EU RISK MANAGEMENT PLAN

BRUKINSA (ZANUBRUTINIB)

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP Version number: 6.0

Data lock point for this RMP	Clinical data: 25 October 2022 Global Safety Database: 13 May 2023 Post-marketing exposure data: 13 May 2023	Version number	6.0
Date of final sign off	27 June 2025		

Rationale for submitting an updated RMP:

Addition of film-coated tablet

Summary of Significant Changes in This RMP:

Part	Module/Annex	Significant Changes in Each Module
Part I Product overview		Addition of film-coated tablets.
Part II Safety specification		No updates.
Part III Pharmacovigilance plan (including postauthorisation safety studies)		No updates.
Part IV Plan for postauthorisation efficacy studies		No updates.
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)		No updates
Part VI Summary of risk management plan for BRUKINSA (zanubrutinib)		No updates
Part VII Annexes	**ANNEX 4** Specific adverse drug reaction follow up forms	No updates.
	ANNEX 6 Details of proposed additional risk minimisation activities (if applicable)	No updates.
	ANNEX 7 Other supporting data (including referenced material)	No updates.

Details of the Currently Approved RMP:

RMP Version Number	Approved With Procedure	Date of Approval (opinion date)
5.0	EMEA/H/C/004978/II/0014	15 November 2023

QPPV Name: Dr Olaf Schickling

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LIST OF TABLES

LIST OF ABBREVIATIONS FOR ALL PARTS/MODULES

ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BR	Bendamustine with rituximab
BTK	Bruton tyrosine kinase
CD	Cluster of differentiation
CLL	Chronic lymphocytic lymphoma
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CrCl	Creatinine clearance
CVD	Cardiovascular disease
CYP	Cytochrome P450
CYP3A	Cytochrome P450 family 3 subfamily A
DCO	Data cutoff
DDI	Drug-drug interaction
Del(17p)	Deletions of the short arm of chromosome 17
DLBCL	Diffuse large B-cell lymphoma
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
FL	Follicular lymphoma
HBV	Hepatitis B virus
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration
IGHV	Immunoglobulin heavy-chain variable region gene

IgM	Immunoglobulin M
ILD	Interstitial lung disease
INN	International nonproprietary name
LPL	Lymphoplasmacytic lymphoma
MALT	Mucosa associated lymphoid tissue
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PT	Preferred term
RMP	Risk management plan
R/R	Relapsed or refractory
SEER	Surveillance, epidemiology, and end results
SIR	Standardised incidence ratio
SLL	Small lymphocytic leukaemia
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
TN	Treatment-naive
UK	United Kingdom
US(A)	United States (of America)
WHO	World Health Organisation
WM	Waldenström macroglobulinaemia

Part I PRODUCT(S) OVERVIEW

Table Part I-1: Product Overview

Active substance(s) (INN or common name)	Zanubrutinib (also known as BGB-3111)
Pharmacotherapeutic group(s) (ATC Code)	L01EL03
Marketing Authorisation Applicant	BeiGene Ireland, Ltd. 10 Earlsfort Terrace Dublin 2 D02 T380 Ireland
Medicinal products to which this RMP refers	2
Invented name(s)	BRUKINSA®
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Small-molecule inhibitor of Bruton tyrosine kinase (BTK)
	Summary of mode of action: Zanubrutinib is a small-molecule inhibitor of BTK. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signalling molecule of the B-cell receptor and cytokine receptor pathways. In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.
	Important information about capsule and tablet composition: Capsules: White to off-white opaque hard capsule of 22 mm in length (size 0), marked with "ZANU 80" in black ink containing white to off-white powder.The capsule contains microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate (E487), silica colloidal anhydrous, and magnesium stearate. The capsule shell contains gelatine and titanium dioxide (E171), and the edible black ink contains shellac glaze (E904), iron oxide black (E172), and propylene glycol (E1520). Oval, blue, film-coated tablets of 16 mm in length, with letters "zanu" debossed on one side and a functional score line on the other side The tablet contains lactose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, povidone, microcrystalline cellulose, magnesium stearate, Opadry blue (coating agent).
Hyperlink to the product information	Zanubrutinib Summary of Product characteristics (SmPC)

Table Part I-1: Product Overview

Indication(s)	Current: Zanubrutinib as monotherapy is indicated for the treatment of adult patients with Waldenström macroglobulinaemia (WM) who have received ≥ 1 prior therapy, or in first line treatment for patients unsuitable for chemoimmunotherapy. Zanubrutinib 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. Zanubrutinib as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL). Zanubrutinib in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least 2 prior systemic therapies.
Dosage	Current: The recommended daily dose of zanubrutinib is 320 mg, taken orally either once daily (four 80 mg capsules) or twice daily (two 80 mg capsules). Addition of: Treatment with zanubrutinib should be continued until disease progression or unacceptable toxicity.
	Proposed: The recommended total daily dose of zanubrutinib is 320 mg, taken either once daily (four 80 mg capsules or two 160 mg tablets) or divided into two doses of 160 mg twice daily (two 80 mg capsules or one 160 mg tablet). Treatment with Brukinsa should be continued until disease progression or unacceptable toxicity.
Pharmaceutical form(s) and strengths	Current: Zanubrutinib 80 mg hard capsules
	Proposed: Zanubrutinib 80 mg hard capsules Zanubrutinib 160 mg film-coated tablets
Is/will the product be subject to additional monitoring?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Waldenström Macroglobulinaemia

Indication

WM is the predominant form of lymphoplasmacytic lymphoma (LPL). LPL is divided into 2 subsets, immunoglobulin M (IgM) LPL and nonIgM LPL. These variants present with similar symptoms and pathological features and follow the same treatment guidelines (Anderson et al 2012; Dimopoulos et al 2014). IgM LPL comprises most cases and is referred to and diagnosed as WM (Swerdlow et al 2016). WM presents with distinct clinical features such as IgM paraproteinaemia, serum hyperviscosity, cryoglobulinaemia, demyelinating neuropathy, and occasionally, amyloidosis (Morice et al 2009; Gertz 2017; Gertz 2019). The World Health Organization (WHO) defines WM as an LPL associated with a monoclonal IgM protein (Owen et al 2003).

Incidence

WM is a rare disease that accounts for 1% to 2% of all haematological neoplasms. The RARECARE 2002 database (a list of tumour entities from which rare tumours are identified as those with an incidence < 6 per 100,000 person-year) reported an annual incidence of 0.81 per 100,000 population for all LPL cases across Europe. This data resource has been updated to RARECARE 2007 but does not provide a revised estimate from that previously noted from 2002 (RARECAREnet). The European Waldenström's Macroglobulinemia Network reported an annual incidence of approximately 5 cases per million for WM and an incidence of 1 in 260,000 persons per year in the United States of America (USA) (EWMnetwork 2020). The reported age-adjusted incidence rate has also been reported as 0.73 and 0.42 cases, for males and females, respectively, per 100,000 European standard population (Groves et al 1998; Phekoo et al 2008) and 0.34 per 100,000 among males and 0.17 per 100,000 among females in the USA (Buske et al 2013). In a population-based study undertaken in the USA (Kyle et al 2018), the age-adjusted incidence rate for males was reported as 0.92 per 100,000 person-years and for females as 0.30 per 100,000 person-years, with an age- and sex-adjusted incidence of 0.57 per 100,000 person-years. There was no convincing evidence that a change in the incidence of WM had occurred over the past 50 years.

Prevalence

The paucity of reporting of prevalence and/or incidence of LPL or WM reflects the rarity of the condition. Additionally, LPL and WM may be reported as if medically synonymous and, in some cases, reporting is made in combination with other cancers; in the United Kingdom (UK), for example, cancer registries report solitary plasmacytoma, multiple myeloma, plasma cell leukaemia, and WM together (McNally and Cartwright 1998). Therefore, the overall prevalence and incidence of LPL specifically is not available in most countries. However, in Europe, the prevalence is reported by Orphanet as 1 to 9 per 100,000 and as a disease of the elderly (Orphanet). Further available epidemiological data are provided in Table Part II: Module SI-1

below.

Table Part II: Module SI-1: Incidence and Prevalence of Lymphoplasmacytic Lymphoma Reported in Studies of European Data

Citation State Study Year(s)	Prevalence per 100,000	Incidence per 100,000	Notes
(RARECAREnet) [a] Trans-European 2002	NR	0.81	None
(Leisten and Tomeczkowski 2015) Germany 2012	6.0	NR	Meeting abstract only
(Phekoo et al 2008) United Kingdom 1999 and 2001	NR	0.55	WM only, ESR
(Brandefors et al 2016a) Sweden 2000 to 2012	NR	1.05	Stable incidence across study years
(Brandefors et al 2016b) Sweden 2000 to 2014	NR	1.06	Meeting abstract only

Abbreviations: ESR, European standardised rate; NR, not reported; WM, Waldenström macroglobulinaemia.
[a] The RARECARE 2002 data resource has been updated to RARECARE 2007.

A sickness funds data analysis of the prevalence and treatment of WM in Germany was conducted in 2012, which reported a prevalence of 6 per 100,000 population (Leisten and Tomeczkowski 2015). These data are reported from a meeting abstract, with limited study design detail provided.

A more recent population-based study from Sweden has recorded the age-adjusted overall annual incidence of LPL of 1.05 cases per 100,000 population (Brandefors et al 2016a). Prevalence was not reported in this publication. A second Swedish paper by the same group (Brandefors et al 2016b) reported an annual incidence of 1.06 cases per 100,000 population for all LPL and a median survival of 96 months for WM (2008 to 2016). An estimate of prevalence can be made from these data of 8.5 per 100,000 population (1.06 x 8 years) but this assumes that median and mean survival are the same and that survival is the same in WM and all LPL. The paper notes a high incidence of LPL in Sweden.

The Thames Cancer Registry in the UK is a population-based registry covering 14 million residents in Southeast England. In collaboration with local haematologists, the registry developed a haematology register (South Thames Haematology Committee, 2002) for the South Thames area to collect more detailed clinical data on patients diagnosed with haematological cancers between 1999 and 2003. One of the aims of this study was to use data from the register to describe the incidence of WM in the population of South Thames. The study reported that

between 1999 and 2001, there were 152 new cases of WM recorded in the South Thames Haematology Register, giving an age-standardised rate of 0.55 per 100,000 European standard population (0.73 for males and 0.42 for females). The incidence increased with age, and the median age at diagnosis was 75 years (range: 45 to 93 years). Between 1985 and 2002, the Thames Cancer Registry recorded 750 cases of WM occurring in the wider area of Southeast England. Prevalence data were not reported (Phekoo et al 2008).

The RARECARE data are trans-European but provide only incidence data, not prevalence or trend data. Assuming that the survival is approximately 8 years based on Swedish WM median rates (2000 to 2014) (Brandefors et al 2016b), the annual incidence of 0.81 per 100,000 would give a prevalence of 6.5 per 100,000 population (0.81 x 8). No other European data on LPL survival have been identified.

WM prevalence is higher among white people than among black people (incidence rate ratio: 1.75) (Teras et al 2016).

Demographics of the Population in the Authorised Indication – Sex, Age, Racial and/or Ethnic Origin, Geographic Distribution, and Risk Factors for the Disease

WM is a disease of the elderly, with the median age at the time of diagnosis being 63 to 68 years (Teras et al 2016; Kastritis et al 2015b; Treon 2009a). The incidence rate of WM is twice as high in men as in women and higher in white people than in black people (Gertz 2017; Leukemia and Lymphoma Society 2018). The most important prognostic factor predicting survival in patients with WM from Surveillance, Epidemiology, and End Results (SEER) data is age (Gertz 2018). Patients under the age of 70 have a median survival in excess of 10 years; those 70 to 79 years, approximately 7 years; and those ≥ 80 years, approximately 4 years. The reported age-adjusted incidence rate is 0.34 per 100,000 among males and 0.17 per 100,000 among females in the USA, and 0.73 and 0.42, respectively, per 100,000 European standard population (Buske et al 2013).

A strong familial predisposition has been reported (McMaster 2003; Treon et al 2006; Treon et al 2012) and first-degree relatives of WM patients have up to 20-fold increased risk for developing WM (risk for other B-cell disorders is also increased but at a lower level) (Kristinsson et al 2008).

Main Existing Treatment Options

According to the International Prognostic Scoring System for Waldenström macroglobulinaemia, patients are stratified into low-, intermediate-, and high-risk groups with respective 5-year survival rates of 87%, 68%, and 36% based upon age, IgM level, β2-microglobulin level, haemoglobin, and platelet count (Morel et al 2009). There is no cure for WM. Some patients with WM can be asymptomatic, in which case treatment is not indicated and patients are monitored. However, most patients with WM will become symptomatic during the course of the disease, because of anaemia, hyperviscosity, neuropathy, or other disease processes, necessitating therapy. Furthermore, a significant proportion of patients with WM die after large-cell transformation (Durot et al 2017) or myelodysplastic syndrome (Castillo and Gertz 2017; Ricci et al 2011), which needs to be considered when choosing treatment regimens, particularly for younger patients.

Specifically, anti-cluster of differentiation (CD)20-based (rituximab-based) combinations are the mainstay of first-line treatment. A transient increase in serum IgM (IgM flare) occurs in 30% to 80% of patients treated with rituximab-based therapies, which may exacerbate IgM-related complications (Dimopoulos et al 2002; Ghobrial et al 2004). Pre-emptive use of plasmapheresis may be considered in symptomatic patients with very high levels of IgM and at high risk for hyperviscosity or IgM-related complications before commencing anti-CD20-based chemoimmunotherapy. Rituximab alone as a single agent has consistently been shown to be an inferior regimen in meta-analyses with partial response rates of < 50% compared to combination chemotherapy regimens where response rates are in the 80% range (Santos-Lozano et al 2016). However, combinations of rituximab with oral or intravenous cyclophosphamide and dexamethasone (for 6 cycles) induce higher response rates than rituximab alone, but complete responses are infrequent. The dexamethasone, rituximab, cyclophosphamide regimen is associated with a progression-free survival (PFS) of about 3 years, a treatment-free interval > 4 years, and median overall survival (OS) of approximately 8 years with favourable short- and long-term safety profiles (Kastritis et al 2015a). For patients where therapy is indicated because of progressive marrow infiltration or for symptoms for hyperviscosity, multi-agent chemotherapy is preferred over single-agent rituximab. Bendamustine with rituximab ([BR] for 4 to 6 cycles) is associated with longer PFS and OS than rituximab with cyclophosphamide/doxorubicin/vincristine/prednisolone, based on a subanalysis of a randomised study (Rummel et al 2013). Dose intensity of bendamustine should be adapted to the individual characteristics of the patients by reducing the number of cycles and/or by reducing the dosing per cycle.

Bortezomib alone or in combination with rituximab is very active in WM (Gavriatopoulou et al 2017; Ghobrial et al 2010; Treon et al 2009b) and should preferably be given subcutaneously and at weekly intervals (1.6 mg/m^2). Long-term follow-up of a Phase 2 study of bortezomib/dexamethasone/rituximab (for 5 cycles) has shown a median PFS of 3.5 years, median duration of major response of 5.5 years and OS rate of 66% at 7 years (Gavriatopoulou et al 2017). Neurotoxicity remains a significant concern with bortezomib.

The first-in-class Bruton tyrosine kinase (BTK) inhibitor ibrutinib (IMBRUVICA®) demonstrated a major response rate of 70% (including 14% very good partial response and 56% partial response) in a single arm study (Study 1118) in 63 previously treated patients. The median PFS was not reached at a median duration of treatment of 14.8 months (IMBRUVICA SmPC 2022). No patients with wild type *MYD88* disease had a major response (partial response and above) (Treon et al 2015b). At the time of publication, 20/63 (32%) patients had discontinued ibrutinib treatment, including 7 with progressive disease and 2 with disease transformation, highlighting limitations of ibrutinib as a chronic treatment in WM (Treon et al 2015a).

The approval of ibrutinib alone and in combination with rituximab has expanded the treatment options for WM patients. Ibrutinib is highly active when given as monotherapy or in combination with rituximab in the treatment of WM, with response rates and durability that compare favourably to that achieved with highly intensive combination chemoimmunotherapy regimens. In the randomised Phase 3 (iNNOVATE) study of ibrutinib given in combination with rituximab versus rituximab monotherapy in WM, ibrutinib combined with rituximab prolonged PFS compared to rituximab alone, with a hazard ratio (HR) of 0.20 (95% CI: 0.11 to 0.38). (Dimopoulos et al 2017).

An advantage of BTK inhibitors is that they offer a relatively nonmyelosuppressive, nonimmunosuppressive treatment option, limiting 2 of the major toxicities of conventional therapies that confound the management of these patients. While the therapeutic response rate to ibrutinib has been high, with therapy well-tolerated overall, some patients have experienced relapse, while others have discontinued therapy because of toxic effects or other reasons (Maddocks et al 2015; Jain et al 2015). A recent retrospective report of 189 patients confirms the relatively high frequency of treatment discontinuation with ibrutinib in WM. In this study, 51 (27%) patients had discontinued ibrutinib after a median treatment duration of 13 months (range: 0.3 to 60 months), 27 (14%) owing to disease progression, 15 (8%) owing to toxicity, 5 (3%) owing to nonresponse and 4 (2%) owing to other unrelated reasons. Together, these data highlight the importance of maintaining BTK inhibitor treatment in patients with WM (Gustine et al 2018). In Study BGB-3111-302, the cumulative incidence of ibrutinib discontinuation at 12, 24, 36, and 48 months from treatment initiation was 22%, 26%, 35%, and 43%, respectively. Of the 51 patients who discontinued ibrutinib, 75% of patients required additional rescue therapy for WM at a median of 5 weeks after ibrutinib discontinuation.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

WM is defined as a B-cell LPL. WM is an indolent, chronic disease in most patients. The median survival has varied in studies, from 5 years to nearly 11 years (Oza and Rajkumar 2015). At least 25% of patients are asymptomatic at diagnosis, and 50% of asymptomatic patients who are observed will not require therapy within 3 years and 1 in 10 will not require therapy for 10 years (Morel and Merlini 2012). At the time of diagnosis, WM most commonly involves the blood and bone marrow; however, WM can start almost anywhere and spread to almost any part of the body, affecting the lymph nodes, liver, or spleen as well as the stomach, intestines, or lungs (Leukemia and Lymphoma Society 2012). Most patients present with symptoms attributable to tumour burden, including anaemia, pancytopenia, organomegaly, neuropathy, amyloidosis, cryoglobulinemia, night sweats and symptomatic hyperviscosity (Oza and Rajkumar 2015). Approximately 20% of patients will experience hepatosplenomegaly and lymphadenopathy, and some patients may present with 'B' symptoms, including night sweats, fever, and weight loss (Ghobrial 2012). Median life expectancy at diagnosis is between 5 and 10 years, but varies considerably according to disease aggressiveness and tumour mass (Souchet-Cömpain et al 2014). The main causes of death of WM include disease progression, transformation to high-grade lymphoma or complications of therapy (Oza and Rajkumar 2015). However, because of the advanced age of these patients, approximately 50% die of unrelated causes (Ansell et al 2010).

Mortality and Morbidity

A Swedish population-based study of 1555 LPL/WM patients diagnosed from 1980 to 2005 observed survival of LPL/WM patients to have improved significantly over time (Kristinsson et al 2013). Specifically, the 5-year relative survival ratios increased from 0.57 (95% CI: 0.46 to 0.68) to 0.78 (95% CI: 0.71 to 0.85) for patients diagnosed during the calendar periods 1980 to 2005.

In a UK study of patients with WM recorded within the South Thames Haematology Registry during 1999 to 2001, the estimated 5-year survival was 57% (95% CI: 47% to 66%). Relative 5-year survival was 70% among patients ≤ 70 years and 50% for patients aged 70 and older (Phekoo et al 2008).

Similar findings were observed in a SEER-based US study of 5784 WM cases from 1991 to 2010, where the median OS was 7 years, and the 5- and 10-year OS rates were 62% and 39%, respectively (Castillo et al 2015a). Median survival for 600 patients with WM, diagnosed and treated before January 2002, and classified based on the International Prognostic Scoring System for WM were 12, 8, and 3.5 years for low-, medium-, and high-risk groups, respectively (American Cancer Society 2018).

Important Comorbidities

Important comorbidities in patients with WM include peripheral neuropathy, infection (McShane et al 2014), other malignancies (Castillo et al 2015b), and cardiovascular disease (CVD; Leukemia and Lymphoma Society 2012).

Marginal Zone Lymphoma

Indication

MZL is a subtype of indolent B-cell non-Hodgkin lymphoma (NHL) that accounts for approximately 5% to 17% of all adult NHLs in the USA, and 5% to 15% of all NHLs in the Western World (Teras et al 2016; Zucca et al 2020). Depending on the sites involved, and other features, the WHO has identified 3 subtypes of MZL: extranodal MZL of mucosa associated lymphoid tissue (MALT), nodal MZL, and splenic MZL (Swerdlow et al 2016).

Incidence

Data sources in Europe and in the USA show that the incidence of MZL is low. For example, the incidence (95% CI) of MZL as reported by 44 European Cancer Registries (HAEMACARE project) representing 20 European countries in 2000 to 2002 was 0.42 (0.40 to 0.45) per 100,000 (Sant et al 2010).

Information obtained from the European Cancer Information System is consistent with the above estimates. Although it does not have estimates for the incidence of MZL, the European Cancer Information System indicates that the incidence of NHL in the European Union-27 in 2020 was 19.4 per 100,000 (European Cancer Information System 2021). Because MZL contributes to about 8% of all NHL (Lymphoma Research Foundation), the incidence of MZL from the European Cancer Information System could be calculated as 19.4 per 100,000 (incidence of NHL) x 8% (percentage of MZL in NHL) = 1.6 per 100,000.

Findings from the USA also indicate that the incidence of MZL is low. The age-standardised incident rate for MZL based on data from 2001 to 2017 from the National Cancer Institute SEER Program was 19.6 per 1,000,000 person-years (Cerhan and Habermann 2021).

Prevalence

Published estimates of the prevalence of MZL are rare. Only 1 published study from the UK (Smith et al 2015) includes an estimate of the prevalence of MZL for a European population. Using data from the University of York's Haematological Malignancy Research Network (HMRN) from 2004 through 2012, the estimated 3-year prevalence (95% CI) of MZL in the UK

was 10.1 (9.0, 11.1) per 100,000 persons. Estimates for 5- and 10-year prevalence rates were 15.2 (13.9, 16.5) and 23.8 (22.2, 25.4) per 100,000 persons, respectively.

Updated prevalence estimates incorporating data from 2007 through 2016 are available from the HMRN website (Haematological Malignancy Research Network). The estimated 3-, 5-, and 10-year prevalence estimates were 12.5, 17.8, and 26.4 per 100,000 persons in the UK, respectively.

Demographics of the Population in the Proposed Indication – Sex, Age, Racial and/or Ethnic Origin, Geographic Distribution, and Risk Factors for the Disease

The risk of MZL increases substantially with age (Cerhan and Habermann 2021) with a median age of 67 years at diagnosis (Leukemia and Lymphoma Society). Other risk factors for MZL include family history of NHL; genetic loci in the human leukocyte antigen region; *Helicobacter pylori* infection; and autoimmune diseases such as Sjogren syndrome, systemic lupus erythematosus and Hashimoto thyroiditis (Cerhan and Habermann 2021). In the USA, the age-standardised incidence of MZL per 1,000,000 persons has been reported to be highest among non-Hispanic whites (20.7) and somewhat lower in Hispanics of all races (17.6), non-Hispanic blacks (15.4), and Asian/Pacific islanders (15.0).

Main Existing Treatment Options

The treatment approach for MZL is largely based on the subtype, location, presence or absence of symptoms, and stage of the disease.

Pathogenesis of extranodal MZL of MALT involves persistent proliferation of B-cells and stimulation of the B-cell receptor signalling pathway, which can often be induced by chronic inflammation as a result of either infectious or autoimmune causes, including *Helicobacter pylori* infection in gastric MALT and *Chlamydophila psittaci* in the ocular adnexa. Eradication of the infectious agent can, in some cases, be effective in inducing tumour regression (Zucca et al 2014; Wotherspoon 1998; Kuo et al 2017). For patients with chromosomal aberrations such as t(11;18) that predicts for lack of response to antibiotics, radiation therapy may be considered (NCCN Version 5.2022). Rituximab is an option for patients with contraindications to radiation therapy (Martinelli et al 2005). For asymptomatic patients, a watch-and-wait approach is an option. For patients presenting with advanced stage disease (stage III or IV), treatment is commonly approached with regimens used for other indolent NHL such as FL; first-line options include systemic therapy with either single-agent or combination chemotherapy, anti-CD20 monoclonal antibody, or chemoimmunotherapy. For patients who experience disease progression, the preferred therapy is not clearly defined and most data in this population originate from retrospective series or extrapolation of data from other indolent NHLs.

Viral hepatitis C has been implicated in the pathogenesis of splenic MZL. Treatments for splenic MZL include a watch-and-wait approach in asymptomatic patients; antiviral therapy (in viral hepatitis C-positive cases), splenectomy, rituximab, and chemotherapy are available options in patients requiring treatment (Arcaini et al 2014).

There is no single preferred therapy for nodal MZL, but treatment options in general follow the principles applied for FL, including rituximab alone or in combination with chemotherapy (NCCN Version 5.2022).

In patients with recurrent disease, asymptomatic patients may be observed, and radiotherapy may be considered for localised relapses. If systemic treatment is needed, chemoimmunotherapy can be repeated or an alternate chemoimmunotherapy regimen can be used. Autologous transplantation may be considered in fit patients with aggressive disease (NCCN Version 5.2022).

Until recently, treatment of MZL included products approved for broader indications such as NHL, which is common in rare diseases with high unmet medical need. These include rituximab, chlorambucil, fludarabine and bendamustine. Older drugs such as vincristine and cyclophosphamide are also being utilised. While these agents provide additional options to patients with MZL, the toxicity associated with these regimens (including long-term effects such as second malignancy) is considerable and duration of benefit for these agents is limited (Sindel et al 2019).

Lenalidomide in combination with rituximab is also used in the treatment of adult patients with previously treated MZL. The approval is based on data from 2 studies, MAGNIFY and AUGMENT. MAGNIFY is a single-arm study of 222 patients with relapsed or refractory (R/R) indolent lymphoma, including 45 patients with MZL (Revlimid USPI 2022). AUGMENT is a Phase 3 study comparing the combination (rituximab plus lenalidomide) with rituximab plus placebo in 358 patients with R/R indolent lymphoma, including 63 with MZL (31 patients received lenalidomide plus rituximab). The ORR for patients with MZL who received lenalidomide plus rituximab was 51% (by investigator assessment) in the MAGNIFY study and 65% (by Independent Review Committee assessment, compared with 44% in the control arm) in the AUGMENT study. Although the primary endpoint of PFS was significantly improved for lenalidomide compared with placebo for the AUGMENT study population overall, there was no PFS benefit in patients with MZL (HR of 1.00; 95% CI: 0.47 to 2.13) (Leonard et al 2019). Important toxicities for the lenalidomide plus rituximab arm, which occurred more frequently than in the control arm were infections (63% versus 49%, respectively), cutaneous reactions (32% versus 12%) and Grade 3 or higher neutropenia (50% versus 13%). Adverse events that led to treatment discontinuation occurred in 14.6% of patients who received lenalidomide plus rituximab (Revlimid USPI 2022).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

MZLs originate from B lymphocytes in the “marginal zone” of secondary lymphoid follicles within the spleen, lymph node, and MALT. Evidence indicates that MZL of MALT, splenic, and nodal types are associated with chronic antigenic stimulation by autoantigens and/or microbial pathogens (Thieblemont 2005).

Clinical presentation of MALT lymphomas varies according to the lymphoma location. Most MALT lymphoma patients present at diagnosis with an indolent disease with good performance status, absence of B symptoms, and no adverse biological prognostic factors such as high lactate dehydrogenase or β2 microglobulin levels (Zucca et al 2003; Thieblemont 2005). Disease is localized for the majority of the patients, but multifocal lesions are present in 30% to 40% of patients (Thieblemont 2005). Dissemination of the disease occurs either to other mucosal sites or, more often, by extension from a mucosal site to a nonmucosal site such as spleen, bone marrow, or liver. Bone marrow involvement is detected in 20% of the cases. Risk of dissemination is significantly higher for non-gastrointestinal tract lymphomas.

Splenic MZL is rare and overlaps with other indolent lymphomas. The hallmark of the clinical presentation is usually splenomegaly (Thieblemont 2005). The splenomegaly becomes symptomatic when massive and/or associated with cytopenias. Early in the disease, however, the splenomegaly may be detectable only on computed tomography scanning. Small involved splenic hilar lymph nodes are frequently present. Bone marrow and blood involvement are present in 95% of patients with splenic MZL. Whereas the serum lactate dehydrogenase level is usually normal in splenic MZL, the β2-microglobulin level is increased. A large proportion of patients have a serum monoclonal paraprotein (M-component), mainly of the μ (IgM) isotype.

The vast majority of patients with nodal MZL present with disseminated, peripheral, and visceral nodal involvement with bone marrow involvement in less than half of these patients (28%, 43%, and 44%, respectively) (Thieblemont 2005; Berger et al 2000; Arcaini et al 2004). There is no difference among these groups with respect to B symptoms, elevated lactate dehydrogenase, performance status, or International Prognostic Index score compared with other primary nodal B-cell lymphomas such as FLs (Thieblemont 2005). Elevated β2-microglobulin is found in one-third of the patients, and an M-component is infrequently detected (8%) (Thieblemont 2005). Cytopenias are rare (Arcaini et al 2004).

Mortality and Morbidity

For cases diagnosed between 2000 and 2017 in the USA, the 5-year relative survival rate for MZL, accounting for competing causes of death, was 89.8%, and was similar across racial/ethnic groups (Cerhan and Habermann 2021). Nodal MZL had the lowest survival (82.8%), with higher survival for splenic MZL (85.3%) and MALT (93.8%), and survival rates were similar across race/ethnicity except for a lower survival for splenic MZL in Hispanics of all races (76.3%). Of MALT sites, 5-year survival was highest for skin (100%) and lowest for small intestine (87.9%).

The 5-year relative survival rate for MZL in the UK was 77.2% for cases diagnosed from 2004 to 2012 (Smith et al 2015), and 90% in the Netherlands from 1989 to 2008 (van de Schans et al 2014). Based on data from HAEMACARE (48 registries in 20 European countries), the estimated 5-year relative survival for MZL cases diagnosed between 2000 and 2002 was 81.4%, with only minor differences by sex (79.3% for males versus 83.2% for females) or region of Europe (range: 73.2% to 84.2%) (Marcos-Gragera et al 2011). In Singapore, 5-year age-standardized relative survival for MZL increased from 76.4% between 1998 and 2002 to 86.7% between 2008 and 2012 (Lim et al 2015).

An analysis of the SEER database revealed that of the patients with splenic MZL, nodal MZL, and MALT, 55%, 54%, and 34% of patients died due to events related to lymphoma (Olszewski and Castillo 2013).

Important Comorbidities

Important comorbidities in patients with MZL include CVD, other malignancies and lung pathology (Olszewski and Castillo 2013).

Chronic Lymphocytic Leukaemia

Indication

CLL and small lymphocytic lymphoma (SLL) are forms of NHL arising from B lymphocytes (Lymphoma Research Foundation 2020). CLL is characterised by clonal proliferation and

accumulation of mature, typically CD5-positive B cells within the blood, bone marrow, lymph nodes, and spleen (Hallek 2019). SLL is essentially the same disease as CLL, characterised by lymphadenopathy or other tissue infiltrated by CLL phenotype lymphocytes in the absence of clonal lymphocytosis in peripheral blood (Hallek et al 2018; Hallek 2019). The WHO classification considers CLL and SLL to be different clinical manifestations of the same disease (Swerdlow et al 2016); therefore CLL and SLL are considered collectively. Often the disease may be initiated by the loss or addition of large amounts of chromosomal material (eg, deletion 13q, deletion 11q, trisomy 12), followed later by additional mutations that may render the leukaemia more aggressive (Landau et al 2015). In all cases, CLL is preceded by a premalignant counterpart called monoclonal B-cell lymphocytosis, and the capacity to generate clonal B cells in CLL is already acquired at the haematopoietic stem cell stage (Parikh 2018; Kikushige et al 2011).

The presence of ≥ 5000 clonal B lymphocytes/µL in the peripheral blood for ≥ a 3-month period is required to diagnose CLL (Hallek 2019). Lymph node or tissue biopsy to indicate the infiltration of clonal CLL cells is important for SLL diagnosis (Hallek et al 2018).

CLL can be divided into 2 main subsets which differ in their clinical behaviour and are distinguished by whether CLL cells express an unmutated or mutated immunoglobulin heavy-chain variable region gene (IGHV) (Kipps et al 2017). Cells expressing unmutated IGHV originate from a B cell that has not undergone differentiation in germinal centres, while those with mutated IGHV arise from a postgerminal centre B cell that expresses immunoglobulin that has undergone somatic hypermutation and sometimes also immunoglobulin isotype switching. Cells with unmutated IGHV typically cause more aggressive disease than those expressing mutated IGHV.

Deletions of the short arm of chromosome 17 (del[17p]) are found in 5% to 8% of chemotherapy-naive patients with CLL (Hallek 2019). These deletions almost always include band 17p13, where the prominent tumour suppressor gene TP53 is located. The CLL patients carrying a del(17p) clone show marked resistance against genotoxic chemotherapies that cannot be overcome by the addition of anti-CD20 antibodies in the context of state of the art chemoimmunotherapy.

Histologic transformation (Richter transformation) of CLL to more aggressive tumours such as diffuse large B-cell lymphoma (DLBCL; a type of NHL) or Hodgkin lymphoma occurs in 2% to 10% of CLL cases (Wierda et al 2019). hepLess commonly, CLL may progress to prolymphocytic leukaemia.

Incidence

CLL is the most common type of leukaemia in Western countries, with an age-adjusted incidence of 4.1 per 100,000 inhabitants in the USA (Hallek 2019; Jemal et al 2007). The lifetime risk of getting CLL is estimated at 1 in 176 (0.57%) (American Cancer Society 2021). Estimates from the American Cancer Society indicate around 21,250 new CLL cases, and 4320 deaths from CLL in the USA in 2021. CLL therefore accounts for about a quarter of new leukaemia cases. CLL/SLL constitutes approximately 7% of newly diagnosed cases of NHL (Wierda et al 2019). The death rate from CLL based on 2014 to 2018 data was 0.9 per 100,000 persons per year with a 5-year relative survival (2011 to 2017 data) of 86.9% (NCI SEER Program: Chronic Lymphocytic Leukaemia 2021).

Prevalence

Published estimates of the prevalence of CLL are rare, but CLL remains the most prevalent adult leukaemia in Western countries (Wierda et al 2020). Prevalence estimates using data from 2007 to 2016 are available from the HMRN website (Haematological Malignancy Research Network). Estimated 3-, 5-, and 10-year prevalence in the UK was 19.0, 29.1, and 47.0 per 100,000 persons. A study of the prevalence of CLL in Sweden calculated an actual prevalence of 52.0 per 100,000 inhabitants in 2015 (Mattsson et al 2020). Assuming relative survival remains unchanged, the study estimated prevalence of 60.6 and 66.5 per 100,000 inhabitants in 2025 and 2035, respectively.

Demographics of the Population in the Authorised Indication – Sex, Age, Racial and/or Ethnic Origin, Geographic Distribution, and Risk Factors for the Disease

The risk of getting CLL is slightly higher in men than women (1.7:1) (American Cancer Society 2021; Hallek 2019). The US National Cancer Institute's SEER Program has estimated the rate of new cases of CLL/SLL to be 6.0 per 100,000 men and 3.4 per 100,000 women (4.6 per 100,000 persons) (NCI SEER Program: Chronic Lymphocytic Leukaemia 2021). The disease mainly affects older adults, with a median age of 72 years at diagnosis (Hallek 2019). It is rarely seen in people under 40, with about 90% of patients with CLL over 50 years old (American Cancer Society 2021).

CLL is the most common adult leukaemia in Western countries but is less common in Asia and relatively rare in Japan and Korea (Kipps et al 2017). Average incidence of CLL ranges from < 0.01% of individuals in eastern Asia to approximately 0.06% of individuals in Europe and the USA. In each racial group in the SEER program, women had a lower prevalence of CLL/SLL than men (NCI SEER Program: Chronic Lymphocytic Leukaemia 2021).

An increased risk of CLL has been linked to exposure to Agent Orange, and it has been suggested that farming and long-term exposure to certain pesticides may also increase the risk (American Cancer Society 2021). First-degree relatives of patients with CLL have an 8.5-fold higher risk of developing CLL (Goldin et al 2009).

Main Existing Treatment Options

If patients show no or few symptoms, watchful waiting is employed. Active treatment is started if the patient begins to develop CLL/SLL-related symptoms or there are signs that the disease is progressing (Lymphoma Research Foundation 2020).

Treatment of CLL is based on the consideration of the clinical stage of the disease, the presenting symptoms, the fitness, and concomitant diseases of the patient, and genetic risk factors (Hallek 2019). Chemoimmunotherapies improve OS when used in CLL patients, although resistance to chemoimmunotherapy is conferred by del(17p) and/or TP53 gene mutations. Specific inhibitors, such as ibrutinib, which disrupt important pathways for survival of CLL cells, have been approved and have started to replace chemoimmunotherapy.

Front-line treatment recommended as per European Society for Medical Oncology (ESMO) guidelines include chemoimmunotherapy such as fludarabine + cyclophosphamide + rituximab for fit patients up to the age of 65-years, BR for fit patients above the age of 65-years, or chlorambucil + obinutuzumab for unfit treatment-naive (TN) patients with mutated- or unmutated-IGHV and without TP53 mutation or del(17p) (Eichhorst et al 2021). However, in

patients with unmutated-IGHV and without TP53 mutation or del(17p), chemoimmunotherapy is recommended only if there is a contraindication to targeted therapies or if those agents are not available. Patients with TP53 mutation or del(17p) should not receive chemoimmunotherapy because of the poor prognosis with those regimens. Recommended targeted therapies include acalabrutinib, ibrutinib, and venetoclax (± obinutuzumab) (Eichhorst et al 2021), or idelalisib as monotherapy or in combination with rituximab (NCCN Version 1.2023). The preferred regimens in the National Comprehensive Cancer Network guideline for all TN CLL/SLL patient groups include zanubrutinib, acalabrutinib (± obinutuzumab), ibrutinib or venetoclax + obinutuzumab. Bendamustine + anti-CD20 monoclonal antibody regimen is included in other recommended regimens and is recommended as a first-line treatment for patients without TP53 mutation or del(17p) for fit patients < 65 years of age and patients with significant comorbidities without age limitation (NCCN Version 1.2023).

Second-line treatment is guided by the duration of the first remission for R/R CLL/SLL patients, defined as no response or relapse within 6 months to the last treatment (Leukemia and Lymphoma Society 2021). ESMO guidelines recommend change of therapeutic regimen in case of symptomatic relapse within 3 years, or refractory disease; treatment with venetoclax + rituximab, or ibrutinib, acalabrutinib, or other BTK inhibitor monotherapy should be considered (Eichhorst et al 2021). Patients with remissions of more than 3 years may be re-exposed to the same time limited regimen, however, repetition of fludarabine + cyclophosphamide + rituximab regimen is not recommended. Other options are acalabrutinib or ibrutinib, venetoclax ± rituximab, or idelalisib + rituximab. For fit patients with TP53 mutation or del(17p), allogenic stem-cell transplantation should be considered. The preferred regimens in the National Comprehensive Cancer Network guideline for R/R CLL/SLL patients are the same, except venetoclax monotherapy is recommended only for patients with TP53 mutation or del(17p) (NCCN Version 1.2023). Ibrutinib is also approved in a number of regions for the treatment of CLL/SLL, including CLL/SLL with 17p deletion, and zanubrutinib is approved in the EU and UK for treatment of both TN and R/R CLL.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

CLL/SLL is a lymphoproliferative disorder, involving peripheral blood, bone marrow, and lymphoid organs (Scarfò et al 2016). The clinical manifestations of CLL range from an asymptomatic patient with minimal B-cell lymphocytosis to a progressive clinical picture of enlarging lymph nodes, splenomegaly, anaemia, thrombocytopenia, and life-threatening infections (Kempin 2013). Some patients live with stable disease for many years without intervention, while 20% to 30% follow an aggressive course, sometimes with rapid progression requiring treatment (Huang et al 2014). Advanced stage patients can show fatigue and intolerance to physical exercise because of anaemia, secondary to bone marrow infiltration, while the presence of bleeding manifestations caused by low platelet count is very rare. The nonspecific B symptoms, which include fever, chills, night sweats, weight loss, fatigue, and/or malaise, are indicators of increased disease activity and need for treatment. Other symptoms indicating the need for treatment are anaemia, thrombocytopenia, and progressive lymphadenopathy (Tees and Flinn 2017). Patients with CLL have a higher vulnerability to infections, with bacterial infections involving upper and lower respiratory tract and urinary tract being the most frequent, though an increased risk of viral reactivation (eg, herpes zoster infection) has also been reported (Scarfò et al 2016). About 5% to 10% of patients with CLL

develop Richter transformation which refers to the development of aggressive lymphoma with rapidly enlarging lymph nodes (Jain and O'Brien 2012). Advanced disease is frequently characterised by worsening infectious complications which represent the main cause of death (Scarfò et al 2016).

Mortality and Morbidity

For CLL, the 5-year relative survival in Europe was estimated to be 70.4%, is better in women than men (73.7% versus 68%) and ranged from 58% in Eastern Europe to about 74% in Central and Northern Europe (De Angelis et al 2015). In the USA, the 5-year survival is estimated at 87.2% based on data from 2011 to 2017 (NCI SEER Program: Chronic Lymphocytic Leukaemia 2021). For those with CLL, 5-year survival for low risk, intermediate risk, high risk, and very high risk groups is approximately 95%, 80%, 65%, and 25%, respectively (Cancer Research UK, Survival for CLL 2021).

The mortality for 2021 is estimated to be 4320 CLL deaths in the USA (NCI SEER Program: Chronic Lymphocytic Leukaemia 2021). From 2015 to 2019 in the USA, the median age at death from CLL was 82 years. Of the CLL deaths, less than 0.1% died under age 20; 0.1% between 20 and 34; 0.2% between 35 and 44; 1.3% between 45 and 54; 7.2% between 55 and 64; 18.8% between 65 and 74; 32.6% between 75 and 84; and 39.7% 84 years of age and older. The age-adjusted death rate was 1.1 per 100,000 men and women per year. The death rates by race and sex between 2015 and 2019 in the USA are detailed in Table Part II: Module SI-2 (NCI SEER Program: Chronic Lymphocytic Leukaemia 2021).

Table Part II: Module SI-2: Death Rates by Race and Sex, United States of America, 2015 to 2019

Race/Ethnicity	Males per 100,000 Men	Females per 100,000 Women
All races	1.6	0.7
White	1.7	0.8
Black	1.3	0.7
Asian/Pacific Islander	0.3	0.1
American Indian/Alaska Native	0.6	0.2
Hispanic	0.6	0.3
Non-Hispanic	1.7	0.8

Source: NCI SEER Program: Chronic Lymphocytic Leukaemia 2021.

Important Comorbidities

Important comorbidities in patients with CLL/SLL include infections (Dearden 2008), neurological disorders (Lopes da Silva 2012), other malignancies (Tsimberidou et al 2009), CVD, and renal insufficiencies (Schmidt et al 2011).

Follicular Lymphoma

Indication

FL is a heterogeneous clinicopathologic entity that includes tumours derived from germinal centre B cells, both centrocytes and centroblasts (Freedman and Aster 2022). FL most commonly presents either as clinically enlarged lymph nodes or incidentally on imaging performed for other reasons. Over 90% of cases are associated with a specific translocation between the immunoglobulin heavy chain gene on chromosome 14 and the *BCL2* oncogene on chromosome 18. FL is the second most common subtype of NHL, accounting for around 20% of all cases of NHL (Freedman 2018; Swerdlow et al 2016). The majority (80%) of cases do not have B-type symptoms or cytopenia at the time of diagnosis (Hanel and Epperla 2021).

Incidence

Age-adjusted incidence rate of FL in the US was 3.4 per 100,000 person-years from 2011 to 2012 and estimated new cases of FL was 13,960 in 2016 (Teras et al 2016). In the UK, the crude incidence rate from the HMRN from 2004 to 2012 was 3.23 (95% CI: 3.03 to 3.45) per 100,000 persons; age-standardized (European 2013) incidence rate was 2.81 (95% CI: 2.74 to 2.88) per 100,000 persons (Smith et al 2015). The age-standardized incidence rate in France in 2012 has been estimated to be 2.5 and 2.1 in males and females, respectively, per 100,000 persons (Le Guyader-Peyrou et al 2016).

Prevalence

The 3-, 5-, and 10-year prevalence rates per 100,000 estimated from the UK HMRN database were 9.7 (95% CI: 8.7 to 10.7), 14.8 (95% CI: 13.6 to 16.1), and 25.2 (95% CI: 23.5 to 26.9) respectively (Smith et al 2015).

According to Kanas et al (2022), the 10-year prevalence of FL (defined as the number of patients diagnosed within the past 10 years who survived to the given year) in the USA and in Western Europe including France, Germany, Italy, Spain and the UK in 2020 is estimated to be 103,708 and 94,658 cases, respectively. By 2025, the 10-year prevalence of FL in 2025 is projected to reach 106,671 cases in the US and 101,370 cases in Western Europe. The 10-year prevalence is projected to increase at a lower rate of 3% over the period for the US compared to 7% for Western Europe. For the US, the historic incidence rate for FL is declining, resulting in a slower increase in the 10-year prevalence. In addition, the 20-year prevalence of FL in the US and in Western Europe in 2020 is 163,217 and 137,930 cases, respectively, projecting to be 171,837 and 153,915 by 2025. According to Orphanet (Orphanet), prevalence of FL in Europe is estimated at about 1/3,000.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

The natural history of FL is indolent in nature, with most patients developing several relapses over their lifetime. As the disease progresses, subsequent relapses can become progressively aggressive and refractory, and some cases may transform into aggressive lymphoma (Becnel and Nastoupil 2018).

According to the WHO criteria, FL tumours are histologically divided into three grades: Grade 1 (< 5 centroblasts per high-power field [hpf]), Grade 2 (6 to 15 centroblasts/hpf) and Grade 3

(> 15 centroblasts/hpf). Grade 3 is further subdivided into Grade 3a (centrocytes still present) and Grade 3b (the follicles consist almost entirely of centroblasts). Grades 1 through 3a are considered to be indolent and incurable, whereas Grade 3b is considered an aggressive but curable disease similar to DLBCL (Ma 2012). The Ann Arbor staging system includes: Stage I (IE) – single lymph node region or extralymphatic site; Stage II (IIE) – multiple lymph node regions or at least one lymph node region plus a localized extralymphatic site on the same side of the diaphragm; Stage III (IIIE, IIIS) – multiple lymph node regions or lymphoid structures (eg, thymus, Waldeyer's ring) on both sides of the diaphragm with optional localized extranodal site (IIIE) or spleen (IIIS); Stage IV – diffuse or disseminated extralymphatic organ involvement. The Follicular Lymphoma International Prognostic Index risk factors include number of nodal sites or long diameter of largest lymph node; age > 60 years; elevated lactate dehydrogenase or elevated β2-microglobulin; Ann Arbor Stage III to IV or bone marrow involvement; and haemoglobin < 12 g/dL (Dreyling et al 2021).

The overwhelming majority of FL patients have advanced stage disease at diagnosis, whereas less than 10% of patients have Stage I/II disease at diagnosis. Studies have reported that 10% to 70% of patients transform to DLBCL over time, with an estimated risk of 3% per year. Symptoms include rapid progression of lymphadenopathy, extranodal disease, and B symptoms (fever, night sweats, and weight loss) (Freedman and Aster 2022).

5-year relative survival rates (the ratio of observed survival in the patient group to expected survival in a comparable group of the general population assumed to be free of the cancer of interest) for patients with FL ranged from 81% in black males to 87% in white females in the US (Teras et al 2016).

5-year overall and relative survival rates in the UK HMRN patients diagnosed between 2004 and 2012 and followed through to 2014 were 75.6% (95% CI: 72.4 to 78.5) and 86.5% (95% CI: 83.0 to 89.4), respectively (Smith et al 2015).

Risk Factors for the Disease

Risk factors for FL are poorly understood. Based on data from the US SEER program, FL incidence is 1.2 times higher in men than women, increases with age, and is highest in non-Hispanic whites (4.1 per 100,000 vs Hispanics of all races [2.9], non-Hispanic blacks [2.4], American-Indian/Alaska Natives [1.7], and Asian or Pacific Islanders [1.7]) (Cerhan 2020). Other than age, gender and ethnicity, environmental and occupational exposure to benzenes and pesticides have been implicated, but a clear association has not been established. Lifestyle factors such as smoking, alcohol use, and obesity have also been implicated in various studies, but conflicting results have not established a clear association with increased risk of FL (Ma 2012).

Risk factors for transformation to DLBCL have been controversial. Clinical risk factors include elevated β2-microglobulin levels, high international prognostic index, high Follicular Lymphoma International Prognostic Index score, and advanced stage (III and IV). However, due to the variable follow-up time, inclusion criteria and treatments, findings in various studies have been inconsistent (Fischer et al 2018).

Demographic Profile of Target Population

The median age at diagnosis is 60 to 65 years, and incidence is 1.2 times higher in men than women (Cerhan 2020). In the US, Caucasians have a higher incidence than African Americans (Ma 2012).

In the UK HMRN population, median age at diagnosis was 64.9 (interquartile range [IQR]: 55.8 to 73.3) (Smith et al 2015). Similarly, in the EUROCARE study, the median age at diagnosis was 62 years (IQR 51 to 72) and females accounted for 53% of all 13,988 cases (Mounier et al 2015).

Main Treatment Options

Treatment options are currently recommended for patients with FL by ESMO (Dreyling et al 2021) and NCCN (NCCN Version 5.2022).

At relapse, the selection of salvage treatment depends on the patient's prior regimens. In symptomatic cases with low tumour burden, rituximab monotherapy may be utilized. In early relapses (< 12 to 24 months), consideration should be given to a noncross-resistant therapy. This could include rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone or rituximab plus cyclophosphamide, vincristine and prednisolone or BR. Fludarabine, platinum, or alkylator based regimens are other treatment options. Obinutuzumab also can be used as monotherapy or in combination with bendamustine in select patients. In patients with short lived remissions (< 2 to 3 years), high dose chemotherapy followed by autologous stem cell transplantation, should be considered (Dreyling et al 2021). Other options include phosphoinositide 3-kinase (PI3K) inhibitors such as copanlisib, tazemetostat in patients who have mutations in EHZ2 or lack other treatment options, lenalidomide plus rituximab, or radioimmunotherapy (Y90 ibritumomab tiuxetan). Fit patients can also receive chimeric antigen receptor T-cells (CAR-T cells) or bispecific antibodies.

Important Comorbidities

It is common that FL patients have comorbidities. An analysis of 414 FL patients showed that 40% of patients had at least one Charlson comorbidity. In one study, 28% of patients had arterial hypertension and 20% of patients had hyperlipidaemia (Mozas et al 2021). Another study including 1346 FL patients mostly receiving rituximab-based regimens yielded similar findings. In this study, approximately 38% of FL patients had at least one Charlson comorbidity such as diabetes (14.5%) and chronic pulmonary disease (11.2%) (Morrison et al 2019). In addition, a SEER-Medicare analysis of 6109 patients with FL found that 78.8% of patients had pre-existing hypertension; 18.9% had pre-existing diabetes; 7.6% had pre-existing chronic heart failure; and 7.1% had CVD/acute myocardial infarction (Kenzik et al 2018). Having a Charlson Comorbidity Index score ≥ 2 is reported to lower 10-year OS with a HR of 2.5 (Mozas et al 2021).

PART II: MODULE SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human use are shown in Table Part II: Module SII-1.

Table Part II: Module SII-1: Key Safety Findings From Nonclinical Studies

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single-dose toxicity No mortality or severe toxicity was noted in rats or dogs at single oral doses up to 1000 mg/kg, which is approximately 30- and 101-fold, respectively, higher than the recommended therapeutic dose (320 mg/day) in patients, based on body surface area.	The risk of acute toxicities in patients is considered minimal due to the safety margin of larger than 30-fold.
Repeated-dose toxicity Repeated-dose toxicities were characterised orally in both rats and dogs for 28-day, 13-week, and 6- or 9-month treatment duration. Treatment-related mortality was noted only in rats at 1000 mg/kg/day after 5 days of treatment in a 6-month repeated-dose study, which was associated with histopathologic changes in the gastrointestinal tract (erosion/necrosis/ulceration, atrophy, and/or neutrophilic infiltration). The dose of 1000 mg/kg/day was approximately 81-fold higher than the systemic exposure (area under the curve [AUC]) in patients receiving the recommended dose. The treatment-related clinical findings were noted in the gastrointestinal tract (soft/watery/mucoid stool) and skin (rash, red discoloration, and thickened/scaling) mainly in dogs at doses ≥ 10 mg/kg/day (3 x the clinical AUC). Test article related, dose dependent and reversible changes were limited to slight increases in inflammatory cells in peripheral blood, lymphoid depletion in peripheral lymph nodes, and slight inflammatory cell infiltration in multiple tissues. The histopathologic changes noted in rat pancreases were considered a species-specific class effect of BTK inhibitors and are not likely relevant to humans (Bhaskaran et al 2018).	The risk of severe gastrointestinal toxicity in patients is considered minimal because it occurred only at the dose approximately 81-fold higher than the recommended therapeutic dose (320 mg/day) in patients, based on systemic exposure (AUC). No specific safety or toxicity issues were identified in rats at doses up to 100 mg/kg/day for 6 months or in dogs at doses up to 10 mg/kg/day for 9 months. The toxicities noted in both rats and dogs were generally related to the pharmacological activity of zanubrutinib. Margins of exposure were approximately 13-fold to 3-fold higher than the systemic exposure (AUC) in patients receiving the recommended dose.
Reproductive/developmental toxicity	
Embryo-foetal developmental toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts at the incidence of 0.3% to 1.5%) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5-fold higher than the systemic exposure (AUC) in patients receiving the recommended dose.	Zanubrutinib may cause foetal harm when administered to a pregnant woman. This is based on teratogenic findings in the foetal rat heart (low incidence of 0.3%) when pregnant rats received 30 mg/kg/day and postimplantation loss in the rabbit

Table Part II: Module SII-1: Key Safety Findings From Nonclinical Studies

Key Safety Findings	Relevance to Human Usage
Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in postimplantation loss at the highest dose. The dose of 70 mg/kg is approximately 25-fold higher than the systemic exposure (AUC) in patients receiving the recommended dose. No teratogenicity was noted in this study.	study at the highest dose of 150 mg/kg. The ophthalmic lesions were noted only in offspring rats. Because the lesions were not noted in rats or dogs in 6- or 9-month repeated-dose
In a pre and postnatal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The main findings for offspring included adverse ocular lesions at all dose levels (eg, cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5-fold higher than the systemic exposure (AUC) in patients receiving the recommended dose.	studies, the risk of ophthalmic lesions is considered low for the adult patients.
Fertility and early embryonic development A male and female fertility and early embryonic development study was conducted in rats with oral administration of zanubrutinib at doses of 30, 100 or 300 mg/kg/day. Male rats were dosed 4 weeks before mating and through mating, and female rats were dosed 2 weeks before mating and through to gestational Day 7. No effect on male or female fertility was noted, but at the high dose of 300 mg/kg tested, morphological abnormalities in sperm and increased postimplantation loss were noted. The dose of 100 mg/kg/day, is approximately 3-fold higher than the human recommended dose, based on body surface area. Additionally, no apparent treatment-related adverse pathological changes in reproductive organs were noted in rats or dogs in 6- or 9-month repeated-dose studies, which suggests a low risk of fertility impairment.	Based on the animal findings, the risk of fertility toxicities in patients is considered low.
Genotoxicity	
Zanubrutinib was not genotoxic in studies evaluating gene mutations in bacteria, erythrocyte micronuclei in the bone marrow of rats, and chromosome aberrations in Chinese hamster ovary cells.	No genotoxic risk was identified based on nonclinical genotoxicity studies.
Carcinogenicity	
No carcinogenicity studies were conducted. Carcinogenicity studies are not required based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline S9 (ICH 2008). No tumour masses were noted in rat repeat-dose studies up to 6 months of treatment or in dog repeat-dose studies up to 9 months of treatment.	The relevance to human usage of carcinogenicity is unknown.

Table Part II: Module SII-1: Key Safety Findings From Nonclinical Studies

Key Safety Findings	Relevance to Human Usage
General safety pharmacology	
Cardiovascular system (including potential for QT interval prolongation)	
A moderate inhibitory effect on human ether-à-go-go-related gene was noted (half maximal inhibitory concentration [IC_{50}] = 9.11 μM). Based on the clinical steady-state unbound maximum observed plasma concentration (C_{max}) of 0.03 μM (total C_{max} 247 ng/mL; plasma protein binding 94.2%) observed at the recommended Phase 2 dose of 160 mg twice daily, there is an approximately 304-fold exposure margin. No effects on blood pressure, heart rate, or electrocardiogram (ECG) were noted in telemetry-instrumented conscious dogs at single oral doses up to 100 mg/kg for 24 hours. No changes in ECG were noted in beagle dogs at doses up to 100 mg/kg/day for 9 months. The dose of 100 mg/kg is approximately 18-fold higher than the systemic exposure (AUC) in patients receiving the recommended dose.	The clinical study demonstrated that single oral doses of zanubrutinib at 160 mg and 480 mg did not have a clinically relevant effect on ECG parameters, including QTc interval and other ECG intervals. Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter is an important identified risk
Central nervous system (CNS)	
No zanubrutinib-related changes were noted in rats at single oral doses up to 300 mg/kg by the functional observational battery test, which included motor activity, behavioural changes, coordination, sensory/motor reflex responses, and body temperature assessments. The dose of 300 mg/kg is approximately 25-fold higher than the systemic exposure (AUC) in patients receiving the recommended dose.	No apparent changes were noted in the completed clinical studies.
Respiratory system	
No significant changes in the respiration rate, tidal volume, or derived minute volume were noted in rats at single oral doses up to 300 mg/kg. The dose of 300 mg/kg is approximately 25-fold higher than the systemic exposure (AUC) in humans at the therapeutic dose.	No apparent changes were noted in the completed clinical studies.
Other toxicity-related information or data	
Gastrointestinal system In the repeat-dose studies in rats, treatment-related soft/tan/yellow stool, correlated with histopathologic changes in the gastrointestinal tract (erosion/necrosis/ulceration, atrophy, and/or neutrophilic infiltration) were only noted at the mortality dose of 1000 mg/kg/day following 5-day dosing, where the systemic exposure was approximately 81-fold higher than the human therapeutic exposure. Soft stool was noted in rats at the dose of 500 mg/kg/day in the 28-day repeat-dose study and 300 mg/kg/day in the 26-week repeat-dose study.	The systemic exposure at the mortality dose of 1000 mg/kg/day in rats with severe gastrointestinal tract toxicity was approximately 81-fold higher than the human therapeutic exposure. Therefore, the risks for severe gastrointestinal tract disorders are considered minimal in patients. In clinical studies, the most

Table Part II: Module SII-1: Key Safety Findings From Nonclinical Studies

Key Safety Findings	Relevance to Human Usage
In the repeat-dose studies in dogs, treatment-related abnormal stool (soft/watery/mucoid) was reported at the doses ≥ 10 mg/kg/day based on the higher incidences and/or frequencies of occurrence, predominant in the 39-week repeat-dose study. No corresponding histopathologic changes were noted. The systemic exposure at the dose of 10 mg/kg/day is approximately 3-fold higher than the human therapeutic exposure.	commonly reported preferred terms (PTs) were diarrhoea, constipation, nausea, vomiting, and abdominal pain. The criteria for seriousness was met in 59 (3.8%) patients.
Skin Erosion/ulcer of the mouth/lips/eyelids were noted in rats at the doses of 500 mg/kg/day; rash, red discoloration and thickened/scaling of the skin were noted in dogs at the doses ≥ 10 mg/kg/day without correlated histopathologic changes. The systemic exposure at the dose of 500 mg/kg/day in rats and 10 mg/kg/day in dogs is approximately 34- and 3-fold higher, respectively, than the human exposure at the therapeutic dose.	In the All Zanubrutinib treatment group (N = 1550) at the 07 May 2021 data cutoff (DCO) date, a cutaneous reactions event occurred in 131 (8.5%) patients, primarily ocular or oral (n = 112). Serious events included 1 (0.1%) case of drug reaction with eosinophilia and systemic symptoms in a combination study, and 1 (0.1%) case of toxic epidermal necrolysis.
Body weight Decreased body weight gain by 5.65% in male rats at doses ≥ 30 mg/kg/day in the 26-week repeat-dose study and decreased body weight by 18.3% in beagle dogs at doses ≥ 10 mg/kg/day in the 39-week repeat-dose study were noted. The systemic exposure at the doses of 30 mg/kg/day in rats and 10 mg/kg/day in dogs was similar and was approximately 3-fold higher than the human exposure at the therapeutic dose.	No apparent changes in body weight were noted in the completed clinical studies.
Haematology Erythrocytes: Marginal decreases in red blood cells, haemoglobin and haematocrit were noted in rats at the dose of 500 mg/kg/day in the 28-day repeat-dose study. The systemic exposure at the dose of 500 mg/kg/day in rats is approximately 34-fold higher than the human exposure at the therapeutic dose. Granulocytes: Marginal increases in white blood cells, neutrophils, and monocytes were noted in rats at the dose ≥ 300 mg/kg/day and in dogs at the dose of 100 mg/kg/day. The systemic exposure at the dose of 300 mg/kg/day in rats and 100 mg/kg/day in dogs is approximately 25- and 20-fold higher, respectively, than the human exposure at the therapeutic dose.	In clinical studies, haemorrhage was an Important Identified Risk. No haemorrhage or reduction of platelet counts was identified in animal studies. Cytopenias (anaemia, neutropenia and thrombocytopenia) and infections were noted in the completed clinical studies, while slight decreases in red blood cells and increases in granulocytes were noted in nonclinical studies without apparent infections.

Table Part II: Module SII-1: Key Safety Findings From Nonclinical Studies

Key Safety Findings	Relevance to Human Usage
Hepatotoxicity and electrolytes Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin/globulin ratio, total cholesterol and fibrinogen; decreases in albumin, total bilirubin, total protein, globulin, triglycerides, calcium and potassium were noted in rats at the dose of 300 mg/kg/day and/or in dogs at the dose of 100 mg/kg/day. All these changes were slightly higher or lower than the historical normal range. The systemic exposure at the dose of 300 mg/kg/day in rats and 100 mg/kg/day in dogs is approximately 25- and 20-fold higher, respectively, than the human exposure at the therapeutic dose.	In clinical studies, the most commonly reported adverse events in PTs were hyperbilirubinaemia, hepatic function abnormal, hepatic steatosis, cholecystitis, and cholelithiasis. No clinically relevant differences were observed for serum chemistry analytes of interest for postbaseline shifts of ≥ 2 toxicity grades. A few cases were reported as potential Hy's law cases. After a comprehensive review, no Hy's law cases were confirmed and most events in the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) of Drug-related hepatic disorders reported with zanubrutinib use were explained by alternative aetiologies, including progression of underlying haematological malignancy. Currently there are no data to associate zanubrutinib treatment and drug-induced liver injury.
Urinalysis Increased incidence of proteinuria and occult blood was observed at ≥ 30 mg/kg/day in rats. The systemic exposure at the dose of 30 mg/kg/day in rats is approximately 3-fold higher than the human exposure at the therapeutic dose.	No apparent changes were noted in the completed clinical studies.

Conclusions of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	Teratogenicity
Missing information	None

PART II: MODULE SIII CLINICAL STUDY EXPOSURE

Overview of Clinical Development

The zanubrutinib clinical development programme summarised in this application includes data from 179 patients with FL treated with zanubrutinib in combination with obinutuzumab in 2 clinical studies (1 Phase 1 study and 1 Phase 2 study). In addition, it includes 1550 B-cell malignancy patients treated with zanubrutinib monotherapy (the Zanubrutinib Monotherapy group) at a dose of 320 mg daily, including patients with MZL, WM, CLL/SLL, and mantle cell lymphoma (MCL) enrolled in 10 additional clinical studies (2 Phase 1 studies, 4 Phase 2 studies, 3 Phase 3 studies, and 1 long-term extension study). Of the 1550 patients, 59 had a diagnosis of FL. These patients were treated with zanubrutinib monotherapy in 2 clinical studies (the Phase 1, single arm study BGB-3111-1002 and the Phase 1/2 study BGB-3111-AU003).

The following studies have been conducted with zanubrutinib as monotherapy:

- Study BGB-3111-1002: A Phase 1, single-arm pharmacokinetics (PK)/pharmacodynamics (PD), safety, and efficacy study in adult patients with B-cell malignancies (conducted in China, N = 44). The long-term extension study BGB-3111-LTE1 includes 11 patients from the 44 patients in this study.
- Study BGB-3111-AU-003: A first-in-human, Phase 1/2, dose-escalation and selection, PK/PD, safety, and efficacy study in adult patients with R/R or TN B-cell malignancies conducted in Australia, New Zealand, Italy, South Korea, the UK, and the USA (373 patients were enrolled, including 33 patients with FL). This study contributes PK, PD, efficacy, and safety data. Safety data from 201 patients who have been rolled over to a long-term extension study (BGB-3111-LTE1) were integrated in the BGB-3111-AU-003 clinical study report and summary of clinical safety.
- Study BGB-3111-205: A Phase 2, single-arm, efficacy and safety study of zanubrutinib monotherapy in adult patients with R/R CLL or SLL (conducted in China, N = 91). The long-term extension study BGB-3111-LTE1 includes 60 patients from this study.
- Study BGB-3111-206: A Phase 2, open-label, single-arm efficacy and safety study of zanubrutinib monotherapy in adult patients with R/R MCL (conducted in China, N = 86). The long-term extension study BGB-3111-LTE1 includes 40 patients from this study.
- Study BGB-3111-210: A Phase 2, single-arm, open-label study assessing the efficacy and safety of zanubrutinib monotherapy in adult patients with R/R WM (conducted in China, N = 44). The long-term extension study BGB-3111-LTE1 includes 25 patients from this study.
- 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. The study enrolled patients from sites in Australia, China, New Zealand, South Korea, the USA, the Czech Republic, France, the UK, and Italy (N = 68). This study contributes efficacy as well as safety data for the MZL indication.

- Study BGB-3111-302: A Phase 3, randomised, open-label study comparing the efficacy and safety of zanubrutinib and ibrutinib in patients with WM. This study contributes PK, PD, efficacy, and safety data. The study enrolled R/R or TN patients from the USA, Europe, and Australia/New Zealand and was amongst the largest prospective Phase 3 studies ever to be conducted in WM (N = 129). Further, Study BGB-3111-302 is the first study in any indication that compared a more selective BTK inhibitor (zanubrutinib) to ibrutinib.
- Study BGB-3111-304: An international, Phase 3, randomised, multicentre study comparing the efficacy and safety of zanubrutinib versus bendamustine plus rituximab in patients with previously untreated CLL/SLL. The study enrolled TN patients from the USA, Europe, China, and Australia/New Zealand (N = 391).
- Study BGB-3111-305: A Phase 3, randomised, multicentre study comparing the efficacy and safety of zanubrutinib versus ibrutinib in patients with R/R CLL/SLL. The study enrolled patients from the USA, Europe, China, and Australia/New Zealand (N = 324).
- Study BGB-3111-LTE1 (long term extension [LTE-1]), a study consisting of patients rolling over from Studies BGB-3111-AU-003, BGB-3111-1002, BGB-3111-113, BGB-3111-205, BGB-3111-206, BGB-3111-207, BGB-3111-210, BGB-3111-213, BGB-3111-214, BGB-3111-302, BGB-3111-GA101, and BGB-3111-A317, and those 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, are combined with data from their respective studies.

The following studies have been conducted with zanubrutinib in combination with obinutuzumab:

- Study BGB-3111-212: An international, Phase 2, open-label, randomized study of zanubrutinib combined with obinutuzumab compared with obinutuzumab monotherapy in R/R FL. The study enrolled patients from the USA, Canada, Europe, China, Taiwan, South Korea, and Australia/New Zealand (N = 143 FL patients treated with zanubrutinib plus obinutuzumab).
- Study BGB-3111-GA101_Study_001: A Phase 1b study to assess safety, tolerability and antitumor activity of the combination of zanubrutinib with obinutuzumab in subjects with B-cell lymphoid malignancies. This study enrolled R/R patients with B-cell malignancies from the USA, Australia, and South Korea (N = 36 FL patients treated with zanubrutinib plus obinutuzumab).

The following bioequivalent studies have been conducted with zanubrutinib tablet, which demonstrated that the safety profile of zanubrutinib tablet is consistent with the safety profile with zanubrutinib capsule.

- Study BGB-3111-114: A Single-dose, Open-label, Randomized, Replicate Crossover Study in Healthy Adult Subjects to Assess the Bioequivalence of a Zanubrutinib 160-mg Tablet Compared to Two BRUKINSA® (Zanubrutinib) 80-mg Capsules. (N=58)

- Study BGB-3111-115: A Single-dose, Open-label, Randomized, Crossover Study in Healthy Adult Subjects to Assess the Relative Bioavailability of a Zanubrutinib 160-mg Tablet Compared to Two BRUKINSA® (Zanubrutinib) 80-mg Capsules and to Evaluate the Effects of Food on the Pharmacokinetics of the Zanubrutinib Tablet. (N=43)

Within this RMP, data are presented for the following 2 patient groups:

All Zanubrutinib Monotherapy group, comprising all patients from the 10 supportive safety studies who were treated with zanubrutinib monotherapy at 160 mg twice a day or 320 mg once a day (n = 1550 patients).

Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, comprising all FL patients who were treated with combination therapy of zanubrutinib and obinutuzumab (n = 143 patients).

Table Part II: Module SIII-1, below, presents a summary of the studies included in assessments of efficacy and safety.

Table Part II: Module SIII-1: Studies Contributing Safety Data

Study and Location	Study Design	Population	Starting Dose	N	First Patient First Dose Data Cutoff Date Study Status
Monotherapy Studies					
214 AU, CN, EU (CZ, FR, IT), NZ, SK, UK, USA	Phase 2, open-label, single-arm	Patients with R/R MZL	160 mg twice daily	68	19 February 2019 04 May 2022 Completed
302 AU, USA, UK, EU (CZ, DE, ES, FR, GR, IT, NL, PO, SW)	Phase 3, randomised, open-label, multicentre	Patients with R/R or TN WM	160 mg twice daily	129	25 January 2017 21 June 2022 Completed
AU-003 AU, NZ, SK, USA, IT, UK	Phase 1/2, single-arm, dose-escalation and cohort-expansion	Patients with R/R or TN CLL/SLL, DLBCL, FL, HCL, MALT, MCL, MZL, NHL, RT, or WM	160 mg twice daily 320 mg once daily	373	16 September 2014 31 March 2021 Completed
LTE1[a] AU, CN, IT, KOR, NZ, UK, USA	Phase 3, open-label, long-term extension of zanubrutinib regimens	Patients from parent studies with B-cell malignancies: CLL/SLL, DLBCL, FL, HCL, MCL, MZL, NHL, RT, transformed FL, WM	160 mg twice daily 320 mg once daily	373	17 October 2022 Ongoing
210 CN	Phase 2, single-arm	Patients with R/R WM	160 mg twice daily	44	31 August 2017 11 January 2021 Completed
1002 CN	Phase 1, single-arm	Patients with R/R CLL/SLL, MCL, WM/LPL, FL, MZL, HCL or nGCB DLBCL	160 mg twice daily 320 mg once daily	44	05 July 2016 30 August 2020 Completed
205 CN	Phase 2, single-arm	Patients with R/R CLL/SLL	160 mg twice daily	91	09 March 2017 11 September 2020 Completed
206 CN	Phase 2, single-arm	Patients with R/R MCL	160 mg twice daily	86	02 March 2017 08 September 2020 Completed

Table Part II: Module SIII-1: Studies Contributing Safety Data

Study and Location	Study Design	Population	Starting Dose	N	First Patient First Dose Data Cutoff Date Study Status
Monotherapy Studies					
304 AU, CN, EU (AT, BE, CZ, ES, FR, IT, PO, SW), NZ, RUS, UK, USA	Phase 3, randomised, open-label, multicentre	Patients with TN CLL/SLL	160 mg twice daily	391	31 October 2017 07 March 2022 Ongoing
305 AU, CN, EU (BE, CZ, DE, ES, FR, IT, NL, PO, SW), TR, NZ, UK, USA	Phase 3, randomised, open-label, multicentre	Patients with R/R CLL/SLL	160 mg twice daily	324	01 November 2018 08 August 2022 Ongoing
Total patients in the integrated monotherapy safety population				**1550**	
Pivotal Combination Therapy Study: Zanubrutinib + Obinutuzumab (Combination Safety Population)					
212 AU, BG, BY, CA, CN, EU (CZ, DE, ES, FR, IT, PO), SK, NZ, RU, TW, UK, USA	Phase 2, randomized, open-label, multicentre study	Patients with R/R FL	160 mg BID	143	14 November 2017 25 October 2022 Ongoing
Supportive Combination Therapy Study: Zanubrutinib + Obinutuzumab					
GA101_Study_001 AU, SK, USA	Phase 1b, open-label, multicentre study	Patients with B-cell malignancies	160 mg BID 320 mg QD	36 (FL subset)	13 January 2016 02 September 2020 Completed

Abbreviations: AT, Austria; AU, Australia; BE, Belgium; BG, Bulgaria; BY, Belarus; CA, Canada; CLL, chronic lymphocytic leukaemia; CN, China; CSR, clinical study report; CZ, Czech Republic; DE, Germany; DLBCL, diffuse large B-cell lymphoma; ES, Spain; EU, European Union; FL, follicular lymphoma; FR, France; GR, Greece; HCL, hairy cell leukaemia; IT, Italy; IV, intravenous; LPL, lymphoplasmacytic lymphoma; LTE1, long-term extension 1; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; N, number of patients treated with zanubrutinib; nGCB, nongerminal centre B-cell-like; NHL, non-Hodgkin lymphoma; NL, Netherlands; NZ, New Zealand; PO, Poland; R/R, relapsed or refractory; RT, Richter transformation; RUS, Russia; SK, South Korea; SLL, small lymphocytic lymphoma; SW, Sweden; TN, treatment-naive; TR, Turkey; TW, Taiwan; UK; United Kingdom; USA, United States of America; WM, Waldenström macroglobulinaemia.

[a] Safety data collected from LTE1 study for 373 patients who were dosed at either 160 mg twice daily or 320 mg once daily in the parent studies (BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, and BGB-3111-210) are grouped with data from the parent studies in all data summaries and analysis described herein.

Extent of Exposure

A summary of treatment exposure to zanubrutinib monotherapy is provided in Table Part II: Module SIII-2.

In the All Zanubrutinib Monotherapy group, the median duration of exposure was 34.41 months; 1270 patients (81.9%) had ≥ 12 months of exposure, 1035 patients (66.8%) had ≥ 24 months of exposure, and 697 patients (45.0%) had ≥ 36 months of exposure. The total exposure (in patient-months) was 52,437.55. The median relative dose intensity was 98.48% (range: 14.6% to 165.9%). A total of 235 patients (15.2%) required ≥ 1 dose reductions (Table Part II: Module SIII-2).

- In the All WM group, the median duration of exposure was 53.55 months; 180 patients (72.3%) had ≥ 24 months of exposure, and 163 patients (65.5%) had ≥ 36 months of exposure. The total exposure (in patient-months) was 10,731.56. The median relative dose intensity was 98.09% (range: 21.2% to 101.4%). A total of 41 patients (16.5%) required ≥ 1 dose reductions (Table Part II: Module SIII-2).
- In the All MCL group, the median duration of exposure was 26.09 months; 62 patients (51.7%) had ≥ 24 months of exposure, and 52 patients (43.3%) had ≥ 36 months of exposure. The total exposure (in patient-months) was 3911.72. The median relative dose intensity was 99.72% (range: 45.4% to 165.9%). A total of 12 patients (10.0%) required ≥ 1 dose reductions (Table Part II: Module SIII-2).
- In the 214+AU003 MZL group, the median duration of exposure was 28.16 months; 47 patients (53.4%) had ≥ 24 months of exposure, 31 patients (35.2%) had ≥ 36 months of exposure. The total exposure (in patient-months) was 2307.29. The median relative dose intensity was 98.83% (range: 71.4% to 100.0%). A total of 5 patients (5.7%) required ≥ 1 dose reductions (Table Part II: Module SIII-2).
- In the All CLL/SLL group, the median duration of exposure was 34.71 months; 695 patients (74.1%) had ≥ 24 months of exposure, and 414 patients (44.1%) had ≥ 36 months of exposure. The total exposure (in patient-months) was 32,309.16. The median relative dose intensity was 98.28% (range: 14.6% to 101.7%). A total of 165 patients (17.6%) required ≥ 1 dose reductions (Table Part II: Module SIII-2).

A summary of treatment exposure to zanubrutinib in FL studies is provided in Table Part II: Module SIII-3.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, the median duration of exposure was 12.35 months; 73 patients (51.0%) had ≥ 12 months of exposure, 37 patients (25.9%) had ≥ 24 months of exposure, and 9 patients (6.3%) had ≥ 36 months of exposure. The total exposure (in patient-months) was 2297.36. The median relative dose intensity was 98.86% (range: 30.7% to 100.0%). A total of 19 patients (13.3%) required ≥ 1 dose reductions (Table Part II: Module SIII-3).

In the Zanubrutinib Monotherapy group (FL patients; N = 59), the median duration of exposure was 8.34 months; 21 patients (35.6%) had ≥ 12 months of exposure, 12 patients (20.3%) had ≥ 24 months of exposure, and 9 patients (15.3%) had ≥ 36 months of exposure. The total exposure (in patient-months) was 1067.33. The median relative dose intensity was 99.63%

(range: 81.9% to 100.0%). A total of 1 patient (1.7%) required ≥ 1 dose reductions (Table Part II: Module SIII-3).

Table Part II: Module SIII-2: Summary of Treatment Exposure: Zanubrutinib Monotherapy Studies (Safety Analysis Set)

	Zanubrutinib Monotherapy													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101)	All WM (N = 249)	AU003 (N = 32)	206 (N = 86)	AU003 + 206 Total (N = 118)	All MCL (N = 120)	BGB-3111-214 (N = 68)	214 + AU003 MZL (N = 88)	All MZL (N = 93)	304 (N = 391)	305 (N = 324)	All R/R CLL/ SLL (N = 525)	All CLL/ SLL (N = 938)	All Zanu Mono (N = 1550)[a]
Duration of exposure (months)[b]														
n	101	249	32	86	118	120	68	88	93	391	324	525	938	1550
Mean (SD)	44.61 (19.797)	43.10 (23.547)	28.53 (24.393)	33.81 (25.159)	32.38 (24.962)	32.60 (25.060)	22.43 (14.638)	26.22 (19.218)	25.67 (19.620)	33.02 (10.443)	26.92 (9.817)	34.41 (18.685)	34.44 (16.446)	33.83 (20.202)
Median	53.82	53.55	18.35	27.61	26.09	26.09	27.70	28.16	27.79	36.27	28.42	33.25	34.71	34.41
Min, max	0.8, 68.7	0.6, 85.3	0.4, 72.9	0.2, 67.5	0.2, 72.9	0.2, 72.9	0.9, 40.5	0.9, 83.1	0.9, 83.1	0.5, 52.1	0.4, 41.6	0.2, 90.0	0.2, 90.0	0.1, 90.0
Total exposure (patient-months)	4505.63	10,731.56	912.82	2907.76	3820.58	3911.72	1525.06	2307.29	2387.25	12,908.88	8722.86	18,063.05	32,309.16	52,437.55
Duration of exposure, n (%)														
< 3 months	6 (5.9)	16 (6.4)	4 (12.5)	12 (14.0)	16 (13.6)	16 (13.3)	7 (10.3)	7 (8.0)	10 (10.8)	5 (1.3)	9 (2.8)	18 (3.4)	23 (2.5)	104 (6.7)
3 to < 6 months	1 (1.0)	11 (4.4)	3 (9.4)	6 (7.0)	9 (7.6)	9 (7.5)	9 (13.2)	11 (12.5)	11 (11.8)	6 (1.5)	10 (3.1)	15 (2.9)	22 (2.3)	76 (4.9)
6 to < 9 months	3 (3.0)	9 (3.6)	2 (6.3)	4 (4.7)	6 (5.1)	6 (5.0)	3 (4.4)	6 (6.8)	6 (6.5)	8 (2.0)	7 (2.2)	14 (2.7)	22 (2.3)	57 (3.7)
9 to < 12 months	1 (1.0)	7 (2.8)	2 (6.3)	3 (3.5)	5 (4.2)	5 (4.2)	4 (5.9)	5 (5.7)	6 (6.5)	6 (1.5)	4 (1.2)	9 (1.7)	15 (1.6)	43 (2.8)
12 to < 24 months	10 (9.9)	26 (10.4)	7 (21.9)	14 (16.3)	21 (17.8)	22 (18.3)	10 (14.7)	12 (13.6)	12 (12.9)	53 (13.6)	86 (26.5)	107 (20.4)	161 (17.2)	235 (15.2)
24 to < 36 months	8 (7.9)	17 (6.8)	2 (6.3)	8 (9.3)	10 (8.5)	10 (8.3)	15 (22.1)	16 (18.2)	16 (17.2)	108 (27.6)	155 (47.8)	170 (32.4)	281 (30.0)	338 (21.8)

Table Part II: Module SIII-2: Summary of Treatment Exposure: Zanubrutinib Monotherapy Studies (Safety Analysis Set)

	Zanubrutinib Monotherapy													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101)	All WM (N = 249)	AU003 (N = 32)	206 (N = 86)	AU003 + 206 Total (N = 118)	All MCL (N = 120)	BGB-3111-214 (N = 68)	214 + AU003 MZL (N = 88)	All MZL (N = 93)	304 (N = 391)	305 (N = 324)	All R/R CLL/ SLL (N = 525)	All CLL/ SLL (N = 938)	All Zanu Mono (N = 1550)[a]
≥ 36 months	72 (71.3)	163 (65.5)	12 (37.5)	39 (45.3)	51 (43.2)	52 (43.3)	20 (29.4)	31 (35.2)	32 (34.4)	205 (52.4)	53 (16.4)	192 (36.6)	414 (44.1)	697 (45.0)
Cumulative dose administered (g)														
n	101	249	32	86	118	120	68	88	93	391	324	525	938	1550
Mean (SD)	402.65 (196.682)	397.02 (229.009)	243.92 (213.507)	326.65 (244.589)	304.21 (238.546)	306.42 (239.495)	211.96 (139.121)	247.35 (182.632)	242.41 (186.648)	302.63 (101.667)	247.69 (95.416)	315.52 (179.044)	316.30 (158.370)	311.62 (193.105)
Median	506.32	497.76	178.16	261.60	236.16	236.16	254.08	269.68	266.24	337.92	248.40	305.48	322.48	318.40
Min, max	6.6, 626.6	4.9, 828.8	3.5, 696.3	1.4, 654.2	1.4, 696.3	1.4, 696.3	6.4, 392.2	6.4, 790.4	6.4, 790.4	4.5, 497.6	2.9, 379.9	1.1, 870.6	1.1, 870.6	1.0, 870.6
Actual dose intensity (mg/day) [c]														
n	101	249	32	86	118	120	68	88	93	391	324	525	938	1550
Mean (SD)	292.77 (49.606)	297.66 (43.232)	290.16 (48.265)	316.71 (31.998)	309.51 (38.749)	309.67 (38.443)	309.76 (16.133)	308.88 (17.071)	309.38 (16.739)	300.57 (31.397)	302.13 (36.666)	300.70 (42.821)	300.89 (37.951)	301.90 (38.145)
Median	313.41	313.87	312.72	319.47	319.12	319.12	316.86	316.24	316.77	311.35	315.76	316.32	314.47	315.10
Min, max	82.9, 324.5	67.8, 324.5	145.2, 320.0	147.3, 531.0	145.2, 531.0	145.2, 531.0	228.6, 320.1	228.6, 320.1	228.6, 320.1	126.1, 321.0	129.3, 325.6	46.7, 325.6	46.7, 325.6	46.7, 531.0
Relative dose intensity (%) [d]														
n	101	249	32	86	118	120	68	88	93	391	324	525	938	1550
Mean (SD)	91.54 (15.444)	93.04 (13.482)	90.68 (15.090)	98.97 (9.999)	96.72 (12.111)	96.77 (12.015)	96.83 (5.026)	96.55 (5.324)	96.70 (5.220)	93.93 (9.812)	94.42 (11.458)	93.97 (13.382)	94.03(11.860)	94.35 (11.915)
Median	97.92	98.09	97.87	99.83	99.72	99.72	98.98	98.83	98.91	97.30	98.68	98.85	98.28	98.48
Min, max	25.9, 101.4	21.2, 101.4	45.4, 100.0	46.0, 165.9	45.4, 165.9	45.4, 165.9	71.4, 100.0	71.4, 100.0	71.4, 100.0	39.4, 100.3	40.4, 101.7	14.6, 101.7	14.6, 101.7	14.6, 165.9
Patients with dose reduction														
n (%)	20 (19.8)	41 (16.5)	6 (18.8)	6 (7.0)	12 (10.2)	12 (10.0)	2 (2.9)	5 (5.7)	6 (6.5)	81 (20.7)	52 (16.0)	83 (15.8)	165 (17.6)	235 (15.2)

Table Part II: Module SIII-2: Summary of Treatment Exposure: Zanubrutinib Monotherapy Studies (Safety Analysis Set)

	Zanubrutinib Monotherapy													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101)	All WM (N = 249)	AU003 (N = 32)	206 (N = 86)	AU003 + 206 Total (N = 118)	All MCL (N = 120)	BGB-3111-214 (N = 68)	214 + AU003 MZL (N = 88)	All MZL (N = 93)	304 (N = 391)	305 (N = 324)	All R/R CLL/ SLL (N = 525)	All CLL/ SLL (N = 938)	All Zanu Mono (N = 1550)[a]
Patients with dose reduction due to AE														
n (%)	19 (18.8)	33 (13.3)	4 (12.5)	6 (7.0)	10 (8.5)	10 (8.3)	1 (1.5)	4 (4.5)	4 (4.3)	52 (13.3)	36 (11.1)	58 (11.0)	111 (11.8)	166 (10.7)
Number of dose reductions per patient														
n	20	41	6	6	12	12	2	5	6	81	52	83	165	235
Mean (SD)	1.3 (0.57)	1.5 (0.92)	1.3 (0.52)	1.3 (0.52)	1.3 (0.49)	1.3 (0.49)	1.0 (0.00)	1.2 (0.45)	1.2 (0.41)	1.3 (0.65)	1.3 (0.54)	1.5 (0.79)	1.4 (0.72)	1.4 (0.73)
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Min, max	1, 3	1, 6	1, 2	1, 2	1, 2	1, 2	1, 1	1, 2	1, 2	1, 4	1, 3	1, 5	1, 5	1, 6
Number of dose reductions per patient, n (%)														
1	15 (14.9)	28 (11.2)	4 (12.5)	4 (4.7)	8 (6.8)	8 (6.7)	2 (2.9)	4 (4.5)	5 (5.4)	63 (16.1)	38 (11.7)	56 (10.7)	120 (12.8)	170 (11.0)
2	4 (4.0)	10 (4.0)	2 (6.3)	2 (2.3)	4 (3.4)	4 (3.3)	0 (0.0)	1 (1.1)	1 (1.1)	12 (3.1)	12 (3.7)	19 (3.6)	31 (3.3)	48 (3.1)
3	1 (1.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	2 (0.6)	6 (1.1)	11 (1.2)	13 (0.8)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	2 (0.1)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
≥ 6	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Patients with dose interruptions due to AE[c]														
n (%)	62 (61.4)	138 (55.4)	20 (62.5)	21 (24.4)	41 (34.7)	42 (35.0)	28 (41.2)	39 (44.3)	40 (43.0)	149 (38.1)	149 (46.0)	255 (48.6)	418 (44.6)	690 (44.5)
Patients with dose modification (reduction or interruption) due to AE														
n (%)	63 (62.4)	139 (55.8)	21 (65.6)	22 (25.6)	43 (36.4)	44 (36.7)	29 (42.6)	40 (45.5)	41 (44.1)	175 (44.8)	156 (48.1)	264 (50.3)	453 (48.3)	730 (47.1)

Abbreviations: CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; MCL, Mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed or refractory; WM, Waldenström's macroglobulinemia.

[a] Total for All Zanubrutinib Monotherapy group includes other indications in addition to those detailed in this table.

[b] Duration of exposure (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients.

[c] Actual dose intensity (mg/day) is defined as the cumulative dose administration (mg) received by a patient divided by the duration of exposure (days).

[d] Relative dose intensity is defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (mg/day).

[e] Derived as any interruption due to an AE with duration > 1 day from drug administration eCRF in BGB-3111-AU-003; from drug administration eCRF in BGB-3111-304, BGB-3111-305, BGB-3111-205, BGB-3111-206, BGB-3111-210 (interruption due to AE), BGB-3111-214, and BGB-3111-302; from AE eCRF in BGB-3111-1002 (action taken = drug held).

Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data Source: ADSL, ADEXSUM.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.

Table Part II: Module SIII-3: Summary of Treatment Exposure: FL Studies (Safety Analysis Set)

	Combination Therapy: Zanubrutinib + Obinutuzumab		Monotherapy Zanubrutinib
	BGB-3111-212 (N = 143)	BGB-3111-GA101-101 (N = 36)	BGB-3111-1002 + AU003 (N = 59)
Duration of exposure (months) [a]			
n	143	36	59
Mean (SD)	16.07 (11.754)	24.91 (17.119)	18.09 (21.583)
Median	12.35	26.66	8.34
Min, max	0.5, 48.1	0.5, 52.4	0.1, 79.1
Total exposure (patient-months)	2297.36	896.69	1067.33
Duration of exposure, n (%)			
< 3 months	19 (13.3)	3 (8.3)	13 (22.0)
3 to < 6 months	18 (12.6)	2 (5.6)	7 (11.9)
6 to < 9 months	16 (11.2)	5 (13.9)	11 (18.6)
9 to < 12 months	17 (11.9)	5 (13.9)	7 (11.9)
12 to < 24 months	36 (25.2)	2 (5.6)	9 (15.3)
24 to < 36 months	28 (19.6)	7 (19.4)	3 (5.1)
≥ 36 months	9 (6.3)	12 (33.3)	9 (15.3)
Cumulative dose administered (g)			
n	143	36	59
Mean (SD)	145.80 (109.504)	233.08 (162.468)	172.05 (207.501)
Median	116.16	233.68	81.12
Min, max	4.6, 468.3	4.5, 510.1	1.3, 763.1
Actual dose intensity (mg/day) [b]			
n	143	36	59
Mean (SD)	299.30 (42.922)	308.92 (24.889)	310.84 (15.208)
Median	316.36	318.32	318.57
Min, max	98.2, 320.0	186.6, 320.0	262.2, 320.0
Relative dose intensity (%) [c]			
n	143	36	59
Mean (SD)	93.53 (13.413)	96.54 (7.778)	97.16 (4.763)
Median	98.86	99.48	99.63
Min, max	30.7, 100.0	58.3, 100.0	81.9, 100.0
Patients with dose reduction			
n (%)	19 (13.3)	1 (2.8)	1 (1.7)

Table Part II: Module SIII-3: Summary of Treatment Exposure: FL Studies (Safety Analysis Set)

	Combination Therapy: Zanubrutinib + Obinutuzumab		Monotherapy Zanubrutinib
	BGB-3111-212 (N = 143)	BGB-3111-GA101-101 (N = 36)	BGB-3111-1002 + AU003 (N = 59)
Patients with dose reduction due to AE			
n (%)	15 (10.5)	1 (2.8)	1 (1.7)
Number of dose reductions per patient			
n	19	1	1
Mean (SD)	1.6 (0.83)	1.0 (N/A)	1.0 (NE)
Median	1.0	1.0	1.0
Min, max	1, 4	1, 1	1, 1
Number of dose reductions per patient, n (%)			
1	10 (7.0)	1 (2.8)	1 (1.7)
2	7 (4.9)	0 (0.0)	0 (0.0)
3	1 (0.7)	0 (0.0)	0 (0.0)
≥ 4	1 (0.7)	0 (0.0)	0 (0.0)
Patients with dose interruptions due to AE [d]			
n (%)	63 (44.1)	12 (33.3)	14 (23.7)
Patients with dose modification (reduction or interruption) due to AE			
n (%)	65 (45.5)	12 (33.3)	15 (25.4)

Abbreviations: AE, adverse event; BID, twice daily; eCRF, electronic case report form; FL, follicular lymphoma; max, maximum; min, minimum; N/A, not applicable; QD, once daily; SD, standard deviation.

[a] Duration of exposure (months) was calculated as (last dose date - first dose date + 1)/30.4375, where data cutoff date is used as last dose date for ongoing patients.

[b] Actual dose intensity (mg/day) is defined as the cumulative dose administration (mg) received by a patient divided by the duration of exposure (days).

[c] Relative dose intensity is defined as the ratio of the actual dose intensity (mg/day) and the planned dose intensity (mg/day).

[d] Derived as any interruption due to an AE with duration > 1 day from drug administration eCRF in BGB-3111-AU-003; from drug administration eCRF in BGB 3111-304, BGB-3111-305, BGB-3111-205, BGB-3111-206, BGB-3111-210 (interruption due to AE), BGB-3111-214, and BGB-3111-302; from AE eCRF in BGB 3111-1002 (action taken = drug held).

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003); Data Source: ADSL, ADEXSUM

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.

In the tables below, patient exposure in the 12 clinical studies summarised in this risk management plan (RMP) is presented by duration of exposure (Table Part II: Module SIII-4 and Table Part II: Module SIII-5), exposure by age group and sex (Table Part II: Module SIII-6 and

Table Part II: Module SIII-7), by dose (Table Part II: Module SIII-8 and Table Part II: Module SIII-9), and by ethnic origin (Table Part II: Module SIII-10 and Table Part II: Module SIII-11).

Table Part II: Module SIII-4: Duration of Exposure With Zanubrutinib Monotherapy (Safety Analysis Set)

Duration of Exposure	Patients	Person-Months
Cumulative for all zanubrutinib monotherapy indications		
≤ 3 months	104	163.9
≤ 6 months	180	515.1
≤ 9 months	237	942.9
≤ 12 months	280	1391.8
≤ 18 months	372	2795.7
≤ 24 months	515	5836.2
> 24 months	1035	46,601.3
Total	**1550**	**52,437.6**
Mantle cell lymphoma [a]		
≤ 3 months	19	28.3
≤ 6 months	30	79.8
≤ 9 months	36	128
≤ 12 months	42	187.7
≤ 18 months	56	405.3
≤ 24 months	66	606.6
> 24 months	74	3847.7
Total	**140**	**4454.3**
Marginal zone lymphoma		
≤ 3 months	10	17.6
≤ 6 months	21	66.1
≤ 9 months	27	111.6
≤ 12 months	33	174.7
≤ 18 months	41	293.6
≤ 24 months	45	378.8
> 24 months	48	2008.5
Total	**93**	**2387.3**
Waldenström macroglobulinaemia		
≤ 3 months	16	30.6
≤ 6 months	27	81.4

Table Part II: Module SIII-4: Duration of Exposure With Zanubrutinib Monotherapy (Safety Analysis Set)

Duration of Exposure	Patients	Person-Months
≤ 9 months	36	145.8
≤ 12 months	43	221.4
≤ 18 months	57	430.1
≤ 24 months	69	682.9
> 24 months	180	10,048.7
Total	**249**	**10,731.6**
Duration of Exposure	**Patients**	**Person-Months**
Chronic lymphocytic leukaemia/small lymphocytic lymphoma		
≤ 3 months	23	33.6
≤ 6 months	45	137.2
≤ 9 months	67	303.1
≤ 12 months	82	459.3
≤ 18 months	132	1220.3
≤ 24 months	243	3595.2
> 24 months	695	28,713.9
Total	**938**	**32,309.2**

[a] Including 120 patients with relapsed or refractory mantle cell lymphoma and 20 patients with treatment-naïve mantle cell lymphoma.

Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data source: ADSL, ADEXSUM.

Clinical studies included are BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-210, BGB-3111-214, BGB-3111-302, BGB-3111-304, BGB-3111-305.

Table Part II: Module SIII-5: Duration of Exposure for Follicular Lymphoma Patients with Zanubrutinib + Obinutuzumab (Study BGB-3111-212; Safety Analysis Set)

Duration of Exposure	Patients	Person-Months
Follicular lymphoma patients with zanubrutinib + obinutuzumab		
≤ 3 months	19	35
≤ 6 months	37	122.4
≤ 9 months	53	235.6
≤ 12 months	70	418.2
≤ 18 months	84	636.5
≤ 24 months	106	1097.4
> 24 months	37	1200
Total	**143**	**2297.4**

Data cutoff: 25OCT2022(212); Data snapshot: 16DEC2022(212); Data Source: ADSL, ADEXSUM
Clinical studies included are BGB-3111-212.

Table Part II: Module SIII-6: Exposure by Age Group and Gender With Zanubrutinib Monotherapy (Safety Analysis Set)

	Sex			
	Male		Female	
Age Group	Person	Person-Months	Person	Person-Months
All zanubrutinib monotherapy indications				
< 35 years	6	49.5	5	50.8
≥ 35 to 49 years	61	2250.7	41	1418.7
≥ 50 to 64 years	325	12,239.7	162	5328
≥ 65 to 69 years	218	7441.6	92	3064.7
≥ 70 to 74 years	196	6429	109	3519.7
≥ 75 years	221	6962.7	114	3682.4
Total	**1027**	**35,373.2**	**523**	**17,064.3**
Mantle cell lymphoma [a]				
< 35 years	1	12.9	0	0
≥ 35 to 49 years	6	302.6	5	174.8
≥ 50 to 64 years	47	1726.3	15	444.1
≥ 65 to 69 years	20	694.8	3	54
≥ 70 to 74 years	13	272.4	3	126.3
≥ 75 years	19	353.5	8	292.6

Table Part II: Module SIII-6: Exposure by Age Group and Gender With Zanubrutinib Monotherapy (Safety Analysis Set)

	Sex			
	Male		Female	
Age Group	Person	Person-Months	Person	Person-Months
Total	**106**	**3362.5**	**34**	**1091.8**
Marginal zone lymphoma				
≥ 35 to 49 years	3	84.2	2	39.9
≥ 50 to 64 years	15	384.5	15	406.1
≥ 65 to 69 years	8	299.5	5	105.2
≥ 70 to 74 years	11	306.4	11	204.3
≥ 75 years	13	371.7	10	185.4
Total	**50**	**1446.3**	**43**	**940.9**
Waldenström macroglobulinaemia				
≥ 35 to 49 years	7	373.6	5	269.1
≥ 50 to 64 years	58	2717.3	23	960.1
≥ 65 to 69 years	32	1377.3	11	457.2
≥ 70 to 74 years	26	1163.1	15	659.7
≥ 75 years	46	1750.9	26	1003.2
Total	**169**	**7382.1**	**80**	**3349.4**
Chronic lymphocytic leukaemia/small lymphocytic lymphoma				
< 35 years	1	21.4	2	21.2
≥ 35 to 49 years	34	1243	20	844.7
≥ 50 to 64 years	176	6477	89	3174.3
≥ 65 to 69 years	147	4927.5	61	2200.2
≥ 70 to 74 years	134	4492	79	2527.4
≥ 75 years	131	4305	64	2075.3
Total	**623**	**21,466**	**315**	**10,843.2**

[a] Including 120 patients with relapsed or refractory mantle cell lymphoma and 20 patients with treatment-naïve mantle cell lymphoma.

Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data source: ADSL, ADEXSUM.
Clinical studies included are BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-210, BGB-3111-214, BGB-3111-302, BGB-3111-304, BGB-3111-305.

Table Part II: Module SIII-7: Exposure by Age Group and Gender for Follicular Lymphoma Patients with Zanubrutinib + Obinutuzumab (Study BGB-3111-212; Safety Analysis Set)

Age Group	Gender			
	Male		Female	
	Person	Person-Months	Person	Person-Months
Follicular lymphoma patients with zanubrutinib + obinutuzumab				
< 35 years	0	0	2	53.8
≥ 35 to 49 years	14	242.8	11	240
≥ 50 to 64 years	31	504	25	387.8
≥ 65 to 69 years	8	121.9	13	198.2
≥ 70 to 74 years	13	195.8	12	146.1
≥ 75 years	7	114.9	7	92.1
Total	**73**	**1179.4**	**70**	**1118**

Data cutoff: 25OCT2022(212); Data snapshot: 16DEC2022(212); Data Source: ADSL, ADEXSUM.
Clinical studies included are BGB-3111-212.

Table Part II: Module SIII-8: Exposure by Assigned Dose With Zanubrutinib Monotherapy (Safety Analysis Set)

Dosing Regimen	Patients	Person-Months
All zanubrutinib monotherapy indications		
160 mg twice daily	1445	47,431.9
320 mg once daily	105	5005.6
Total	**1550**	**52,437.6**
Mantle cell lymphoma [a]		
160 mg twice daily	118	3727.2
320 mg once daily	22	727.1
Total	**140**	**4454.3**
Marginal zone lymphoma		
160 mg twice daily	90	2160.9
320 mg once daily	3	226.4
Total	**93**	**2387.3**
Waldenström macroglobulinaemia		
160 mg twice daily	225	9489.5
320 mg once daily	24	1242.1

Table Part II: Module SIII-8: Exposure by Assigned Dose With Zanubrutinib Monotherapy (Safety Analysis Set)

Dosing Regimen	Patients	Person-Months
Total	**249**	**10,731.6**
Chronic lymphocytic leukaemia/small lymphocytic lymphoma		
160 mg twice daily	894	29,827.8
320 mg once daily	44	2481.3
Total	**938**	**32,309.2**

[a] Including 120 patients with relapsed or refractory mantle cell lymphoma and 20 patients with treatment-naïve mantle cell lymphoma.

Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data source: ADSL, ADEXSUM.

Clinical studies included are BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-210, BGB-3111-214, BGB-3111-302, BGB-3111-304, BGB-3111-305.

Table Part II: Module SIII-9: Exposure by Dose for Follicular Lymphoma Patients with Zanubrutinib + Obinutuzumab (Study BGB-311-212; Safety Analysis Set)

Zanubrutinib Dosing Regimen	Patients	Person-Months
Follicular lymphoma patients with zanubrutinib + obinutuzumab		
160 mg twice daily	143	2297.4
Total	**143**	**2297.4**

Data cutoff: 25OCT2022(212); Data snapshot: 16DEC2022(212); Data Source: ADSL, ADEXSUM.

Clinical studies included are BGB-3111-212.

Table Part II: Module SIII-10: Exposure by Ethnic Origin With Zanubrutinib Monotherapy (Safety Analysis Set)

Ethnic Origin	Patients	Person-Months
All zanubrutinib monotherapy indications		
White	1032	36,304.5
Asian	424	13,274.6
Black or African American	13	298
Native Hawaiian or Other Pacific Islander	6	153
Other/missing	75	2407.5
Total	**1550**	**52,437.6**

Table Part II: Module SIII-10: Exposure by Ethnic Origin With Zanubrutinib Monotherapy (Safety Analysis Set)

Ethnic Origin	Patients	Person-Months
Mantle cell lymphoma [a]		
White	41	1201.6
Asian	92	3116.1
Black or African American	1	1.9
Other/missing	6	134.8
Total	**140**	**4454.3**
Marginal zone lymphoma		
White	55	1610.6
Asian	22	456.7
Other/missing	16	319.9
Total	**93**	**2387.3**
Waldenström macroglobulinaemia		
White	178	7823.6
Asian	56	2216.8
Black or African American	1	11.1
Other/missing	14	680.1
Total	**249**	**10,731.6**
Chronic lymphocytic leukemia/small lymphocytic lymphoma		
White	696	24,087.3
Asian	194	6652.1
Black or African American	11	285
Native Hawaiian or Other Pacific Islander	5	152.5
Other/missing	32	1132.3
Total	**938**	**32,309.2**

[a] Including 120 patients with relapsed or refractory mantle cell lymphoma and 20 patients with treatment-naïve mantle cell lymphoma.

Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data source: ADSL, ADEXSUM.
Clinical studies included are BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, BGB-3111-210, BGB-3111-214, BGB-3111-302, BGB-3111-304, BGB-3111-305.

Table Part II: Module SIII-11: Exposure by Ethnic Origin for Follicular Lymphoma Patients with Zanubrutinib + Obinutuzumab (Study BGB-3111-212; Safety Analysis Set)

Ethnic Origin	Patients	Person-Months
Follicular lymphoma patients with zanubrutinib + obinutuzumab		
White	90	1366.8
Asian	30	525.8
Other/missing	23	404.8
Total	**143**	**2297.4**

Data cutoff: 25OCT2022(212); Data snapshot: 16DEC2022(212); Data Source: ADSL, ADEXSUM
Clinical studies included are BGB-3111-212.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL STUDIES

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Eligibility criteria vary by study and, consequently, the following exclusion criteria are representative of those used in the studies supporting registration of all indications (WM, MCL, MZL, CLL/SLL, and FL).

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Central Nervous System (CNS) Involvement by Lymphoma	
Reason for being an exclusion criterion	This is an oncology clinical study standard practice. Inclusion of patients with known CNS involvement can confound the efficacy and safety assessments of the study. **WM only** Bing-Neel Syndrome (WM with CNS infiltration) is a rare complication of WM. In order to keep the study population homogeneous, Bing-Neel Syndrome was excluded. **MZL and CLL/SLL only** CNS infiltration is a rare complication of MZL and CLL/SLL. In order to keep the study population homogeneous, patients with CNS involvement were excluded.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Patients may have their lymphoma treated with zanubrutinib, yet the additional pharmacotherapy needed to treat the CNS involvement can confound the efficacy and safety assessments of the study.
Pregnant or lactating women	
Reason for being an exclusion criterion	Based on findings in animal studies, zanubrutinib has the potential to cause foetal harm when administered to pregnant women.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Not applicable

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Known history of HIV or active infection with hepatitis B virus (HBV) or hepatitis C virus or any uncontrolled active systemic infection. Uncontrolled active systemic infection or recent infection requiring parenteral antimicrobial therapy that was completed ≤ 14 days before the first dose of study drug	
Reason for being an exclusion criterion	The potential of BTK inhibitors to cause immunosuppression could pose a risk to patients with active infections. It is common clinical practice to exclude patients with severe active infections because they potentially confound the interpretation of safety.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Infections (including lower respiratory tract infections and hepatitis B reactivation) are included as an important identified risk. The treating physician should weigh the benefit and risks in individual patients.
Currently active, clinically significant CVD such as uncontrolled arrhythmia, congestive heart failure, any class III or IV cardiac disease (congestive heart failure) as defined by the New York Heart Association Functional Classification, myocardial infarction in prior 6 months, ECG abnormalities (including second-degree atrioventricular block Type II, or third-degree atrioventricular block) or QTc > 480 ms	
Reason for being an exclusion criterion	It is common practice to exclude patients with severe and potentially life-threatening concurrent cardiac conditions from clinical studies. These patients can confound the efficacy and safety assessments of the study.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Cardiac arrhythmias are included as an important identified risk. The treating physician would be expected to weigh the benefit and risks in individual patients. **WM only** Patients with controlled atrial fibrillation were allowed, 10 of whom received study drug and were considered in the Safety Analysis Set. **CLL/SLL only** Patients with controlled atrial fibrillation were allowed. In Study BGB-3111-305, 4.9% of patients who received study drug had a medical history of atrial fibrillation and were considered in the Safety Analysis Set.

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Corticosteroids given with antineoplastic intent within 7 days, or chemotherapy, targeted therapy, or radiation therapy within 4 weeks, or antibody-based therapy within 4 weeks of the start of study drug	
Reason for being an exclusion criterion	These treatments in patients can confound the efficacy and safety assessments of monotherapy studies.
Considered to be included as missing information	No
Rationale (if not included as missing information)	These treatments are evaluated in combination studies. The treating physician would be expected to weigh the benefit and risks of combination treatments in individual patients.
Major surgery within 4 weeks of study treatment	
Reason for being an exclusion criterion	Haemorrhage is an important identified risk; such patients may be at risk and were excluded for their safety. Patients with planned or elective surgery are commonly excluded from clinical studies to avoid any procedure-related bleeding risk.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Patients with recent major surgery are not reasonably considered to have missing information. The treating physician would be expected to weigh the benefit and risks in individual patients.
Known CNS haemorrhage or stroke within 6 months before study entry	
Reason for being an exclusion criterion	Haemorrhage is an important identified risk; such patients may be at risk and were excluded for their safety. Also, patients with recent severe and potentially life-threatening haemorrhage can confound the efficacy and safety assessments of the study.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Haemorrhage is an important identified risk. The treating physician would be expected to weigh the benefit and risks in individual patients.

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

At time of study entry, taking any medications that are strong cytochrome P450 (CYP), family 3, subfamily A (CYP3A) inhibitors or strong CYP3A inducers	
Reason for being an exclusion criterion	These treatments in patients can confound the efficacy and safety assessments of monotherapy studies. Strong CYP3A inhibitors or inducers may alter the PK/PD of zanubrutinib. Use of these treatments by patients at time of study entry can confound the initial efficacy and safety assessments of the study.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Patients were permitted to take strong CYP3A inhibitors or inducers after study enrolment. The treating physician would be expected to weigh the benefit and risks in individual patients. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and to consider using alternative agents. If these agents will be used, the dose modification guidance in Table Part V-1 should be followed. Drug-drug interaction with CYP3A inducers is an Important Potential Risk. **WM only** Enrolment in Study BGB-3111-302 generally required discussion with the BeiGene medical monitor.
At time of study entry, taking warfarin or other vitamin K antagonists	
Reason for being an exclusion criterion	This is an ibrutinib treatment recommendation and was included because ibrutinib is the comparator in Study BGB-3111-302 and Study BGB-3111-305.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Haemorrhage is an important identified risk. The treating physician would be expected to weigh the benefit and risks in individual patients.

Table Part II: Module SIV-1: Important Exclusion Criteria in Pivotal Clinical Studies Across the Development Programme

Presence of del(17p)-positive CLL/SLL	
Reason for being an exclusion criterion	Patients with CLL/SLL with del(17p) were excluded from Cohort 1 (primary objective) of Study BGB-3111-304 as they have poor clinical outcome and poor response to chemoimmunotherapy.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Patients with del(17p) were included in Cohorts 2 and 3 (secondary objectives) of Study BGB-3111-304.
Evidence of transformation from FL to DLBCL or other aggressive histology (such as large cells seen on biopsy or high PET avidity in a single node seen on PET scan)	
Reason for being an exclusion criterion	Patients with transformed disease have a different diagnosis than FL.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The exclusion criteria was intended to ensure studies in FL enrolled patients with the correct diagnosis.
History of severe bleeding disorder such as haemophilia A, haemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention	
Reason for being an exclusion criterion	Haemorrhage is an important identified risk; such patients may be at risk and were excluded for their safety. Also, patients with recent severe and potentially life-threatening haemorrhage can confound the efficacy and safety assessments of the trial.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Haemorrhage is an important identified risk. The treating physician would be expected to weigh the benefit and risks in individual patients.
Allogeneic hematopoietic stem cell transplantation within 12 months of study enrolment	
Reason for being an exclusion criterion	The early toxicities of allogeneic transplant can confound the efficacy and safety.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The treating physician would be expected to weigh the benefit and risks of allogeneic transplant in individual patients.

SIV.2 Limitations to Detect Adverse Reactions in the Zanubrutinib Clinical Study Development Programme

The clinical development programme is unlikely to detect certain adverse drug reactions (ADRs), including rare ADRs.

As presented above in Table Part II: Module SIII-4 , 515 of the 1550 patients who have received zanubrutinib monotherapy have accrued exposure of ≤ 24 months. Thus, 1035 patients (66.8%) representing 46,601.3 person-months of person exposure have accrued exposure of > 24 months with zanubrutinib monotherapy. A further 37 patients with FL in the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group have had > 24 months of exposure representing 1200 person-months of exposure Table Part II: Module SIII-5. The zanubrutinib clinical development programme is expected to be able to detect ADRs following prolonged exposure or events that may have a long latency.

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Study Development Programme

Table Part II: Module SIV-2: Exposure of Special Populations Included or Not in Clinical Study Development Programme

Type of Special Population	Exposure
Children	As discussed in Section Part II: Module SI, the target indication(s) are typically described in elderly patients. The safety and efficacy of zanubrutinib in children aged 1 to < 18 years in other B-cell lymphomas have not yet been established.
Elderly	Of the 1550 adult subjects in the All Zanubrutinib Monotherapy population, 950 (61.3%) subjects (with 31,100.1 person-months of person exposure) were 65 years of age or older, and 335 (21.6%) subjects with 10,645.1 person-months of exposure were 75 years of age or older (Table Part II: Module SIII-6). Of the 143 subjects with FL in the Study BGB-311-212 (Zanubrutinib + Obinutuzumab) group, 60 (42.0%) subjects (with 869 person-months of person exposure) were 65 years of age or older, and 14 (9.8%) subjects with 207 person-months of exposure were 75 years of age or older (Table Part II: Module SIII-7).
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical studies	Patients were eligible for study enrolment having met the following criteria: creatinine clearance (CrCl) of ≥ 30 mL/min (as calculated by the Cockcroft-Gault equation); AST and ALT ≤ 3 x upper limit of normal; and bilirubin ≤ 2 x upper limit of normal (unless documented Gilbert syndrome). A Phase 1 hepatic impairment study (BGB-3111-107) was assessed in accordance with the Child-Pugh classification system at screening. Enrolment was N = 29 (n = 6 each in Child-Pugh class A, B, and C, and n = 11 healthy controls) (Ou et al 2020). This study showed that there was no substantial difference in plasma exposure (C_{max} and AUC) between patients with mild/moderate hepatic impairment and healthy subjects (Ou et al 2020). The total

Table Part II: Module SIV-2: Exposure of Special Populations Included or Not in Clinical Study Development Programme

Type of Special Population	Exposure
	and unbound AUC of zanubrutinib in patients with severe hepatic impairment were 1.60- and 2.94-fold, respectively, of those in healthy controls. No studies in patients with renal or cardiovascular impairment have been undertaken. Safety in patients with severe hepatic impairment and Safety in patients with severe renal impairment/on dialysis are considered missing information in the RMP.
Population with relevant different ethnic origins	Of the 1550 adult patients in the All Zanubrutinib Monotherapy population, 1032 (66.6%) patients with 36,304.5 person-months of exposure were white, 424 (27.4%) patients with 13,274.6 person-months of exposure were Asian, and 94 (6.1%) patients with 2858.5 person-months of exposure were Black or African American, Native Hawaiian or Other Pacific Islander, or "Other/Missing" race (Table Part II: Module SIII-10). Of the 143 subjects with FL in the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 90 (62.9%) subjects with 1366.8 person-months of exposure were White, while 30 (21.0%) subjects with 525.8 person-months of exposure were Asian, and 23 (16.1%) subjects with 404.8 person months of exposure were "Other/Missing" race (Table Part II: Module SIII-11).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

PART II: MODULE SV POSTAUTHORISATION EXPERIENCE

SV.1 Postauthorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Exposure in person-months was estimated from the data for the distribution of zanubrutinib to countries in which marketing authorisation has been obtained and was based on the recommended daily dose of four 80 mg capsules per day.

It should be noted that the estimations of postauthorisation exposure use the number of units distributed and do not reflect actual utilisation by the patients. Therefore, the calculation of patient exposure will generally be an overestimate for reasons including the holding of drug stocks at pharmacies, distributors or business partners.

SV.1.2 Exposure Estimate

Cumulatively, as of 13 May 2023, approximately 47,163,525 capsules of zanubrutinib have been supplied to the global market (equivalent to 11,790,881 daily doses based on the recommended daily dose of four 80 mg capsules per day; approximately 387,857.9 person-months; 32,321.5 person-years).

Table Part II: Module SV-1: Estimated Cumulative Exposure From Marketing Experience

Territory	Number of Capsules Supplied	Equivalent Number of Daily Doses [a]	Person-Months	Person-Years
Australia	[redacted]			
Canada				
China				
Europe [b]				
Hong Kong, China				
New Markets [c]				
Singapore				
South Korea				
Taiwan, China				
USA				
Total	**47,163,525**	**11,790,881**	**387,857.9**	**32,321.5**

Abbreviations: UAE, United Arab Emirates; USA, United States of America.
[a] Based on the recommended daily dose of four 80 mg capsules per day.
[b] Germany, United Kingdom (UK), Spain, Italy, Belgium, Austria, Netherlands, Denmark, Switzerland, Norway, Ireland, Luxembourg, France, Iceland, Poland.
[c] Brazil, Chile, Ecuador, Egypt (pre registration sales only), Israel, Kuwait, Mexico, Saudi Arabia, UAE, and Uruguay. Data are reported up to and including April 2023.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Commonly misused classes of prescription drugs include opioid pain relievers, stimulants, and CNS depressants (sedatives and tranquilisers). Zanubrutinib is a small-molecule BTK inhibitor that specifically inhibits activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion, through which it has demonstrated antineoplastic activity. Zanubrutinib does not share any characteristics with drugs that have recognised misuse potential and should not reasonably be regarded as having misuse potential.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

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 with CYP3A 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)

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- **Cutaneous reactions**

  Inhibition of the epidermal growth factor (EGF) receptor (*EGFR*; a transmembrane glycoprotein cell surface receptor) increases expression of genes that stimulate inflammation, apoptosis, and cell attachment. Clinical adverse effects such as rash, dry skin, dry mucus membranes, ocular abnormalities, hair changes and alopecia, nail changes, and hand and foot reactions have been observed with EGFR inhibition (Nanney et al 1990). Skin cells exposed to EGFR inhibitors may also release cytokines that recruit neutrophils, monocytes, and lymphocytes to the area, resulting in an inflammatory reaction, manifested as a papulopustular rash (Lacouture 2006).

  A total of 16 serious events were identified following a search of the global safety database using the severe cutaneous adverse reactions SMQ (broad) up to 13 May 2023. The most frequently reported serious events were stomatitis (4) and conjunctivitis, dermatitis exfoliative generalised, pemphigoid, and toxic epidermal necrolysis (2 each). In summary, the events retrieved from the global safety database are heavily confounded, and a clear association between zanubrutinib and these serious cutaneous events cannot be established. Assessment of these cases does not support severe cutaneous adverse reactions being added as an identified risk.

- **Gastrointestinal disorders** (including severe gastrointestinal disorders)

  Dysregulation of intestinal ion transport systems (eg, through *EGFR* inhibition) can increase chloride secretion and lead to secretory diarrhoea, a possible mechanism for *EGFR* tyrosine kinase inhibitor associated secretory diarrhoea (Rugo et al 2019). Specifically, when EGF binds to its receptor, this signals several pathways that

regulate intestinal barrier function (Tang et al 2016). It has been shown that EGF suppresses cell shedding in the intestinal epithelium through a selective mitogen-activated protein kinase-dependent pathway affecting multiple extrusion mechanisms (Miguel et al 2017).

In the Gastrointestinal Disorders System Organ Class (SOC) in the global safety database up to 13 May 2023, the most frequently reported serious events were diarrhoea (43), abdominal pain (30), haematochezia (20), nausea and gastrointestinal haemorrhage (19 each), rectal haemorrhage (18), vomiting (17), ascites (13), intestinal obstruction and small intestinal obstruction (11 each), abdominal pain upper, colitis, dysphagia, inguinal hernia, and upper gastrointestinal haemorrhage (8 each). Overall, no new serious ADR events of drug-related gastrointestinal morbidity relating to the use of zanubrutinib has been identified.

- **Progressive multifocal leukoencephalopathy**

  Progressive multifocal leukoencephalopathy (PML) is a rare, mostly fatal, demyelinating disease of the CNS primarily affecting immunocompromised individuals. It is caused by the opportunistic, lytic infection of oligodendrocytes by the John Cunningham virus. PML is typically described in immunocompromised individuals, particularly those infected with HIV, but which was first described in patients with lymphoma.

  Cases of PML (within the context of a prior or concomitant immunosuppressive therapy), including fatal ones, in association with ibrutinib have been reported in completed clinical studies and during postmarketing experience. PML is also mentioned in the current prescribing information for ibrutinib (IMBRUVICA SmPC 2022 [SmPC, Section 4.4 Special warnings and precautions for use]).

  No cases of PML have been reported in association with the use of zanubrutinib in the global safety database up to 13 May 2023.

- **Hypertension**

  Hypertension is commonly observed in patients with haematologic malignancies, primarily because of toxicity related to the use of chemotherapy (Florescu et al 2013). Drugs used in the treatment of haematological malignancies can induce hypertension through several mechanisms. Such mechanisms include inhibition of vascular endothelial growth factor receptor, vascular fibrosis, and cellular remodelling secondary to the inhibition of the PI3K pathway with downregulation of nitric oxide (Dickerson et al 2019). In an in vitro study, ibrutinib has been shown to have dose-dependent anti-vascular endothelial growth factor effects suppressing production by macrophages (Ping et al 2017). Vascular endothelial growth factor inhibition can lead to hypertension by the activation of the endothelin-1 system, suppression of the renin-angiotensin system, leading to generalised microvascular dysfunction and ultimately increased blood pressure (Kappers et al 2010).

  Hypertension is known to be associated with older age. In the USA, based on National Health and Nutrition Examination Survey 1999 to 2002, hypertension prevalence increased from 6.7% in persons 20 to 39 years to 65.2% in persons

60 years or older. The greatest increase in hypertension prevalence between 1988 to 1991 (57.9%) and 1999 to 2000 (65.4%) occurred in individuals 60 years or older (Hajjar et al 2006).

Hypertension is a commonly noted adverse event for patients with CLL who are treated with ibrutinib in the clinical study setting (incidence, 18%; ≥ Grade 3 hypertension, 6%) (Coutre et al 2019). Hypertension is described to be a common adverse event affecting those with and without pre-existing hypertension (Jones et al 2019; Caldeira et al 2019, Mahida et al 2018). In a study of 562 patients, 78.3% of ibrutinib users developed new or worsened hypertension over a median of 30 months. New hypertension developed in 71.6% of ibrutinib users, and among those without preceding hypertension, 17.7% developed hypertension with blood pressure > 160 per 100 mmHg (Dickerson et al 2019).

In the All Zanubrutinib Monotherapy group, 259 (16.7%) patients had ≥ 1 hypertension event; these events were most commonly reported as hypertension (242 [15.6%] patients), blood pressure increased (16 [1.0%] patients), and hypertensive crisis (4 [0.3%] patients). Serious events were reported in 7 (0.5%) patients and ≥ Grade 3 events were reported in 129 (8.3%) patients. No patients had hypertension events that led to treatment discontinuation. There was 1 patient with an adverse event of special interest of hypertension (PT: Hypertensive heart disease) that led to death. The median time to onset for any grade hypertension event was 303.0 days (range: 1 to 1889 days). The exposure adjusted incidence rate (EAIR) for all-grade hypertension events was 0.57 persons/100 person-months, and for ≥ Grade 3 hypertension events was 0.26 persons/100 person-months. Additional analysis suggested that the risk of hypertension may be higher in patients with a history of hypertension. A total of 138 (8.9%) patients had a reported treatment-emergent adverse event of hypertension that required new antihypertensive therapy; 12 (0.8%) patients had these adverse events that required changes in the dose of pre-existing antihypertensive therapy.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 6 (4.2%) patients had ≥ 1 hypertension event; in 5 of these patients the events were reported as Hypertension, and in 1 patient as Blood pressure increased. No patients reported serious events, while ≥ Grade 3 hypertension events were reported in 1 (0.7%) patient. No patients had hypertension events that led to treatment discontinuation or death. The median time to onset for any grade hypertension event was 127.0 days (range: 2 to 428 days). The EAIR for all grade hypertension events was 0.26 persons/100 person-months, and for ≥ Grade 3 hypertension events was 0.04 persons/100 person-months.

There were 20 serious cases of hypertension identified following a search of the global safety database using the Hypertension MedDRA SMQ (narrow) up to 13 May 2023. The most frequently reported serious events were hypertension (21), blood pressure increased (6) and hypertensive crisis (2).

The hypertension data in zanubrutinib-treated patients are evolving as results from longer follow-up time become available. Hypertension is included as an ADR in the Company Core Data Sheet (CCDS;Zanubrutinib_CCDS_2024).

- **Interstitial lung disease (ILD)**

  ILD has been identified as an adverse reaction during postmarketing experience of ibrutinib. These events are described in the current prescribing information for ibrutinib. In addition to patients receiving ibrutinib, other treatments for MCL and CLL have been associated with ILD, including cases of ILD in patients who received, for example, bortezomib (Yoshizawa et al 2014).

  Searches were conducted in the BeiGene clinical and global safety databases using the SMQ of Interstitial lung disease (narrow). Of the 1550 patients in the All Zanubrutinib Monotherapy group in the clinical database, ILD was reported in 43 (2.8%) patients. The PTs reported in these 43 patients were interstitial lung disease and pneumonitis (16 patients each), lung opacity (4 patients), lung infiltration and pulmonary fibrosis (3 patients each), bronchiolitis (2 patients), and pulmonary necrosis (1 patient).

  In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, ILD was reported in 4 (2.8%) patients. The PTs reported in these 4 patients were pneumonitis (3 patients) and lung opacity (1 patient).

  A search of the global safety database revealed 17 serious events of pneumonitis, 9 of ILD, 3 of lung infiltration and 1 each of bronchiolitis, lung opacity, and pulmonary fibrosis reported in the ILD SMQ (narrow) up to 13 May 2023.

  Assessment of these cases does not indicate a causal relationship between zanubrutinib and ILD, and does not support ILD being added as an identified risk to the RMP.

  Differences in both the molecular structure and pharmacological footprint of zanubrutinib and ibrutinib mean that comparison between the two is not applicable (Wen et al 2021). There is a lack of clear understanding of mechanism of action of ILD by ibrutinib, and an evaluation of case level details of patients who had received zanubrutinib identified events but failed to identify cases demonstrating a clear causal association.

- **Hepatotoxicity (including hepatic failure)**

  An event of Grade 4 hepatic enzyme elevation in association with ibrutinib has been observed in a healthy volunteer in a clinical study. Hepatic failure has been identified as an adverse reaction during postmarketing experience. These events are described in the current prescribing information for ibrutinib. Literature case reports (Nandikolla et al 2017; Kahn et al 2018) have detailed additional cases of ibrutinib-associated hepatotoxicity in 2 patients who were being treated for WM and 1 with CLL. In these patients, the onset of liver injury appeared to be idiosyncratic with a latency period between 2 and 36 weeks from the beginning of ibrutinib treatment. All 3 patients had very high ALT levels, 2 had a coagulopathy (elevated international normalised ratio), and 1 had encephalopathy, indicating severe liver damage in all 3 patients.

  In Study BGB-3111-212, the median baseline values were generally within the respective normal ranges for most parameters. No clinically relevant changes over time were observed in serum chemistry parameters.

No patients met all of the criteria for Hy's law. Four patients met 2 of the 3 criteria for Hy's Law; however, each case had an alternative aetiology for the laboratory abnormalities, and none of these 4 cases were determined to meet all of the criteria of Hy's Law.

- Patient [redacted] (Study BGB-3111-206), with hepatic hilar nodal disease had transient elevation of liver function tests on Study Day 285. The patient's ALT, total bilirubin, and alkaline phosphatase were all within normal limits at the next test point, on Study Day 309, without interval study treatment interruption.
- For Patient [redacted] (Study BGB-3111-210) liver function test abnormalities were determined to be a consequence of acute hepatitis B (Common Terminology for Adverse Events Grade 5).
- Patient [redacted] (Study BGB-3111-214) had increased levels of ALT, AST, alkaline phosphatase, and bilirubin. Liver function test abnormalities were attributed to concurrent administration of prophylactic antibiotics (trimethoprim sulfamethoxazole) and incidentally identified cholelithiasis (Grade 3). Treatment with zanubrutinib was interrupted for 7 days for the increases in ALT and AST.
- Patient [redacted] (Study BGB-3111-302) was hospitalised with acute, severe hepatocellular injury (serum ALT > 50 x ULN, bilirubin > 7 x ULN unaccompanied by alkaline phosphatase elevation) on Study Day 832. A complete evaluation for viral aetiologies was unrevealing and the patient had normal liver chemistries up until the time of the event. Liver biopsy revealed findings consistent with drug-induced liver injury. Treatment with zanubrutinib was permanently discontinued. Immediately prior to the detection of the liver injury, the patient had received treatment for 4 days with phenoxymethylpenicillin (Pen V) for sinus congestion (500 mg orally once daily). He was recovering from the injury with a fall in serum bilirubin to 82 μmol/L from a peak of 271 μmol/L about 1 month after the injury was detected (the last liver function studies reported). A role for zanubrutinib in the development of drug-induced liver injury appears unlikely because 1) there is a more likely aetiology (ie, Pen V), and 2) the long latency between initiation of zanubrutinib and onset of the event.

Of the 47 serious events identified from a search of the global safety database up to 13 May 2023, the most frequent events were ascites (13), hepatic failure and hepatic function abnormal (4 each), ALT increased, AST increased, drug-induced liver injury, liver function test abnormal, and liver injury (3 each), and hepatitis and transaminases increased (2 each). The search terms used were as follows: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) (broad); Hepatitis, non-infectious (SMQ) (broad); Liver-related investigations, signs and symptoms (SMQ) (broad).

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table Part II: Module SVII-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Summary of Safety Concerns	
Important identified risks	• Haemorrhage • Infections (including lower respiratory tract infections and hepatitis B reactivation) • Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter
Important potential risks	• Second primary malignancies (other than non-melanoma skin cancer) • Second primary non-melanoma skin cancer • Drug-drug interaction with CYP3A 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)

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

No changes.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks:

Haemorrhage:

Potential Mechanisms:

BTK plays a role in platelet signalling through glycoprotein 1b and glycoprotein VI, which mediate platelet aggregation and adhesion through von Willebrand factor and collagen, respectively. Although the precise mechanisms for BTK inhibition-associated (ibrutinib-associated) bleeding have not been fully elucidated, published data suggest that both disease- and therapy-related platelet dysfunction may contribute to clinical bleeding. Within a Phase 2 study of single-agent ibrutinib in patients with CLL, Lipsky et al (2015) evaluated platelet function and coagulation factors at baseline and 4 weeks after initiation of therapy. Platelet aggregation was impaired in all patients with CLL as compared with healthy controls, and responses to both collagen and adenosine 5′-diphosphate agonists were reduced in ibrutinib-treated and TN patients compared with normal controls, consistent with a direct disease effect on platelet aggregation. Ibrutinib therapy was associated with further reduction in platelet aggregation with collagen while responses to adenosine 5′-diphosphate improved over time on therapy.

Bye et al (2015) studied the effects of ibrutinib on platelet function by comparing signalling in suspension and during adhesion to immobilised ligands. Defects in glycoprotein VI and integrin αIIbβ3 platelet signalling resulted in the formation of unstable thrombi that may contribute to bleeding. These and other findings suggest that deficiencies in several signalling pathways may ultimately contribute to ibrutinib-associated bleeding.

The mechanism for the bleeding events related to BTK inhibitor therapy is thought to be due to a platelet function defect mediated by the platelet collagen receptor (Kamel et al 2015; Levade et al 2014). Furthermore, ibrutinib has been shown to inhibit collagen-induced platelet aggregation in healthy donors, donors taking warfarin, and donors with severe renal dysfunction with IC_{50} values between 0.8 and 4.6 µmol/L (Chen et al 2018). This concept is further supported by studies showing that addition of untreated platelets reverses ibrutinib-induced inhibition of platelet aggregation in vitro (Levade et al 2014).

Evidence Source(s) and Strength of Evidence:

No apparent haemorrhage was observed in animal studies. No bleeding or apparent changes in haematology or coagulation were noted in rat and dog studies for up to 26 and 39 weeks, respectively, at doses (AUC) up to 20-fold to 28-fold higher than the human therapeutic dose level (320 mg/day, twice daily). Minimal or mild haemorrhage, which was only noted microscopically in the pancreas of interstitial material and islet in rat repeated-dose studies for up to 26 weeks, was not considered adverse based on the lack of correlating clinical pathology findings and lack of detrimental effects on overall health.

Haemorrhagic events have been reported relating to the use of zanubrutinib in ongoing and completed clinical studies.

Such events, in addition to recommendations to prescribers regarding the use of zanubrutinib in patients that are also receiving antiplatelet or anticoagulant therapies, are described in the prescribing information. This includes the recommendation to consider the benefit-risk of withholding zanubrutinib for 3 to 7 days pre and post surgery depending upon the type of surgery and the risk of bleeding (Zanubrutinib SmPC 2024). Data from ibrutinib monotherapy clinical studies demonstrate that the incidence rate of Grade 3/4 bleeding events is generally very low. A relatively high incidence of 14% was reported in a Phase 2 MCL clinical study with the therapy of high-dose regimen, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine. Grade 3 or higher bleeding events (intracranial haemorrhage [including subdural haematoma], gastrointestinal bleeding, haematuria, and post procedural haemorrhage) have occurred in up to 6% of ibrutinib patients (Bernstein et al 2013). Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib (Huang et al 2018).

Characterisation of the Risk - Data:

In the All Zanubrutinib group (cutoff 25 October 2022), 799 (51.5%) patients had ≥ 1 occurrence of haemorrhage (Table Part II: Module SVII-2). The most frequently reported events were contusion (303 [19.5%] patients), haematuria (166 [10.7%] patients), epistaxis (122 [7.9%] patients), petechiae (105 [6.8%] patients), and purpura (84 [5.4%] patients). Serious and ≥ Grade 3 events were reported in 67 (4.3%) and 77 (5.0%) patients, respectively. Haemorrhage events leading to treatment discontinuation were reported in 19 (1.2%) patients.

Haemorrhage events leading to death were reported in 6 (0.4%) patients, an increase of 1 patient (cerebral haemorrhage [2 patients], subdural haematoma [2 patients] and aortic aneurysm rupture and Haemorrhagic transformation stroke [1 patient each]). The median time to onset for any grade haemorrhage was 55.0 days (range: 1 to 1759 days). The EAIR for all grade haemorrhage was 3.00 persons/100 person-months, and for ≥ Grade 3 haemorrhage was 0.15 persons/100 person-months. The incidence of all-grade haemorrhage was highest (39.5%) in the first 6 months of zanubrutinib exposure and decreased substantially (to 5.0%) in Months 6 to 12.

Major haemorrhage is defined as Subdural haematoma (PT), Subdural haemorrhage (PT) and all Haemorrhage PTs if the AE SOC is 'nervous system disorders' or serious or Grade 3 and above Haemorrhage PTs if the AE SOC is not 'nervous system disorders'. In the All Zanubrutinib Monotherapy group, 88 patients (5.7%) reported ≥ 1 occurrence of major haemorrhage. The most frequently reported events were haematuria (16 [1.0%] patients), subdural haematoma (6 [0.4%] patients), upper gastrointestinal haemorrhage (5 [0.3%] patients), and cerebral haemorrhage, gastrointestinal haemorrhage, post procedural haemorrhage and purpura (4 [0.3%] patients each). Serious and ≥ Grade 3 events were reported in 67 (4.3%) patients and 77 (5.0%) patients, respectively. Major haemorrhage led to treatment discontinuation in 16 (1.0%) patients. Major haemorrhage events leading to death were reported in 6 (0.4%) patients, an increase of 1 patient (cerebral haemorrhage [2 patients], subdural haematoma [2 patients] and aortic aneurysm rupture and haemorrhagic transformation stroke [1 patient each]). The median time to onset for any grade major haemorrhage was 343.0 days (range: 2 to 2003 days). The EAIR for all-grade major haemorrhage was 0.17 persons/100 person-months and for ≥ Grade 3 major haemorrhage was 0.15 persons/100 person-months.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 40 (28.0%) patients had ≥ 1 haemorrhage event (Table Part II: Module SVII-3). The most frequently reported events were contusion (12 [8.4%] patients), petechiae (9 [6.3%] patients), and epistaxis (7 [4.9%] patients). Serious and ≥ Grade 3 haemorrhage events were reported in 1 (0.7%) and 2 (1.4%) patients, respectively. No patients reported haemorrhage events leading to treatment discontinuation or death. The median time to onset for any grade haemorrhage was 28.0 days (range: 2 to 1002 days). The EAIR for all grade haemorrhage was 2.22 persons/100 person-months, and for ≥ Grade 3 haemorrhage was 0.08 persons/100 person-months.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 2 (1.4%) patients had ≥ 1 major haemorrhage event; these events were haemoptysis and retroperitoneal haematoma (1 [0.7%] patient each) and were both ≥ Grade 3. The event of retroperitoneal haematoma (1 [0.7%] patient) was serious. No patients reported major haemorrhage events leading to treatment discontinuation or death. The median time to onset for any grade major haemorrhage was 247.5 days (range: 120 to 375 days). The EAIR for all grade and ≥ Grade 3 major haemorrhage was 0.08 persons/100 person-months.

Table Part II: Module SVII-2: Haemorrhage in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI Category Preferred Term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111-214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu-brutinib (N = 1550) n (%)
Hemorrhage	**57 (56.4)**	**143 (57.4)**	**20 (62.5)**	**33 (38.4)**	**53 (44.9)**	**53 (44.2)**	**30 (44.1)**	**42 (47.7)**	**44 (47.3)**	**192 (49.1)**	**137 (42.3)**	**284 (54.1)**	**491 (52.3)**	**799 (51.5)**
Contusion	19 (18.8)	55 (22.1)	14 (43.8)	2 (2.3)	16 (13.6)	16 (13.3)	16 (23.5)	23 (26.1)	23 (24.7)	71 (18.2)	44 (13.6)	97 (18.5)	181 (19.3)	303 (19.5)
Haematuria	12 (11.9)	27 (10.8)	5 (15.6)	7 (8.1)	12 (10.2)	12 (10.0)	3 (4.4)	4 (4.5)	5 (5.4)	26 (6.6)	15 (4.6)	72 (13.7)	106 (11.3)	166 (10.7)
Epistaxis	18 (17.8)	34 (13.7)	3 (9.4)	3 (3.5)	6 (5.1)	6 (5.0)	4 (5.9)	6 (6.8)	6 (6.5)	23 (5.9)	24 (7.4)	39 (7.4)	63 (6.7)	122 (7.9)
Petechiae	7 (6.9)	18 (7.2)	1 (3.1)	1 (1.2)	2 (1.7)	2 (1.7)	3 (4.4)	5 (5.7)	5 (5.4)	29 (7.4)	29 (9.0)	39 (7.4)	69 (7.4)	105 (6.8)
Purpura	4 (4.0)	18 (7.2)	0 (0.0)	2 (2.3)	2 (1.7)	2 (1.7)	2 (2.9)	3 (3.4)	4 (4.3)	12 (3.1)	6 (1.9)	46 (8.8)	59 (6.3)	84 (5.4)
Haematoma	6 (5.9)	11 (4.4)	2 (6.3)	0 (0.0)	2 (1.7)	2 (1.7)	1 (1.5)	2 (2.3)	2 (2.2)	24 (6.1)	15 (4.6)	15 (2.9)	39 (4.2)	57 (3.7)
Ecchymosis	1 (1.0)	9 (3.6)	1 (3.1)	2 (2.3)	3 (2.5)	3 (2.5)	2 (2.9)	2 (2.3)	2 (2.2)	15 (3.8)	4 (1.2)	9 (1.7)	24 (2.6)	41 (2.6)
Increased tendency to bruise	3 (3.0)	7 (2.8)	2 (6.3)	0 (0.0)	2 (1.7)	2 (1.7)	1 (1.5)	2 (2.3)	2 (2.2)	6 (1.5)	7 (2.2)	10 (1.9)	18 (1.9)	32 (2.1)
Gingival bleeding	2 (2.0)	7 (2.8)	0 (0.0)	1 (1.2)	1 (0.8)	1 (0.8)	1 (1.5)	1 (1.1)	1 (1.1)	6 (1.5)	7 (2.2)	9 (1.7)	15 (1.6)	26 (1.7)
Urinary occult blood positive	0 (0.0)	1 (0.4)	0 (0.0)	11 (12.8)	11 (9.3)	11 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	12 (2.3)	12 (1.3)	26 (1.7)
Skin haemorrhage	1 (1.0)	4 (1.6)	0 (0.0)	1 (1.2)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	9 (2.8)	12 (2.3)	17 (1.8)	23 (1.5)
Conjunctival haemorrhage	5 (5.0)	9 (3.6)	1 (3.1)	1 (1.2)	2 (1.7)	2 (1.7)	0 (0.0)	1 (1.1)	1 (1.1)	2 (0.5)	6 (1.9)	7 (1.3)	9 (1.0)	22 (1.4)
Haemoptysis	1 (1.0)	3 (1.2)	1 (3.1)	2 (2.3)	3 (2.5)	3 (2.5)	0 (0.0)	2 (2.3)	2 (2.2)	5 (1.3)	2 (0.6)	7 (1.3)	12 (1.3)	22 (1.4)
Haemorrhage subcutaneous	0 (0.0)	3 (1.2)	0 (0.0)	3 (3.5)	3 (2.5)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.9)	10 (1.9)	12 (1.3)	18 (1.2)

Table Part II: Module SVII-2:Haemorrhage in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

AESI Category Preferred Term	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111-214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu-brutinib (N = 1550) n (%)
Rectal haemorrhage	5 (5.0)	8 (3.2)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	1 (1.1)	1 (1.1)	4 (1.0)	2 (0.6)	2 (0.4)	6 (0.6)	17 (1.1)
Mouth haemorrhage	2 (2.0)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	5 (1.3)	2 (0.6)	5 (1.0)	10 (1.1)	15 (1.0)
Post procedural haemorrhage	2 (2.0)	4 (1.6)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	0 (0.0)	2 (0.4)	7 (0.7)	13 (0.8)
Haemorrhoidal haemorrhage	3 (3.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	3 (3.4)	3 (3.2)	2 (0.5)	1 (0.3)	2 (0.4)	5 (0.5)	12 (0.8)
Post procedural contusion	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	2 (0.5)	0 (0.0)	5 (1.0)	7 (0.7)	10 (0.6)
Subcutaneous haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	2 (2.3)	2 (2.2)	5 (1.3)	3 (0.9)	3 (0.6)	8 (0.9)	10 (0.6)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	4 (4.7)	4 (3.4)	4 (3.3)	0 (0.0)	1 (1.1)	1 (1.1)	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	9 (0.6)
Haematochezia	0 (0.0)	1 (0.4)	0 (0.0)	1 (1.2)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.6)	4 (0.8)	6 (0.6)	8 (0.5)
Eye haemorrhage	1 (1.0)	2 (0.8)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)	1 (0.2)	3 (0.3)	7 (0.5)
Haemorrhagic diathesis	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.6)	3 (0.6)	5 (0.5)	7 (0.5)
Oral blood blister	3 (3.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.9)	3 (0.6)	4 (0.4)	7 (0.5)
Retinal haemorrhage	0 (0.0)	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	7 (0.5)
Ear haemorrhage	1 (1.0)	1 (0.4)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	3 (0.6)	4 (0.4)	6 (0.4)

Table Part II: Module SVII-2:Haemorrhage in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

AESI Category Preferred Term	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111-214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu-brutinib (N = 1550) n (%)
Subdural haematoma	2 (2.0)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	6 (0.4)
Vaginal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	1 (0.3)	3 (0.6)	3 (0.3)	6 (0.4)
Eye contusion	1 (1.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.4)	3 (0.3)	5 (0.3)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	1 (3.1)	1 (1.2)	2 (1.7)	2 (1.7)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	5 (0.3)
Periorbital haemorrhage	3 (3.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	5 (0.3)
Traumatic haematoma	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	1 (0.3)	1 (0.3)	2 (0.4)	3 (0.3)	5 (0.3)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.4)	3 (0.3)	4 (0.3)
Melaena	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	4 (0.3)
Pharyngeal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	4 (0.8)	4 (0.4)	4 (0.3)
Post procedural haematoma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)	1 (0.2)	3 (0.3)	4 (0.3)
Blood blister	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	3 (0.2)
Blood urine present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.6)	3 (0.3)	3 (0.2)
Bone contusion	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.2)
Eyelid bleeding	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	3 (0.2)
Haemarthrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.6)	3 (0.3)	3 (0.2)

Table Part II: Module SVII-2:Haemorrhage in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI Category Preferred Term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111-214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu-brutinib (N = 1550) n (%)
Haemorrhage	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)
Heavy menstrual bleeding	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.2)
Procedural haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)
Subdural haemorrhage	1 (1.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)
Vessel puncture site bruise	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.2)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAE

Abbreviations: AESI, adverse events of special interest; CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; MCL, Mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed or refractory; WM, Waldenström's macroglobulinemia.

N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or ibrutinib. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.

Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.

MedDRA Version: 24.0.

Table Part II: Module SVII-3: Haemorrhage in Zanubrutinib FL Studies (Safety Analysis Set)

AESI Category Preferred Term	Combination Therapy: Zanubrutinib + Obinutuzumab		Monotherapy Zanubrutinib
	BGB-3111-212 (N = 143) n (%)	BGB-3111-GA101-101 (N = 36) n (%)	BGB-3111-1002 + AU003 (N = 59) n (%)
Haemorrhage	40 (28.0)	18 (50.0)	25 (42.4)
Contusion	12 (8.4)	11 (30.6)	8 (13.6)
Petechiae	9 (6.3)	6 (16.7)	5 (8.5)
Epistaxis	7 (4.9)	2 (5.6)	5 (8.5)
Haematoma	6 (4.2)	1 (2.8)	0 (0.0)
Gingival bleeding	4 (2.8)	1 (2.8)	0 (0.0)
Haemoptysis	2 (1.4)	1 (2.8)	0 (0.0)
Mouth haemorrhage	1 (0.7)	2 (5.6)	0 (0.0)
Purpura	3 (2.1)	0 (0.0)	1 (1.7)
Conjunctival haemorrhage	2 (1.4)	0 (0.0)	0 (0.0)
Ecchymosis	2 (1.4)	0 (0.0)	0 (0.0)
Haematuria	1 (0.7)	1 (2.8)	7 (11.9)
Increased tendency to bruise	0 (0.0)	2 (5.6)	0 (0.0)
Injection site haemorrhage	2 (1.4)	0 (0.0)	0 (0.0)
Retinal haemorrhage	2 (1.4)	0 (0.0)	0 (0.0)
Anal haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Ear haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Haemorrhage subcutaneous	1 (0.7)	0 (0.0)	0 (0.0)
Haemorrhagic diathesis	1 (0.7)	0 (0.0)	0 (0.0)
Injection site bruising	1 (0.7)	0 (0.0)	0 (0.0)
Injection site haematoma	1 (0.7)	0 (0.0)	0 (0.0)
Penile contusion	1 (0.7)	0 (0.0)	0 (0.0)
Periorbital haemorrhage	0 (0.0)	1 (2.8)	0 (0.0)
Post procedural haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Rectal haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Retroperitoneal haematoma	1 (0.7)	0 (0.0)	0 (0.0)
Skin haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Tongue haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Traumatic haematoma	1 (0.7)	0 (0.0)	0 (0.0)
Upper gastrointestinal haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Vaginal haemorrhage	1 (0.7)	0 (0.0)	1 (1.7)
Vascular access site haematoma	1 (0.7)	0 (0.0)	0 (0.0)

Table Part II: Module SVII-3: Haemorrhage in Zanubrutinib FL Studies (Safety Analysis Set)

AESI Category Preferred Term	Combination Therapy: Zanubrutinib + Obinutuzumab		Monotherapy Zanubrutinib
	BGB-3111-212 (N = 143) n (%)	BGB-3111-GA101-101 (N = 36) n (%)	BGB-3111-1002 + AU003 (N = 59) n (%)
Vascular purpura	1 (0.7)	0 (0.0)	0 (0.0)
Vitreous haemorrhage	1 (0.7)	0 (0.0)	0 (0.0)
Heavy menstrual bleeding	0 (0.0)	0 (0.0)	1 (1.7)
Post procedural contusion	0 (0.0)	0 (0.0)	1 (1.7)
Urinary occult blood positive	0 (0.0)	0 (0.0)	2 (3.4)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAE.
Abbreviations: FL, follicular lymphoma.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or obinutuzumab. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.
Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.
MedDRA Version: 24.0.

The validated safety database search outputs (13 May 2023; utilising the Haemorrhage terms SMQ (narrow) (excluding laboratory terms)) revealed 1763 events, of which 562 were serious. Of note, 388 of these serious events reported in 355 cases are part of the major haemorrhage subset. The search terms that comprise this subset are included below.

MedDRA Terms Used in Clinical Database Search:

Haemorrhage: Haemorrhage terms (excluding laboratory terms) SMQ (narrow)

Major Haemorrhage:

- All Subdural haematoma (PT), Subdural haemorrhage (PT)
- All Haemorrhage PTs if the adverse event SOC is ‘nervous system disorders’ or
- Serious or Grade 3 and above Haemorrhage PTs if the adverse event SOC is not ‘nervous system disorders’

Characterisation of the Risk - Discussion:

Mild to moderate haemorrhage is a commonly observed adverse reaction. Severe haemorrhage was uncommonly reported in zanubrutinib clinical studies but can be potentially life-threatening or associated with a fatal outcome. Patients with haemorrhage should be managed according to the usual standard of care.

Risk Factors and Risk Groups:

Risks include advanced age, history of bleeding, dose of chemotherapy, baseline platelet count, poor performance and/or nutritional status, and concomitant use of antiplatelet or anticoagulant therapy, especially warfarin use in the elderly population.

Preventability:

Zanubrutinib may increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. In the event of emergency surgery, patients should be closely monitored perioperatively for unusual or excessive bleeding, and the provision of blood products should be considered. In the event of planned or elective surgery, the patient's treating physician should carefully consider the benefits and risks of withholding zanubrutinib treatment for up to 7 days pre and postoperatively.

Impact on the Benefit-Risk Balance of the Product:

Bleeding events have been reported frequently in clinical studies with zanubrutinib. Most bleeding events are Grade 1 to 2, and include spontaneous bruising, petechiae, and haematomas, but, in some patients, they are ≥ Grade 3. More serious bleeding events have been reported less frequently but some events have been associated with a fatal outcome. The local label and patient information leaflet provide information both to the prescriber and patient as to how to identify and manage any bleeding risk. In the context of the underlying disease process and associated outcomes, this risk is manageable with the provision of such information. Overall, the benefit-risk balance is positive given the clinical efficacy associated with the use of the product.

Public Health Impact:

Haemorrhage is known to occur in the context of underlying haematological malignancy, which can be life-threatening or fatal. Patients should be closely monitored for such events and instructed by their treating physician to be vigilant for any signs and symptoms of bleeding. Patients with haemorrhage should be treated according to the standard of care. Because the incidence of ≥ Grade 3 haemorrhage in patients with B-cell malignancies treated with zanubrutinib is low, haemorrhage is unlikely to represent a significant risk to public health.

Infections (Including Lower Respiratory Tract Infections and Hepatitis B Reactivation)

Potential Mechanisms:

Infection is one of the most common complications of cancer or cancer treatment and can result in morbidity and mortality. It is not unusual for CLL to present as recurrent infections. In untreated patients with CLL, the most common infections include respiratory tract and urinary tract infections, predominantly secondary to bacteria (67%), viruses (25%), and fungi (7%) (Forconi and Moss 2015). There is some evidence for direct immunosuppression by the tumour/malignancy itself, manifested through the activity of cytokines and cell-cell interactions in the tumour microenvironment. Neutrophil function is also impaired with defects in phagocytic killing and altered chemotaxis. Furthermore, the adaptive immune response is altered with impairments in CD4 and CD8 T cell function and often hypogammaglobulinemia that also increases risk of infection (Forconi and Moss 2015).

The association between kinase inhibition, either BTK or off-target inhibition of Janus kinase 3 or other kinases, and infection risk in patients treated with BTK inhibitors is unclear. Ibrutinib

has been shown to inhibit TEC family kinases BTK, TEC, interleukin-2-inducible T-cell kinase, and BMX with the potential for effects on a large number of immune cell types including T and B cells, macrophages, dendritic cells, natural killer cells, and mast cells (Berglöf et al 2015). Of these, zanubrutinib has less inhibition of Janus kinase 3, TEC, and interleukin-2-inducible T-cell kinase compared to ibrutinib.

Patients with a haematological malignancy have an increased risk of infection. In addition, BTK inhibition affects the B-cell receptor signalling pathway and may interfere with the function to synthesise all classes of immunoglobulins, which may lead to serious bacterial infections and increased susceptibility to viral and parasitic infections. Loss of BTK expression, as seen in individuals with X-linked agammaglobulinaemia, results in the absence of circulating B cells and an increased risk for infections with encapsulated pyogenic bacteria and enteroviruses (Varughese et al 2018).

Evidence Source(s) and Strength of Evidence:

Fatal and non-fatal infections (including bacterial, viral, or fungal infections or sepsis) and opportunistic infections (eg, aspergillus, cryptococcal, herpes viral, and pneumocystis jirovecii infections) have occurred in patients treated with zanubrutinib. Infections due to HBV reactivation have also occurred.

Characterisation of the Risk - Data:

In the All Zanubrutinib Monotherapy group, 1153 (74.4%) patients reported ≥ 1 infection. The most commonly reported infection events were upper respiratory tract infection (461 [29.7%] patients), pneumonia (224 [14.5%] patients), urinary tract infection (212 [13.7%] patients), and COVID-19 (208 [13.4%] patients). Serious and ≥ Grade 3 infection events were reported in 409 (26.4%) and 448 (28.9%) patients, respectively.
Seventy (4.5%) patients reported infection events leading to treatment discontinuation, and 57 (3.7%) patients had infection events leading to death; the most common infection events leading to death were COVID-19 (14 [0.9%] patients), and pneumonia and COVID-19 pneumonia (13 [0.8%] patients each).

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 83 (58.0%) patients reported ≥ 1 infection. The most commonly reported infection events were pneumonia and COVID-19 (18 [12.6%] patients each), urinary tract infection (13 [9.1%] patients) and nasopharyngitis (11 [7.7%] patients). Serious and ≥ Grade 3 infection events were reported in 42 (29.4%) and 45 (31.5%) patients, respectively. Thirteen (9.1%) patients reported infection events leading to treatment discontinuation, and 7 (4.9%) patients had infection events leading to death (COVID-19 and pneumonia [2 patients each] and COVID-19 pneumonia, pulmonary mucormycosis, and septic shock [1 patient each]).

In the All Zanubrutinib Monotherapy group, 38 (2.5%) patients reported opportunistic infection events (Table Part II: Module SVII-5). The most commonly reported opportunistic infection events were pneumonia fungal (9 [0.6%] patients) and bronchopulmonary aspergillosis (7 [0.5%] patients). Serious and ≥ Grade 3 opportunistic infection events were each reported in 26 (1.7%) patients. Five (0.3%) patients reported opportunistic infection events leading to treatment discontinuation and 4 (0.3%) patients had opportunistic infection events leading to death (pneumonia fungal [2 patients] and pneumonia cryptococcal and scedosporium infection

[1 patient each]). The EAIR for opportunistic infection events of any grade was 0.07 persons/100 person-months.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 4 (2.8%) patients reported opportunistic infection events. The most commonly reported infection event was oesophageal candidiasis (2 [1.4%] patients); no other opportunistic infection was reported by > 1 patient (Table Part II: Module SVII-6). Serious and ≥ Grade 3 opportunistic infection events were each reported in 2 (1.4%) patients. No patients reported opportunistic infection events leading to treatment discontinuation, while 1 (0.7%) patient had an opportunistic infection event leading to death (pulmonary mucormycosis). The EAIR for opportunistic infection events of any grade was 0.17 persons/100 person-months.

A summary of the incidence of concurrent ≥ Grade 3 infection events in patients with neutropenia events is presented in Table Part II: Module SVII-4. The majority of ≥ Grade 3 infections were not preceded by neutropenia; the proportion of patients with neutropenia who had concurrent ≥ Grade 3 infections was < 10% across all patient groups.

Table Part II: Module SVII-4: Incidence Summary of Grade 3 or Higher Infections for Patients with Neutropenia (Safety Analysis Set)

	Combination Therapy Trials		Monotherapy Trials	
	BGB-3111-212 Zanu + Obi (N = 143) n (%)	BGB-3111-212 Obi (N = 71) n (%)	All Zanu Monotherapy (N = 1550) n (%)	FL Patients (N = 59) n (%)
Patients with at least one AESI of Neutropenia	44 (30.8)	20 (28.2)	467 (30.1)	19 (32.2)
With any concurrent grade 3 or higher AESI of infection [a]	4 (9.1)	1 (5.0)	40 (8.6)	1 (5.3)

Abbreviations: AESI, adverse event of special interest; FL, follicular lymphoma; Obi, Obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, Zanubrutinib.

[a] Concurrent infection was defined as the grade 3 or higher infection started on or after (within 14 days of) any grade neutropenia start date and on or before treatment emergent period end date. Percentages are based on number of patients with at least one Neutropenia AESI.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD and/or obinutuzumab. Percentages are based on N, unless otherwise specified.

Source: ADSL, ADAE. Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304).

TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days or initiation of new anti-cancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond last zanubrutinib dose date + 30 days/last obinutuzumab infusion date + 90 days and prior to initiation of new anti-cancer therapy is also considered as treatment-emergent.

Table Part II: Module SVII-5:Opportunistic Infections in Zanubrutinib Clinical Studies (Safety Analysis Set)

AESI Category Preferred Term	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Opportunistic infections	**2 (2.0)**	**7 (2.8)**	**2 (6.3)**	**2 (2.3)**	**4 (3.4)**	**4 (3.3)**	**3 (4.4)**	**4 (4.5)**	**4 (4.3)**	**3 (0.8)**	**7 (2.2)**	**16 (3.0)**	**21 (2.2)**	**38 (2.5)**
Pneumonia fungal	0 (0.0)	1 (0.4)	0 (0.0)	2 (2.3)	2 (1.7)	2 (1.7)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	2 (0.6)	4 (0.8)	4 (0.4)	9 (0.6)
Bronchopulmonary aspergillosis	0 (0.0)	1 (0.4)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	1 (1.1)	1 (1.1)	1 (0.3)	2 (0.6)	2 (0.4)	3 (0.3)	7 (0.5)
Meningitis cryptococcal	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	3 (0.2)
Pneumonia cryptococcal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.6)	3 (0.3)	3 (0.2)
Disseminated varicella zoster virus infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	2 (0.1)
Pneumocystis jirovecii pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	2 (2.3)	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cerebral aspergillosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cryptococcal fungaemia	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cryptococcosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Encephalitis fungal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Fungal abscess central nervous system	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Herpes ophthalmic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Herpes simplex viraemia	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Herpes zoster meningoencephalitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Herpes zoster oticus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

Table Part II: Module SVII-5:Opportunistic Infections in Zanubrutinib Clinical Studies (Safety Analysis Set)

AESI Category Preferred Term	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Listeria sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Lower respiratory tract infection fungal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Mycobacterium ulcerans infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Oesophageal candidiasis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pulmonary tuberculosis	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Scedosporium infection	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAE

Abbreviations: AESI, adverse events of special interest; CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; MCL, Mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed or refractory; WM, Waldenström's macroglobulinemia; Zanu, Zanubrutinib.

N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or ibrutinib. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.

Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.

MedDRA Version: 24.0.

Table Part II: Module SVII-6: Opportunistic Infections in Zanubrutinib FL Studies (Safety Analysis Set)

AESI Category Preferred Term	Combination Therapy: Zanubrutinib + Obinutuzumab BGB-3111-212 (N = 143) n (%)	Combination Therapy: Zanubrutinib + Obinutuzumab BGB-3111-GA101-101 (N = 36) n (%)	Monotherapy Zanubrutinib BGB-3111-1002 + AU003 (N = 59) n (%)
Opportunistic Infections	**4 (2.8)**	**2 (5.6)**	**1 (1.7)**
Oesophageal candidiasis	2 (1.4)	0 (0.0)	0 (0.0)
Disseminated varicella zoster virus infection	0 (0.0)	1 (2.8)	0 (0.0)
Herpes zoster oticus	1 (0.7)	0 (0.0)	0 (0.0)
Ophthalmic herpes simplex	0 (0.0)	1 (2.8)	0 (0.0)
Pulmonary mucormycosis	1 (0.7)	0 (0.0)	0 (0.0)
Pneumonia fungal	0 (0.0)	0 (0.0)	1 (1.7)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAE.
Abbreviations: FL, follicular lymphoma.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or obinutuzumab. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.
Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.
MedDRA Version: 24.0

In the SmPC, very commonly reported ADRs with zanubrutinib monotherapy are upper respiratory tract infection (grouped terms; 36% [all grades], 2% [≥ Grade 3]), and the PT of pneumonia (15% [all grades], 8% [≥ Grade 3]) and urinary tract infection (grouped terms; 14% [all grades], 2% [≥ Grade 3]). Grouped terms for pneumonia ADRs are also very commonly reported (24% [all grades], 14% [≥ Grade 3]). Commonly reported ADRs in the SOC of infections and infestations are the PTs of lower respiratory tract infection (5% of 1550 patients with B-cell malignancies [all grades], < 1% [≥ Grade 3]) and bronchitis (4% [all grades], < 1% [≥ Grade 3]). Hepatitis B reactivation is uncommon (≤ 1% [all grades], ≤ 1% [≥ Grade 3]).

The validated safety database search outputs (13 May 2023; utilising the Opportunistic Infections SMQ narrow) revealed 86 events (84 of which were serious) in 80 cases. Of the 80 cases, 50 were from sponsored clinical studies, 12 were from an organised data collection programme, 11 were spontaneous cases, 5 were from investigator sponsored research, and 1 each of compassionate use and postmarketing literature cases. The most commonly occurring serious infections were pneumonia fungal (15), bronchopulmonary aspergillosis and pneumocystis jirovecii pneumonia (8 each), meningitis cryptococcal (5), disseminated cryptococcosis and pneumonia cryptococcal (4 each), and pneumonia legionella (3).

MedDRA Terms Used in Clinical Database Search:

Infections and infestations SOC, Opportunistic infections SMQ (narrow).

Characterisation of the Risk - Discussion:

As is typical for the B-cell malignancies represented herein (principally MCL, CLL/SLL, WM), many of the infection events reported were mucosal infections involving the sinopulmonary and urinary tracts. No opportunistic infections were reported with a frequency of > 5% in any treatment group. Due to the causal relationship of important infection events, ie, ADRs in Table 3 of the SmPC and according to Good Pharmacovigilance Practices guidance (Annex I [Rev 4] and Module V [Rev 2]), infections (including lower respiratory tract infections and hepatitis B reactivation) is considered to be an important identified risk.

Risk Factors and Risk Groups:

Predictors include advanced age, underlying immunosuppression that is inherent to the primary disease process, therapy-related immunosuppression, absence of antibiotic prophylaxis, and poor performance and/or nutritional status.

Preventability:

The SmPC states that prophylaxis, according to the standard of care in patients who are at increased risk for infections, should be considered. Monitor patients for signs and symptoms of infection and treat appropriately.

Impact on the Benefit-Risk Balance of the Product:

Infections are frequently observed in patients with haematological malignancies. However, without appropriately controlled clinical studies, assessment of the relative contribution of zanubrutinib to the incidence and severity of infections is difficult; based on an understanding of the mechanism of action, an association of zanubrutinib use with infection risk appears biologically plausible. The SmPC and patient information leaflet provide information to the prescriber and patient as to how to manage the risk. Overall, the benefit-risk balance is positive for the product considering the severity of the diseases treated and the potential efficacy in patients treated with zanubrutinib. In addition, control of the underlying disease may also alleviate the immunodysfunction due to underlying disease and improve immunity against infections.

Public Health Impact:

The incidence of ≥ Grade 3 infections is similar between zanubrutinib and comparators (used in Phase 3 randomised controlled clinical studies). In addition, because of the relatively small number of patients in the targeted populations, infections associated with zanubrutinib therapy are not likely to have a significant impact on public health.

Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter:

Potential Mechanisms:

Preclinical studies have shown that ibrutinib therapy leads to atrial fibrillation and other cardiac damage through the off-target inhibition of C-terminal src kinase (Xiao et al 2020), and zanubrutinib has been shown to have 48-fold less inhibition of C-terminal src kinase than ibrutinib (Guo et al 2019). The C_{max} of zanubrutinib at 160 mg twice daily is estimated to be around 30 to 40 nM which is approximately 5 to 7-fold less than zanubrutinib's IC_{50} of 218 nM for C-terminal src kinase. Therefore, it is expected that zanubrutinib at the therapeutic dose results in minimal, if any, inhibition of C-terminal src kinase. In addition, ibrutinib inhibits

Erb-B2 receptor tyrosine kinase 2/human epidermal growth factor receptor 2 more potently than zanubrutinib (IC_{50} = 9.4 nM versus IC_{50} = 660 nM, respectively), which results in cardiac myocyte dysfunction and reduced heart contractile efficiency, leading to impaired cardiac function (Berglöf et al 2015).

The unintended impact of BTK inhibition results in potentially beneficial or adverse events including atrial fibrillation, which is putatively related either to reduced activity of the BTK-regulated PI3K/protein kinase B pathway in cardiac myocytes, to reduced activity of other relevant tyrosine kinase pathways, or to as-yet unidentified mechanisms. It has been hypothesised (McMullen et al 2014) that ibrutinib-induced atrial fibrillation may be due to on-target inhibition of BTK and related kinases such as TEC, which hitherto were not known to have functions in the human heart. McMullen et al (2014) have shown that both BTK and TEC transcripts were expressed in human heart tissue and that the expression of BTK and TEC transcripts was higher in atrial tissue under conditions of atrial fibrillation than sinus rhythm ($p < 0.05$), suggesting that BTK and TEC may have functional roles under conditions of cardiac stress. Furthermore, one of the pathways regulated by BTK and TEC is the PI3K pathway, which is a critical regulator of cardiac protection under stress conditions. Pretorius et al (2009) have shown that mice with reduced cardiac PI3K activity were highly susceptible to the development of atrial fibrillation.

Evidence Source(s) and Strength of Evidence:

Reports of atrial fibrillation have been identified in completed and ongoing clinical studies, particularly in patients with a history of cardiac disease and known cardiac risk factors (eg, hypertension, previous history of atrial fibrillation, and concurrent active infections). Atrial fibrillation is described in the current prescribing information for ibrutinib.

Characterisation of the Risk - Data:

Nonclinical studies of zanubrutinib showed that no effects on QT or Fridericia's corrected QT interval were observed in telemetry-instrumented conscious dogs at single doses of zanubrutinib up to 100 mg/kg. In addition, no abnormal changes in ECG or cardiovascular function were noted in repeated-dose toxicity studies in dogs at doses up to 100 mg/kg. The QT interval prolongation potential of zanubrutinib was evaluated in Study BGB-3111-106, a thorough QT study in healthy male and female subjects conducted in 2 parts, Part A and Part B. Part A of this study was a randomised, double-blind, placebo-controlled, single-dose study to evaluate the safety, tolerability, and PK of a single oral dose of zanubrutinib 480 mg. Part B of this study was a randomised, placebo- and positive-controlled, 4-way crossover, single-dose, thorough QT study to investigate the effects of zanubrutinib on ECG parameters, and to assess the safety, tolerability, and PK of zanubrutinib. The study demonstrated that single oral doses of zanubrutinib at 160 mg and 480 mg did not have a clinically relevant effect on ECG parameters, including Fridericia's corrected QT interval and other ECG intervals. Because of the short half-life and no accumulation observed following multiple-dosing, these results are also applicable for steady-state conditions.

Results from Study BGB-3111-302 (cutoff date 31 October 2021) demonstrated that atrial fibrillation occurred in a statistically higher proportion (> 10% difference) of ibrutinib-treated patients compared with zanubrutinib (23 of 98 [23.5%] patients versus 8 of 101 [7.9%] patients). The EAIR difference was -0.56 (95% CI: -0.93 to -0.20; p = 0.0024). In the CLL/SLL

Study BGB-3111-304, the rates of atrial fibrillation/flutter for zanubrutinib were similar to the BR comparator group. In Study BGB-3111-305 (cutoff date 01 December 2021), patients with CLL/SLL in the zanubrutinib arm (15 of 324 [4.6%] patients) had a significantly lower frequency of atrial fibrillation/flutter compared with those in the ibrutinib arm (39 of 324 [12.0%] patients). The rate difference between the 2 arms was -7.4% (95% CI: -11.6% to -3.2%, p = 0.0006).

In the All Zanubrutinib Monotherapy group, 75 (4.8%) patients had at least 1 occurrence of atrial fibrillation or flutter (Table Part II: Module SVII-5). Sixty-nine (4.5%) patients had events of atrial fibrillation and 7 (0.5%) patients had events of Atrial flutter. A majority of patients with atrial fibrillation or flutter events had known risk factors including hypertension (57.3%), and/or a prior history of atrial fibrillation or flutter (20.0%). Serious events and ≥ Grade 3 events were reported in 25 (1.6%) and 31 (2.0%) patients, respectively. Two (0.1%) patients had atrial fibrillation or flutter events leading to discontinuations. No patients had atrial fibrillation or flutter events leading to death. The median time to onset for any grade atrial fibrillation or flutter was 599.0 days (range: 1 to 1988 days). The EAIR for all-grade atrial fibrillation or flutter was 0.15 persons/100 person-months, and for ≥ Grade 3 atrial fibrillation or flutter was 0.06 persons/100 person-months.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 4 (2.8%) patients reported events of atrial fibrillation or flutter. Two (50.0%) patients with atrial fibrillation or flutter had a medical history of hypertension. The events of atrial fibrillation were serious in 2 (1.4%) patients and ≥ Grade 3 in 2 (1.4%) patients. No patients had atrial fibrillation or flutter events that led to treatment discontinuation or death. The median time to onset for any grade atrial fibrillation or flutter was 272.5 days (range: 64 to 396 days). The EAIR for all grade atrial fibrillation or flutter was 0.17 persons/100 person-months, and for ≥ Grade 3 atrial fibrillation or flutter was 0.08 persons/100 person-months.

Table Part II: Module SVII-7: Cardiac Arrhythmia, Mainly Presented as Atrial Fibrillation and Flutter, in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI Category Preferred Term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Atrial fibrillation	8 (7.9)	18 (7.2)	2 (6.3)	0 (0.0)	2 (1.7)	2 (1.7)	1 (1.5)	2 (2.3)	2 (2.2)	15 (3.8)	15 (4.6)	25 (4.8)	41 (4.4)	69 (4.5)
Atrial flutter	1 (1.0)	2 (0.8)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	2 (0.6)	3 (0.6)	3 (0.3)	7 (0.5)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAE

Abbreviations: CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; MCL, Mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed or refractory; WM, Waldenström's macroglobulinemia; Zanu, Zanubrutinib.

N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or ibrutinib. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.

Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.

MedDRA Version: 24.0.

Table Part II: Module SVII-8: Cardiac Arrhythmia, Mainly Presented as Atrial Fibrillation and Flutter in Zanubrutinib FL Studies (Safety Analysis Set)

AESI Category Preferred Term	Combination Therapy: Zanubrutinib + Obinutuzumab		Monotherapy Zanubrutinib
	BGB-3111-212 (N = 143) n (%)	BGB-3111-GA101-101 (N = 36) n (%)	BGB-3111-1002 + AU003 (N = 59) n (%)
Atrial fibrillation	4 (2.8)	0 (0.0)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	0 (0.0)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAE.
Abbreviations: FL, follicular lymphoma.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or obinutuzumab. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.
Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.
MedDRA Version: 24.0.

A supplementary search of the global safety database was undertaken (13 May 2023) using the Cardiac arrhythmias (SMQ) (broad). A total of 388 cardiac arrhythmia events reported in 350 cases were identified, of which 270 events were serious, as shown in Table Part II: Module SVII-9 below.

Table Part II: Module SVII-9: Serious Cardiac Arrhythmia Events in the Cumulative Global Safety Database

Cardiac Arrhythmia (MedDRA Version 26.0)	
Preferred Term	**n**
Atrial fibrillation	123
Syncope	40
Loss of consciousness	21
Arrhythmia	13
Cardiac arrest	11
Atrial flutter	9
Cardiac flutter	9
Heart rate increased	5
Palpitations	5
Atrioventricular block complete	4
Ventricular tachycardia	4
Bradycardia	4

Table Part II: Module SVII-9:Serious Cardiac Arrhythmia Events in the Cumulative Global Safety Database

Cardiac Arrhythmia (MedDRA Version 26.0)	
Preferred Term	**n**
Tachycardia	3
Ventricular arrhythmia	3
Atrioventricular block second degree	3
Ventricular extrasystoles	2
Heart rate irregular	2
Cardiac fibrillation	2
Pulseless electrical activity	1
Supraventricular tachycardia	1
Ventricular flutter	1
Sinus bradycardia	1
Sinus node dysfunction	1
Sudden death	1
Sudden cardiac death	1
Total	**270**

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities.
Data lock point: 13 May 2023

Of the 270 serious events, there were 132 events of atrial fibrillation and flutter, reported in 131 patients, 40 events of syncope, and low numbers of other cardiac arrhythmia events, including loss of consciousness (21), arrhythmia (13), cardiac arrest (11) and cardiac flutter (9). Of these serious cases, 1 case of a sustained ventricular tachycardia was reported in a patient with SLL and previously undiagnosed coronary artery disease, prior myocardial inferolateral infarction, and ventricular segmental dysfunction. The remaining case of ventricular tachycardia verbatim term states not sustained. These observations, together with the prolonged latency, are not supportive of a causal relationship with zanubrutinib administration. Overall, low numbers of cardiac arrhythmia events, predominantly atrial fibrillation and flutter, have been reported in zanubrutinib clinical studies.

MedDRA Terms Used in Clinical Database Search:

Cardiac arrhythmias (SMQ) (broad)

Characterisation of the Risk - Discussion:

Atrial fibrillation is the most common type of cardiac arrhythmia (Roberts et al 1993). Overall, patients with any cancer diagnosis are associated with increased risk of atrial fibrillation (Yuan et al 2019; Jakobsen et al 2019; O'Neal et al 2015). Atrial fibrillation is the most common sustained arrhythmia and is increasing in both prevalence and incidence as demonstrated by the Framingham Heart Study (Schnabel et al 2015). In atrial fibrillation, the atrial chambers of the

heart do not function correctly as a result of abnormal electrical signalling (Falk 2001). Atrial fibrillation is characterised by rapid and irregular atrial depolarisation with a discrete lack of P waves on ECGs. As a result, the blood within the atria remains static which can promote blood clot formation and thus increase the risk of thromboembolic stroke (Copley and Hill 2016). Atrial fibrillation can cause detrimental symptoms, impair functional status and reduce the quality of life (Gutierrez and Blanchard 2011; Menezes et al 2013).

With rare exceptions, atrial fibrillation is generally not life-threatening, but it can have considerable effects on quality of life and can cause considerable distress for some patients. Atrial fibrillation is a major risk factor for stroke, and the incidence of stroke remains high in patients with atrial fibrillation with or without valvular heart disease.

Risk Factors and Risk Groups:

Atrial fibrillation is the most common heart rhythm disorder worldwide (Chugh et al 2014). Between 1990 and 2010, there was a modest increase in prevalence and a major increase in incidence of atrial fibrillation (Chugh et al 2014). In 2010, the prevalence rates per 100,000 persons were 596.2 (95% uncertainty intervals: 558.4 to 636.7) in men (5% increase since 1990) and 373.1 (95% uncertainty intervals: 347.9 to 402.2) in women (4% increase since 1990). Atrial fibrillation incidence per 100,000 persons was 77.5 (95% uncertainty intervals: 65.2 to 95.4) in men (28% increase from 1990) and 59.5 (95% uncertainty intervals: 49.9 to 74.9) in women (35% increase from 1990) (Chugh et al 2014).

Atrial fibrillation is more common in men than women. There are also indications that individuals of white European descent have a higher risk of atrial fibrillation compared with individuals of other races (Chugh et al 2014). The prevalence rate of atrial fibrillation/flutter increases with advancing age, such that the mean annual change was 4.3% among patients aged 66 to 69 years and 5.4% among patients aged 90 years or older in the period 1993 to 2007 (Piccini et al 2012). Atrial fibrillation is present in 0.12% to 0.16% of subjects younger than 49 years, 3.7% to 4.2% of those aged 60 to 70 years, and 10% to 17% of those aged 80 years or older (Zoni-Berisso et al 2014). The rate of atrial fibrillation among those in the general US population aged 75 years or older is estimated to be 7.3% to over 10% (Go et al 2001). Of the 1550 patients in the updated Zanubrutinib Monotherapy group, 635 of 1027 (61.8%) male patients and 315 of 523 (60.2%) female patients were aged ≥ 65 years.

A study in CLL reported that a prior history of atrial fibrillation was present at CLL diagnosis in 148 (6.1%) patients. Among the 2292 patients without history of atrial fibrillation, 139 (6.1%) developed incident atrial fibrillation during follow-up (incidence approximately 1%/year). Older age ($p < 0.0001$), male sex ($p = 0.01$), valvular heart disease ($p = 0.001$), and hypertension ($p = 0.04$) were associated with risk of incident atrial fibrillation on multivariate analysis (Shanafelt et al 2017).

As of 2017, genetic studies have reported 17 independent signals for atrial fibrillation at 14 genomic regions (Staerk et al 2017). It has been established that advanced age, male sex, and European ancestry are prominent atrial fibrillation risk factors. Other modifiable risk factors that predispose individuals to atrial fibrillation include sedentary lifestyle, smoking, obesity, diabetes mellitus, obstructive sleep apnoea, cardiac conditions, hypertension, and hyperlipidaemia. Each factor has been shown to induce structural and electric remodelling of the atria. Both heart failure

and myocardial infarction increase the risk of atrial fibrillation and vice versa, creating a feed-forward loop that increases mortality (Staerk et al 2017).

Preventability:

The zanubrutinib SmPC states that atrial fibrillation and atrial flutter have occurred in patients treated with zanubrutinib, particularly in patients with cardiac risk factors, hypertension, acute infections, and the elderly (≥ 65 years). Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate. The incidence of atrial fibrillation was comparable among patients with different Eastern Cooperative Oncology Group (ECOG) Performance Status.

Impact on the Benefit-Risk Balance of the Product:

Events of atrial fibrillation and flutter have been uncommonly reported in patients receiving treatment with zanubrutinib. Overall, the benefit-risk balance is positive for the product considering the seriousness of the underlying disease being treated and the efficacy for patients treated with zanubrutinib.

Public Health Impact:

Atrial fibrillation/flutter is a commonly encountered supraventricular tachycardia, which is associated with aging and CVD (including hypertension). Its presence is associated with an increased risk of thromboembolic stroke and may be exacerbated by concurrent acute illness (eg, infection). Atrial fibrillation and flutter are rarely life-threatening unless complicated by acute thromboembolic events (eg, ischaemic stroke).

Important Potential Risks:

Second Primary Malignancies (Other Than Non-Melanoma Skin Cancer):

Potential Mechanisms:

BTK expression is restricted to cell lineages of the hematopoietic system (Pal Singh et al 2018; Weber et al 2017). There are no data confirming a strong link between BTK inhibition and the development of or suppression of malignancy beyond the well understood pathways associated with B-cell malignancies. Cases of malignancy have been observed in patients with X-linked agammaglobulinaemia; however, latency is in decades, although still occurring earlier than anticipated in the general population, and the overall frequency of malignancies is relatively low (Lougaris et al 2020).

Evidence Source(s) and Strength of Evidence:

Zanubrutinib was not genotoxic in studies evaluating gene mutations in bacteria (Ames assay), was not clastogenic in an in vivo bone marrow erythrocyte micronucleus assay in rats, nor was it clastogenic in a chromosome aberration assay in Chinese hamster ovary cells. No malignancy or premalignancy was identified in rat repeated-dose studies for 26 weeks and in dog repeated-dose studies for 39 weeks. No carcinogenicity studies were conducted.

Zanubrutinib has a favourable PK profile with short half-life and shows a lack of accumulation in the skin or other tissues in absorption, distribution, metabolism, and excretion studies with ^{14}C-zanubrutinib. In addition, ^{14}C-zanubrutinib-related material was not extensively associated

with melanin in rats. In summary, preclinical data do not describe any risk that zanubrutinib may be carcinogenic.

Second primary malignancies (other than non-melanoma skin cancer) have been reported in patients participating in ongoing and completed clinical studies of zanubrutinib.

Characterisation of the Risk - Data:

Second primary malignancies (other than non-melanoma skin cancer) have been reported in patients participating in ongoing and completed clinical studies. Cases below have been included regardless of time to onset or past medical history.

In the All Zanubrutinib Monotherapy group, 127 (8.2%) patients reported second primary malignancies (other than non-melanoma skin cancer). The most frequently reported events were prostate cancer (1.2% of patients) and malignant melanoma (0.8% of patients); all other events were reported in ≤ 0.5% of patients. Refer to Table Part II: Module SVII-7 below.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, 8 patients (5.6%) reported second primary malignancies (other than non-melanoma skin cancer). Myelodysplastic syndrome was reported in 2 (1.4%) patients) and no other malignancy was reported by more than a single patient. Refer to Table Part II: Module SVII-12 below.

Table Part II: Module SVII-10: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI category Preferred term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Second primary malignancies (other than nonmelanoma skin cancer)	8 (7.9)	23 (9.2)	1 (3.1)	3 (3.5)	4 (3.4)	4 (3.3)	4 (5.9)	8 (9.1)	9 (9.7)	34 (8.7)	21 (6.5)	45 (8.6)	81 (8.6)	127 (8.2)
Prostate cancer	0 (0.0)	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	2 (2.3)	2 (2.2)	5 (1.3)	2 (0.6)	5 (1.0)	10 (1.1)	18 (1.2)
Malignant melanoma	1 (1.0)	1 (0.4)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	1 (0.3)	4 (0.8)	9 (1.0)	13 (0.8)
Lung adenocarcinoma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	1 (0.3)	2 (0.4)	6 (0.6)	7 (0.5)
Breast cancer	1 (1.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.2)	3 (0.3)	5 (0.3)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.4)	2 (0.2)	4 (0.3)
Lung neoplasm malignant	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.4)	3 (0.3)	4 (0.3)
Acute myeloid leukaemia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	2 (2.3)	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Adenocarcinoma gastric	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	3 (0.2)
Bladder cancer	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.2)
Bladder transitional cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	2 (0.4)	3 (0.3)	3 (0.2)

Table Part II: Module SVII-10: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

AESI category Preferred term	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Clear cell renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)	1 (0.2)	3 (0.3)	3 (0.2)
Rectal adenocarcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.2)	3 (0.3)	3 (0.2)
Squamous cell carcinoma of lung	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	3 (0.2)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Chronic myeloid leukaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	2 (0.1)
Endometrial adenocarcinoma	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Intraductal proliferative breast lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Invasive ductal breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Lung cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Malignant melanoma in situ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	2 (0.1)

Table Part II: Module SVII-10: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI category Preferred term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Myelodysplastic syndrome	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Neuroendocrine carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Neuroendocrine tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Rectal cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.4)	2 (0.2)	2 (0.1)
Renal cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Squamous cell carcinoma of the parotid gland	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	2 (0.1)
Anal cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Anal squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Anaplastic large cell lymphoma T- and null-cell types	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bladder cancer recurrent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Choroid melanoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)

Table Part II: Module SVII-10: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI category Preferred term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Chronic myelomonocytic leukaemia	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Colon cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Follicular lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Glioblastoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Hepatocellular carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Laryngeal cancer	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Lentigo maligna	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Malignant melanoma stage I	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Malignant melanoma stage II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Metastatic squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Myeloproliferative neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

Table Part II: Module SVII-10: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI category Preferred term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Neoplasm prostate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Neuroendocrine carcinoma metastatic	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Neuroendocrine carcinoma of prostate	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Nodular melanoma	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Non-small cell lung cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Ocular surface squamous neoplasia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Oesophageal squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ovarian cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Papillary thyroid cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table Part II: Module SVII-10: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI category Preferred term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Peritoneal sarcoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Perivascular epithelioid cell tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Pituitary tumour	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Plasma cell myeloma	1 (1.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pleomorphic malignant fibrous histiocytoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Polycythaemia vera	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Sarcomatoid carcinoma of the lung	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Small cell lung cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Small cell lung cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)

Table Part II: Module SVII-10: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
AESI category Preferred term	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Spindle cell sarcoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Squamous cell carcinoma of the oral cavity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Transitional cell cancer of the renal pelvis and ureter	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Transitional cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAEG

Abbreviations: AESI, adverse events of special interest; BID, twice daily; CLL, chronic lymphocytic leukaemia; MCL, mantle cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; MZL, marginal zone lymphoma; QD, once daily; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinaemia.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.

Notes: MedDRA Version 24.0.

Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.

Events of disease under study and transformation of disease under study were excluded.

Table Part II: Module SVII-11: Second Primary Malignancies (Other Than Non-melanoma Skin Cancer) in Zanubrutinib FL Studies (Safety Analysis Set)

AESI Category Preferred Term	Combination Therapy: Zanubrutinib + Obinutuzumab		Monotherapy Zanubrutinib
	BGB-3111-212 (N = 143) n (%)	BGB-3111-GA101-101 (N = 36) n (%)	BGB-3111-1002 + AU003 (N = 59) n (%)
Second primary malignancies (other than non-melanoma skin cancer)	**8 (5.6)**	**2 (5.6)**	**2 (3.4)**
Myelodysplastic syndrome	2 (1.4)	0 (0.0)	0 (0.0)
Acute myeloid leukaemia	1 (0.7)	0 (0.0)	0 (0.0)
Adenocarcinoma pancreas	1 (0.7)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.7)	0 (0.0)	0 (0.0)
Breast cancer metastatic	0 (0.0)	1 (2.8)	0 (0.0)
Invasive ductal breast carcinoma	1 (0.7)	0 (0.0)	0 (0.0)
Medullary thyroid cancer	0 (0.0)	1 (2.8)	0 (0.0)
Metastatic neoplasm	1 (0.7)	0 (0.0)	0 (0.0)
Thyroid cancer	0 (0.0)	1 (2.8)	0 (0.0)
Transitional cell carcinoma	1 (0.7)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	1 (1.7)
Sarcomatoid carcinoma of the lung	0 (0.0)	0 (0.0)	1 (1.7)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAEG.
Abbreviations: FL, follicular lymphoma.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or obinutuzumab. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.
Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.
MedDRA Version: 24.0.
Events of disease under study and transformation of disease under study were excluded

A global safety database search was performed up to 13 May 2023 using the following MedDRA terms:

a. SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps).
b. Exclude: High Level Group Terms with ‘benign’ in their wording, Skin Neoplasms Malignant and Unspecified (excl. Melanoma), Neoplasm related morbidities, and Metastases.

This search revealed 345 events reported in 324 cases, of which 331 were serious events. The most frequently occurring serious events (excluding non-melanoma skin cancers) were malignant neoplasm progression and prostate cancer (19 each), squamous cell carcinoma (17), neoplasm malignant (14), neoplasm progression (13), lung neoplasm malignant (12), lymphoma and

malignant melanoma (10 each), lung adenocarcinoma (9), and acute myeloid leukaemia, breast cancer and myelodysplastic syndrome (7 each).

MedDRA Terms Used in Clinical Database Search:

From all cases reported in the SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps), benign tumours events were removed if the reported PT is included in any High Level Grouped Terms containing 'benign' in their wording. Similarly, events related to morbidities or metastasis were excluded using the High Level Grouped Terms of Neoplasm related morbidities and Metastases. Medical review was conducted to exclude events of disease under study and transformation of disease under study. Non-melanoma skin cancer events were excluded if the reported PT is included in the High Level Term of Skin neoplasms malignant and unspecified.

Characterisation of the Risk - Discussion:

The risk of developing a second malignancy in patients with B-cell malignancies treated with zanubrutinib has been shown to reduce with duration of exposure. In addition, when compared with an earlier, smaller dataset (n = 779) for zanubrutinib exposure in clinical studies, the EAIRs remain stable (0.61 per 100 person-months versus 0.57 per 100 person-months). This is converse to the pattern expected in the presence of a carcinogen and despite the fact that the numbers of patients >65 years and >75 years (who are at greatest bystander malignancy risk) has increased (from 51.9% to 61.3% and from 19.5% to 21.6%, respectively) and the number of patients treated for more than 3 years (and hence more likely to manifest a drug induced cancer) has increased (from 21.6% to 30.2%). The malignancies observed were consistent with the pattern and frequency expected in the population treated based on age, gender, and geographical location.

Risk Factors and Risk Groups:

The risk of developing a second malignancy depends on several factors, including type of primary cancer, age at diagnosis, sex, types of therapy given, environmental exposures, genetic predisposition, and health decisions. Radiation has long been associated with the development of primary cancers and, when used as treatment, imparts a risk for the development of a second cancer. Risk factors that may increase the risk of second primary malignancies in patients with haematological malignancies include immune dysregulation, the immunosuppressive effects of chemotherapeutic agents and radiation therapy. In patients with CLL, proposed risk factors for second primary malignancy include environmental and occupational exposures, genetic risk factors, immune dysfunction inherent to the disease itself, and deoxyribonucleic acid damage from prior chemotherapy (Bond et al 2020), which are independent of zanubrutinib exposure.

Patients with B-cell malignancies may have a potential for increased development of second malignancy associated with the inherently impaired immune function caused by the disease. Standardised incidence ratios (SIRs) for the development of second malignancies in B-cell malignancy patients reported in the literature range from 1.19 (95% CI: 1.13 to 1.25) to 2.20 (95% CI: 1.93 to 2.51) (Sacchi et al 2008, Morton et al 2010, Kumar et al. 2019, Tsimberidou et al 2009). In an analysis of the SEER database from 1973 to 2015, 6,487 out of 38,754 patients (16.7%) with CLL developed second primary malignancies (excluding non-melanoma skin cancer) during an average follow-up of 7.0 years, with a 20% increased risk of developing any malignancies compared to the US general population (SIR=1.20, 95% CI: 1.17 to 1.23) (Kumar

et al 2019). In a retrospective review of electronic medical records from The Ohio State University Comprehensive Cancer Center, the risk of second primary malignancies from a large cohort of patients with CLL who were previously treated with a BTK inhibitor (545 ibrutinib-treated patients and 146 acalabrutinib-treated patients) between 2009 and 2017, was 2.2-fold (95% CI: 1.7 to 2.9) higher than that expected in the general population (Bond et al 2020). On multivariable analysis, smoking was associated with increased second primary malignancy risk (HR 2.8 [95% CI: 1.6 to 4.8]) and higher baseline CD8 count was associated with lower second primary malignancy risk (HR 0.9 for 2-fold increase [95% CI: 0.8 to 0.9]). Together, these data indicate that CLL patients treated with BTK inhibitors remain at increased risk for second primary malignancies.

A geographic difference for the risk of developing a second primary malignancy has also been observed in patients with B-cell malignancy in different regions/countries. The SIR of second primary malignancy in European patients varies from 1.71 to 1.94 (Sacchi et al 2008), similar to that in the US patients from 1.19 to 2.20 (Tsimberidou et al 2009, Morton et al 2010, Kumar et al 2019), but lower than that observed for Australian patients (SIR = 5.44) (Shen et al 2022).

Preventability:

Identifying patients who are at greater risk of multiple neoplasms can help medical providers to better monitor for second primary malignancies, as well as advise patients on ways of reducing risks. Many groups of high-risk individuals are already known, and certain agents and regimens increase the risk of second primary malignancies. Specifically for the prevention of melanoma, patients should be advised to seek regular medical examination of sun-exposed areas (particularly if resident in geographic areas where exposure to UV radiation is high), avoid sun exposure, and use protective clothing and sunscreen/sun block with high sun-protection factors.

Impact on the Benefit-Risk Balance of the Product:

This safety concern is not considered to have a significant impact on the otherwise favourable benefit-risk assessment.

Public Health Impact:

As presented at the American Society of Hematology 2018 meeting, 46/598 (7.7%) patients in the Greek Myeloma Study Group database who were treated for WM (equating to 1 case per 100 patients per year) developed a second primary malignancy, the most common of which were cancers of the prostate (18%), stomach, colon, lung, CNS, and acute myeloid leukaemia/myelodysplastic syndrome (6% each). The cumulative incidence of second primary malignancy was 3.6% at 5 years and 6.6% at 10 years (Gavriatopoulou et al 2018). In a recent retrospective review of electronic medical records by Bond et al (2020), during the follow-up period (median 44 months; range 0.7 to 95.7 months) after starting BTK inhibitor treatment, 64 (9%) patients were diagnosed with second primary malignancies (other than non-melanoma skin cancer) with a 3-year cumulative incidence rate of 7.1% (95% CI: 5.3% to 9.3%). Given the low number of reports of second primary malignancies (other than non-melanoma skin cancers) with zanubrutinib treatment, the risk to public health is considered to be low.

Second Primary Non-Melanoma Skin Cancer:

Potential Mechanisms:

BTK expression is restricted to cell lineages of the hematopoietic system (Pal Singh et al 2018; Weber et al 2017). There are no substantive data showing a mechanistic link between BTK inhibition and the pathogenesis of non-hematologic malignancies, especially non-melanoma skin cancer. The off-target kinases inhibited by zanubrutinib are not clearly associated with non-melanoma skin cancer induction. Zanubrutinib is not mutagenic or genotoxic, does not accumulate in the skin and is not associated with melanin. The risk of phototoxicity was low in clinical studies. No other mechanism by which zanubrutinib might induce non-melanoma skin cancer has been identified.

Evidence Source(s) and Strength of Evidence:

Zanubrutinib was not genotoxic in studies evaluating gene mutations in bacteria (Ames assay), was not clastogenic in an in vivo bone marrow erythrocyte micronucleus assay in rats, nor was it clastogenic in a chromosome aberration assay in Chinese hamster ovary cells. In vivo animal studies did not identify premalignant lesions at any site including the skin. ^{14}C-zanubrutinib demonstrated no accumulation in skin and zanubrutinib was not associated with melanocytes. The risk of phototoxicity was low in clinical studies. No malignancy was identified in rat repeated-dose studies for 26 weeks and in dog repeated-dose studies for 39 weeks. No carcinogenicity studies were conducted.

The most frequent second primary malignancy reported in zanubrutinib clinical studies was skin cancer. Skin cancers were observed predominantly in patients at high risk of developing skin cancer (white, elderly males from Australia, which has a high known prevalence of skin cancers). Second primary skin cancers were rarely observed in patients of Asian origin or in any non-white patient, confirming that race and geographic location are the main drivers of non-melanoma skin cancer generation.

Characterisation of the Risk – Data:

Second primary non-melanoma skin cancer has been reported in patients participating in ongoing and completed clinical studies. Cases below have been included regardless of time to onset or past medical history.

In the All Zanubrutinib Monotherapy group, 138 (8.9%) patients reported second primary non-melanoma skin cancer. Consistent with prior experience, the most frequently reported events included basal cell carcinoma (5.9%) and squamous cell carcinoma of skin (3.7%); all other events were reported in < 1% of patients. Refer to Table Part II: Module SVII-8 below.

In the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group, second primary non-melanoma skin cancer was reported in 5 (3.5%) patients. Reported events were all basal cell carcinoma; no other non-melanoma skin cancer was reported. Refer to Table Part II: Module SVII-13 below.

Table Part II: Module SVII-12: Second Primary Non-melanoma Skin Cancer in Zanubrutinib Monotherapy Clinical Studies (Safety Analysis Set)

AESI Category Preferred Term	Zanubrutinib													
	WM		R/R MCL				MZL			CLL				Summary
	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 249) n (%)	AU003 (N = 32) n (%)	206 (N = 86) n (%)	AU003 + 206 Total (N = 118) n (%)	All MCL (N = 120) n (%)	BGB-3111 -214 (N = 68) n (%)	214 + AU003 MZL (N = 88) n (%)	All MZL (N = 93) n (%)	304 (N = 391) n (%)	305 (N = 324) n (%)	All R/R CLL/ SLL (N = 525) n (%)	All CLL/ SLL (N = 938) n (%)	All Zanu (N = 1550) n (%)
Second primary non-melanoma skin cancer	12 (11.9)	35 (14.1)	7 (21.9)	0 (0.0)	7 (5.9)	7 (5.8)	2 (2.9)	2 (2.3)	2 (2.2)	40 (10.2)	20 (6.2)	37 (7.0)	84 (9.0)	138 (8.9)
Basal cell carcinoma	6 (5.9)	22 (8.8)	5 (15.6)	0 (0.0)	5 (4.2)	5 (4.2)	2 (2.9)	2 (2.3)	2 (2.2)	32 (8.2)	11 (3.4)	20 (3.8)	55 (5.9)	91 (5.9)
Squamous cell carcinoma of skin	3 (3.0)	13 (5.2)	2 (6.3)	0 (0.0)	2 (1.7)	2 (1.7)	1 (1.5)	1 (1.1)	1 (1.1)	12 (3.1)	12 (3.7)	20 (3.8)	36 (3.8)	58 (3.7)
Bowen's disease	2 (2.0)	6 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	4 (1.2)	6 (1.1)	8 (0.9)	14 (0.9)
Skin cancer	3 (3.0)	6 (2.4)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	1 (0.2)	4 (0.4)	11 (0.7)
External ear neoplasm malignant	1 (1.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	5 (0.3)
Squamous cell carcinoma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.2)
Skin squamous cell carcinoma recurrent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Lip squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Queyrat erythroplasia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin neoplasm bleeding	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Squamous cell carcinoma of head and neck	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAEG

Abbreviations: AESI, adverse events of special interest; BID, twice daily; CLL, chronic lymphocytic leukaemia; MCL, mantle cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; MZL, marginal zone lymphoma; QD, once daily; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinaemia.

N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.

Notes: MedDRA Version 24.0.

Patients with multiple events within an AESI category or multiple preferred terms within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the All Zanubrutinib column.

Events of disease under study and transformation of disease under study were excluded.

Table Part II: Module SVII-13: Second Primary Non-melanoma Skin Cancer in Zanubrutinib FL Studies (Safety Analysis Set)

	Combination Therapy: Zanubrutinib + Obinutuzumab		Monotherapy Zanubrutinib
AESI Category Preferred Term	BGB-3111-212 (N = 143) n = (%)	BGB-3111-GA101-101 (N = 36) n = (%)	BGB-3111-1002 + AU003 (N = 59) n = (%)
Second Primary Non-Melanoma Skin Cancer	5 (3.5)	4 (11.1)	1 (1.7)
Basal cell carcinoma	5 (3.5)	3 (8.3)	0 (0.0)
Squamous cell carcinoma of skin	0 (0.0)	2 (5.6)	1 (1.7)
Bowen's disease	0 (0.0)	1 (2.8)	0 (0.0)

Data cutoff: 25OCT2022(212), 02SEP2020(GA101), 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 04MAY2022(214), 21JUN2022(302), 17OCT2022(LTE1), 08AUG2022(305), 07MAR2022(304); Data snapshot: 16DEC2022(212), 27NOV2020(GA101), 15OCT2020(1002), 03MAY2021(AU-003), 16OCT2020(205), 10NOV2020(206), 04FEB2021(210), 31MAY2022(214), 29JUL2022(302), 13DEC2022(LTE1), 27SEP2022(305), 06MAY2022(304); Data Source: ADSL, ADAEG.
Abbreviations: FL, follicular lymphoma.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD or obinutuzumab. All doses of comparator drugs are excluded. Percentages are based on N, unless otherwise specified.
Patients with multiple events within an AESI category or multiple events within a preferred term are counted only once, respectively. Events are sorted by order of AESI category and then by decreasing frequency of preferred term within each AESI category in the all zanubrutinib column.
MedDRA Version: 24.0.
Events of disease under study and transformation of disease under study were excluded

A global safety database search for MedDRA High Level Term of Skin Neoplasms Malignant and Unspecified (excl. Melanoma) up to 13 May 2023, revealed 86 events reported in 83 cases, of which 85 events were serious. The most frequently occurring serious events of non-melanoma skin cancer were skin cancer (31), basal cell carcinoma (26), squamous cell carcinoma of skin (20), and Bowen's disease (4).

MedDRA Terms Used in Clinical Database Search:

High Level Term: Skin neoplasms malignant and unspecified.

Characterisation of the Risk - Discussion:

Skin cancer is the most common type of cancer in light skinned populations around the world (Breitbart et al 2006), with an estimated 2 to 3 million cases of non-melanoma skin cancers occurring worldwide each year (Foster et al 2008). As presented at the American Society of Hematology 2018 meeting, 46/598 (7.7%) patients in the Greek Myeloma Study Group database who were treated for WM (equating to 1 case per 100 patients per year) developed a second primary malignancy, of which 3% were non melanoma skin cancers (Gavriatopoulou et al 2018). In a recent retrospective review of electronic medical records by Bond et al (2020), during the follow-up period (median 44 months; range 0.7 to 95.7 months) after starting BTK inhibitor treatment, 137 (20%) patients were diagnosed with non-melanoma skin cancer with a 3 year cumulative incidence rate of 15.4% (95% CI: 12.7% to 18.3%).

Risk Factors and Risk Groups:

An individual's risk of developing skin cancer depends on both constitutional and environmental factors. The constitutional risk factors of skin cancer include family history, red hair colour, melanocytic nevi, and sun exposure sensitivity (Gandini et al 2005), whereas solar UV radiation is a well-established environmental risk factor (Gandini et al 2005; Armstrong et al 1997). Sunlight can also cause immunosuppression (Onajin and Brewer 2012; Brin et al 2014). Skin cancer is the most common type of cancer in light-skinned populations around the world (Breitbart et al 2006), with skin cancers most frequent in Australia/New Zealand with an age-adjusted standardised rate of 295.9 in 100,000, followed by Northern America (113.7), and Western Europe (52.9). Basal cell carcinoma, the most common malignancy in white people accounting for 80% to 85% of all non-melanoma skin cancers, has a higher occurrence in men than women, consistent with greater sun exposure (often occupational) (Diepgen and Mahler 2002). Albert et al (1990) describe incidence rates 16-fold greater in Caucasians than African Americans and 10-fold greater than that observed in Hispanics.

Preventability:

Early diagnosis often leads to successful treatment of most non-melanoma skin cancers. Identifying patients who are at greater risk of multiple neoplasms can help medical providers to better monitor for second neoplasms, as well as advise patients on ways of reducing risks. Cutaneous carcinomas are known to be related to exposure to UV radiation. As noted above, the incidence of skin cancers was highest in patients from Australia/New Zealand, areas that report the highest incidence of skin cancer worldwide; and patients in North America, compared with the European Union and Asia. Patients should be advised to seek regular medical examination of sun-exposed areas (particularly if resident in geographic areas where exposure to UV radiation is high), avoid sun exposure, and use protective clothing and sunscreen/sun block with high sun-protection factors.

Impact on the Benefit-Risk Balance of the Product:

This safety concern is not considered to have a significant impact on the otherwise favourable benefit-risk assessment.

Public Health Impact:

Given the low numbers of reports of second primary non-melanoma skin cancer with zanubrutinib treatment, the high level of awareness of the risk of UV-associated skin malignancies, and the availability of protective measures, the risk to public health is considered to be low.

Drug-Drug Interaction With CYP3A Inducers:

Potential Mechanisms:

Phenotyping studies using human liver microsomes with selective CYP inhibitors, recombinant CYP enzymes, and uridine 5'-diphospho-glucuronosyltransferase enzymes suggested that CYP3A was the major CYP isoform responsible for zanubrutinib metabolism. The drug-drug interaction (DDI) potential for zanubrutinib as a victim or perpetrator of P450 enzymes was evaluated in P450 and uridine 5'-diphospho-glucuronosyltransferase phenotyping, human hepatocyte P450 induction, and reversible and time-dependent P450 inhibition studies.

Zanubrutinib is metabolised primarily by CYP3A, and its PK can be affected by strong and moderate CYP3A inducers.

Evidence Source(s) and Strength of Evidence:

CYP3A inducers have been shown to significantly modulate drug exposure of other BTK inhibitors, including ibrutinib.

Characterisation of the Risk - Data:

CYP3A inducers: The DDI potential of zanubrutinib coadministered with a strong CYP3A inducer was assessed in Study BGB-3111-104, an open-label, parallel-group, fixed-sequence study in healthy male and female subjects. Part A of the study investigated the effect of CYP3A induction by steady-state rifampin on the single-dose PK of zanubrutinib.

Statistical analysis demonstrated that systemic exposure to zanubrutinib was significantly lower after coadministration of 320 mg zanubrutinib with 600 mg rifampin than after administration of 320 mg zanubrutinib alone, with geometric mean AUC approximately 93% lower and C_{max} approximately 92% lower. This represents a decreased exposure of 13.5-fold for $AUC_{0-\infty}$, and 12.6-fold for C_{max}.

The DDI potential of zanubrutinib coadministered with a moderate CYP3A inducer was assessed in Study BGB-3111-112, an open-label, fixed-sequence study in healthy male subjects. It investigated the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib.

Statistical analysis demonstrated that systemic exposure to zanubrutinib was moderately lower after coadministration of 320 mg zanubrutinib with 300 mg rifabutin than after administration of 320 mg zanubrutinib alone, with geometric mean AUC approximately 44% lower and C_{max} approximately 48% lower. This represents a decreased exposure of 1.8-fold for $AUC_{0-\infty}$, and 1.9-fold for C_{max}.

CYP3A inhibitors: An integrated assessment of safety data from 7 single agent zanubrutinib studies was undertaken in patients with B-cell malignancies receiving zanubrutinib before, during, and after concomitant treatment with moderate or strong CYP3A inhibitors. The analysis included 138 patients to whom zanubrutinib and strong and moderate CYP3A inhibitors were coadministered for a median duration of approximately 2 months. During coadministration, the majority of the patients (89.1%) received a full dose of 320 mg zanubrutinib daily. The number of patients experiencing a treatment-emergent adverse event and the EAIRs of adverse events of special interest (adverse events known to be associated with the class of BTK inhibitors) did not show any trend for safety concerns across the 3 study periods (Prior to Coadministration, During Coadministration, and After Coadministration Periods). The patterns of adverse events of special interest in this analysis appeared to be generally consistent with the known safety profile of zanubrutinib in clinical studies. Treatment-emergent adverse events leading to death, treatment discontinuation, or dose reduction were generally consistent with the known safety profile of zanubrutinib.

In Study BGB-3111-113, the magnitude of the DDI between zanubrutinib and moderate (diltiazem, fluconazole) and strong (clarithromycin, voriconazole) CYP3A inhibitors was further evaluated in patients with B cell malignancies. Zanubrutinib steady-state exposures upon concurrent administration with moderate and strong CYP3A inhibitors (under the 2-fold or

4-fold dose reduction per zanubrutinib prescribing information) were lower than exposures at the 320 mg once-a-day dose of zanubrutinib. Overall, the safety findings were consistent with the safety profile of zanubrutinib and no changes to the dosing recommendations for use of zanubrutinib with moderate or strong CYP3A inhibitors was considered necessary.

Based upon this extensive CYP3A inhibitor data, the risk of DDI with CYP3A inhibitors is well characterised and therefore not considered to be an important risk with zanubrutinib.

There were no adverse events reported in the All Zanubrutinib Monotherapy population or in the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group that were clearly attributed to a potential DDI. There were 4 serious adverse events related to potential DDIs reported in the global safety database up to 13 May 2023.

MedDRA Terms Used in Clinical Database Search:

Drug interaction (PT), Labelled drug-drug interaction medication error (PT), Potentiating drug interaction (PT)

Characterisation of the Risk - Discussion:

There is DDI potential between zanubrutinib and other concomitant medications, particularly those with strong CYP3A inhibitors and inducers. The DDI potential of zanubrutinib was assessed in 3 dedicated clinical DDI studies: BGB-3111-104, BGB-3111-108 and BGB-3111-113. In addition, a physiologically-based PK model was developed to predict the effect of moderate and mild CYP3A inhibitors and CYP3A inducers on the PK of zanubrutinib.

Risk Factors and Risk Groups:

Zanubrutinib is metabolised primarily by CYP3A enzymes and a clinical DDI study and physiologically-based PK simulations show that strong/moderate CYP3A inhibitors or inducers can modulate exposure of zanubrutinib. Coadministration of the strong CYP3A inhibitor itraconazole has been shown to increase exposure of zanubrutinib. Coadministration of zanubrutinib with the strong CYP3A inducer rifampin decreased exposure of zanubrutinib in healthy volunteers.

Preventability:

Based on the results of the DDI studies and understanding of exposure-response relationships, the following dose modifications are recommended for zanubrutinib:

Table Part II: Module SVII-14: Recommended Dose Modifications When Coadministered With Other Medicinal Products

CYP3A	**Coadministered Medicinal Products**	**Recommended Dose** (starting dose: 320 mg once daily or 160 mg twice daily)
Inhibition	Strong CYP3A inhibitor (eg, posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily

Table Part II: Module SVII-14: Recommended Dose Modifications When Coadministered With Other Medicinal Products

CYP3A	Coadministered Medicinal Products	Recommended Dose (starting dose: 320 mg once daily or 160 mg twice daily)
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort).	Avoid concomitant use; Consider alternative agents with less CYP3A induction
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	

Abbreviations: CYP3A, cytochrome P450 family 3 subfamily A.

Impact on the Benefit-Risk Balance of the Product:

The impact on benefit-risk is considered to be low, given the above dose-modification criteria.

Public Health Impact:

Not applicable.

Teratogenicity:

Potential Mechanisms:

The potential mechanism for teratogenicity noted in the rat study was not clear. Our animal data demonstrated a low incidence rate in heart abnormalities (0.3% to 1.5%) at the dose of ≥ 5 times the human therapeutic dose based on systemic exposure. No other teratogenicity in rats or any teratogenicity in rabbits was noted in the embryo-foetal toxicity studies.

Evidence Source(s) and Strength of Evidence:

Embryo-foetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts at the incidence of 0.3% to 1.5%) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the systemic exposure (AUC) in patients receiving the recommended dose. Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in postimplantation loss at the highest dose. The dose of 150 mg/kg is approximately 25 times the systemic exposure (AUC) in patients receiving the recommended dose and was associated with maternal toxicity. No teratogenicity was noted in this study. In a pre- and postnatal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The main findings for offspring included adverse ocular lesions at all dose levels (eg, cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the systemic exposure (AUC) in patients receiving the recommended dose.

Characterisation of the Risk - Data:

In the All Zanubrutinib Monotherapy group in the clinical database, abortion induced and pulmonary air leakage occurred in 1 (0.1%) patient each. The event of pulmonary air leakage occurred in a [redacted] patient who experienced an air leak following a lung biopsy. No events relating to teratogenicity were reported in the Study BGB-3111-212 (Zanubrutinib + Obinutuzumab) group.

A global safety database search was performed up to 13 May 2023 using the following MedDRA terms:

Congenital, familial and genetic disorders (SMQ), Foetal disorders (SMQ) narrow, Neonatal disorders (SMQ) narrow, Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ) narrow, Termination of pregnancy and risk of abortion (SMQ).

This search revealed 1 serious adverse event with the PT 'abortion induced'. The 38-year-old patient diagnosed with stage IV NHL became pregnant (serum pregnancy test and urine pregnancy test) while taking zanubrutinib. Dosing with zanubrutinib took place between 08 September 2017 and 18 April 2018. The stated method of birth control was condom use. Ultrasonography (19 April 2018) confirmed early intrauterine pregnancy with live foetus (equivalent to 6 weeks) and revealed foetal abnormality. While the precise duration of the pregnancy was not reported, available information suggests that exposure to zanubrutinib occurred throughout the first trimester. The event 'abortion induced' was reported as completed on 20 April 2018. No other suspect medications were reported.

MedDRA Terms Used in Clinical Database Search:

Congenital, familial and genetic disorders SMQ, Foetal disorders SMQ (narrow), Neonatal disorders SMQ (narrow), Pregnancy, labour and delivery complications and risk factors (excl. abortions and stillbirth) SMQ (narrow), and Termination of pregnancy and risk of abortion SMQ.

Characterisation of the Risk - Discussion:

Based on findings in animal studies, zanubrutinib may cause harm to the unborn child. The 1 case of pregnancy while taking zanubrutinib is described above.

Risk Factors and Risk Groups:

Female subjects of childbearing potential.

Preventability:

Any potential risk relating to the development of foetus/unborn child is considered to be preventable by the provision of appropriate information by the prescribing physician to the patient. Pregnancy testing is recommended for women of reproductive potential prior to initiating therapy, and women of childbearing potential must use highly effective contraceptive measures while taking zanubrutinib and for up to 1 month after stopping treatment.

Impact on the Benefit-Risk Balance of the Product:

The impact on benefit-risk is considered to be low.

Public Health Impact:

Any impact on public health is considered to be low.

SVII.3.2 Presentation of the Missing Information

Missing information: Safety in patients with severe hepatic impairment

Evidence source:

There are limited data on the clinical safety and efficacy of zanubrutinib when administered to patients with severe hepatic impairment. Zanubrutinib is metabolised in the liver. As mentioned in Table Part II: Module SIV-2, the results of a hepatic impairment study (BGB-3111-107) showed that zanubrutinib exposure was higher in patients with severe hepatic impairment (Child-Pugh class C) compared to matched healthy subjects and patients with mild hepatic impairment (Child-Pugh class A) (Ou et al 2020). Patients taking zanubrutinib should be monitored for adverse reactions.

Anticipated risk/consequence of the missing information:

Based on exposure data in patients with liver impairment, dose modifications are recommended in patients with severe hepatic impairment.

Missing information: Safety in patients with severe renal impairment/on dialysis

Evidence source:

There are limited data on the effect of severe renal impairment (CrCl < 30 mL/min) and dialysis on zanubrutinib PK. In the population PK study BGB-3111-CP-08, 10 patients with B-cell lymphoma had severe renal impairment and1 patient had end-stage renal disease. These patients had sparse PK data. The population PK model predicted steady-state PK exposures of zanubrutinib following 160 mg twice daily in patients with severe renal impairment and end-stage renal disease (N = 11) are comparable with those of patients with normal renal function (N = 204), given the variability of exposures. Renal excretion of unchanged zanubrutinib was very low in humans. No dosage modification is recommended in patients with mild to moderate renal impairment (CrCl ≥ 30 mL/min, estimated by Cockcroft-Gault). The SmPC states that patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis should be monitored for adverse reactions.

Anticipated risk/consequence of the missing information:

Safety monitoring is recommended for patients with severe renal impairment.

Missing information: Long-term safety (> 2 years)

Evidence source:

There are limited data on the clinical safety and efficacy of zanubrutinib when administered to patients for > 2 years. In zanubrutinib monotherapy clinical studies, 979 subjects have accrued ≥ 24 months of exposure to zanubrutinib. As data from patients with > 2 years exposure accrue, the zanubrutinib clinical development programme is expected to be able to detect adverse reactions following prolonged exposure or, otherwise, events that may have a long latency.

Population in need of further characterisation:

Patients with long-term exposure (> 2 years) exposure to zanubrutinib.

PART II: MODULE SVIII SUMMARY OF SAFETY CONCERNS

Table Part II: Module SVIII-1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Haemorrhage • Infections (including lower respiratory tract infections and hepatitis B reactivation) • Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter
Important potential risks	• Second primary malignancies (other than non-melanoma skin cancer) • Second primary non-melanoma skin cancer • Drug-drug interaction with CYP3A 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)

PART III PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Pharmacovigilance procedures and policies are established to promote optimum patient safety, product stewardship, and regulatory compliance. Routine pharmacovigilance practices are in accordance with standards set by regional and local health authorities, with global procedures being specified to meet the expectations of the authorities with the most comprehensive regulatory requirements. Routine pharmacovigilance activities are conducted for all identified and potential risks. BeiGene's approaches for conducting routine pharmacovigilance activities for zanubrutinib are summarised as follows:

- Collection, monitoring, evaluation, and reporting of individual adverse events and literature reports
- Preparation of aggregate safety reports, including Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports, Development Safety Update Reports, and equivalent safety summaries required by local health authorities
- Signal detection by monitoring frequencies and severities of adverse events and serious adverse events
- Review of 6 months Suspected Unexpected Serious Adverse Reaction line listing
- Evaluation of relevant epidemiological findings as required

Specific Adverse Reaction Follow-Up Questionnaires:

None proposed.

Other Forms of Routine Pharmacovigilance Activities:

None proposed.

III.2 Additional Pharmacovigilance Activities

Study BGB-3111-LTE1	
Short name and title	BGB-3111-LTE1 - An Open-label, Multicenter, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies
Rational and study objectives	Rationale: To evaluate the long-term safety and efficacy of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who are or were previously enrolled in a BeiGene parent study and who are still benefiting or may benefit from treatment with zanubrutinib, or who are willing to have long-term survival follow up.
	Objective: To evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who participated in a BeiGene parent study for zanubrutinib.
Safety concern addressed	Long-term safety (> 2 years)
Study design	Open-label, long-term extension study

Study BGB-3111-LTE1	
Study population	Patients with B-cell malignancies who are or were previously enrolled in a BeiGene parent study and who are still benefiting or may benefit from treatment with zanubrutinib, or who are willing to have long-term survival follow up.
Milestones	Information on the progress of the study in the PSURs until study completion Interim report submission: December 2025 Estimated study completion date: December 2026 Final report submission: planned for June 2027

III.3 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 authorization				
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-LTE1 An Open-label, Multicenter, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies Ongoing	To evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who participated in a BeiGene parent study for zanubrutinib.	Long-term safety (> 2 years)	Information on study progress in PSURs: Interim report submission: Estimated study completion date: Final report submission:	In each periodic report until study completion December 2025 December 2026 Planned June 2027

Part IV PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

Table Part IV-1: Planned and Ongoing Postauthorisation Efficacy Studies That are Conditions of the Marketing Authorisation or That are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorisation				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
BGB-3111-308[a] A Phase 3 Randomized, Open-label, Multicenter Study of Zanubrutinib (BGB-3111) Plus Anti-CD20 Antibodies Versus Lenalidomide Plus Rituximab in Patients With Relapsed/Refractory Follicular or Marginal Zone Lymphoma. Ongoing	To evaluate the efficacy of zanubrutinib in combination with anti-CD20 monoclonal antibodies compared with lenalidomide plus rituximab in patients with R/R FL or R/R MZL.	To further confirm the efficacy of zanubrutinib in patients with R/R MZL	Estimated study completion date: Final report submission:	2028 Quarter 4, 2028

Abbreviations: CD, cluster of differentiation; FL, follicular lymphoma ; MZL, marginal zone lymphoma ; R/R, relapsed or refractory.

[a] Study BGB-3111-308 has been initiated in response to a postapproval request from the European Medicines Agency in MZL, and in response to a United States postmarketing request in MZL and FL.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

As part of routine risk management activities, dose modifications are included in Section 4.2 of the zanubrutinib SmPC, as follows:

Dosage Modification for Use in Hepatic Impairment

Dose modifications are not needed in patients with mild or moderate hepatic impairment. Patients with mild or moderate hepatic impairment were treated in zanubrutinib clinical studies. The recommended dose of zanubrutinib for patients with severe hepatic impairment is 80 mg orally twice daily. The safety of zanubrutinib has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse events of zanubrutinib.

Dosage Modifications for Drug Interactions

Recommended dose modifications of zanubrutinib for drug interactions are provided below in Table Part V-1.

Table Part V-1: Recommended Dose Modifications When Coadministered with Other Medicinal Products

CYP3A	Coadministered Medicinal Product	Recommended Dose (starting dose: 320 mg once daily or 160 mg twice daily)
Inhibition	Strong CYP3A inhibitor (eg, posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort).	Avoid concomitant use; consider alternative agents with less CYP3A induction
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	

Abbreviations: CYP3A, cytochrome P450 family 3 subfamily A.

Dosage Modifications for Adverse Reactions

Recommended dose modifications of zanubrutinib for ≥ Grade 3 adverse reactions are provided in Table Part V-2 below.

Table Part V-2: Recommended Dose Modification for Adverse Reactions

Adverse Reaction	Adverse Reaction Occurrence	Dose Modification (Starting dose: 320 mg once daily or 160 mg twice daily)
≥ Grade 3 nonhaematological toxicities Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting > 10 consecutive days) Grade 4 thrombocytopenia (lasting > 10 consecutive days)	First	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
	Third	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue zanubrutinib

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

Table Part V-3 below presents the routine risk minimisation activities.

Table Part V-3: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Haemorrhage	Routine risk communication: 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 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration. Recommendations for dose modifications in the case of Grade 3 thrombocytopenia with significant bleeding. SmPC Section 4.4 Special warnings and precautions for use. Patients should be monitored for signs and symptoms of bleeding and monitor complete blood counts. Consider the risks and benefits of anticoagulant or antiplatelet therapy when coadministered with zanubrutinib. Dose modification may be necessary for Grade 3 or greater adverse reactions. Warfarin or other vitamin K antagonists should not be administered concomitantly with zanubrutinib. Consider the benefit-risk of withholding zanubrutinib for 3 to 7 days pre and post surgery depending upon the type of surgery and the risk of bleeding. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes information on the risk of bleeding and direction for patients to inform their doctor if taking medicines that increase their risk of bleeding. Package leaflet: Information for the patient Section 4: Possible side effects. Includes direction for patients to tell a doctor straight away in the case of bleeding.

Table Part V-3: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
	Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Infections (including lower respiratory tract infections and hepatitis B reactivation)	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package leaflet: Information for the patient Section 2: Warning and precautions Package leaflet: Information for the patient Section 4: Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 Special warnings and precautions for use. Before initiating treatment with zanubrutinib, the patient's HBV status should be established. Consider prophylaxis according to standard of care in patients who are at increased risk for infections. Monitor patients for signs and symptoms of infection and treat appropriately. Consultation with a liver disease expert physician is recommended for patients who test positive for HBV or have positive hepatitis B serology, before initiating treatment. The patient should be monitored and managed according to the medical standards to prevent hepatitis B reactivation. Consider prophylaxis according to standard of care in patients who are at increased risk for infections. Monitor patients for signs and symptoms of infection and treat appropriately. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes direction for patients to talk to their doctor, pharmacist or nurse before taking zanubrutinib if they have been advised they are at higher risk of infections and if they have ever had or might have hepatitis B. Includes details of the type of infections that might occur and their symptoms. Package leaflet: Information for the patient Section 4: Possible side effects. Includes direction for patients to tell a doctor, pharmacist or nurse straight away in the case of fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath, and frequent and painful urination as these could be signs of an infection (viral, bacterial or fungal). Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter	Routine risk communication: 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 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 Special warnings and precautions for use. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes direction for patients to talk to their doctor, pharmacist or nurse before taking zanubrutinib if they have an irregular heartbeat, a history of irregular heartbeat or severe

Table Part V-3: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
	heart failure, shortness of breath, weakness, dizziness, light headedness, fainting or near fainting, chest pain, or swollen legs. Package leaflet: Information for the patient Section 4: Possible side effects. Includes direction for patients to tell a doctor straight away in the case of dizziness. Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Second primary malignancies (other than non-melanoma skin cancer)	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 Special warnings and precautions for use. Advise patients to use sun protection. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes direction for patients to tell a doctor, pharmacist or nurse if they had other carcinomas in the past. Advises patients to use sun protection. Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Second primary non-melanoma skin cancer	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 Special warnings and precautions for use. Advise patients to use sun protection. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes direction for patients to tell a doctor, pharmacist or nurse if they had skin cancer in the past (eg, basal cell carcinoma or squamous cell carcinoma). Advises patients to use sun protection. Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
DDI with CYP3A inducers	Routine risk communication: 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

Table Part V-3: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration, Table 2 Recommended dose modifications of zanubrutinib when coadministered with other medicinal products are described. SmPC Section 4.4 Special warnings and precautions for use. Warfarin or other vitamin K antagonists should not be administered concomitantly with zanubrutinib. SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction. Interactions between zanubrutinib and other medicinal products are described, with advice and instructions provided. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes direction for patients to tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines, including details of specific medicines, supplements and food that may have an effect on zanubrutinib when taken together. Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Teratogenicity	Routine risk communication: SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Preclinical safety data Package leaflet: Information for the patient Section 2: Warnings and precautions Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.6 Fertility, pregnancy and lactation. Zanubrutinib should not be used during pregnancy. There are no data from the use of zanubrutinib in pregnant women. Women should avoid becoming pregnant while taking zanubrutinib and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking zanubrutinib and for up to 1 month after stopping treatment. It is currently unknown whether zanubrutinib may reduce the efficacy of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. Pregnancy testing is recommended for women of reproductive potential prior to initiating therapy. Package leaflet: Information for the patient Section 2: Warnings and precautions. Informs patients not to get pregnant or to breastfeed while taking zanubrutinib as it is not known if zanubrutinib will harm the unborn baby or if it may pass into breast milk. Includes direction on the use of highly effective methods of birth control and for patients to tell their doctor immediately if they become pregnant. Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Safety in patients with severe hepatic impairment	Routine risk communication: 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

Table Part V-3: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration. The safety of zanubrutinib has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for AEs of zanubrutinib. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes direction for patients to tell their doctor, pharmacist or nurse if they have liver problems. Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Safety in patients with severe renal impairment/on dialysis	Routine risk communication: 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 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 Posology and method of administration. There are limited data on patients with severe renal impairment and end-stage renal disease (n = 12). Patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis should be monitored for adverse reactions. Package leaflet: Information for the patient Section 2: Warnings and precautions. Includes direction for patients to tell their doctor, pharmacist or nurse if they have kidney problems. Other routine risk minimisation measures beyond the product information: Legal status: medical prescription
Long-term safety (> 2 years)	Routine risk communication: Not specifically addressed Routine risk minimisation activities recommending specific clinical measures to address the risk: Not specifically addressed Other routine risk minimisation measures beyond the product information: Legal status: medical prescription

Abbreviation: AE, adverse event; CrCl, creatinine clearance; CYP3A, cytochrome P450 family 3 subfamily A; DDI, drug-drug interaction; HBV, hepatitis B virus; SmPC, Summary of Product Characteristics
Note: SmPC refers to approved zanubrutinib [BRUKINSA] SmPC.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Additional Risk Minimisation

Not applicable.

Removal of Additional Risk Minimisation Activities

Not applicable.

V.3 Summary of Risk Minimisation Measures

Table Part V-4: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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
Infections (including lower respiratory tract infections and 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
Cardiac arrhythmia, mainly presenting 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 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

Table Part V-4: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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 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: None
Teratogenicity	Routine risk minimisation measures: SmPC Section 4.6 Fertility 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

Table Part V-4: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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, Multicenter, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies Information on study progress in PSURs until study completion Interim report submission: December 2025 Estimated study completion date: December 2026 Final report submission: planned for June 2027

Abbreviation: CYP3A, cytochrome P450 family 3 subfamily A; DDI, drug-drug interaction; PSUR, Periodic Safety Update Report; SmPC, Summary of Product Characteristics.
Note: SmPC refers to approved zanubrutinib [BRUKINSA] SmPC.

PART VI SUMMARY OF RISK MANAGEMENT PLAN FOR BRUKINSA (ZANUBRUTINIB)

This is a summary of the risk management plan (RMP) for BRUKINSA®. The RMP describes important risks of BRUKINSA, how these risks can be minimised, how more information will be obtained about BRUKINSA and uncertainties (missing information).

The BRUKINSA Summary of Product Characteristics (SmPC) and its package leaflet provide essential information to healthcare professionals and patients as to how BRUKINSA should be used.

This summary of the RMP for BRUKINSA should be read in the context of all information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report. Important new concerns or changes to the current ones will be included in updates of the BRUKINSA RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

BRUKINSA is an anticancer medicine that contains the active substance zanubrutinib. It belongs to a class of medicines called protein kinase inhibitors. BRUKINSA works by blocking Bruton tyrosine kinase, a protein in the body that helps cancer cells grow and survive. By blocking this protein, BRUKINSA helps kill and reduce the number of cancer cells, which can slow down the worsening of the cancer.

Waldenström Macroglobulinaemia

Waldenström macroglobulinaemia is a rare, slow growing type of cancer that begins in the white blood cells. In this condition, the bone marrow produces too many abnormal white blood cells that can overcome healthy blood cells. Waldenström macroglobulinaemia is considered a type of non-Hodgkin lymphoma, which is a rare type of blood cancer, and is sometimes called lymphoplasmacytic lymphoma. Waldenström macroglobulinaemia belongs to a group of blood cancers called non-Hodgkin lymphomas (NHLs) that affect B lymphocytes. It is also a rare disease that affects about 4 to 5 people per 1,000,000 in Europe and less than 1 in 100,000 people throughout the rest of the world. Waldenström macroglobulinaemia occurs more frequently in older adults, the average age at diagnosis being in the mid-60s. It is more common in men than women and white people are at a higher risk than black people.

The abnormal white blood cells produce a large protein called a macroglobulin that builds up in the blood where it can impair circulation and cause complications. Some people with Waldenström macroglobulinaemia may not experience many symptoms early on when the disease is first diagnosed. However, the macroglobulin in Waldenström macroglobulinaemia makes the blood more viscous, ie, thick and stickier, so that it does not flow easily. This is called hyperviscosity which can cause easy bruising, headaches, nose bleeds, and blurred vision.

In a main study involving 201 patients who had never received treatment for Waldenström macroglobulinaemia or either did not respond to or had come back after previous treatment, BRUKINSA was shown to be an effective treatment with favourable responses to treatment when compared with another medicine used to treat this condition. Furthermore, patients treated

with BRUKINSA demonstrated a favourable safety and tolerability profile in patients with Waldenström macroglobulinaemia. The average treatment duration was > 18 months.

Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is a group of indolent (slow growing) non-Hodgkin lymphoma B-cell lymphomas, which account for approximately eight percent of all non-Hodgkin lymphoma cases. The average age at diagnosis is 60 years, and it is slightly more common in women than in men.

There are 3 types of MZL. Mucosa associated lymphoid tissue lymphoma is the most common type of MZL. Mucosa associated lymphoid tissue lymphoma does not start in the lymph nodes. It starts in the mucosa, which is a soft, moist tissue layer that protects and covers organs in different parts of the body. The second type of MZL, nodal MZL, starts within the lymph nodes. The third type of MZL, splenic MZL, starts in the spleen but can also be found in the bloodstream.

Chronic Lymphocytic Leukaemia

Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are malignant blood disorders in which there are an increased number of white blood cells in the lymphoid tissue. CLL and SLL are different forms of the same disorder, differing in the location of unhealthy blood cells, and are treated in the same way. In CLL/SLL, abnormal B lymphocytes (a type of white blood cell responsible for the production of antibodies to help fight infection) are produced instead of healthy white blood cells, and then accumulate over time. As the number of unhealthy blood cells grows, there is less room for healthy cells. The combination of fewer healthy cells and the fact that the CLL/SLL lymphocytes are poor at fighting infections can lead to frequent infection, anaemia, and easy bleeding. The uncontrolled build up and enlargement of lymphoid tissue can occur in various sites of the body such as the lymph nodes, spleen, bone marrow, and lungs. CLL/SLL can be slow-growing or fast-growing. The slower-growing form has an increased number of lymphocytes but a normal or slightly below normal level of red cells, platelets, and neutrophils in the blood. This form can remain stable for years. The faster-growing form has too many CLL/SLL cells in the blood that block normal cell production. As a result, the number of fully functioning red cells and platelet levels drop lower than normal. CLL/SLL is the most common type of leukaemia in adults and very rarely occurs in children. It is more common in older people, is rare in people younger than 40 and men are more likely to develop CLL/SLL than women.

Follicular Lymphoma

Follicular lymphoma (FL) is a type of non-Hodgkin lymphoma, which is a rare form of blood cancer. FL is most commonly diagnosed due to enlarged lymph nodes or during imaging performed for other reasons. On average, FL is diagnosed in patients around the ages of 60 to 65 years. FL is slightly more common in women than men, and white people are at a higher risk than black people.

Most patients with FL experience several relapses over their lifetime and some patients go onto develop another form of lymphoma called diffuse large B-cell lymphoma (DLBCL). Symptoms of DLBCL include rapid progression of lymph node swelling, extranodal disease, and symptoms

such as fever, night sweats, and weight loss. The factors that increase the risk of FL transforming to DLBCL are still being investigated.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of BRUKINSA, together with measures to minimise such risks and the proposed studies for learning more about BRUKINSA risks, are described below. These are risks that require special risk management activities in order to investigate them more thoroughly, to help understand how BRUKINSA can be used safely. There are 2 kinds of risks, identified and potential risks. Concerns are called identified risks when there is evidence of a link with the use of BRUKINSA. Concerns are called potential risks where this evidence is not as strong and where this needs further investigation. In addition, there is missing information that refers to concerns where information is missing or insufficient and where further evidence needs to be collected. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise any risks that may be associated with its use

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and analysed regularly, including periodic assessment, so that immediate action relating to the safety of BRUKINSA can be taken if considered necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of BRUKINSA is not yet available, it is listed under 'missing information', below.

II.A List of Important Risks and Missing Information

Summary of Safety Concerns	
Important identified risks	• Haemorrhage • Infections (including lower respiratory tract infections and hepatitis B reactivation) • Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter
Important potential risks	• Second primary malignancies (other than non-melanoma skin cancer) • Second primary non-melanoma skin cancer • Drug-drug interaction with CYP3A inducers • Teratogenicity

Summary of Safety Concerns	
Missing information	• Safety in patients with severe hepatic impairment • Safety in patients with severe renal impairment/on dialysis • Long-term safety (> 2 years)

II.B Summary of Important Risks

Important Identified Risk: Haemorrhage	
Evidence for linking the risk to the medicine	Haemorrhage events have been reported relating to the use of BRUKINSA in ongoing and completed clinical studies. Such events, in addition to recommendations to prescribers regarding the use of BRUKINSA in patients that are also receiving treatment with anticoagulants or medications that inhibit platelet function, are described in the SmPC for BRUKINSA. This includes the recommendation to consider the benefit-risk of withholding zanubrutinib for 3 to 7 days pre and post surgery depending upon the type of surgery and the risk of bleeding.
Risk factors and risk groups	Risks include advanced age, history of bleeding, dose of chemotherapy, baseline platelet count, poor performance and/or nutritional status, and concomitant use of antiplatelet or anticoagulant therapy, especially warfarin use in the elderly population.
Risk minimisation measures	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

Important Identified Risk: Infections (including lower respiratory tract infections and hepatitis B reactivation)	
Evidence for linking the risk to the medicine	Fatal and non-fatal infections (including bacterial, viral, or fungal infections or sepsis) and opportunistic infections (eg, aspergillus, cryptococcal, herpes viral and pneumocystis jirovecii infections) have occurred in patients treated with zanubrutinib. Infections due to hepatitis B virus (HBV) reactivation have also occurred.
Risk factors and risk groups	Predictors of infection include advanced age, underlying immunosuppression that is inherent to the primary disease process, therapy-related immunosuppression, absence of antibiotic prophylaxis, and poor performance and/or nutritional status.
Risk minimisation measures	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

Important Identified Risk: Cardiac arrhythmia, mainly presenting as atrial fibrillation and flutter	
Evidence for linking the risk to the medicine	Reports of atrial fibrillation have been identified in completed and ongoing clinical studies, particularly in patients with a history of cardiac disease and known cardiac risk factors (eg, hypertension, previous history of atrial fibrillation and concurrent active infections). Atrial fibrillation is described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Atrial fibrillation is the most common heart rhythm disorder. Atrial fibrillation is more common in men than women. There are also indications that individuals of white European descent have a higher risk of atrial fibrillation compared with individuals of other races. Most patients with atrial fibrillation/flutter had known risk factors in addition to age, including a history of atrial fibrillation, hypertension, pre-existing cardiovascular disease, or concurrent infection.
Risk minimisation measures	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

Important Potential Risk: Second primary malignancies (other than non-melanoma skin cancer)	
Evidence for linking the risk to the medicine	BRUKINSA was not genotoxic in studies evaluating gene mutations in bacteria (Ames assay), was not clastogenic in an in vivo bone marrow erythrocyte micronucleus assay in rats, nor was it clastogenic in a chromosome aberration assay in Chinese hamster ovary cells. No malignancy or premalignancy was identified in rat repeated-dose studies for 26 weeks and in dog repeated-dose studies for 39 weeks. No carcinogenicity studies were conducted. Zanubrutinib has a favourable pharmacokinetic (PK) profile with short half-life and shows a lack of accumulation in the skin or other tissues in absorption, distribution, metabolism, and excretion studies with ^{14}C-zanubrutinib. In addition, ^{14}C-zanubrutinib related material was not extensively associated with melanin in rats. In summary, preclinical data do not describe any risk that zanubrutinib may be carcinogenic. Second primary malignancies (other than non-melanoma skin cancer) have been reported in patients participating in ongoing and completed clinical studies of BRUKINSA.
Risk factors and risk groups	The risk of developing a second malignancy depends on several factors, including type of primary cancer, age at diagnosis, sex, types of therapy given, environmental exposures, genetic predisposition, and health decisions. Radiation has long been associated with the development of primary cancers and, when used as treatment, imparts a risk for the development of a second cancer. Risk factors that may increase the risk of second primary malignancies in patients with haematological malignancies include immune dysregulation, the immunosuppressive effects of chemotherapeutic agents and radiation therapy. In patients with CLL, proposed risk factors for second primary malignancy include environmental and occupational exposures, genetic risk factors, immune dysfunction inherent to the disease itself, and deoxyribonucleic acid damage from prior chemotherapy (Bond et al 2020), which are independent of BRUKINSA exposure. In a retrospective review of electronic medical records from The Ohio State University Comprehensive

Important Potential Risk: Second primary malignancies (other than non-melanoma skin cancer)	
	Cancer Center, the risk of second primary malignancies from a large cohort of patients with CLL who were previously treated with a Bruton tyrosine kinase inhibitor (545 ibrutinib-treated patients and 146 acalabrutinib-treated patients) between 2009 and 2017, was 2.2-fold (95% confidence interval: 1.7 to 2.9) higher than that expected in the general population (Bond et al 2020). On multivariable analysis, smoking was associated with increased second primary malignancy risk (hazard ratio [HR] 2.8 [95% confidence interval: 1.6 to 4.8]) and higher baseline CD8 count was associated with lower second primary malignancy risk (HR 0.9 for 2-fold increase [95% confidence interval: 0.8 to 0.9]). Together, these data indicate that CLL patients treated with Bruton tyrosine kinase inhibitors remain at increased risk for second primary malignancies.
Risk minimisation measures	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

Important Potential Risk: Second primary non-melanoma skin cancer	
Evidence for linking the risk to the medicine	BRUKINSA was not genotoxic in studies evaluating gene mutations in bacteria (Ames assay), was not clastogenic in an in vivo bone marrow erythrocyte micronucleus assay in rats, nor was it clastogenic in a chromosome aberration assay in Chinese hamster ovary cells. In vivo animal studies did not identify premalignant lesions at any site including the skin. ^{14}C-zanubrutinib demonstrated no accumulation in skin and BRUKINSA was not associated with melanocytes. The risk of phototoxicity was low in clinical studies. No malignancy was identified in rat repeated-dose studies for 26 weeks and in dog repeated-dose studies for 39 weeks. No carcinogenicity studies were conducted. The most frequent second primary malignancy reported in BRUKINSA clinical studies was skin cancer. Skin cancers were observed predominantly in patients at high risk of developing skin cancer (white, elderly males from Australia, which has a high known prevalence of skin cancers). Second primary skin cancers were not observed in patients of Asian origin, or in any nonwhite patient, confirming that race and geographic location are the main drivers of non-melanoma skin cancer generation.
Risk factors and risk groups	An individual's risk of developing skin cancer depends on both constitutional and environmental factors. The constitutional risk factors of skin cancer include family history, red hair colour, melanocytic nevi, and sun exposure sensitivity (Gandini et al 2005), whereas solar ultraviolet radiation is a well-established environmental risk factor (Gandini et al 2005; Armstrong et al 1997). Sunlight can also cause immunosuppression (Onajin and Brewer 2012; Brin et al 2014). Skin cancer is the most common type of cancer in light-skinned populations around the world (Breitbart et al 2006), with skin cancers most frequent in Australia/New Zealand with an age adjusted standardised rate of 295.9 in 100.000, followed by Northern America (113.7), and Western Europe (52.9). Basal cell carcinoma, the most common malignancy in white people accounting for 80% to 85% of all non-melanoma skin cancers, has a higher occurrence in men than women, consistent with greater sun exposure (often occupational) (Diepgen and Mahler 2002). Albert et al (1990) describe incidence rates 16-fold greater in Caucasians than African Americans and > 10-fold than that observed in Hispanics.

Important Potential Risk: Second primary non-melanoma skin cancer	
Risk minimisation measures	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

Important Potential Risk: Drug-drug interaction with CYP3A inducers	
Evidence for linking the risk to the medicine	There is drug-drug interaction (DDI) potential between BRUKINSA and other concomitant medications, particularly those with strong CYP3A inhibitors and inducers. The DDI potential of BRUKINSA was assessed in 3 dedicated clinical DDI studies: BGB-3111-104, BGB-3111-108 and BGB-3111-113. In addition, a physiologically-based pharmacokinetics model was developed to predict the effect of moderate and mild CYP3A inhibitors and CYP3A inducers on the pharmacokinetics of BRUKINSA. The DDI potential of zanubrutinib coadministered with a moderate CYP3A inducer was assessed in Study BGB-3111-112, an open-label, fixed-sequence study in healthy male subjects. It investigated the effect of CYP3A induction by steady-state rifabutin on the single-dose PK of zanubrutinib. Statistical analysis demonstrated that systemic exposure to zanubrutinib was moderately lower after coadministration of 320 mg zanubrutinib with 300 mg rifabutin than after administration of 320 mg zanubrutinib alone, with geometric mean AUC approximately 44% lower and C_{max} approximately 48% lower. This represents a decreased exposure of 1.8-fold for AUC0-∞, and 1.9-fold for C_{max}. In Study BGB-3111-113, the magnitude of the DDI between zanubrutinib and moderate (diltiazem, fluconazole) and strong (clarithromycin, voriconazole) CYP3A inhibitors was further evaluated in patients with B cell malignancies. Zanubrutinib steady-state exposures upon concurrent administration with moderate and strong CYP3A inhibitors (under the 2-fold or 4-fold dose reduction per zanubrutinib prescribing information) were lower than exposures at the 320 mg once-a-day dose of zanubrutinib. Overall, the safety findings were consistent with the safety profile of zanubrutinib and no changes to the dosing recommendations for use of zanubrutinib with moderate or strong CYP3A inhibitors was considered necessary.
Risk factors and risk groups	BRUKINSA is metabolised primarily by CYP3A enzymes and a clinical DDI study and physiologically-based pharmacokinetics simulations show that strong and moderate CYP3A inhibitors or inducers can modulate exposure of BRUKINSA. Based on the results of the DDI studies and understanding of exposure-response relationships, patients receiving medications that act as moderate to strong CYP3A inducers are at risk of DDIs.
Risk minimisation measures	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

Important Potential Risk: Teratogenicity	
Evidence for linking the risk to the medicine	Embryo-foetal development toxicity studies were conducted in both rats and rabbits. Malformations in the heart (2- or 3-chambered hearts at the incidence of 0.3% to 1.5%) were noted at all dose levels (in the absence of maternal toxicity) when administered orally to pregnant rats during the period of organogenesis. Administration of BRUKINSA to pregnant rabbits during the period of organogenesis resulted in post implantation loss at the highest dose, but no teratogenicity was noted in this study. Embryo-foetal toxicity may cause embryo-foetal harm.
Risk factors and risk groups	Sexually active female patients of childbearing potential not practising birth control methods, or those known to be pregnant or lactating.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Fertility, 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

II.C Postauthorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

Short Name and Title:

BGB-3111-308 A Phase 3 Randomized, Open-label, Multicenter Study of Zanubrutinib (BGB-3111) Plus Anti-CD20 Antibodies Versus Lenalidomide Plus Rituximab in Patients With Relapsed/Refractory Follicular or Marginal Zone Lymphoma.

Purpose of the Study:

Rationale: To evaluate whether the addition of zanubrutinib to obinutuzumab (for patients with R/R FL) or rituximab (for patients with R/R MZL) will result in a favourable benefit-risk profile when compared with rituximab in combination with lenalidomide in patients with R/R FL or R/R MZL.

Objective: To evaluate the efficacy of zanubrutinib in combination with anti-CD20 monoclonal antibodies compared with lenalidomide plus rituximab in patients with R/R FL or R/R MZL.

II.C.2 Other Studies in Postauthorisation Development Plan

BGB-3111-LTE1

Short Name and Title:

BGB-3111-LTE1 - An Open-label, Multicenter, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies

Purpose of the Study:

Rationale: To evaluate the long-term safety and efficacy of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who are or were previously enrolled in a

BeiGene parent study and who are still benefiting or may benefit from treatment with zanubrutinib, or who are willing to have long-term survival follow-up.

Objective: To evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who participated in a BeiGene parent study for zanubrutinib.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None proposed.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

None proposed.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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