AU003.

In order to substantiate the efficacy results (ORR) the MAH provided updated efficacy results of the pivotal study BGB-3111-214 with a data cutoff date of 04 May 2022 which represents approximately 15.5 months of additional follow-up from the initial data cut on 18 January 2021. While the observed CR rate of 25.8% is not particularly high, an ORR of 68.2% in an indolent disease such as MZL with a median follow-up time for DOR of almost 2 years and median DOR not reached (72.9% at 24 months) could be regarded as promising taking into account the single arm design of the study. Thus, results from the ongoing phase 3 study should provide additional data on time-to-event endpoints to further confirm the observed efficacy results from the pivotal study BGB-3111-214.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

2.4.4. Conclusions on the clinical efficacy

Efficacy results from single-arm trial 214 show relevant response rates for zanubrutinib in patients with R/R MZL. Responses are durable upon longer follow-up and endorse the clinical benefit from this treatment.

In order to further confirm the efficacy of zanubrutinib in patients with R/R MZL, the MAH will submit the final study report of the post-authorisation efficacy study (PAES): Study BGB-3111-308: a global, multicenter, phase 3, open-label, randomized study of zanubrutinib plus rituximab versus lenalidomide plus rituximab in patients with relapsed/refractory marginal zone lymphoma (NCT05100862).

2.5. Clinical safety

Introduction

The safety profile for zanubrutinib monotherapy is derived from 847 patients with MZL and other B-cell malignancies enrolled into 7 clinical studies (2 Phase 1 studies, 4 Phase 2 studies and 1 Phase 3 study):

Table 31 Studies included in the SCS

Study Location	Study Design	Population	Starting Dose	N	First Patient First Dose/ Data Cutoff Date/ Study Status
BGB-3111-214 (AU, China, EU [CZ, FR, UK, IT], NZ, SK, US)	Phase 2, open-label, single-arm study	Patients with R/R MZL	160 mg BID	68	19 February 2019/ 18 January 2021/ Ongoing
BGB-3111-AU-003[a] Ex-China (AU, NZ, SK, US, IT, UK)	Phase1/2, single-arm, dose escalation and cohort expansion	Patients with R/R or T-N CLL/SLL, DLBCL, FL, HCL, MALT, MCL, MZL, NHL, RT, or WM	160 mg BID 320 mg QD 40 mg QD 80 mg QD 160 mg QD	278 95 3 4 5	25 August 2014/ 02 October 2020/ Ongoing
BGB-3111-1002 China[b]	Phase 1, single-arm	Patients with R/R CLL/SLL, MCL, WM/LPL, FL, MZL, HCL or nGCB DLBCL	160 mg BID 320 mg QD	34 10	05 July 2016/ 30 August 2020/ Closed
BGB-3111-205 China	Phase 2, single-arm	Patients with R/R CLL/SLL	160 mg BID	91	09 March 2017/ 11 September 2020/ Completed
BGB-3111-206 China	Phase 2, single-arm	Patients with R/R MCL	160 mg BID	86	02 March 2017/ 08 September 2020/ Completed
BGB-3111-210 China	Phase 2, single-arm	Patients with R/R WM	160 mg BID	44	31 August 2017/ 15 September 2020/ Ongoing
BGB-3111-302 Ex-China (AU, USA, EU [CZ, SP, GE, FR, UK, GR, IT, NL, PO, SW])	Phase 3, Randomized, Open-Label, Multicentre Study	Patients with R/R or T-N WM	160 mg BID	129	25 January 2017/ 31 August 2020/ Ongoing
Total Patients in the Integrated Safety Population				**847**	NA

Safety data are presented for the following 4 patient groups:

1. The **214+AU-003 MZL** patient group, which includes BGB-3111-214 (n = 68) + patients with MZL (n = 20) enrolled to Study BGB-3111-AU-003, collectively comprising n = 88 patients who received at least 1 dose of zanubrutinib.
2. The **All Non-China** patient group, which includes zanubrutinib-treated patients enrolled to studies outside of China including Study BGB-3111-214 and all patients in BGB-3111-AU-003 and -302 (n = 571).
3. The **All China** patient group, which includes zanubrutinib-treated patients enrolled to BGB-3111-214 in China and all patients in studies BGB-3111-1002, -205, -206 and -210, (n = 276).

4. The **All Zanubrutinib** patient group, which includes zanubrutinib-treated patients in the aforementioned 7 studies (n = 847).

Additional safety data from Study BGB-3111-LTE1 (long-term extension [LTE-1]), a study consisting of patients rolling over from study BGB-3111-AU-003 who were continuing study treatment or who were on long-term safety and survival follow-up at the time of transition to BGB-3111-LTE1 from the BGB-3111-AU-003 are combined with Study BGB-3111-AU-003 and included in this filing.

For an additional perspective, selected summaries of comparative safety data from the Phase 3 study of zanubrutinib versus ibrutinib in patients with *MYD88*^{MUT} WM (Study BGB-3111-302, Cohort 1) are provided as these data provide head-to-head comparison of the 2 BTK inhibitors in a single randomized.

Patient exposure

Exposure data for all patient groups are summarized below. Across all patient groups, the median relative dose intensity was near 100%.

Table 32 Summary of treatment exposure

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Duration of exposure (months)				
Mean (SD)	15.57 (11.272)	23.54 (14.125)	26.63 (17.284)	25.62 (16.378)
Median	14.51	29.26	28.29	28.45
Min, Max	0.9, 58.6	0.1, 49.7	0.1, 71.4	0.1, 71.4
Total exposure (patient-months)	1369.99	6497.05	15204.34	21701.39
Duration of exposure, n (%)				
< 3 months	7 (8.0)	35 (12.7)	56 (9.8)	91 (10.7)
3 to < 6 months	11 (12.5)	20 (7.2)	41 (7.2)	61 (7.2)
6 to < 9 months	6 (6.8)	14 (5.1)	28 (4.9)	42 (5.0)
9 to < 12 months	5 (5.7)	11 (4.0)	22 (3.9)	33 (3.9)
12 to < 18 months	37 (42.0)	25 (9.1)	57 (10.0)	82 (9.7)
18 to < 24 months	10 (11.4)	18 (6.5)	41 (7.2)	59 (7.0)
24 to < 30 months	0 (0.0)	22 (8.0)	65 (11.4)	87 (10.3)
30 to < 36 months	6 (6.8)	73 (26.4)	101 (17.7)	174 (20.5)
36 to < 48 months	4 (4.5)	56 (20.3)	85 (14.9)	141 (16.6)
≥ 48 months	2 (2.3)	2 (0.7)	75 (13.1)	77 (9.1)
Cumulative dose administered (g)				
Mean (SD)	142.84 (105.930)	222.97 (136.452)	237.83 (159.156)	232.99 (152.209)
Median	133.92	265.92	246.08	250.72
Min, Max	6.4, 546.1	1.3, 483.8	1.0, 642.1	1.0, 642.1
Average daily dose (mg/day)				
Mean (SD)	309.97 (16.872)	310.66 (30.190)	296.72 (46.953)	301.27 (42.713)
Median	317.64	319.37	314.66	316.94
Min, Max	228.6, 320.0	97.1, 321.9	46.7, 348.6	46.7, 348.6
Relative dose intensity (%)[a]				
Mean (SD)	96.86 (5.272)	97.08 (9.434)	96.64 (38.312)	96.79 (31.905)
Median	99.26	99.80	98.41	99.11
Min, Max	71.4, 100.0	30.4, 100.6	14.6, 691.3	14.6, 691.3

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with dose reduction[b], n (%)	2 (2.3)	11 (4.0)	61 (10.7)	72 (8.5)
Number of dose reductions				
n	2	11	61	72
Mean (SD)	1.0 (0.00)	1.1 (0.30)	1.5 (0.92)	1.4 (0.87)
Median	1.0	1.0	1.0	1.0
Min, Max	1, 1	1, 2	1, 5	1, 5
Number of dose reductions, n (%)				
1	2 (2.3)	10 (3.6)	43 (7.5)	53 (6.3)
2	0 (0.0)	1 (0.4)	12 (2.1)	13 (1.5)
3	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.4)
4	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
5	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
≥ 6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with dose interruptions due to adverse event, n (%)				
COVID-19 related event	3 (3.4)	0 (0.0)	5 (0.9)	5 (0.6)

Source: Table 2.7.4.1.2.1
Abbreviations: COVID-19, coronavirus disease 2019; eCRF, electronic case report form; MZL, marginal zone lymphoma; SD, standard deviation
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Duration of exposure is defined as first dose date to last dose date for patients that ended treatment on or before the data cutoff date or to the data cutoff date for ongoing patients.
[a] Relative dose intensity is the ratio of actual daily dose and the planned daily dose.
[b] No patient required a dose reduction for a COVID-19 related event.

Demographics

Table 33 Demographics and baseline characteristics (Safety Analysis Set)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Age (years)				
Mean (SD)	68.2 (10.63)	59.3 (10.19)	67.2 (11.27)	64.6 (11.54)
Median	70.0	61.0	69.0	65.0
Min, Max	37, 95	28, 87	20, 95	20, 95
Age group, n (%)				
< 65 years	31 (35.2)	192 (69.6)	210 (36.8)	402 (47.5)
≥ 65 and < 75 years	34 (38.6)	69 (25.0)	205 (35.9)	274 (32.3)
≥ 75 years	23 (26.1)	15 (5.4)	156 (27.3)	171 (20.2)
Sex, n (%)				
Male	46 (52.3)	177 (64.1)	387 (67.8)	564 (66.6)
Female	42 (47.7)	99 (35.9)	184 (32.2)	283 (33.4)
Race, n (%)				
Asian	17 (19.3)	276 (100.0)	59 (10.3)	335 (39.6)
White	56 (63.6)	0 (0.0)	458 (80.2)	458 (54.1)
Black or African American	0 (0.0)	0 (0.0)	5 (0.9)	5 (0.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Multiple	2 (2.3)	0 (0.0)	3 (0.5)	3 (0.4)
Other	2 (2.3)	0 (0.0)	21 (3.7)	21 (2.5)
Not Reported	10 (11.4)	0 (0.0)	20 (3.5)	20 (2.4)
Unknown	1 (1.1)	0 (0.0)	2 (0.4)	2 (0.2)
Missing	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Region, n (%)				
Asia	16 (18.2)	276 (100.0)	41 (7.2)	317 (37.4)
European Union	31 (35.2)	0 (0.0)	127 (22.2)	127 (15.0)
North America	8 (9.1)	0 (0.0)	81 (14.2)	81 (9.6)
Oceania	33 (37.5)	0 (0.0)	322 (56.4)	322 (38.0)
HBcAb, n (%)				
Positive	8 (9.1)	101 (36.6)	56 (9.8)	157 (18.5)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Negative	78 (88.6)	175 (63.4)	484 (84.8)	659 (77.8)
Equivocal	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Missing	2 (2.3)	0 (0.0)	29 (5.1)	29 (3.4)
ECOG performance status, n (%)				
0	46 (52.3)	152 (55.1)	251 (44.0)	403 (47.6)
1	35 (39.8)	112 (40.6)	279 (48.9)	391 (46.2)
2	7 (8.0)	12 (4.3)	41 (7.2)	53 (6.3)
Weight (kg)				
Mean (SD)	74.33 (16.092)	64.95 (10.879)	77.62 (17.611)	73.50 (16.815)
Median	72.00	64.05	75.40	70.90
Min, Max	45.5, 114.0	44.5, 105.0	36.0, 145.1	36.0, 145.1
Height (cm)				
n	88	276	566	842
Mean (SD)	167.82 (10.105)	165.88 (8.044)	170.33 (9.994)	168.87 (9.624)
Median	167.00	166.00	171.00	169.75
Min, Max	146.0, 195.5	146.0, 187.0	143.0, 195.5	143.0, 195.5

Source: Table 2.7.4.1.3.1
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; MZL, marginal zone lymphoma; SD, standard deviation
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

Table 34 Disease Characteristics (Safety Analysis Set)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Diagnosis, n (%)				
NHL	88 (100.0)	130 (47.1)	214 (37.5)	344 (40.6)
MZL	88 (100.0)	16 (5.8)	77 (13.5)	93 (11.0) [a]
MCL	--	88 (31.9)	57 (10.0)	145 (17.1)
FL	--	26 (9.4)	33 (5.8)	59 (7.0)
DLBCL	--	--	45 (7.9)	45 (5.3)
Other[b]	--	--	2 (0.4)	2 (0.2)
WM	--	46 (16.7)	207 (36.3)	253 (29.9)
CLL/SLL	--	100 (36.2)	125 (21.9)	225 (26.6)
Other[c]	--	--	25 (4.4)	25 (3.0)
Prior treatment status, n (%)				
Treatment-naive	0 (0.0)	0 (0.0)	91 (15.9)	91 (10.7)
Relapsed/refractory	88 (100.0)	276 (100.0)	480 (84.1)	756 (89.3)
Time from initial diagnosis to first study dose (years)				
Mean (SD)	6.67 (5.514)	3.47 (2.825)	6.35 (5.563)	5.41 (5.027)
Median	5.21	2.70	5.02	3.92
Min, Max	0.2, 29.5	0.3, 20.1	0.0, 29.5	0.0, 29.5
Time from most recent progression to first study dose (months)				
n	83	224	438	662
Mean (SD)	7.01 (12.601)	4.14 (5.479)	4.55 (8.496)	4.41 (7.608)
Median	2.73	2.14	2.09	2.10
Min, Max	0.7, 90.1	0.2, 47.3	0.0, 90.1	0.0, 90.1
Baseline neutropenia[d], n (%)				
Yes	5 (5.7)	35 (12.7)	63 (11.0)	98 (11.6)
No	83 (94.3)	241 (87.3)	506 (88.6)	747 (88.2)
Missing	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Baseline anaemia[e], n (%)				
Yes	20 (22.7)	104 (37.7)	242 (42.4)	346 (40.9)
No	68 (77.3)	172 (62.3)	329 (57.6)	501 (59.1)
Baseline platelet group, n (%)				
$\leq 100 \times 10^9$/L	12 (13.6)	76 (27.5)	109 (19.1)	185 (21.8)
$> 100 \times 10^9$/L	76 (86.4)	200 (72.5)	462 (80.9)	662 (78.2)

Source: Table 2.7.4.1.3.2

Abbreviations: CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma (subdiagnosis of NHL); FL, follicular lymphoma (subdiagnosis of NHL); MCL, mantle cell lymphoma (subdiagnosis of NHL); MZL, marginal zone lymphoma (subdiagnosis of NHL); NHL, non-Hodgkin lymphoma; SD, standard deviation; WM, Waldenström macroglobulinaemia

N = number of patients who received at least 1 dose of zanubrutinib.

[a] Five MZL patients enrolled in BGB-3111-1002 were not included in the **214+AU003 MZL** group. However, they are included in the **All China** and **All Zanubrutinib** groups for all safety summaries reported herein.

[b] Includes 1 patient with "B lineage lymphoma" and 1 patient with "indolent lymphoma".

[c] Includes 13 patients with Richter's transformation and 12 patients with hairy cell leukaemia.

[d] Neutropenia is defined as absolute neutrophil count $\leq 1.5 \times 10^9$/L.

[e] Anaemia is defined as haemoglobin ≤ 110 g/L.

Table 7. Prior Anticancer Therapies (Safety Analysis Set)

	214+AU003 MZL (N = 88)	All China (N = 276)	All Non-China (N = 571)	All Zanubrutinib (N = 847)
Patients with any prior systemic anticancer drug therapy, n (%)	88 (100.0)	276 (100.0)	480 (84.1)	756 (89.3)
Number of prior lines of therapy/regimens[a]				
Mean (SD)	2.0 (1.20)	2.4 (1.52)	2.2 (1.58)	2.3 (1.56)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 6	1, 9	1, 12	1, 12
Number of prior lines of therapy/regimens[a], n (%)				
n	88	276	480	756
1	39 (44.3)	97 (35.1)	213 (44.4)	310 (41.0)
2	26 (29.5)	81 (29.3)	114 (23.8)	195 (25.8)
3	13 (14.8)	50 (18.1)	77 (16.0)	127 (16.8)
4	6 (6.8)	23 (8.3)	37 (7.7)	60 (7.9)
5	2 (2.3)	12 (4.3)	19 (4.0)	31 (4.1)
≥ 6	2 (2.3)	13 (4.7)	20 (4.2)	33 (4.4)
Best response to last therapy, n (%)				
Complete response	30 (34.1)	20 (7.2)	121 (25.2)	141 (18.7)
Complete response with incomplete bone marrow recovery	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Very good partial response	0 (0.0)	1 (0.4)	10 (2.1)	11 (1.5)
Partial response	29 (33.0)	56 (20.3)	167 (34.8)	223 (29.5)
Partial response with lymphocytosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodular partial response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Minor response	0 (0.0)	2 (0.7)	7 (1.5)	9 (1.2)
Stable disease	17 (19.3)	77 (27.9)	74 (15.4)	151 (20.0)
Progressive disease	9 (10.2)	71 (25.7)	52 (10.8)	123 (16.3)
NA	3 (3.4)	48 (17.4)	49 (10.2)	97 (12.8)

	214+AU003 MZL (N = 88)	All China (N = 276)	All Non-China (N = 571)	All Zanubrutinib (N = 847)
Time from end of last therapy to first study dose (months)				
n	88	276	463	739
Mean (SD)	31.00 (33.915)	11.25 (16.499)	24.89 (28.345)	19.80 (25.457)
Median	19.98	4.58	14.95	9.07
Min, Max	1.0, 176.6	0.0, 93.9	0.0, 176.6	0.0, 176.6
Prior transplant, n (%)				
Yes	4 (4.5)	9 (3.3)	35 (6.1)	44 (5.2)
No	84 (95.5)	267 (96.7)	535 (93.7)	802 (94.7)
Unknown	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

Source: Table 2.7.4.1.3.4.1
Abbreviations: MZL, marginal zone lymphoma; NA, Not applicable; SD, standard deviation
N = number of patients who received at least 1 dose of zanubrutinib.
For patients with any prior anticancer drug therapy or any transplants, percentages were based on N; for others, percentages are based on the number of patients with any prior anticancer therapy.
[a] n is number of patients with 1 or more prior lines of therapy/regimens.

Adverse events

Table 35 Overview of all TEAEs reported by patient group (SAS).

	214+AU003 MZL (N = 88)	All China (N = 276)	All Non-China (N = 571)	All Zanubrutinib (N = 847)
Patients with a least 1 TEAE	85 (96.6)	271 (98.2)	561 (98.2)	832 (98.2)
≥ Grade 3	38 (43.2)	181 (65.6)	373 (65.3)	554 (65.4)
Serious	35 (39.8)	111 (40.2)	288 (50.4)	399 (47.1)
Leading to death	3 (3.4)	17 (6.2)	29 (5.1)	46 (5.4)
Leading to treatment discontinuation	5 (5.7)	30 (10.9)	61 (10.7)	91 (10.7)
Leading to dose reduction	2 (2.3)	11 (4.0)	52 (9.1)	63 (7.4)
Leading to dose interruption[a]	29 (33.0)	84 (30.4)	241 (42.2)	325 (38.4)
Treatment-related	56 (63.6)	258 (93.5)	426 (74.6)	684 (80.8)

	214+AU003 MZL (N = 88)	All China (N = 276)	All Non-China (N = 571)	All Zanubrutinib (N = 847)
Patients with a least 1 AESI	68 (77.3)	257 (93.1)	513 (89.8)	770 (90.9)
≥ Grade 3 AESI	28 (31.8)	160 (58.0)	295 (51.7)	455 (53.7)
Serious AESI	22 (25.0)	85 (30.8)	193 (33.8)	278 (32.8)

Source: Table 2.7.4.2.1.1 and Table 2.7.4.1.2.1
Abbreviations: AE, Adverse event; AESI, Adverse event of special interest; eCRF, electronic case report form; MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
[a] Derived as any interruption because of an adverse event with duration > 1 day from drug administration eCRF in BGB-3111-AU-003; from drug administration eCRF in BGB-3111-214, BGB-3111-205, BGB-3111-206, BGB-3111-210 (interruption because of AE), and BGB-3111-302; from AE eCRF in BGB-3111-1002 (action taken = drug held).
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

Table 36 An overview of TEAEs occurring within the first 6 months of starting treatment

Overall Summary of Treatment-Emergent Adverse Events: First 6 Months (Safety Analysis Set)

	214+AU003 MZL Zanubrutinib (N = 88) n (%)	All China Zanubrutinib (N = 276) n (%)	All Non-China Zanubrutinib (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with at least one TEAE	81 (92.0)	263 (95.3)	542 (94.9)	805 (95.0)
Grade 3 or Higher	26 (29.5)	122 (44.2)	213 (37.3)	335 (39.6)
Serious	22 (25.0)	48 (17.4)	147 (25.7)	195 (23.0)
Leading to Death	1 (1.1)	10 (3.6)	12 (2.1)	22 (2.6)
Leading to Treatment Discontinuation [a]	3 (3.4)	17 (6.2)	27 (4.7)	44 (5.2)
Leading to Dose Reduction	1 (1.1)	7 (2.5)	25 (4.4)	32 (3.8)
Treatment-Related	47 (53.4)	238 (86.2)	360 (63.0)	598 (70.6)
Treatment-Related Grade 3 or Higher	9 (10.2)	91 (33.0)	93 (16.3)	184 (21.7)
Treatment-Related Serious	4 (4.5)	23 (8.3)	43 (7.5)	66 (7.8)
Treatment-Related Leading to Death	0 (0.0)	4 (1.4)	3 (0.5)	7 (0.8)
Treatment-Related Leading to Treatment Discontinuation [a]	1 (1.1)	8 (2.9)	13 (2.3)	21 (2.5)
Treatment-Related Leading to Dose Reduction	1 (1.1)	7 (2.5)	21 (3.7)	28 (3.3)
Patients with at least one AESI	62 (70.5)	237 (85.9)	450 (78.8)	687 (81.1)
Grade 3 or Higher AESI	18 (20.5)	102 (37.0)	158 (27.7)	260 (30.7)
Serious AESI	14 (15.9)	38 (13.8)	92 (16.1)	130 (15.3)

Common Treatment-Emergent Adverse Events

TEAEs reported in ≥ 10% of patients in the 214+AU003 MZL group include diarrhoea (25.0%), contusion (23.9%), upper respiratory tract infection and pyrexia (15.9% each), constipation (14.8%), nausea (12.5%), neutropenia and fatigue (11.4% each), and rash, back pain and abdominal pain (10.2% each).

Table 37 TEAEs reported in ⩾ 10% of patients by SOC and PT (SAS)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with a least 1 TEAE	85 (96.6)	271 (98.2)	561 (98.2)	832 (98.2)
Infections and infestations	46 (52.3)	201 (72.8)	423 (74.1)	624 (73.7)
Upper respiratory tract infection	14 (15.9)	115 (41.7)	200 (35.0)	315 (37.2)
Pneumonia	4 (4.5)	70 (25.4)	59 (10.3)	129 (15.2)
Urinary tract infection	5 (5.7)	39 (14.1)	85 (14.9)	124 (14.6)
Gastrointestinal disorders	48 (54.5)	133 (48.2)	364 (63.7)	497 (58.7)
Diarrhoea	22 (25.0)	47 (17.0)	152 (26.6)	199 (23.5)
Constipation	13 (14.8)	20 (7.2)	107 (18.7)	127 (15.0)
Nausea	11 (12.5)	4 (1.4)	94 (16.5)	98 (11.6)
Abdominal pain	9 (10.2)	7 (2.5)	47 (8.2)	54 (6.4)
Skin and subcutaneous tissue disorders	29 (33.0)	140 (50.7)	309 (54.1)	449 (53.0)
Rash	9 (10.2)	64 (23.2)	98 (17.2)	162 (19.1)
Purpura	3 (3.4)	46 (16.7)	18 (3.2)	64 (7.6)
Pruritus	2 (2.3)	5 (1.8)	58 (10.2)	63 (7.4)
Respiratory, thoracic and mediastinal disorders	22 (25.0)	100 (36.2)	278 (48.7)	378 (44.6)
Cough	7 (8.0)	47 (17.0)	126 (22.1)	173 (20.4)
Investigations	16 (18.2)	236 (85.5)	138 (24.2)	374 (44.2)
Neutrophil count decreased	5 (5.7)	163 (59.1)	30 (5.3)	193 (22.8)
Platelet count decreased	6 (6.8)	94 (34.1)	21 (3.7)	115 (13.6)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
White blood cell count decreased	2 (2.3)	81 (29.3)	0 (0.0)	81 (9.6)
Alanine aminotransferase increased	4 (4.5)	40 (14.5)	18 (3.2)	58 (6.8)
Aspartate aminotransferase increased	1 (1.1)	31 (11.2)	11 (1.9)	42 (5.0)
General disorders and administration site conditions	30 (34.1)	77 (27.9)	281 (49.2)	358 (42.3)
Fatigue	10 (11.4)	10 (3.6)	115 (20.1)	125 (14.8)
Pyrexia	14 (15.9)	30 (10.9)	79 (13.8)	109 (12.9)
Oedema peripheral	6 (6.8)	11 (4.0)	61 (10.7)	72 (8.5)
Musculoskeletal and connective tissue disorders	32 (36.4)	38 (13.8)	291 (51.0)	329 (38.8)
Back pain	9 (10.2)	9 (3.3)	89 (15.6)	98 (11.6)
Arthralgia	7 (8.0)	13 (4.7)	78 (13.7)	91 (10.7)
Injury, poisoning and procedural complications	27 (30.7)	31 (11.2)	273 (47.8)	304 (35.9)
Contusion	21 (23.9)	4 (1.4)	174 (30.5)	178 (21.0)
Blood and lymphatic system disorders	16 (18.2)	105 (38.0)	197 (34.5)	302 (35.7)
Anaemia	7 (8.0)	73 (26.4)	73 (12.8)	146 (17.2)
Neutropenia	10 (11.4)	19 (6.9)	94 (16.5)	113 (13.3)
Metabolism and nutrition disorders	13 (14.8)	150 (54.3)	153 (26.8)	303 (35.8)
Hypokalaemia	4 (4.5)	53 (19.2)	20 (3.5)	73 (8.6)
Hyperglycaemia	1 (1.1)	48 (17.4)	11 (1.9)	59 (7.0)
Hyperuricaemia	1 (1.1)	44 (15.9)	9 (1.6)	53 (6.3)
Nervous system disorders	26 (29.5)	49 (17.8)	235 (41.2)	284 (33.5)
Headache	5 (5.7)	15 (5.4)	90 (15.8)	105 (12.4)
Renal and urinary disorders	9 (10.2)	76 (27.5)	129 (22.6)	205 (24.2)
Haematuria	3 (3.4)	57 (20.7)	58 (10.2)	115 (13.6)
Vascular disorders	11 (12.5)	37 (13.4)	129 (22.6)	166 (19.6)
Hypertension	2 (2.3)	29 (10.5)	66 (11.6)	95 (11.2)

Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events are sorted by decreasing frequency of system organ class and preferred term in the **All Zanubrutinib** column.

Table 38 TEAEs in ≥10% of patients in any patient group by SOC and PT (SAS)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with a least 1 treatment-related TEAE	56 (63.6)	258 (93.5)	426 (74.6)	684 (80.8)
Skin and subcutaneous tissue disorders	14 (15.9)	126 (45.7)	140 (24.5)	266 (31.4)
Rash	4 (4.5)	50 (18.1)	48 (8.4)	98 (11.6)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Purpura	3 (3.4)	44 (15.9)	13 (2.3)	57 (6.7)
Investigations	10 (11.4)	208 (75.4)	52 (9.1)	260 (30.7)
Neutrophil count decreased	5 (5.7)	158 (57.2)	22 (3.9)	180 (21.3)
Platelet count decreased	4 (4.5)	88 (31.9)	13 (2.3)	101 (11.9)
White blood cell count decreased	2 (2.3)	74 (26.8)	0 (0.0)	74 (8.7)
Alanine aminotransferase increased	2 (2.3)	31 (11.2)	3 (0.5)	34 (4.0)
Infections and infestations	7 (8.0)	99 (35.9)	132 (23.1)	231 (27.3)
Pneumonia	1 (1.1)	42 (15.2)	28 (4.9)	70 (8.3)
Upper respiratory tract infection	1 (1.1)	37 (13.4)	32 (5.6)	69 (8.1)
Blood and lymphatic system disorders	11 (12.5)	85 (30.8)	111 (19.4)	196 (23.1)
Neutropenia	7 (8.0)	17 (6.2)	66 (11.6)	83 (9.8)
Anaemia	3 (3.4)	54 (19.6)	12 (2.1)	66 (7.8)
Gastrointestinal disorders	18 (20.5)	54 (19.6)	141 (24.7)	195 (23.0)
Diarrhoea	8 (9.1)	16 (5.8)	60 (10.5)	76 (9.0)
Injury, poisoning and procedural complications	18 (20.5)	2 (0.7)	135 (23.6)	137 (16.2)
Contusion	17 (19.3)	2 (0.7)	124 (21.7)	126 (14.9)
Renal and urinary disorders	1 (1.1)	58 (21.0)	27 (4.7)	85 (10.0)
Haematuria	1 (1.1)	49 (17.8)	25 (4.4)	74 (8.7)

Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events were sorted by decreasing frequency of system organ class and preferred term in the **All Zanubrutinib** column.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

Grade 3 and higher adverse events

Table 39 Grade 3 and higher adverse events reported in ≥ 3% of patients by SOC and PT (SAS)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with a least 1 ≥ Grade 3 TEAE	38 (43.2)	181 (65.6)	373 (65.3)	554 (65.4)
Infections and infestations	15 (17.0)	86 (31.2)	145 (25.4)	231 (27.3)
Pneumonia	3 (3.4)	46 (16.7)	35 (6.1)	81 (9.6)
Upper respiratory tract infection	1 (1.1)	20 (7.2)	0 (0.0)	20 (2.4)
COVID-19 pneumonia	3 (3.4)	0 (0.0)	3 (0.5)	3 (0.4)
Blood and lymphatic system disorders	10 (11.4)	40 (14.5)	126 (22.1)	166 (19.6)
Neutropenia	8 (9.1)	8 (2.9)	77 (13.5)	85 (10.0)
Anaemia	5 (5.7)	23 (8.3)	46 (8.1)	69 (8.1)
Thrombocytopaenia	3 (3.4)	10 (3.6)	22 (3.9)	32 (3.8)
Investigations	7 (8.0)	103 (37.3)	43 (7.5)	146 (17.2)
Neutrophil count decreased	3 (3.4)	88 (31.9)	23 (4.0)	111 (13.1)
Platelet count decreased	2 (2.3)	26 (9.4)	9 (1.6)	35 (4.1)
White blood cell count decreased	0 (0.0)	20 (7.2)	0 (0.0)	20 (2.4)
Gastrointestinal disorders	8 (9.1)	11 (4.0)	52 (9.1)	63 (7.4)
Diarrhoea	3 (3.4)	2 (0.7)	14 (2.5)	16 (1.9)
Metabolism and nutrition disorders	2 (2.3)	27 (9.8)	31 (5.4)	58 (6.8)
Hypokalaemia	1 (1.1)	9 (3.3)	6 (1.1)	15 (1.8)
Vascular disorders	2 (2.3)	10 (3.6)	46 (8.1)	56 (6.6)
Hypertension	2 (2.3)	9 (3.3)	35 (6.1)	44 (5.2)
General disorders and administration site conditions	7 (8.0)	10 (3.6)	40 (7.0)	50 (5.9)
Pyrexia	4 (4.5)	0 (0.0)	14 (2.5)	14 (1.7)

Adverse events of special interest (AESI)

Adverse events of special interest are those that are known to be associated with the class of BTK inhibitors. The search criteria defining events within each category of AEs of special interest are detailed below.

Table 40 Categories of AESI

AESI category	Search Criteria
1. Haemorrhage (including minor bleeding events such as contusion and petechia)	Haemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major haemorrhage	Major haemorrhage is defined as Subdural haematoma PT, Subdural haemorrhage PT and all Haemorrhage PTs if the SOC is "Nervous system disorders" or serious or Grade 3 and above Haemorrhage PTs if the SOC is not "Nervous system disorders"
2. Atrial fibrillation and flutter	Atrial fibrillation PT, Atrial flutter PT
3. Hypertension	Hypertension (SMQ) Narrow
4. Second primary malignancies	Malignant tumours (SMQ) Narrow
Skin cancer	Skin malignant tumours (SMQ) Narrow
5. Tumour lysis syndrome	Tumour lysis syndrome (SMQ) Narrow
6. Infections	Infections and infestations SOC
Opportunistic infections	Subcategory – Opportunistic infections (SMQ) Narrow
7. Cytopenias	
Neutropenia	Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT
Thrombocytopaenia	Thrombocytopaenia PT, Platelet count decreased PT
Anaemia	Anaemia PT, Haemoglobin decreased PT

Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, Standardized MedDRA Query; SOC, system organ class

Table 41 AESIs by category (SAS)

AESI Category	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Anaemia	7 (8.0)	79 (28.6)	73 (12.8)	152 (17.9)
≥ Grade 3	5 (5.7)	23 (8.3)	46 (8.1)	69 (8.1)
Serious	2 (2.3)	4 (1.4)	10 (1.8)	14 (1.7)
Atrial fibrillation and flutter	2 (2.3)	1 (0.4)	26 (4.6)	27 (3.2)
≥ Grade 3	1 (1.1)	0 (0.0)	9 (1.6)	9 (1.1)
Serious	2 (2.3)	0 (0.0)	9 (1.6)	9 (1.1)
All haemorrhage (including major haemorrhage)	37 (42.0)	135 (48.9)	325 (56.9)	460 (54.3)
≥ Grade 3	1 (1.1)	5 (1.8)	27 (4.7)	32 (3.8)
Serious	1 (1.1)	5 (1.8)	23 (4.0)	28 (3.3)
Major haemorrhage	2 (2.3)	8 (2.9)	28 (4.9)	36 (4.3)
≥ Grade 3	1 (1.1)	5 (1.8)	27 (4.7)	32 (3.8)
Serious	1 (1.1)	5 (1.8)	23 (4.0)	28 (3.3)
Hypertension	3 (3.4)	33 (12.0)	67 (11.7)	100 (11.8)
≥ Grade 3	2 (2.3)	9 (3.3)	35 (6.1)	44 (5.2)
Serious	1 (1.1)	1 (0.4)	2 (0.4)	3 (0.4)
All infections (including opportunistic infections)	46 (52.3)	201 (72.8)	423 (74.1)	624 (73.7)
≥ Grade 3	15 (17.0)	86 (31.2)	145 (25.4)	231 (27.3)
Serious	14 (15.9)	67 (24.3)	139 (24.3)	206 (24.3)
Opportunistic infections	3 (3.4)	5 (1.8)	21 (3.7)	26 (3.1)
≥ Grade 3	1 (1.1)	4 (1.4)	12 (2.1)	16 (1.9)
Serious	1 (1.1)	5 (1.8)	11 (1.9)	16 (1.9)
Neutropenia	15 (17.0)	168 (60.9)	124 (21.7)	292 (34.5)
≥ Grade 3	11 (12.5)	91 (33.0)	102 (17.9)	193 (22.8)
Serious	0 (0.0)	4 (1.4)	20 (3.5)	24 (2.8)

AESI Category	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Second primary malignancies (including skin cancers)	8 (9.1)	8 (2.9)	107 (18.7)	115 (13.6)
≥ Grade 3	5 (5.7)	8 (2.9)	39 (6.8)	47 (5.5)
Serious	3 (3.4)	8 (2.9)	28 (4.9)	36 (4.3)
Skin cancers	3 (3.4)	0 (0.0)	74 (13.0)	74 (8.7)
≥ Grade 3	0 (0.0)	0 (0.0)	14 (2.5)	14 (1.7)
Serious	0 (0.0)	0 (0.0)	11 (1.9)	11 (1.3)
Thrombocytopaenia	13 (14.8)	112 (40.6)	71 (12.4)	183 (21.6)
≥ Grade 3	5 (5.7)	35 (12.7)	31 (5.4)	66 (7.8)
Serious	1 (1.1)	6 (2.2)	2 (0.4)	8 (0.9)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.4)
≥ Grade 3	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.4)
Serious	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)

Source: Table 2.7.4.2.6.1.1, Table 2.7.4.2.6.2.1, and Table 2.7.4.2.6.3.1
Abbreviations: AESI, adverse event of special interest; MZL, marginal zone lymphoma
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Patients with multiple events for a given AESI category or multiple preferred terms within a category are counted only once at the AESI category and preferred term levels, respectively. Events are sorted by alphabetical order of AESI category and then by decreasing frequency of preferred term within each AESI category in the **All Zanubrutinib** column.

Table 42 Exposure – adjusted incidence of AESIs (SAS)

AESI Category	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Anaemia				
No. of patients experiencing the event, n (%)	7 (8.0)	79 (28.6)	73 (12.8)	152 (17.9)
Total exposure time (person-months)	1325.2	5309.2	14193.7	19502.9
EAIR (per 100 person-months)	0.53	1.49	0.51	0.78
Atrial fibrillation and flutter				
No. of patients experiencing the event, n (%)	2 (2.3)	1 (0.4)	26 (4.6)	27 (3.2)
Total exposure time (person-months)	1358.3	6485.7	14857.7	21343.4
EAIR (per 100 person-months)	0.15	0.02	0.17	0.13
All haemorrhage (including major haemorrhage)				
No. of patients experiencing the event, n (%)	37 (42.0)	135 (48.9)	325 (56.9)	460 (54.3)
Total exposure time (person-months)	714.8	3421.0	6921.0	10342.0
EAIR (per 100 person-months)	5.18	3.95	4.70	4.45
Major haemorrhage				
No. of patients experiencing the event, n (%)	2 (2.3)	8 (2.9)	28 (4.9)	36 (4.3)
Total exposure time (person-months)	1343.8	6492.8	15027.3	21520.1
EAIR (per 100 person-months)	0.15	0.12	0.19	0.17
Hypertension				
No. of patients experiencing the event, n (%)	3 (3.4)	33 (12.0)	67 (11.7)	100 (11.8)
Total exposure time (person-months)	1361.0	5813.2	13539.8	19352.9
EAIR (per 100 person-months)	0.22	0.57	0.49	0.52
All Infections (including opportunistic infections)				
No. of patients experiencing the event, n (%)	46 (52.3)	201 (72.8)	423(74.1)	624 (73.7)
Total exposure time (person-months)	736.4	2124.2	4925.7	7049.9
EAIR (per 100 person-months)	6.25	9.46	8.59	8.85
Opportunistic Infections				
No. of patients experiencing the event, n (%)	3 (3.4)	5 (1.8)	21 (3.7)	26 (3.1)

AESI Category	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Total exposure time (person-months)	1351.4	6487.8	14809.0	21296.8
EAIR (per 100 person-months)	0.22	0.08	0.14	0.12
Neutropenia				
No. of patients experiencing the event, n (%)	15 (17.0)	168 (60.9)	124 (21.7)	292 (34.5)
Total exposure time (person-months)	1154.9	2807.8	12446.6	15254.4
EAIR (per 100 person-months)	1.30	5.98	1.00	1.91
Second primary malignancies (including skin cancers)				
No. of patients experiencing the event, n (%)	8 (9.1)	8 (2.9)	107 (18.7)	115 (13.6)
Total exposure time (person-months)	1302.1	6463.7	13008.2	19471.9
EAIR (per 100 person-months)	0.61	0.12	0.82	0.59
Skin cancers				
No. of patients experiencing the event, n (%)	3 (3.4)	0 (0.0)	74 (13.0)	74 (8.7)
Total exposure time (person-months)	1336.1	6497.1	13391.4	19888.5
EAIR (per 100 person-months)	0.22	0.00	0.55	0.37
Thrombocytopaenia				
No. of patients experiencing the event, n (%)	13 (14.8)	112 (40.6)	71 (12.4)	183 (21.6)
Total exposure time (person-months)	1242.0	4383.0	14209.2	18592.2
EAIR (per 100 person-months)	1.05	2.56	0.50	0.98
Tumour lysis syndrome				
No. of patients experiencing the event, n (%)	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.4)
Total exposure time (person-months)	1370.0	6497.1	15204.3	21701.4
EAIR (per 100 person-months)	0.00	0.00	0.02	0.01

Source: Table 2.7.4.2.8.1

Abbreviations: AESI, adverse event of special interest; EAIR, exposure-adjusted incidence rate; MZL, marginal zone lymphoma

N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

EAIR is calculated as the number of patients experiencing the event of interest divided by the total time from the first dose date to the first event date or the exposure time if the first event occurred after the last dose date or if there is no event.

Serious adverse event/deaths/other significant events

Deaths

In the 214+AU003 MZL group, 3 TEAEs led to death; myocardial infarction (n = 1) and COVID-19 pneumonia (n = 2). TEAEs with an outcome of death that were reported in > 1 patient in the All Zanubrutinib group were pneumonia (n = 7), multiple organ dysfunction syndrome (n = 5), death (cause unspecified; n = 4), COVID-19 pneumonia (n = 2), and septic shock (n = 2)

Table 43 Summary of all deaths (SAS)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Total number of deaths	10 (11.4)	45 (16.3)	116 (20.3)	161 (19.0)
Cause of death				
Progressive disease[a]	4 (4.5)	20 (7.2)	65 (11.4)	85 (10.0)
Adverse event	4 (4.5)	16 (5.8)	25 (4.4)	41 (4.8)
COVID-19 related event	2 (2.3)	0 (0.0)	3 (0.5)	3 (0.4)
Other	0 (0.0)	9 (3.3)	12 (2.1)	21 (2.5)
Unknown[b]	2 (2.3)	0 (0.0)	14 (2.5)	14 (1.7)
Deaths ≤ 30 days after last dose date	4 (4.5)	18 (6.5)	38 (6.7)	56 (6.6)
Cause of death				
Adverse event	3 (3.4)	13 (4.7)	19 (3.3)	32 (3.8)
COVID-19 related event	1 (1.1)	0 (0.0)	2 (0.4)	2 (0.2)
Progressive disease[a]	1 (1.1)	5 (1.8)	15 (2.6)	20 (2.4)
Unknown[b]	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Other	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Deaths > 30 days of last dose date	6 (6.8)	27 (9.8)	78 (13.7)	105 (12.4)
Cause of death				
Progressive disease[a]	3 (3.4)	15 (5.4)	50 (8.8)	65 (7.7)
Other	0 (0.0)	9 (3.3)	10 (1.8)	19 (2.2)
Unknown[b]	2 (2.3)	0 (0.0)	12 (2.1)	12 (1.4)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Adverse event	1 (1.1)	3 (1.1)	6 (1.1)	9 (1.1)
COVID-19 related event	1 (1.1)	0 (0.0)	1 (0.2)	1 (0.1)

Source: Table 2.7.4.2.16

Abbreviations: COVID-19, coronavirus disease 2019; eCRF, electronic case report form, MZL, marginal zone lymphoma

N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

[a] Includes 'Disease Under Study' from Study BGB-3111-214 and 'Progressive Disease' from all other studies.

[b] Includes 'Indeterminate' from Study BGB-3111-214 and 'Unknown' from all other studies.

Data in this table are based on End-of-Study/End-of-Treatment eCRFs and Deaths eCRFs.

Table 44 TEAEs leading to death by PT (SAS)

Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with a least 1 TEAEs leading to death	3 (3.4)	17 (6.2)	29 (5.1)	46 (5.4)
Pneumonia	0 (0.0)	4 (1.4)	3 (0.5)	7 (0.8)
Multiple organ dysfunction syndrome	0 (0.0)	2 (0.7)	3 (0.5)	5 (0.6)
Death	0 (0.0)	3 (1.1)	1 (0.2)	4 (0.5)
COVID-19 pneumonia	2 (2.3)	0 (0.0)	2 (0.4)	2 (0.2)
Septic shock	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Abdominal sepsis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Acute hepatitis B	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Arthritis bacterial	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Bacteraemia	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
COVID-19	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Escherichia sepsis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pneumonia fungal	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Pneumonia influenza	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pneumonia staphylococcal	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Scedosporium infection	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Sepsis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Acute myocardial infarction	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Cardiac failure	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Cardiomegaly	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Cardiopulmonary failure	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (1.1)	1 (0.4)	0 (0.0)	1 (0.1)
Bone marrow necrosis	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Acute myeloid leukaemia	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Adenocarcinoma gastric	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Lymphoma transformation	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Skin squamous cell carcinoma recurrent	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Central nervous system lesion	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Cerebral haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Brain herniation	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Road traffic accident	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Bronchiectasis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Respiratory failure	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Acute kidney injury	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Toxic epidermal necrolysis	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)

Source: Table 2.7.4.2.2.4
Abbreviations: COVID-19, coronavirus disease 2019; eCRF, electronic case report form, MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Events were sorted by decreasing frequency of preferred term in the **All Zanubrutinib** column.
Data in this table were reported as treatment-emergent Grade 5 adverse events on the adverse event page of the eCRF.

Serious Treatment-Emergent Adverse Events

Table 45 Serious TEAEs reported in >3 patients in any patient group by SOC and PT (SAS)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with a least 1 serious TEAE	35 (39.8)	111 (40.2)	288 (50.4)	399 (47.1)
Infections and infestations	14 (15.9)	67 (24.3)	139 (24.3)	206 (24.3)
Pneumonia	2 (2.3)	43 (15.6)	38 (6.7)	81 (9.6)
Cellulitis	0 (0.0)	0 (0.0)	16 (2.8)	16 (1.9)
Urinary tract infection	1 (1.1)	1 (0.4)	13 (2.3)	14 (1.7)
Upper respiratory tract infection	0 (0.0)	8 (2.9)	1 (0.2)	9 (1.1)
Influenza	2 (2.3)	0 (0.0)	7 (1.2)	7 (0.8)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	7 (1.2)	7 (0.8)
Sepsis	0 (0.0)	0 (0.0)	7 (1.2)	7 (0.8)
Bronchitis	1 (1.1)	4 (1.4)	2 (0.4)	6 (0.7)
Skin infection	1 (1.1)	4 (1.4)	1 (0.2)	5 (0.6)
Gastrointestinal disorders	6 (6.8)	8 (2.9)	37 (6.5)	45 (5.3)
Diarrhoea	2 (2.3)	0 (0.0)	7 (1.2)	7 (0.8)
Abdominal pain	0 (0.0)	0 (0.0)	4 (0.7)	4 (0.5)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
General disorders and administration site conditions	10 (11.4)	6 (2.2)	35 (6.1)	41 (4.8)
Pyrexia	7 (8.0)	0 (0.0)	21 (3.7)	21 (2.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (3.4)	9 (3.3)	31 (5.4)	40 (4.7)
Basal cell carcinoma	0 (0.0)	0 (0.0)	4 (0.7)	4 (0.5)
Respiratory, thoracic and mediastinal disorders	3 (3.4)	6 (2.2)	34 (6.0)	40 (4.7)
Pleural effusion	0 (0.0)	3 (1.1)	8 (1.4)	11 (1.3)
Dyspnoea	0 (0.0)	0 (0.0)	5 (0.9)	5 (0.6)
Respiratory failure	1 (1.1)	1 (0.4)	4 (0.7)	5 (0.6)
Blood and lymphatic system disorders	2 (2.3)	7 (2.5)	31 (5.4)	38 (4.5)
Anaemia	2 (2.3)	4 (1.4)	10 (1.8)	14 (1.7)
Febrile neutropenia	0 (0.0)	1 (0.4)	10 (1.8)	11 (1.3)
Neutropenia	0 (0.0)	0 (0.0)	7 (1.2)	7 (0.8)
Cardiac disorders	5 (5.7)	5 (1.8)	30 (5.3)	35 (4.1)
Atrial fibrillation	1 (1.1)	0 (0.0)	6 (1.1)	6 (0.7)
Injury, poisoning and procedural complications	4 (4.5)	7 (2.5)	27 (4.7)	34 (4.0)
Fall	2 (2.3)	0 (0.0)	7 (1.2)	7 (0.8)
Nervous system disorders	4 (4.5)	13 (4.7)	18 (3.2)	31 (3.7)
Syncope	1 (1.1)	1 (0.4)	4 (0.7)	5 (0.6)
Renal and urinary disorders	1 (1.1)	2 (0.7)	19 (3.3)	21 (2.5)
Acute kidney injury	1 (1.1)	0 (0.0)	7 (1.2)	7 (0.8)
Haematuria	0 (0.0)	0 (0.0)	5 (0.9)	5 (0.6)
Investigations	1 (1.1)	9 (3.3)	6 (1.1)	15 (1.8)
Platelet count decreased	1 (1.1)	6 (2.2)	0 (0.0)	6 (0.7)

Source: Table 2.7.4.2.2.3

Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event

N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively.
Events were sorted by decreasing frequency for system organ class and then by preferred term within each system organ class in the **All Zanubrutinib** column.

Laboratory findings

Table 46 Incidence of high directional abnormalities for Serum chemistry analytes of **Interest at Baseline and Postbaseline (Safety Analysis Set)**

Analyte: High Abnormal Values	214+AU003 MZL (N = 88)	All China (N = 276)	All Non-China (N = 571)	All Zanubrutinib (N = 847)
Alkaline phosphatase (U/L)				
Baseline, n	88	276	571	847
Patients with ≥ Grade 1 toxicity (%)	17 (19.3)	30 (10.9)	105 (18.4)	135 (15.9)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Any postbaseline, n	88	274	570	844
Patients with ≥ Grade 1 toxicity (%)	23 (26.1)	83 (30.3)	212 (37.2)	295 (35.0)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.4)
ALT (U/L)				

Analyte: High Abnormal Values	214+AU003 MZL (N = 88)	All China (N = 276)	All Non-China (N = 571)	All Zanubrutinib (N = 847)
Baseline, n	88	276	571	847
Patients with ≥ Grade 1 toxicity (%)	6 (6.8)	11 (4.0)	41 (7.2)	52 (6.1)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any postbaseline, n	88	274	570	844
Patients with ≥ Grade 1 toxicity (%)	24 (27.3)	79 (28.8)	180 (31.6)	259 (30.7)
Patients with ≥ Grade 3 toxicity (%)	1 (1.1)	4 (1.5)	7 (1.2)	11 (1.3)
AST (U/L)				
Baseline, n	88	276	570	846
Patients with ≥ Grade 1 toxicity (%)	7 (8.0)	15 (5.4)	48 (8.4)	63 (7.4)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any postbaseline, n	88	274	569	843
Patients with ≥ Grade 1 toxicity (%)	15 (17.0)	60 (21.9)	128 (22.5)	188 (22.3)
Patients with ≥ Grade 3 toxicity (%)	1 (1.1)	4 (1.5)	7 (1.2)	11 (1.3)
Bilirubin (µmol/L)				
Baseline, n	88	276	570	846
Patients with ≥ Grade 1 toxicity (%)	3 (3.4)	22 (8.0)	31 (5.4)	53 (6.3)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any postbaseline, n	88	274	570	844
Patients with ≥ Grade 1 toxicity (%)	16 (18.2)	88 (32.1)	141 (24.7)	229 (27.1)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	3 (1.1)	5 (0.9)	8 (0.9)
Creatinine (µmol/L)				
Baseline, n	88	276	571	847
Patients with ≥ Grade 1 toxicity (%)	13 (14.8)	10 (3.6)	99 (17.3)	109 (12.9)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any postbaseline, n	88	275	570	845
Patients with ≥ Grade 1 toxicity (%)	39 (44.3)	47 (17.1)	233 (40.9)	280 (33.1)
Patients with ≥ Grade 3 toxicity (%)	1 (1.1)	1 (0.4)	7 (1.2)	8 (0.9)
Glucose (mmol/L)				
Baseline, n	88	276	553	829
Patients with ≥ Grade 1 toxicity (%)	23 (26.1)	57 (20.7)	165 (29.8)	222 (26.8)
Patients with ≥ Grade 3 toxicity (%)	1 (1.1)	1 (0.4)	6 (1.1)	7 (0.8)

Analyte: High Abnormal Values	214+AU003 MZL (N = 88)	All China (N = 276)	All Non-China (N = 571)	All Zanubrutinib (N = 847)
Any postbaseline, n	87	274	558	832
Patients with ≥ Grade 1 toxicity (%)	60 (69.0)	176 (64.2)	397 (71.1)	573 (68.9)
Patients with ≥ Grade 3 toxicity (%)	5 (5.7)	9 (3.3)	32 (5.7)	41 (4.9)
Urate (µmol/L)				
Baseline, n	20	265	503	768
Patients with ≥ Grade 1 toxicity (%)	3 (15.0)	67 (25.3)	74 (14.7)	141 (18.4)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	7 (2.6)	3 (0.6)	10 (1.3)
Any postbaseline, n	20	264	510	774
Patients with ≥ Grade 1 toxicity (%)	5 (25.0)	119 (45.1)	164 (32.2)	283 (36.6)
Patients with ≥ Grade 3 toxicity (%)	0 (0.0)	17 (6.4)	14 (2.7)	31 (4.0)

Source: Table 2.7.4.3.3.2
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MZL, marginal zone lymphoma
N = number of patients who received at least 1 dose of zanubrutinib.
Percentages were based on n, number of patients with at least 1 assessment at baseline or at any time postbaseline, respectively.
Laboratory results were graded using National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03.

Safety in special populations

INTRINSIC FACTORS

Age

Table 47 Overview of TEAEs by age category (SAS)

	214+AU003 MZL			All Zanubrutinib		
	< 65 Years (N = 31) n (%)	65 to < 75 Years (N = 34) n (%)	≥ 75 Years (N = 23) n (%)	< 65 Years (N = 402) n (%)	65 to < 75 Years (N = 274) n (%)	≥ 75 Years (N = 171) n (%)
Patients with at least 1 TEAE	31 (100)	33 (97.1)	21 (91.3)	394 (98.0)	269 (98.2)	169 (98.8)
≥ Grade 3	11 (35.5)	16 (47.1)	11 (47.8)	249 (61.9)	175 (63.9)	130 (76.0)
Serious	11 (35.5)	14 (41.2)	10 (43.5)	156 (38.8)	136 (49.6)	107 (62.6)
Leading to death	1 (3.2)	2 (5.9)	0 (0.0)	13 (3.2)	17 (6.2)	16 (9.4)
Leading to treatment discontinuation	2 (6.5)	3 (8.8)	0 (0.0)	29 (7.2)	39 (14.2)	23 (13.5)
Leading to dose reduction	0 (0.0)	2 (5.9)	0 (0.0)	22 (5.5)	23 (8.4)	18 (10.5)

Source: Table 2.7.4.2.12.1, Table 2.7.4.2.12.2, and Table 2.7.4.2.12.3
Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

Table 33. TEAEs by System Organ Class and Preferred Term Reported for ≥ 10% in any Study Population by Age Category (Safety Analysis Set)

System Organ Class Preferred Term	214+AU003 MZL			All Zanubrutinib		
	< 65 Years (N = 31) n (%)	65 to < 75 Years (N = 34) n (%)	≥ 75 Years (N = 23) n (%)	< 65 Years (N = 402) n (%)	65 to <75 Years (N = 274) n (%)	≥ 75 Years (N = 171) n (%)
Patients with at least 1 TEAE	31 (100)	33 (97.1)	21 (91.3)	394 (98.0)	269 (98.2)	169 (98.8)
Infections and infestations	17 (54.8)	18 (52.9)	11 (47.8)	296 (73.6)	203 (74.1)	125 (73.1)
Upper respiratory tract infection	6 (19.4)	5 (14.7)	3 (13.0)	173 (43.0)	97 (35.4)	45 (26.3)
Pneumonia	2 (6.5)	0 (0.0)	2 (8.7)	71 (17.7)	39 (14.2)	19 (11.1)
Urinary tract infection	2 (6.5)	2 (5.9)	1 (4.3)	49 (12.2)	40 (14.6)	35 (20.5)
Nasopharyngitis	1 (3.2)	5 (14.7)	0 (0.0)	26 (6.5)	19 (6.9)	14 (8.2)
Sinusitis	4 (12.9)	1 (2.9)	0 (0.0)	25 (6.2)	24 (8.8)	5 (2.9)
Lower respiratory tract infection	1 (3.2)	0 (0.0)	0 (0.0)	18 (4.5)	11 (4.0)	20 (11.7)
Gastrointestinal disorders	16 (51.6)	20 (58.8)	12 (52.2)	221 (55.0)	164 (59.9)	112 (65.5)
Diarrhoea	7 (22.6)	7 (20.6)	8 (34.8)	84 (20.9)	67 (24.5)	48 (28.1)
Constipation	2 (6.5)	6 (17.6)	5 (21.7)	37 (9.2)	47 (17.2)	43 (25.1)
Nausea	6 (19.4)	2 (5.9)	3 (13.0)	36 (9.0)	36 (13.1)	26 (15.2)
Abdominal pain	4 (12.9)	4 (11.8)	1 (4.3)	25 (6.2)	17 (6.2)	12 (7.0)
Skin and subcutaneous tissue disorders	9 (29.0)	11 (32.4)	9 (39.1)	216 (53.7)	138 (50.4)	95 (55.6)
Rash	4 (12.9)	3 (8.8)	2 (8.7)	83 (20.6)	53 (19.3)	26 (15.2)
Purpura	0 (0.0)	0 (0.0)	3 (13.0)	33 (8.2)	18 (6.6)	13 (7.6)
Pruritus	2 (6.5)	0 (0.0)	0 (0.0)	19 (4.7)	23 (8.4)	21 (12.3)
Respiratory, thoracic and mediastinal disorders	3 (9.7)	11 (32.4)	8 (34.8)	152 (37.8)	135 (49.3)	91 (53.2)
Cough	1 (3.2)	2 (5.9)	4 (17.4)	75 (18.7)	55 (20.1)	43 (25.1)
Epistaxis	0 (0.0)	5 (14.7)	0 (0.0)	26 (6.5)	25 (9.1)	18 (10.5)
Productive cough	0 (0.0)	0 (0.0)	3 (13.0)	13 (3.2)	9 (3.3)	10 (5.8)
Investigations	6 (19.4)	4 (11.8)	6 (26.1)	216 (53.7)	103 (37.6)	55 (32.2)
Neutrophil count decreased	2 (6.5)	2 (5.9)	1 (4.3)	123 (30.6)	49 (17.9)	21 (12.3)

System Organ Class Preferred Term	214+AU003 MZL			All Zanubrutinib		
	< 65 Years (N = 31) n (%)	65 to < 75 Years (N = 34) n (%)	≥ 75 Years (N = 23) n (%)	< 65 Years (N = 402) n (%)	65 to <75 Years (N = 274) n (%)	≥ 75 Years (N = 171) n (%)
Platelet count decreased	2 (6.5)	3 (8.8)	1 (4.3)	70 (17.4)	32 (11.7)	13 (7.6)
White blood cell count decreased	2 (6.5)	0 (0.0)	0 (0.0)	61 (15.2)	14 (5.1)	6 (3.5)
General disorders and administration site conditions	10 (32.3)	11 (32.4)	9 (39.1)	148 (36.8)	119 (43.4)	91 (53.2)
Fatigue	3 (9.7)	5 (14.7)	2 (8.7)	47 (11.7)	43 (15.7)	35 (20.5)
Pyrexia	5 (16.1)	5 (14.7)	4 (17.4)	43 (10.7)	40 (14.6)	26 (15.2)
Oedema peripheral	1 (3.2)	1 (2.9)	4 (17.4)	13 (3.2)	28 (10.2)	31 (18.1)
Asthenia	1 (3.2)	0 (0.0)	3 (13.0)	9 (2.2)	9 (3.3)	12 (7.0)
Musculoskeletal and connective tissue disorders	14 (45.2)	10 (29.4)	8 (34.8)	128 (31.8)	118 (43.1)	83 (48.5)
Back pain	4 (12.9)	2 (5.9)	3 (13.0)	39 (9.7)	39 (14.2)	20 (11.7)
Arthralgia	3 (9.7)	2 (5.9)	2 (8.7)	36 (9.0)	37 (13.5)	18 (10.5)
Pain in extremity	1 (3.2)	1 (2.9)	1 (4.3)	18 (4.5)	17 (6.2)	19 (11.1)
Injury, poisoning and procedural complications	5 (16.1)	14 (41.2)	8 (34.8)	109 (27.1)	104 (38.0)	91 (53.2)
Contusion	3 (9.7)	12 (35.3)	6 (26.1)	52 (12.9)	67 (24.5)	59 (34.5)
Fall	0 (0.0)	1 (2.9)	2 (8.7)	8 (2.0)	19 (6.9)	21 (12.3)
Blood and lymphatic system disorders	6 (19.4)	6 (17.6)	4 (17.4)	152 (37.8)	82 (29.9)	68 (39.8)
Anaemia	3 (9.7)	2 (5.9)	2 (8.7)	73 (18.2)	37 (13.5)	36 (21.1)
Neutropenia	4 (12.9)	3 (8.8)	3 (13.0)	57 (14.2)	28 (10.2)	28 (16.4)
Thrombocytopaenia	3 (9.7)	2 (5.9)	2 (8.7)	33 (8.2)	20 (7.3)	22 (12.9)
Nervous system disorders	11 (35.5)	10 (29.4)	5 (21.7)	118 (29.4)	94 (34.3)	72 (42.1)
Headache	3 (9.7)	2 (5.9)	0 (0.0)	50 (12.4)	36 (13.1)	19 (11.1)
Dizziness	4 (12.9)	2 (5.9)	1 (4.3)	25 (6.2)	25 (9.1)	18 (10.5)
Lethargy	1 (3.2)	2 (5.9)	3 (13.0)	4 (1.0)	3 (1.1)	8 (4.7)
Renal and urinary disorders	2 (6.5)	6 (17.6)	1 (4.3)	98 (24.4)	64 (23.4)	43 (25.1)
Haematuria	1 (3.2)	2 (5.9)	0 (0.0)	56 (13.9)	41 (15.0)	18 (10.5)
Vascular disorders	2 (6.5)	5 (14.7)	4 (17.4)	48 (11.9)	62 (22.6)	56 (32.7)
Hypertension	0 (0.0)	1 (2.9)	1 (4.3)	34 (8.5)	39 (14.2)	22 (12.9)

Source: Table 2.7.4.2.13.1, Table 2.7.4.2.13.2, and Table 2.7.4.2.13.3
Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
Notes: N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class were counted only once at the preferred term and system organ class levels, respectively. Events were sorted by decreasing frequency first, by system organ class, and then by preferred term within each system organ class in the **All Zanubrutinib** column.

Table 48 TEAEs of special Interest by demographics and selected baseline characteristics

(Safety Analysis Set)

	All Zanubrutinib (N = 847) n (%)					
	Anemia	Atrial fibrillation and flutter	Hemorrhage	Major hemorrhage	Hypertension	Infections
Age (years)[a]						
Mean (SD)	64.1 (13.03)	75.5 (7.13)	65.9 (11.30)	72.4 (10.81)	66.0 (10.40)	64.7 (11.35)
Median	64.0	76.0	66.0	72.5	67.5	65.0
Min, Max	28, 90	62, 86	24, 90	52, 87	41, 87	20, 90
<65 (N1 = 402)	78 (19.4)	1 (0.2)	196 (48.8)	11 (2.7)	37 (9.2)	296 (73.6)
65 - <75 (N1 = 274)	37 (13.5)	11 (4.0)	156 (56.9)	9 (3.3)	40 (14.6)	203 (74.1)
≥75 (N1 = 171)	37 (21.6)	15 (8.8)	108 (63.2)	16 (9.4)	23 (13.5)	125 (73.1)

Table 49

TEAE of Special Interest by Demographics and Selected Baseline Characteristics in All Zanubrutinib Patients (Safety Analysis Set)

	All Zanubrutinib (N = 847) n (%)					
	Opportunistic infections	Neutropenia	Second primary malignancies	Skin cancers	Thrombocytopenia	Tumor lysis syndrome
Age (years)[a]						
Mean (SD)	67.1 (10.99)	62.6 (10.77)	69.7 (9.33)	70.6 (9.47)	63.6 (11.28)	75.7 (7.51)
Median	70.0	63.0	70.0	71.5	63.0	76.0
Min, Max	46, 85	28, 87	46, 90	46, 90	28, 87	68, 83
<65 (N1 = 402)	9 (2.2)	172 (42.8)	29 (7.2)	16 (4.0)	96 (23.9)	0 (0.0)
65 - <75 (N1 = 274)	10 (3.6)	73 (26.6)	49 (17.9)	31 (11.3)	52 (19.0)	1 (0.4)
≥75 (N1 = 171)	7 (4.1)	47 (27.5)	37 (21.6)	27 (15.8)	35 (20.5)	2 (1.2)

Sex

Table 50 Overview of TEAEs by Sex (SAS)

	214+AU003 MZL		All Zanubrutinib	
	Male (N = 46) n (%)	Female (N = 42) n (%)	Male (N = 564) n (%)	Female (N = 283) n (%)
Patients with at least 1 TEAE	43 (93.5)	42 (100)	553 (98.0)	279 (98.6)
≥ Grade 3	24 (52.2)	14 (33.3)	368 (65.2)	186 (65.7)
Serious	21 (45.7)	14 (33.3)	272 (48.2)	127 (44.9)
Leading to death	3 (6.5)	0 (0.0)	38 (6.7)	8 (2.8)
Leading to treatment discontinuation	4 (8.7)	1 (2.4)	64 (11.3)	27 (9.5)
Leading to dose reduction	0 (0.0)	2 (4.8)	42 (7.4)	21 (7.4)

Source: Table 2.7.4.2.12.4 and Table 2.7.4.2.12.5
Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Adverse event grades were evaluated using National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03.

Weight

Table 51 Overview of TEAEs by baseline weight category

for the 214+AU003 MZL and All Zanubrutinib Patient Groups (Safety Analysis Set)

	214+AU003 MZL		All Zanubrutinib	
	≥ Median Weight (N = 46) n (%)	< Median Weight (N = 42) n (%)	≥ Median Weight (N = 423) n (%)	< Median Weight (N = 424) n (%)
Patients with at least 1 TEAE	45 (97.8)	40 (95.2)	416 (98.3)	416 (98.1)
≥ Grade 3	24 (52.2)	14 (33.3)	267 (63.1)	287 (67.7)
Serious	20 (43.5)	15 (35.7)	201 (47.5)	198 (46.7)
Leading to death	2 (4.3)	1 (2.4)	22 (5.2)	24 (5.7)
Leading to treatment discontinuation	3 (6.5)	2 (4.8)	44 (10.4)	47 (11.1)
Leading to dose reduction	0 (0.0)	2 (4.8)	36 (8.5)	27 (6.4)

Source: Table 2.7.4.2.12.6 and Table 2.7.4.2.12.7
Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

Table 52 TEAEs reported in ≥ 10% in any BMI by SOC and PT (SAS)

System Organ Class Preferred Term	All Zanubrutinib			
BMI groups	**Below 18.5 (below normal)**	**>= 18.5 and < 25.0 (normal)**	**>= 25.0 and < 30.0 (overweight)**	**30.0 and above (obese)**
Patient number (N)	N = 17	N = 411	N = 287	N =127
Infections and infestations	12 (70.6)	298 (72.5)	210 (73.2)	100 (78.7)
Upper respiratory tract infection	4 (23.5)	153 (37.2)	106 (36.9)	50 (39.4)
Urinary tract infection	3 (17.6)	60 (14.6)	32 (11.1)	27 (21.3)
Sinusitis	1 (5.9)	17 (4.1)	18 (6.3)	17 (13.4)
Pneumonia	3 (17.6)	73 (17.8)	38 (13.2)	15 (11.8)
Cellulitis	0 (0.0)	11 (2.7)	18 (6.3)	13 (10.2)

System Organ Class Preferred Term	All Zanubrutinib			
BMI groups	**Below 18.5 (below normal)**	**>= 18.5 and < 25.0 (normal)**	**>= 25.0 and < 30.0 (overweight)**	**30.0 and above (obese)**
Patient number (N)	N = 17	N = 411	N = 287	N =127
Gastrointestinal disorders	10 (58.8)	235 (57.2)	162 (56.4)	87 (68.5)
Diarrhoea	5 (29.4)	90 (21.9)	66 (23.0)	37 (29.1)
Constipation	1 (5.9)	57 (13.9)	44 (15.3)	25 (19.7)
Nausea	2 (11.8)	40 (9.7)	31 (10.8)	24 (18.9)
Skin and subcutaneous tissue disorders	9 (52.9)	209 (50.9)	158 (55.1)	72 (56.7)
Rash	3 (17.6)	74 (18.0)	56 (19.5)	28 (22.0)
Petechiae	0 (0.0)	19 (4.6)	14 (4.9)	14 (11.0)
Pruritus	2 (11.8)	28 (6.8)	22 (7.7)	11 (8.7)
Rash erythematous	2 (11.8)	4 (1.0)	2 (0.7)	2 (1.6)
Musculoskeletal and connective tissue disorders	7 (41.2)	135 (32.8)	117 (40.8)	70 (55.1)
Back pain	3 (17.6)	43 (10.5)	26 (9.1)	26 (20.5)
Arthralgia	2 (11.8)	35 (8.5)	33 (11.5)	21 (16.5)
Muscle spasms	0 (0.0)	19 (4.6)	18 (6.3)	17 (13.4)
Pain in extremity	1 (5.9)	19 (4.6)	20 (7.0)	14 (11.0)
Flank pain	2 (11.8)	4 (1.0)	1 (0.3)	3 (2.4)
General disorders and administration site conditions	9 (52.9)	163 (39.7)	115 (40.1)	69 (54.3)
Fatigue	3 (17.6)	51 (12.4)	39 (13.6)	31 (24.4)
Oedema peripheral	0 (0.0)	27 (6.6)	26 (9.1)	19 (15.0)
Pyrexia	2 (11.8)	63 (15.3)	33 (11.5)	11 (8.7)
Respiratory, thoracic and mediastinal disorders	8 (47.1)	184 (44.8)	119 (41.5)	66 (52.0)
Cough	1 (5.9)	85 (20.7)	52 (18.1)	35 (27.6)
Epistaxis	2 (11.8)	27 (6.6)	25 (8.7)	15 (11.8)

System Organ Class Preferred Term	All Zanubrutinib			
BMI groups	Below 18.5 (below normal)	>= 18.5 and < 25.0 (normal)	>= 25.0 and < 30.0 (overweight)	30.0 and above (obese)
Patient number (N)	N = 17	N = 411	N = 287	N =127
Oropharyngeal pain	2 (11.8)	28 (6.8)	10 (3.5)	6 (4.7)
Nervous system disorders	3 (17.6)	126 (30.7)	89 (31.0)	62 (48.8)
Headache	0 (0.0)	42 (10.2)	40 (13.9)	22 (17.3)
Dizziness	0 (0.0)	30 (7.3)	24 (8.4)	13 (10.2)
Paraesthesia	2 (11.8)	7 (1.7)	11 (3.8)	6 (4.7)
Injury, poisoning and procedural complications	6 (35.3)	125 (30.4)	112 (39.0)	59 (46.5)
Contusion	4 (23.5)	67 (16.3)	68 (23.7)	37 (29.1)
Blood and lymphatic system disorders	6 (35.3)	157 (38.2)	97 (33.8)	42 (33.1)
Neutropenia	1 (5.9)	50 (12.2)	45 (15.7)	17 (13.4)
Anaemia	4 (23.5)	87 (21.2)	39 (13.6)	16 (12.6)
Investigations	8 (47.1)	215 (52.3)	113 (39.4)	37 (29.1)
Neutrophil count decreased	4 (23.5)	125 (30.4)	56 (19.5)	8 (6.3)
Platelet count decreased	3 (17.6)	72 (17.5)	29 (10.1)	10 (7.9)
White blood cell count decreased	2 (11.8)	54 (13.1)	24 (8.4)	1 (0.8)
Carbon dioxide increased	3 (17.6)	20 (4.9)	4 (1.4)	0 (0.0)
Urobilinogen urine increased	2 (11.8)	12 (2.9)	2 (0.7)	0 (0.0)
Renal and urinary disorders	3 (17.6)	107 (26.0)	61 (21.3)	33 (26.0)
Haematuria	3 (17.6)	66 (16.1)	30 (10.5)	15 (11.8)
Proteinuria	2 (11.8)	16 (3.9)	7 (2.4)	1 (0.8)
Vascular disorders	3 (17.6)	74 (18.0)	55 (19.2)	33 (26.0)
Hypertension	2 (11.8)	37 (9.0)	34 (11.8)	21 (16.5)

System Organ Class Preferred Term	All Zanubrutinib			
BMI groups	Below 18.5 (below normal)	>= 18.5 and < 25.0 (normal)	>= 25.0 and < 30.0 (overweight)	30.0 and above (obese)
Patient number (N)	N = 17	N = 411	N = 287	N =127
Metabolism and nutrition disorders	6 (35.3)	161 (39.2)	102 (35.5)	32 (25.2)
Hypokalaemia	3 (17.6)	46 (11.2)	18 (6.3)	5 (3.9)
Decreased appetite	2 (11.8)	33 (8.0)	10 (3.5)	5 (3.9)
Hypercholesterolaemia	2 (11.8)	7 (1.7)	5 (1.7)	0 (0.0)
Hypocalcaemia	2 (11.8)	16 (3.9)	6 (2.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (29.4)	57 (13.9)	48 (16.7)	29 (22.8)
Eye disorders	1 (5.9)	60 (14.6)	27 (9.4)	20 (15.7)
Cardiac disorders	0 (0.0)	68 (16.5)	48 (16.7)	19 (15.0)
Ear and labyrinth disorders	2 (11.8)	27 (6.6)	23 (8.0)	18 (14.2)
Psychiatric disorders	3 (17.6)	38 (9.2)	30 (10.5)	17 (13.4)
Insomnia	3 (17.6)	20 (4.9)	13 (4.5)	2 (1.6)
Reproductive system and breast disorders	2 (11.8)	28 (6.8)	14 (4.9)	10 (7.9)

Race

An overview of TEAEs for patients in the All Zanubrutinib group is presented by race in Table 38. Similar percentages among white and Asian patients reported 1 or more TEAEs (98.5% versus 97.6%, respectively), ≥ Grade 3 TEAEs (64.8% versus 66.3%, respectively) as well as TEAEs leading to treatment discontinuation (10.7% versus 10.4%, respectively) and death (5.0% versus 5.4%, respectively). Events that met the criteria for seriousness were more common in white than Asian patients (49.1% versus 41.8%, respectively), an observation that is consistent with that based on regional differences (All Non-China and All China groups).

Table 38. Overview of TEAEs in the 214+AU003 MZL and All Zanubrutinib Patient Groups by Race (Safety Analysis Set)

	214+AU003 MZL			All Zanubrutinib		
	White (N = 56) n (%)	Asian (N = 17) n (%)	Other (N = 15) n (%)	White (N = 458) n (%)	Asian (N = 335) n (%)	Other (N = 53) n (%)
Patients with at least 1 TEAE	54 (96.4)	16 (94.1)	15 (100.0)	451 (98.5)	327 (97.6)	53 (100.0)
≥ Grade 3	24 (42.9)	6 (35.3)	8 (53.3)	297 (64.8)	222 (66.3)	34 (64.2)
Serious	20 (35.7)	7 (41.2)	8 (53.3)	225 (49.1)	140 (41.8)	33 (62.3)
Leading to death	1 (1.8)	1 (5.9)	1 (6.7)	23 (5.0)	18 (5.4)	5 (9.4)
Leading to treatment discontinuation	2 (3.6)	1 (5.9)	2 (13.3)	49 (10.7)	35 (10.4)	6 (11.3)
Leading to dose reduction	2 (3.6)	0 (0.0)	0 (0.0)	45 (9.8)	16 (4.8)	2 (3.8)

Source: Table 2.7.4.2.14.1

Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event

N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

Table 39. TEAEs by System Organ Class and Preferred Term Reported for ≥ 15% in Any Study Population by Race Category (Safety Analysis Set)

System Organ Class Preferred Term	214+AU003 MZL			All Zanubrutinib		
	White (N = 56) n (%)	Asian (N = 17) n (%)	Other (N = 15) n (%)	White (N = 458) n (%)	Asian (N = 335) n (%)	Other (N = 53) n (%)
Patients with at least 1 TEAE	54 (96.4)	16 (94.1)	15 (100.0)	451 (98.5)	327 (97.6)	53 (100.0)
Infections and infestations	31 (55.4)	7 (41.2)	8 (53.3)	352 (76.9)	237 (70.7)	34 (64.2)
Upper respiratory tract infection	12 (21.4)	2 (11.8)	0 (0.0)	170 (37.1)	130 (38.8)	15 (28.3)
Pneumonia	3 (5.4)	1 (5.9)	0 (0.0)	46 (10.0)	78 (23.3)	5 (9.4)
Urinary tract infection	4 (7.1)	0 (0.0)	1 (6.7)	73 (15.9)	41 (12.2)	9 (17.0)
Gastrointestinal disorders	34 (60.7)	4 (23.5)	10 (66.7)	293 (64.0)	164 (49.0)	39 (73.6)
Diarrhoea	14 (25.0)	2 (11.8)	6 (40.0)	129 (28.2)	56 (16.7)	14 (26.4)
Constipation	10 (17.9)	2 (11.8)	1 (6.7)	85 (18.6)	32 (9.6)	10 (18.9)
Nausea	9 (16.1)	0 (0.0)	2 (13.3)	79 (17.2)	10 (3.0)	8 (15.1)
Skin and subcutaneous tissue disorders	21 (37.5)	2 (11.8)	6 (40.0)	249 (54.4)	168 (50.1)	32 (60.4)
Rash	7 (12.5)	1 (5.9)	1 (6.7)	81 (17.7)	73 (21.8)	8 (15.1)
Respiratory, thoracic and mediastinal disorders	14 (25.0)	2 (11.8)	6 (40.0)	222 (48.5)	127 (37.9)	29 (54.7)
Cough	5 (8.9)	0 (0.0)	2 (13.3)	105 (22.9)	58 (17.3)	10 (18.9)
Epistaxis	3 (5.4)	0 (0.0)	2 (13.3)	44 (9.6)	16 (4.8)	9 (17.0)
Investigations	5 (8.9)	9 (52.9)	2 (13.3)	105 (22.9)	256 (76.4)	13 (24.5)
Neutrophil count decreased	1 (1.8)	4 (23.5)	0 (0.0)	21 (4.6)	171 (51.0)	1 (1.9)
Platelet count decreased	2 (3.6)	4 (23.5)	0 (0.0)	15 (3.3)	99 (29.6)	1 (1.9)
White blood cell count decreased	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	81 (24.2)	0 (0.0)
General disorders and administration site conditions	20 (35.7)	3 (17.6)	7 (46.7)	224 (48.9)	106 (31.6)	28 (52.8)
Fatigue	8 (14.3)	1 (5.9)	1 (6.7)	97 (21.2)	19 (5.7)	9 (17.0)
Pyrexia	9 (16.1)	1 (5.9)	4 (26.7)	59 (12.9)	40 (11.9)	10 (18.9)
Musculoskeletal and connective tissue disorders	22 (39.3)	3 (17.6)	7 (46.7)	240 (52.4)	61 (18.2)	27 (50.9)
Back pain	5 (8.9)	2 (11.8)	2 (13.3)	70 (15.3)	17 (5.1)	11 (20.8)
Injury, poisoning and procedural complications	24 (42.9)	0 (0.0)	3 (20.0)	236 (51.5)	46 (13.7)	22 (41.5)
Contusion	19 (33.9)	0 (0.0)	2 (13.3)	153 (33.4)	11 (3.3)	14 (26.4)
Blood and lymphatic system disorders	11 (19.6)	2 (11.8)	3 (20.0)	164 (35.8)	124 (37.0)	14 (26.4)
Anaemia	3 (5.4)	2 (11.8)	2 (13.3)	56 (12.2)	83 (24.8)	7 (13.2)
Neutropenia	7 (12.5)	0 (0.0)	3 (20.0)	81 (17.7)	25 (7.5)	7 (13.2)
Metabolism and nutrition disorders	7 (12.5)	5 (29.4)	1 (6.7)	111 (24.2)	174 (51.9)	18 (34.0)
Hypokalaemia	2 (3.6)	2 (11.8)	0 (0.0)	14 (3.1)	56 (16.7)	3 (5.7)
Hyperglycaemia	0 (0.0)	0 (0.0)	1 (6.7)	6 (1.3)	51 (15.2)	2 (3.8)
Decreased appetite	0 (0.0)	3 (17.6)	0 (0.0)	21 (4.6)	24 (7.2)	5 (9.4)
Nervous system disorders	15 (26.8)	3 (17.6)	8 (53.3)	186 (40.6)	67 (20.0)	31 (58.5)
Headache	5 (8.9)	0 (0.0)	0 (0.0)	72 (15.7)	23 (6.9)	10 (18.9)
Renal and urinary disorders	5 (8.9)	2 (11.8)	2 (13.3)	104 (22.7)	87 (26.0)	13 (24.5)
Haematuria	0 (0.0)	1 (5.9)	2 (13.3)	45 (9.8)	63 (18.8)	7 (13.2)

Source: Table 2.7.4.2.14.2

Abbreviations: MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event

N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class were counted only once at the preferred term and system organ class levels, respectively. Events were sorted by decreasing frequency first, by system organ class, and then by preferred term within each system organ class in the **All Zanubrutinib** column.

Safety related to drug-drug interactions and other interactions

See the pharmacokinetics section.

Discontinuation due to adverse events

Across all patient groups, the most common reason for treatment discontinuation was progressive disease and the most common reason for study discontinuation was death (Table 4).

In the 214+AU003 MZL group, 36 patients (40.9%) discontinued study treatment. Fourteen patients (15.9%) discontinued study participation. Median follow-up time on study was 16.69 months (range: 1.6 to 59.2 months).

In the All China group, 246 patients (89.1%) discontinued study treatment. A total of 237 patients (85.9%) discontinued study participation. The large percentages of patients discontinued from study treatment and participation are a consequence of the closure of studies BGB-3111-205, 206, and 1002.

In the All Zanubrutinib group, 497 patients (58.7%) discontinued study treatment. A total of 394 patients (46.5%) discontinued study participation. Median follow-up time on study was 32.43 months (range: 0.1 to 71.4 months).

Table 53 Patient disposition and reasons for discontinuation (SAS)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Number of patients treated	88	276	571	847
Patients discontinued from treatment	36 (40.9)	246 (89.1)	251 (44.0)	497 (58.7)
Reason for discontinuation				
Progressive disease	25 (28.4)	97 (35.1)	149 (26.1)	246 (29.0)
Study terminated by sponsor[a]	0 (0.0)	109 (39.5)	0 (0.0)	109 (12.9)
Adverse event	5 (5.7)	31 (11.2)	61 (10.7)	92 (10.9)
COVID-19 related event	2 (2.3)	0 (0.0)	3 (0.5)	3 (0.4)
Withdrawal by subject	3 (3.4)	2 (0.7)	19 (3.3)	21 (2.5)
Investigator's discretion	3 (3.4)	5 (1.8)	15 (2.6)	20 (2.4)
Protocol deviation	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Other	0 (0.0)	1 (0.4)	7 (1.2)	8 (0.9)
Patients remained on treatment	52 (59.1)	30 (10.9)	320 (56.0)	350 (41.3)
Patients discontinued from study	14 (15.9)	237 (85.9)	157 (27.5)	394 (46.5)
Reason for discontinuation				
Death	10 (11.4)	44 (15.9)	115 (20.1)	159 (18.8)
COVID-19 related event	2 (2.3)	0 (0.0)	3 (0.5)	3 (0.4)
Study terminated by sponsor[a]	0 (0.0)	144 (52.2)	0 (0.0)	144 (17.0)
Withdrawal by subject	3 (3.4)	31 (11.2)	30 (5.3)	61 (7.2)
Lost to follow-up	1 (1.1)	16 (5.8)	4 (0.7)	20 (2.4)

	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Adverse event	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Other	0 (0.0)	2 (0.7)	7 (1.2)	9 (1.1)
Patients remaining on study	74 (84.1)	39 (14.1)	414 (72.5)	453 (53.5)
Study follow-up time (months)[b]				
n	88	276	571	847
Mean (SD)	19.83 (10.915)	28.42 (12.304)	31.05 (15.896)	30.19 (14.865)
Median	16.69	33.22	31.57	32.43
Min, Max	1.6, 59.2	0.3, 49.5	0.1, 71.4	0.1, 71.4

Source: Table 2.7.4.1.2.2

Abbreviations: COVID-19, coronavirus disease 2019; MZL, marginal zone lymphoma; SD, standard deviation

N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.

[a] Transitioned from studies BGB-3111-1002, 205, and 206 to long-term extension study BGB-3111-LTE1.

[b] Study follow-up time is defined as the time from the first dose date (randomization date for study BGB-3111-302) to death date or end of study date (whichever occurs earlier) for patients who discontinued the study, or the database cutoff date for ongoing patients.

In the All Zanubrutinib group, TEAEs leading to treatment discontinuation reported in > 1 patient were pneumonia [10 (1.2%)], hepatitis B [3 (0.4%)], multiple organ dysfunction syndrome [3 (0.4%)], and gastric adenocarcinoma, breast cancer, colon cancer, intracranial haemorrhage, anaemia, acute kidney injury, pleural effusion, diarrhoea, COVID-19 pneumonia, haematuria, and subdural haemorrhage, each reported in 2 patients (0.2%) (Table 17).

The incidences of TEAEs leading to treatment discontinuation were similar in the All China and All Non-China groups (10.9% versus 10.7%, respectively).

Table 54 TEAEs leading to treatment discontinuation in ≥ 2 patients by SOC and PT (SAS)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Patients with a least 1 TEAE leading to treatment discontinuation	5 (5.7)	30 (10.9)	61 (10.7)	91 (10.7)

System Organ Class Preferred Term	214+AU003 MZL (N = 88) n (%)	All China (N = 276) n (%)	All Non-China (N = 571) n (%)	All Zanubrutinib (N = 847) n (%)
Infections and infestations	2 (2.3)	12 (4.3)	17 (3.0)	29 (3.4)
Pneumonia	0 (0.0)	7 (2.5)	3 (0.5)	10 (1.2)
Hepatitis B	0 (0.0)	2 (0.7)	1 (0.2)	3 (0.4)
COVID-19 pneumonia	2 (2.3)	0 (0.0)	2 (0.4)	2 (0.2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0.0)	6 (2.2)	12 (2.1)	18 (2.1)
Adenocarcinoma gastric	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.2)
Breast cancer	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.2)
Colon cancer	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (0.7)	6 (1.1)	8 (0.9)
Pleural effusion	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
General disorders and administration site conditions	1 (1.1)	2 (0.7)	4 (0.7)	6 (0.7)
Multiple organ dysfunction syndrome	0 (0.0)	1 (0.4)	2 (0.4)	3 (0.4)
Gastrointestinal disorders	1 (1.1)	1 (0.4)	4 (0.7)	5 (0.6)
Diarrhoea	1 (1.1)	0 (0.0)	2 (0.4)	2 (0.2)
Renal and urinary disorders	0 (0.0)	0 (0.0)	5 (0.9)	5 (0.6)
Acute kidney injury	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Haematuria	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.4)	3 (0.5)	4 (0.5)
Subdural haemorrhage	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)
Nervous system disorders	0 (0.0)	4 (1.4)	3 (0.5)	7 (0.8)
Haemorrhage intracranial	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.2)
Blood and lymphatic system disorders	0 (0.0)	1 (0.4)	3 (0.5)	4 (0.5)
Anaemia	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.2)

Source: Table 2.7.4.2.2.5
Abbreviations: COVID-19, coronavirus disease 2019; MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event
N = number of patients who received at least 1 dose of zanubrutinib. Percentages were based on N, unless otherwise specified.
Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively. Events were sorted by decreasing frequency of system organ class and preferred term in the **All Zanubrutinib** column.

Post marketing experience

Zanubrutinib (BRUKINSA) has received marketing authorization in USA for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy (14 November 2019) (BRUKINSA US Prescribing Information 2019).

On 02 June 2020, BRUKINSA 80 mg was approved in China for the treatment of adult patients with MCL who had received at least 1 prior therapy, and for the treatment of adult patients with CLL/SLL who had received at least 1 prior therapy.

During the reporting period of 14 November 2019 to 13 February 2021, there were 229 serious events reported from approximately 166 cases. General disorders and administration site conditions was the most commonly reported SOC (62 serious events in approximately 55 cases). The most frequently reported preferred term events included death (28 events) and disease progression (15 events). Additional events were reported in the following SOCs: infections and infestations (50 events with the most frequent events of pneumonia [11 events] and urinary tract infection [9 events]); neoplasms benign, malignant, and unspecified (including cysts and polyps) (16 events); respiratory, thoracic and mediastinal disorders (16 events); gastrointestinal disorders (14 events); blood and lymphatic system disorders (14 events); and investigations (12 events).

There were less than 10 events reported in the other SOCs. These events came from postmarketing solicited reports, spontaneous reports, compassionate use program, and investigator sponsored research.

Cumulatively, as of 13 November 2020, approximately 1,659,352 capsules of zanubrutinib have been supplied to the market worldwide (equivalent to 414,838 daily doses based on the recommended daily dose of four 80 mg capsules per day; approximately

13,646.0 person-months; 1,137.2 person-years). The patient exposure was based on postmarketing sales data from the USA and China (data on file).

No changes in the approved product labelling for BRUKINSA are being considered at this time. No regulatory actions concerning safety have been taken since the International Birth Date of 14 November 2019.

2.5.1. Discussion on clinical safety

The safety profile of zanubrutinib has been presented for patients with MZL and other B-cell malignancies. Safety data derived from seven clinical studies involving 847 patients treated with zanubrutinib monotherapy are generally consistent across studies and patient populations. No new safety signal was observed.

Patients in the 214+AU003 MZL group reported lower frequencies for most commonly reported AEs when compared with those in the All Zanubrutinib group, but there the median exposure was twice that of the 214+AU003 MZL group.

The incidences of the various AESIs are also of the same magnitude as the current safety pool (N=779). No major differences between the 214+AU003 group and the All Zanubrutinib group were seen particularly when looking at the first six months for all groups and the Exposure-Adjusted Incidence Rates, and taking into account, that the low number of events for the small 214+AU003 group (N=88) creates some uncertainty regarding the true incidence in this group.

In the 214+AU003 MZL group 39.8% reported at least one SAE. SAEs reported in ≥2% of patients included pyrexia (8%), pneumonia, influenza, diarrhoea, anaemia, and fall (each 2.3%). In the All Zanubrutinib group (where the exposure was longer) 47.1% reported at least one SAE, and PTs reported in ≥ 2% of patients included pneumonia (9.6%) and pyrexia (2.5%).

Additional expert consultations

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable.

2.5.2. Conclusions on clinical safety

The safety observations in patients with R/R MZL were consistent with findings from the integrated safety analyses described in the current SmPC. No new safety signals were found.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicine's web-portal.

2.5.4. Direct Healthcare Professional Communication

Not applicable.

2.6. Significance / Non-Conformity of paediatric studies

Not applicable.

3. Risk management plan

The MAH submitted an updated RMP version 1.1 dated 11 November 2021 with a DLP of 10 July 2021 with this application. The purpose of this RMP update is to include the proposed indication of Marginal Zone Lymphoma (MZL) based on data from 88 patients with R/R MZL from 2 ongoing pivotal studies; Study BGB-3111-214: A Phase 2, open-label, single-arm study designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL, and Study BGB-3111-AU-003: A first-in-human, Phase 1/2, dose-escalation and selection, PK/pharmacodynamic, safety, and efficacy study in adult patients with R/R or treatment-naive B-cell malignancies.

The (main) proposed RMP changes were the following:

1. Updates in part II to include addition information relevant to the proposed indication of MZL and update sections in part II to reflect available information up to the DLP.
2. Updates in Part V to reflect available information up to the DLP
3. Updates in Part VI to reflect changes made to the RMP body.

Part II module SIII clinical trial exposure

Part II module SIII clinical trial exposure was updated with addition of BGB-3111-214 and BGB-3111-AU-003 study for the new proposed indication MZL. The other studies were updated with information on location, population and study status.

The MAH also provided in table Part II Module SIII-2 summary of treatment exposure (safety analysis set) for different indications.

Part II Module SV Post authorisation experience

Patient Exposure From Marketing Experience in the USA and Canada

Cumulatively, as of 30 September 2021, 1,021,090 capsules of zanubrutinib have been supplied to the market in the USA (equivalent to 255,273 daily doses; approximately 8397.1 person months; approximately 699.8 person years) and 13,860 capsules have been supplied in Canada (equivalent to 3465 daily doses; approximately 114.0 person months; 9.5 person-years).

Patient Exposure From Marketing Experience in China

Cumulatively, as of 30 September 2021, approximately 138,103 bottles (8,838,592 capsules) of zanubrutinib have been supplied to the market in China (equivalent to 2,209,648 daily doses; approximately 72,685.8 person -months; 6057.1 person- years).

Patient Exposure From Marketing Experience in Other Countries

It is not possible to calculate exposure for all countries in which zanubrutinib is marketed, including Israel, Russia, the United Arab Emirates, and Chile. Only data for volume shipped is available for these countries and it is not possible to extrapolate this to patient utilisation or exposure.

Up to the data lock point of 21 October 2021, 158 bottles (18,960 capsules) of zanubrutinib had been shipped to Israel, and 86 bottles (10,320 capsules) of zanubrutinib had been shipped to Russia. There had been no shipments to the United Arab Emirates or Chile up the end of the reporting period.

Total Postmarketing Patient Exposure

Cumulatively, as of 30 September 2021, approximately 9,873,542 capsules of zanubrutinib have been supplied to the market in Canada, China and the USA (equivalent to 2,468,386 daily doses; approximately 81,196.9-person months; 6766.4 person-years).

Part II Module SVII identified and potential risks

Following risks not considered important for inclusion in the list of safety concerns were updated based on the new clinical and post marketing data:

4. Rash including severe cutaneous adverse reactions (SCAR)
5. Gastrointestinal disorders (including severe gastrointestinal disorders)
6. Progressive multifocal leukoencephalopathy
7. Hypertension
8. Interstitial Lung Disease (ILD)
9. Hepatotoxicity

Part II SVIII Summary of safety concerns

Summary of safety concerns	
Important identified risks	Haemorrhage
Important potential risks	Cardiac arrhythmia, mainly presented as atrial fibrillation and flutter Infections (including hepatitis B reactivation) Second primary malignancies (other than non-melanoma skin cancer) Second primary non-melanoma skin cancer Drug-drug interaction (DDI) with CYP3A inhibitors and inducers Teratogenicity
Missing information	Safety in patients with severe hepatic impairment Safety in patients with severe renal impairment/on dialysis Long-term safety (> 2 years)

Pharmacovigilance plan

Summary Table of additional Pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
BGB-3111-113 A Drug-Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-cell Malignancies Lymphoma Ongoing	To assess the drug-drug interaction between zanubrutinib and moderate (fluconazole, diltiazem) and strong (voriconazole, clarithromycin) CYP3A inhibitors in patients with B-cell malignancies.	Drug-drug interaction	Study/trial completion (database lock):	2nd Quarter, 2022
			Final report submission:	3rd Quarter, 2022
BGB-3111-LTE1 An Open-label, Multi-centre, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies	To evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who participated in a	Long-term safety (> 2 years)	Annual DSUR	3rd Quarter annually until study completion
			Estimated study completion date	4th Quarter 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing	BeiGene parent study for zanubrutinib			

Except for some editorial changes there were no other changes proposed in summary table of additional pharmacovigilance activities.

As no new safety concerns were identified based on the new study results, no adjustment on additional pharmacovigilance is expected. The proposed table of additional pharmacovigilance plan is accepted.

Part V Summary of Risk Minimisation Measures

Summary of Risk Minimisation Measures was updated with information up to the DLP and some editorial changes.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Haemorrhage	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
Cardiac arrhythmia, mainly presented as atrial fibrillation and flutter	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None

Infections (including hepatitis B reactivation)	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
Second primary malignancies (other than non-melanoma skin cancer)	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
Second primary non-melanoma skin cancer	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
DDI with CYP3A inhibitors and inducers	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction SmPC Section 5.2 Pharmacokinetic properties Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: BGB-3111-113 A Drug-Drug Interaction Study of Zanubrutinib with Moderate/Strong cytochrome P450 family 3 subfamily A Inhibitors in Patients with B-Cell Malignancies Lymphoma

Teratogenicity	Routine risk minimisation measures: SmPC Section 4.6 Use during pregnancy and lactation SmPC Section 5.3 Preclinical safety data Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR. Safety signal detection activities Additional pharmacovigilance activities: None
Safety in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacokinetic properties Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
Safety in patients with severe renal impairment/on dialysis	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacokinetic properties Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
Long-term safety (> 2 years)	Routine risk minimisation measures: Not specifically addressed Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR. Safety signal detection activities Additional pharmacovigilance activities: BGB-3111-LTE1 An Open-label, Multi-center, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies Final study report: Q4 2025

Part V Summary of the risk management plan

This section was updated by inclusion of the new indication and some editorial changes.

3.1. Overall conclusion on the RMP

☒ The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

4. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.5, 4.8, and 5.1 of the SmPC are being updated to include the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti-CD20-based therapy. Several issues have been raised, in particular changes to the wording of the indication and changes to recommendations regarding co-administration of zanubrutinib with moderate CYP3A inducers.

The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Brukinsa. The bridging report submitted by the MAH has been found acceptable. See inserted document.

4.1.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Brukinsa (zanubrutinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

5. Benefit-Risk Balance

5.1. Therapeutic Context

The proposed indication for zanubrutinib is for the treatment of (all subtypes) of MZL in adult patients who have received ≥1 prior therapy.

5.1.1. Disease or condition

MZL (Swerdlow et al., 2016) is an indolent non-Hodgkin lymphoma (NHL) that originates from memory B-lymphocytes normally present in the marginal zone of secondary lymphoid follicles within the spleen, lymph nodes, and mucosal lymphoid tissues (Kahl and Yang 2008). MZL is categorized by the World Health Organization into 3 distinct subtypes: extranodal MZL of mucosa-associated lymphoid tissue (MALT) or MALT lymphoma, nodal MZL, and splenic MZL. MZLs comprise about 5% to 17% of all NHLs in adults, with MALT lymphoma as the most common subtype (50% to 70% of MZLs), followed by the splenic (20% of all MZLs) and nodal (10% of all MZLs) subtypes.

Like other indolent NHLs, advanced-stage disease is considered incurable, with most patients experiencing a continuing pattern of relapse and remission. Relapse is inevitable for many patients, likely due to inadequate response to current therapies, drug resistance, or inability to tolerate treatment due to side effects. Ineffective disease control will eventually lead to poor outcomes, including fatality.

5.1.2. Available therapies and unmet medical need

There are no chemotherapy or immunotherapy products specifically approved for MZL in the European Union (EU) for patients with treatment-naive or relapsed/refractory (R/R) disease.

However, bendamustine is approved for indolent R/R NHLs, including MZL, as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. In addition to bendamustine, several products (corticosteroids and several chemotherapies) have at least partially overlapping indication with the applied indication for zanubrutinib.

Historically, very few prospective clinical trials have been conducted specifically in this patient population, and even fewer comparative, randomized trials have been carried out. Patients with MZL have been enrolled and treated in clinical trials designed for patients with indolent NHL where the ee

As is evident from the ESMO guideline recommendations (Zucca et al., 2020), the primary treatment options depend on the subtype of MZL (see Introduction).

If the relapse of MZL is symptomatic, second-line and subsequent systemic treatments may include single-agent rituximab (while not specifically approved in MZL) or chemoimmunotherapy (the same regimen or an alternative regimen) can be repeated after a long initial remission (≥24 months). However, immunochemotherapy is associated with significant toxicity in these patients, especially in elderly patients and those with comorbidities. Moreover, data that suggest efficacy of these regimens are often based on a small subset of patients and/or retrospectively evaluated (Cheah et al 2019).

There is an unmet medical need for effective and safe therapies to improve long-term outcomes.

5.1.3. Main clinical studies

Study BGB-3111-214: A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma.

Supportive **Study BGB-3111-AU-003**: A Phase 1/2, 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.

5.2. Favourable effects

Zanubrutinib demonstrated high response rates; ORR by IRC of 45/66 (68.2%) in the pivotal study 214 with a CR of 17/66 (25.8%).

5.3. Uncertainties and limitations about favourable effects

The updated analysis of Study BGB-3111-214 provides meaningful additional follow-up data for the evaluation of duration of response: median duration of response follow-up time is 23.4 months compared to 8.31 months in the primary analysis and median DOR not reached (72.9% at 24 months).

However, demonstration of efficacy relies on a small single arm study with few patients (N=66) and initially very limited median follow-up time. In order to further confirm the efficacy of zanubrutinib in patients with R/R MZL, the MAH will submit the final study report of the post-authorisation efficacy study (PAES): Study BGB-3111-308: a global, multicenter, phase 3, open-label, randomized study of zanubrutinib plus rituximab versus lenalidomide plus rituximab in patients with relapsed/refractory marginal zone lymphoma (NCT05100862) (see Annex II).

5.4. Unfavourable effects

The safety observations in patients with R/R MZL were consistent with findings from the integrated safety analyses described in the current SmPC. No new safety signals were found.

5.5. Uncertainties and limitations about unfavourable effects

The pivotal study 214 was a SAT, which comes with a built-in uncertainty. On the other hand, the approved indication (in R/R Waldenström macroglobulinaemia) was based on a phase 3 trial comparing zanubrutinib to ibrutinib, and as safety seems comparable between that study, the entire All zanubrutinib monotherapy pool and the current MZL study, the uncertainty is considered limited. Further, safety of zanubrutinib in patients with R/R MZL, will be studied in the context of BGB-3111-308: a global, multicenter, phase 3, open-label, randomized study of zanubrutinib plus rituximab versus lenalidomide plus rituximab in patients with relapsed/refractory marginal zone lymphoma (NCT05100862) (see Annex II) .

5.6. Effects Table

Table 55. Effects Table for BRUKINSA as monotherapy indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti-

CD20-based therapy. (Study BGB-3111-214, data cut-off: 18 Jan 2021 for safety and 04 May 2022 for Efficacy) SAFETY: +ISS population

Effect	Short description	Unit	Treatment: Brukinsa 160 mg BID	Control N/A	Uncertainties/ Strength of evidence	References
Favourable Effects						
			N = 66			
Primary endpoint	ORR/IRC: (95% CI) CR PR	n (%)	45 (68.2%) (55.56, 79.11) 17 (25.8%) 28 (42.4%)	-	Single-arm trial (SAT) Few patients	Table 1/Q1
Secondary endpoints	mDOR (95% CI)	months	NE (NE, NE)	-	Median follow-up: 23.4 (2.7, 25.8)	Table 1/ Q1
Unfavourable Effects; MZL patients and the All zanubrutinib pool as presented in the ADR table in the SmPC						
			Studies 214+AU003 (n=88)	**All zanubrutinib (n=847)**	Median exposure: MZL (214+AU003): **15.6 months** All Zanubrutinib: **25.6 months**	
Infections by SOC	All ≥Grade 3	n (%)	46 (52.3) 15 (17.0)	624 (73.7) 231 (27.3)		Table 20/ SCS
Neutropenia (AESI)[1]	All ≥Grade 3	n (%)	15 (17.0) 11 (12.5)	292 (34.5) 193 (22.8)		Table 20/ SCS
Haemorrhage[2]	All ≥Grade 3	n (%)	37 (42.0) 1 (1.1)	460 (54.3) 32 (3.8)		Table 20/ SCS
Sec. primary malignancies[3] (AESI)	All ≥Grade 3	n (%)	8 (9.1) 5 (5.7)	115 (13.6) 47 (5.5)		Table 20/ SCS
Skin cancer[4] (AESI)	All ≥Grade 3	n (%)	3 (3.4) 0	74 (8.7) 14 (1.7)		Table 20/ SCS
Diarrhoea, PT	All ≥Grade 3	n (%)	22 (25.0) 3 (3.4)	199 (23.5) 16 (1.9)		Table 11 and 13/SCS
Discontinuation due to AE		n (%)	5 (5.7)	92 (10.9)		Table 4/ SCS

Abbreviations: ORR: overall response rate, CR: complete response, PR: partial response, DOR: duration of response, CI: confidence interval, IRC: independent review committee, NE: not estimable, AESI; adverse events of special interest, SCS: summary of clinical safety (all tables referred to are included in this AR), PT: preferred term

Notes: Tumor response was according to the 2014 Lugano Classification.
[1]Neutropenia was an AESI and defined as Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT.
[2]Includes multiple adverse reaction terms (see AESI section) and includes events with fatal outcome.
[3]Malignant tumours (SMQ) Narrow; includes skin cancers
[4]Skin malignant tumours (SMQ) Narrow

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The MAH has provided efficacy data from one small pivotal SAT (N=66). In study BGB-3111-214 patients with R/R MZL had a high ORR (68.2%), with a CR rate of 25.8%.

Whenever patients with indolent lymphoma (like MZL) needs systemic treatment in case of relapsed (or refractory) disease, the target is to achieve as good response as possible, i.e. complete response. While achieving a response (PR or preferably CR) is of importance, there is no clear correlation of ORR to PFS or OS, at least in relapsed / refractory MZL patients.

In addition, PFS and OS results based on the results from a single arm study, like study 214, are considered only descriptive.

The updated analysis of Study BGB-3111-214 provides meaningful additional follow-up data for the evaluation of duration of response: median duration of response follow-up time is 23.4 months compared to 8.31 months in the primary analysis and median DOR not reached (72.9% at 24 months).

The safety features of zanubrutinib have been earlier characterised in the application concerning WM as an indication. It can be concluded that zanubrutinib is reasonably well tolerated, and that after the addition of this fairly small patient population into the dataset, the safety profile of zanubrutinib remains unchanged.

5.7.2. Balance of benefits and risks

Based on the updated data with a median study follow-up of 28 months and an RCT accepted as a PAES, the benefit/risk is considered positive.

5.7.3. Additional considerations on the benefit-risk balance

Additionally, the applicant applied for an extended (10+1-year) marketing protection.

The MAH has provided a comprehensive review and comparison to the existing therapies for R/R MZL. It is agreed with the MAH that rituximab is not specifically approved for the treatment of MZL and thus the only relevant comparator is bendamustine.

Due to design of the studies (bendamustine monotherapy and bendamustine plus rituximab) with very limited number of patients, the indirect comparisons with regard to efficacy or safety are of limited value and cannot be regarded conclusive.

However, given the fact that zanubrutinib is administered orally compared to bendamustine which is administered intravenously, the significant clinical benefit based on major contribution to patient care has been granted.

A significant clinical benefit of Brukinsa in the claimed indication, in order to benefit from an extended (10+1-year) marketing protection period, has been demonstrated provided the responses are satisfactory to RSI.

5.8. Conclusions

The overall B/R of Brukinsa for the treatment of adult patients with marginal zone lymphoma (MZL) is considered positive.

6. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti-CD20-based therapy, based on data from 88 patients with R/R MZL from 2 ongoing pivotal studies; Study BGB-3111-214: A Phase 2, open-label, single-arm study designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL, and Study BGB-3111-AU-003: A first-in-human, Phase 1/2, dose-escalation and selection, PK/pharmacodynamic, safety, and efficacy study in adult patients with R/R or treatment-naive B-cell malignancies. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated, and the Package Leaflet is updated in accordance.
Version 1.1 of the RMP has also been submitted.
In addition, the one additional year of market protection requested by the MAH has been granted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

7. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Brukinsa-H-C-004978-II-0002’