13 October 2022
EMA/CHMP/896488/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Brukinsa

International non-proprietary name: zanubrutinib

Procedure No. EMEA/H/C/004978/II/0003

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

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

NHL	non-Hodgkin lymphoma
NMPA	China National Medical Products Administration
PCR	polymerase chain reaction
PET	positron-emission tomography
PFS	progression-free survival
PI3K	phosphoinositide 3-kinases
PK	pharmacokinetic
PR	partial response
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SOC	system organ class
SPD	sum of product diameters
TEC	tyrosine kinase expressed in hepatocellular carcinoma
ULN	upper limit of normal
US	United States
VAS	visual analogue scale

1 Background information on the procedure

1.1 Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BeiGene Ireland Ltd submitted to the European Medicines Agency on 31 January 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL) based on results from Study BGB-3111-304; an ongoing, international, Phase 3, open-label, multiple-cohort, randomized study designed to evaluate the efficacy of zanubrutinib versus B+R in patients with previously untreated CLL/SLL, and Study BGB-3111-305; an ongoing, international Phase 3, open-label, randomized study of zanubrutinib versus ibrutinib with R/R CLL/SLL.
As a consequence, sections 4.1, 4.2, 4.4, 4,5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are being updated.
The Package Leaflet is updated in accordance.
An updated RMP version 1.1 (specific for the proposed indication CLL/SLL) was also submitted.
In addition, as part of the application the MAH requested a 1-year extension of the market protection.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0398/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did seek Scientific Advice at the CHMP in 2016; EMEA/H/SA/3376/1/2016/II and in 2017a follow up EMEA/H/SA/3376/1/FU/1/2017/II. The overall study design features for study 304 (1L CLL)

were agreed upon with EMA, although the interim analysis was discouraged. Initially, the MAH proposed one pivotal study to support the use of zanubrutinib in treatment-naïve (TN) and R/R CLL patients. However, the CHMP did not support this proposal and expressed several concerns regarding the design and power of the study to support the claimed indication. In the follow-up advice in 2017 the MAH proposed study 304 in TN patients. For study 304 the proposed study design and primary endpoint (PFS by IRC) were endorsed by the CHMP. The MAH changed the originally proposed study design in patients with R/R CLL without further interaction with the CHMP (primary endpoint of PFS was changed to ORR).

1.2 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Johanna Lähteenvuo

Timetable	Actual dates
Submission date	31 January 2022
Start of procedure:	19 February 2022
CHMP Rapporteur Assessment Report	13 April 2022
PRAC members comments	26 April 2022
CHMP Co-Rapporteur Critique	26 April 2022
PRAC Outcome	5 May 2022
CHMP members comments	6 May 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 May 2022
Request for supplementary information (RSI)	19 May 2022
CHMP Rapporteur Assessment Report	19 September 2022
PRAC Rapporteur Assessment Report	19 September 2022
PRAC members comments	21 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	03 October 2022
Updated CHMP Rapporteur Assessment Report	6 October 2022
Opinion	13 October 2022

2 Scientific discussion

2.1 Introduction

Problem statement

Disease or condition

The claimed the therapeutic indication was applied as: BRUKINSA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The final approved indication is: Brukinsa as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL).

Epidemiology

CLL/SLL is the most common leukemia in the Western world, with an incidence of 4.2 cases in every 100,000 persons per year. The incidence increases to > 30 in 100,000 per year in people aged more than 80 years. In the US, incidence of CLL is 4.9 cases per 100, in Europe, 4.9 CLL/SLL cases per 100,000 persons. It is estimated that there are approximately 191,000 cases and 61,000 deaths per year attributed to CLL/SLL worldwide.
The median age at time of diagnosis is 70 years, and approximately two-thirds of patients are over 65 years of age. The disease is more common in men versus women, and in Caucasian versus black, Hispanic, or Asian populations.

Biologic features

The World Health Organization (WHO) classification considers CLL and SLL to be different clinical manifestations of the same disease; therefore, CLL and SLL are considered collectively.
While CLL/SLL is a highly heterogenous disease in terms of disease course, with several patient-related (such as age and comorbidity) and disease-related (such as stage and immunoglobulin heavy chain gene rearrangement status) factors that carry prognostic significance, the loss of the TP53 locus on chromosome 17p13.1 (del(17p)) is the most significant poor prognostic feature in this disease.

Clinical presentation, diagnosis and stage/prognosis

Patients with loss of 17p13.1, as well as those that harbor a mutation of the TP53 gene, have a grim prognosis in response to chemoimmunotherapy and tend to show marked resistance against genotoxic chemotherapies that cannot be overcome by the addition of anti-CD20 antibodies. While the overall 5-year survival rate is high (> 85% in the USA) for those who receive appropriate treatment, fewer than 25% of the highest-risk subset of patients (based on TP53 gene dysfunction and clinical factors) would be expected to survive 5 years. Staging of CLL/SLL is typically per either the modified Rai or Binet staging system.
CLL/SLL is considered a treatable but essentially incurable disease.

Management

Until recently, the treatment of CLL/SLL was based on chemotherapy, particularly the alkylating agents chlorambucil, cyclophosphamide, and more recently, bendamustine. In the 1990s, the purine analogue fludarabine was shown in clinical trials to improve progression-free survival (PFS) compared to chlorambucil, except for elderly CLL/SLL patients, and became a standard initial therapy in younger patients with CLL/SLL. The addition of anti-CD20 antibodies, such as rituximab, to chemotherapy resulted in significant improvements in the clinical outcomes of previously untreated CLL. Treatment standards for CLL/SLL have evolved since the advent of effective inhibitors of B-cell receptor (BCR) signaling, allowing for several choices of treatment regimens and single-agent therapies for the general population of both treatment-naïve (TN) and previously treated CLL/SLL.

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

1. Patients without TP53 mutation or del(17p)
    1. IGVH unmutated
        1. Fit: ibrutinib or FCR (or BR in patients above 65 years)
        2. Unfit: venetoclax + obinutuzumab or ibrutinib or acalabrutinib or chemo-immunotherapy (if contraindicated to targeted therapy or if they are not available) or chlorambucil + obinutuzumab
    2. IGVH mutated
        1. Fit: FCR (or BR in patients above 65 years) or ibrutinib
        2. Unfit: venetoclax + obinutuzumab or chlorambucil + obinutuzumab or ibrutinib or acalabrutinib
2. All patients WITH TP53 mutation or del(17p): ibrutinib or acalabrutinib or venetoclax +/- obinutuzumab or idelalisib + rituximab

Second-line CLL/SLL treatment is guided by the duration of the first remission for relapsed disease. Refractory disease is defined as having either no response to treatment or relapse within 6 months after the last treatment. ESMO guidelines recommend a change of therapeutic regimen in case of symptomatic relapse within 3 years, or refractory disease, in which case treatment with venetoclax (+/- rituximab), ibrutinib, acalabrutinib, or other BTKi monotherapy should be considered. Patients with remissions of more than 3 years may be re-exposed to the same time-limited regimen; however, repetition of the FCR regimen is not recommended. Other treatment options include acalabrutinib, ibrutinib, venetoclax + rituximab, or idelalisib + rituximab. For patients with TP53 mutation or del(17p), allogenic stem-cell transplantation should be considered for fit patients. The US NCCN guidelines' list of preferred regimens for RR CLL/SLL patients are the same as for frontline treatment except venetoclax monotherapy is recommended only for patients with TP53 mutation or del(17p).

About the product

Zanubrutinib is a potent and irreversible next-generation BTK inhibitor. Zanubrutinib is more selective than ibrutinib for BTK inhibition. Zanubrutinib has been studied in an extensive ongoing clinical development program in a number of B-cell malignancies.

BGB-3111 -301 Europe, USA, RoW	3	Randomized, open-label, multicentre NI study of BGB-3111 vs ibrutinib CLL/SLL who require therapy, defined as: - R/R disease after ≥1 prior therapy, or - ≥65 years of age with treatment-naïve disease who have at least 1 indication for treatment per IWCLL criteria	~ 600	Primary: Demonstration of NI measured by PFS (2012 modification of the 2008 IWCLL Guidelines) Secondary: Compare the 2 treatment groups for - ORR, DOR, 18m PFS, OS - haematologic improvement - incidence and severity of AEs by NCI CTCAEv4.03 - incidence of AEs of interest, including severe bleeding (bleeding >G3 in severity or CNS bleeding of any grade), new onset atrial fibrillation (any grade), AEs leading to treatment discontinuation

The development programme/compliance with CHMP guidance/scientific advice

The overall study design features for study 304 (1L CLL) were agreed upon with EMA in the context of the EMA Scientific Advice EMEA/H/SA/3376/1/2016/II and in a follow up EMEA/H/SA/3376/1/FU/1/2017/II although the interim analysis was discouraged. Initially, the MAH proposed one pivotal study to support the use of zanubrutinib in treatment-naïve (TN) and R/R CLL patients. However, the CHMP did not support this proposal and expressed several concerns regarding the design and power of the study to support the claimed indication. In the follow-up advice in 2017 the MAH proposed study 304 in TN patients. For study 304 the proposed study design and primary endpoint (PFS by IRC) were endorsed by the CHMP. The MAH changed the originally proposed study design in patients with R/R CLL without further interaction with the CHMP (primary endpoint of PFS was changed to ORR.

2.2 Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. An environmental risk assessment (ERA) in the course of the initial MAA for treatment of Waldenström macroglobulinemia (WM) is ongoing, and BeiGene committed to provide the final ERA report by December 2022. This summary was written to support the type II variation application of zanubrutinib for the treatment of adult patients with relapsed/refractory marginal zone lymphoma (MZL) and the current type II variation on CLL.

Introduction

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

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

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

Some of these studies were submitted with this variation.

Ecotoxicity/environmental risk assessment

Summary of ongoing Environment Risk Assessment program for MZL

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

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

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

<table>
<tr><td colspan="4">Substance (INN/Invented Name):</td></tr>
<tr><td colspan="4">CAS-number (if available):</td></tr>
<tr><td>PBT screening</td><td></td><td>Result</td><td>Conclusion</td></tr>
<tr><td>Bioaccumulation potential- log K_{ow}</td><td>OECD107 and OECD123</td><td>Log K_{OW} = 3.2 (pH 5)

Log K_{OW} = 3.6 (pH 7)

Log K_{OW} = 3.7 (pH 9)</td><td>Log K_{OW} < 4.5, no need to conduct definitive PBT assessment.
Log K_{OW} > 3, bioconcentration factor (BCF) in fish study (OECD 305) is triggered.</td></tr>
<tr><td colspan="4">PBT-assessment</td></tr>
<tr><td>Parameter</td><td>Result relevant for conclusion</td><td></td><td>Conclusion</td></tr>
<tr><td rowspan="2">Bioaccumulation</td><td>log K_{ow}</td><td><4.5</td><td>not B</td></tr>
<tr><td>BCF</td><td>Awaits final report (OECD 305)</td><td>B/not B</td></tr>
<tr><td>Persistence</td><td>DT50</td><td>Not persistent, but accumulation of two transformation products.
<table><tr><td>Compartment</td><td>DT50, 12 °C [d]</td></tr><tr><td>SW total system</td><td>32.0</td></tr><tr><td>SW water</td><td>12.4</td></tr><tr><td>SW sediment</td><td>38.3</td></tr><tr><td>EV total system</td><td>74.6</td></tr><tr><td>EV water</td><td>9.8</td></tr><tr><td>EV sediment</td><td>55.4</td></tr></table></td><td>Not P</td></tr>
<tr><td>Toxicity</td><td>NOEC or CMR</td><td>Awaiting conclusions on OECD 210 and 218</td><td>T/not T</td></tr>
</table>

PBT-statement:	Zanubrutinib is persistent (P), however whether it is B or T awaits reporting on ongoing studies and final conclusions on the environmental risk assessment				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.022 for Waldenströms macroglobulinemia	µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Test system / $K_{F,oc}^{ads}$ (mL/g) / $K_{F,oc}^{des}$ (mL/g): Speyer 2.2: 1602 / 2119; Speyer 2.3: 1835 / 2825; Speyer 6S: 2845 / 3257; Tilburg: 516 / 525; Aa & Maas: 635 / 640			KOC < 10,000 mL/g, the terrestrial assessment is not triggered.
Ready Biodegradability Test	OECD 301B	3% and 6% based on ThCO2 in an aerobic aqueous medi-um with microbial activity introduced by inoculation with activated sludge.			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Compartment / $DT_{50,\ 20\ °C}$ [d]: SW total system: 15; SW water: 5.8; SW sediment: 18; EV total system: 35; EV water: 4.6; EV sediment: 26 % shifting to sediment = 92-100% on Day 101			Phase II Tier B assessment for sediment is triggered. Accumulation of two transformation products >10% in sediment which have to be considered as very persistent.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.37	mg/L	*Raphidocelis subcapitata* Risk Quotient (RQ) < 1
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.71	mg/L	Risk Quotient (RQ) < 1
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	<0.017 for larval growth	mg/L	*Pimephales promelas* Another study is planned and will be completed by December 2022.
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	NOEC = 32 mg/L; EC50 > 1000 mg/L	mg/L	No effects on microbial communities.
Phase IIb Studies					

Bioaccumulation	OECD 305-I	BCF	BCF_L at low concentration (1.6 µg/L) = 23 ± 3.1 L/kg; BCF_L at high concentration (16 µg/L) = 32 ± 5.3 L/kg	L/kg	%lipids: 2.7 in fish in study Not considered to be bioaccumulative in fish as BCF<2000. However, although BCF was low, it increased slowly during the study of 28 days. Hence steady state was not reached. Reported BCF is normalised to 5% lipid. Depuration was not determined due to low uptake.
Sediment dwelling organism	OECD 218	NOEC for emergence	89 mg/kg d.w.	mg/kg	Triggered Development was not deemed affected even at the highest concentration of 289 mg/kg d.w, although only 5% of larvae emerged as midges at this concentration.

Discussion on non-clinical aspects

The ERA assessment leaded to the conclusions below:

1. Log K_{OW} > 3, hence a bioconcentration factor (BCF) in fish study (OECD 305) is triggered. This study is ongoing.

   However, the fish tissues were solubilised by Solvable (Perkin Elmer) and bleached by hydrogen peroxide (30%). This procedure was probably used for de-colouring of the bilirubin content of the fish tissues. Unfortunately, oxidation of the parent or even a loss of the label due to the formation of 14CO2 cannot be ruled out. BCF data could be strongly underestimated and would also explain the low recovery in the fish samples.

   Further, the applicant stopped the uptake phase after 28 d (despite an >20% increase of tissue concentration) and waived the depuration phase of the study. An extended uptake and/or a depuration phase could have given further information about the kinetics and quality assessment of the BCF data.

   Therefore, the applicant is asked to explain why hydrogen peroxide was used as bleaching agent after solubilisation, although the 14C parent substance can be subject to strong oxidation and loss of the label as 14CO2 is possible.

   Further, the applicant should clarify for what reason the uptake phase wasn't extended although an increase of the tissue concentration >20% (mean measured) was observed.

A new study is expected, if no reasonable explanations for the aspects as shown in the rationale are provided (OC).

1. Brukinsa is not readily biodegradable (OECD 301B).

2. A study based on Technical Guidance OECD 308 was submitted to concluding that a Phase II Tier B assessment for sediment is triggered.

   The applicant is asked to extend the evaluation of the water/sediment study to the transformation products TP-1 and TP-3. Both TPs accumulate in the course of the study in sediment and have, therefore, to be considered as very persistent **(CHMP recommendation)**.

   The applicant is kindly asked to revise the persistence classification of Zanubrutinib in the PBT assessment part of the ERA into not persistent. Rationale: In the PBT assessment part of the EPAR table Zanubrutinib is wrongly classified as persistent. This classification is based on the results of a study according to OECD TG 301B, whereas, the results of the study according to OECD TG 308, normalised to 12 °C, are relevant for the classification. Since the provided study according to OECD TG 308 indicates that Zanubrutinib is not persistent, the classification should be changed, but the formation of persistent transformation products could be mentioned **(CHMP recommendation)**.

3. Brukinsa is not a risk to microbial communities (OECD 209), algae (OECD 201) or daphnia (OECD 211), however a Fish early life cycle test did not provide a NOEC for larval growth of the fathead minnow (NOEC<0.017 mg/L, OECD 210). A new study is planned to be completed December 2022.

4. In support of a Phase II Tier B assessment, a sediment-water Chironomid toxicity test (OECD 218) is submitted. At 289 mg/kg d.w. sediment emergence of midges was 5% of control. NOEC was 89 mg/kg d.w.

   However, the data are missing in the study report. According to the guideline OECD 218 these data have to be submitted. In order to evaluate whether no significant difference exists between emergence of males and females the numbers of emerged males and females per vessel and per day should be provided. Without this information cumulative emergence as sole result cannot be used.

   The applicant is asked to provide details on the sex ratio of the Sediment-Water Chironomid Toxicity Test (OECD 218). Although it was indicated that sex and number of emerged midges had been recorded according to the test protocol, the respective results on the sex ratio had not been included in the study results. Therefore, separate number of emerged male and female midges should be provided (numbers of emerged males and females per vessel and per day).

   In addition, the information on LOQ and LOD of the analysis are missing. These should also be submitted **(CHMP recommendation)**.

The MAH has accepted the CHMP recommendations and a final environmental risk assessment is awaited post-approval. This should include the last ongoing study, adequate response to OCs and an updated $PEC_{SURFACEWATER}$ with the new indication.

Assessment of paediatric data on non-clinical aspects

The MAH was granted a deferral and a waiver in children below 18 years of age in treatment of lymphoplasmacytic lymphoma and 1 year of age for treatment of mature B-cell neoplasms on the

grounds that these two diseases do not occur in the respective paediatric subsets of the population, in October 2019. At that time, the paediatric investigation plan was planned to be completed by 2026. In vitro and in vivo nonclinical studies investigating efficacy of zanubrutinib in paediatric B-cell tumour cell lines were deferred.

In the most recent PIP compliance check report (outcome 15 October 2021), the non-clinical studies were referred and assessed by the PDCO; the PIP was deemed compliant and no further non-clinical studies were required.

Conclusion on the non-clinical aspects

The environmental risk assessment is still ongoing. The final report, including the last study to support Phase II tier A assessment and updated $PEC_{SURFACEWATER}$ with the new indication, including adequate response to outstanding issues, is awaited by the end of 2022/beginning of 2023.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points are recommended for further investigation:

1. OECD 305: The applicant is asked to explain why hydrogen peroxide was used as bleaching agent after solubilisation, although the ^{14}C parent substance can be subject to strong oxidation and loss of the label as $^{14}CO_2$ is possible.
2. Further, the applicant should clarify for what reason the uptake phase wasn't extended although an increase of the tissue concentration >20% (mean measured) was observed.
3. A new study is expected, if no reasonable explanations for the aspects as shown in the rationale are provided.
4. OECD 218: The applicant is asked to provide details on the sex ratio of the Sediment-Water Chironomid Toxicity Test. Although it was indicated that sex and number of emerged midges had been recorded according to the test protocol, the respective results on the sex ratio had not been included in the study results. Therefore, separate number of emerged male and female midges should be provided (numbers of emerged males and females per vessel and per day).
5. In addition, the information on LOQ and LOD of the analysis are missing. These should also be submitted.
6. OECD 308: The applicant is asked to extend the evaluation of the water/sediment study to the transformation products TP-1 and TP-3. Both TPs accumulate in the course of the study in sediment and have, therefore, to be considered as very persistent.
7. Moreover, the applicant is asked to revise the persistence classification of Zanubrutinib in the PBT assessment part of the ERA into not persistent. Rationale: In the PBT assessment part of the EPAR table Zanubrutinib is wrongly classified as persistent. This classification is based on the results of a study according to OECD TG 301B, whereas, the results of the study according to OECD TG 308, normalised to 12 °C, are relevant for the classification. Since the provided study according to OECD TG 308 indicates that Zanubrutinib is not persistent, the classification should be changed, but the formation of persistent transformation products could be mentioned.

2.3 Clinical aspects

Introduction

GCP

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

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

- Tabular overview of clinical studies

Pharmacokinetics

Studies BGB-3111-304 and BGB-3111-305

Title of Studies

Study BGB-3111-304: An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.

Study BGB-3111-305: A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.

Methods

Study drug administration

Study BGB-3111-304:

The study included approximately 450 patients in Cohort 1 without the 17p deletion (del(17p)) mutation and approximately 80 additional patients from Chinese sites in Cohort 1a to support further analysis in the Chinese population.

Central randomization (1:1) was used to assign patients in Cohort 1/1a to one of the following study drug treatments:

- Arm A: zanubrutinib
- Arm B: bendamustine + rituximab (B+R)

There are 2 additional cohorts in the study which were not randomized: Cohort 2/Arm C (with del17p), with approximately 100 planned patients, and Cohort 3/Arm D (zanubrutinib in combination with venetoclax), with approximately 80 planned patients. Cohort 3 data are not included [in the current submission].

In all cohorts, zanubrutinib was administered orally at 160 mg twice daily.

Study BGB-3111-305:

Patients were randomized in a 1:1 manner to one of the following treatment arms:

- Arm A: Zanubrutinib 160 mg orally twice daily

- Arm B: Ibrutinib 420 mg orally once daily

The study was planned to enroll approximately 600 patients.

Sampling

Study BGB-3111-304:

Sparse pharmacokinetic (PK) samples to assess zanubrutinib plasma concentrations were collected from all patients assigned to Arm A (Cohort 1/1a) and Arm C prior to dosing (within 30 minutes of dosing), 2 hours (± 30 minutes) after dosing on Day 1 of Cycle 1 and Cycle 2 (each cycle is 28 days or 4 weeks).

Study BGB-3111-305:

Sparse PK samples were collected from all patients assigned to Arm A (zanubrutinib) on Cycle 1 Day 1 predose (within 30 min prior to the morning dose), 2 hours postdose (± 30 minutes), and before patient discharge (4-6 hours post-dose); and predose (within 30 min prior to the morning dose) on Cycle 3 Day 1 and Cycle 4 Day 1. (1 cycle = 28 days).

Bioanalytical methods

Plasma samples were analyzed using a validated liquid chromatography with tandem mass spectrometry method for the determination of zanubrutinib in K2EDTA human plasma. The lower limit of quantitation was 1.0 ng/mL. The updated performance of the bioanalytical method for determination of

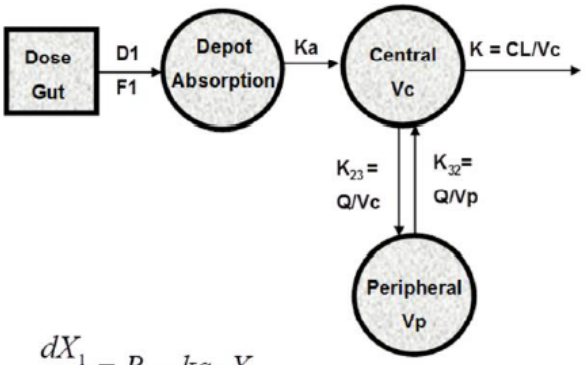
Zanubrutinib concentrations in Study BGB-3111-112, Study BGB-3111-304, and Study BGB-3111-305 is assessed.

Population PK analyses

PopPK analysis was performed using nonlinear mixed effects modelling in NONMEM 7, Version 7.4.3, Perl-Speaks-NONMEM (PsN) Version 4.2 and R 4.1.0 or above. Population PK estimation was performed using the first-order conditional estimation with interaction (FOCEI) method in NONMEM.

A population PK model for zanubrutinib has previously been developed and validated based on data from 632 subjects enrolled in 9 clinical studies (BGB-3111-103, BGB-3111-104, BGB-3111-105, BGB-3111-106, BGB-3111-AU-003, BGB-3111-1002, BGB-3111-205, BGB-3111-206, and BGB-3111-302). The previous model was a two-compartment model with sequential zero-order then first-order absorption and first-order elimination. The previous model was updated with sparse data (data cut-off 21 June 2021) from two Phase 3 studies (BGB-3111-304 and BGB-3111-305) in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) following 160 mg BID zanubrutinib. The previous covariate relationships impacting the PK of zanubrutinib were re-assessed. Observations with |CWRES| >5 were considered as outliers and excluded from the PK analysis dataset. A total of 6500 samples from 1291 subjects were included in the updated Pop PK analysis. Studies 304 and 305 contributed with 1044 and 534 data points from 389 and 271 subjects respectively, where 44 data points were excluded from study 304 and 457 data points (mainly due to missing dosing time) were excluded from study 305.

Figure 1 ***Pop PK model diagram for zanubrutinib***



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

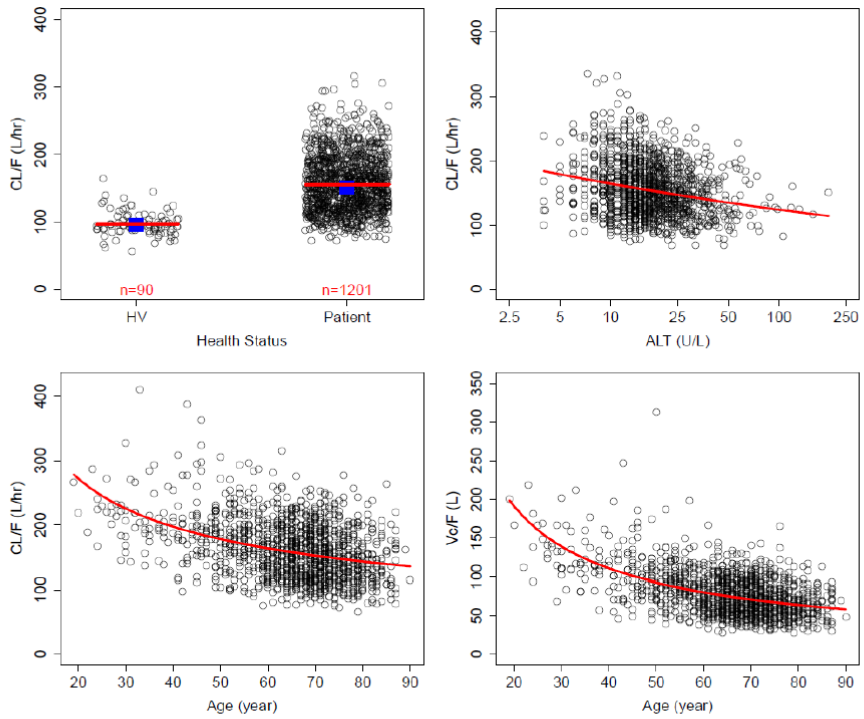
$$\frac{dX_2}{dt} = ka \cdot X_1 - (k + k_{23}) \cdot X_2 + k_{32} \cdot X_3$$

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

D1 = duration for depot compartment
F1 = bioavailability
R1 = rate for depot compartment = Dose/D1
Ka = absorption rate constant
K = elimination rate constant
K_{23} = rate constant from central to peripheral
K_{32} = rate constant from peripheral to central
CL = clearance
Q = inter-compartmental clearance
Vc = central volume
Vp = peripheral volume
X1= the quantity of drug in the absorption compartment
X2 = the quantity of drug in the central compartment
X3 = the quantity of drug in the peripheral compartment
t = time

Testing of covariates one-at-a-time using a stepwise forward addition showed that effect of health status, age, race, and ALT on CL/F and age on Vc/F were significant ($p<0.01$). Race on CL/F was removed in the backward elimination process ($p<0.001$).

Figure 2 PK parameter- covariate relationship for the final PopPK model



Points are the individual parameter estimates after correcting for other covariates. Red lines represent the typical (population) predicted covariate relationship and blue squares represent the geometric mean of the group for categorical covariates.

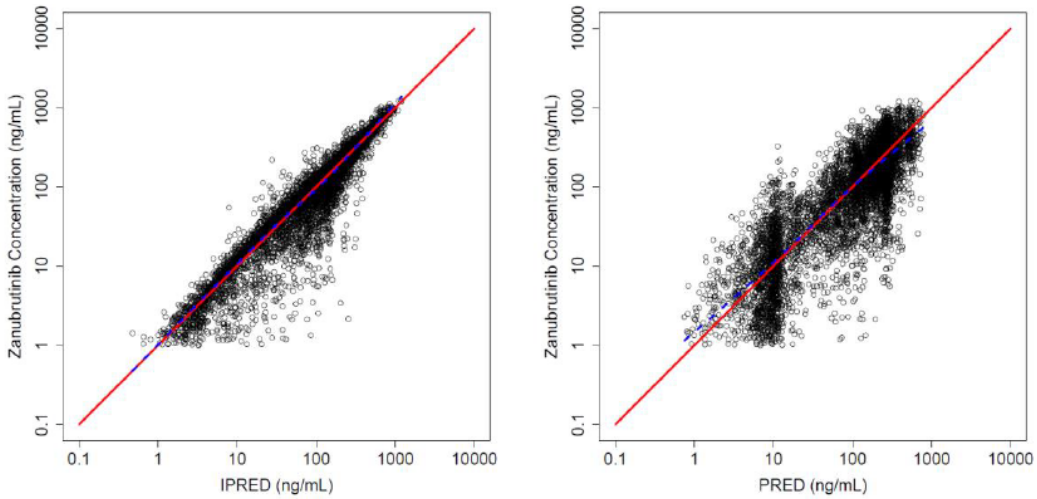
The final updated PopPK model was evaluated by goodness-of-fit plots, pcVPC, NPC, bootstrap (n=1000), and shrinkage assessments.

Table 2 ***Summary of the final population PK parameters.***

Parameter	Parameter Description		Population Estimate (%RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
$exp(\theta_1+\theta_{10})$	Apparent oral clearance, CL/F (L/hr)	Patient	155 (19.5 %)	157 (124, 199)	—
$exp(\theta_1)$		HV	96.4 (19.5%)	95.8 (84.5, 107)	—
θ_{11}	Influence of ALT on CL/F		-0.123 (1.34%)	-0.130 (-0.189, -0.0769)	—
θ_{12}	Influence of age on CL/F		-0.463 (0.302%)	-0.455 (-0.608, -0.300)	—
$exp(\theta_2)$	Apparent central volume, V_c/F (L)		73.6 (0.819%)	71.3 (58.7, 85.2)	—
θ_{13}	Influence of age on V_c/F		-0.788 (0.0482%)	-0.762 (-0.963, -0.455)	—
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)		15.5 (2.67%)	15.6 (13.6, 18.3)	—
$exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)		472 (9.48%)	487 (410, 585)	—
$exp(\theta_5)$	Absorption rate constant, k_a (hr^{-1})		0.477 (1.59%)	0.480 (0.462, 0.501)	—
$exp(\theta_6)$	Duration, D_1 (hr)		1.26 (1.32%)	1.27 (1.16, 1.38)	—
$\omega^2_{CL,Vc}$	Covariance (CL/F,V_c/F)		0.147 (31.7%)	0.142 (0.0681, 0.200)	—
θ_9	Additive residual error (ng/mL, TFDS<5 hr)		72.4 (0.659%)	72.4 (65.1, 80.0)	—
θ_7	Additive residual error (ng/mL, TFDS≥5 hr)		0.730 (2.33%)	0.719 (0.411, 1.10)	—
θ_8	Proportional residual error (%)		45.6 (0.664%)	45.2 (42.7, 47.2)	20.9
IIV (%RSE)	CL/F		37.0 (10.5%)	37.0 (33.8, 40.1)	29.2
	V_c/F		55.1 (26.5%)	55.1 (36.1, 76.6)	44.1
	Q/F		123 (27.9%)	125 (114, 138)	36.5
	V_p/F		70.0 (3.32%)	70.3 (58.9, 85.7)	73.7

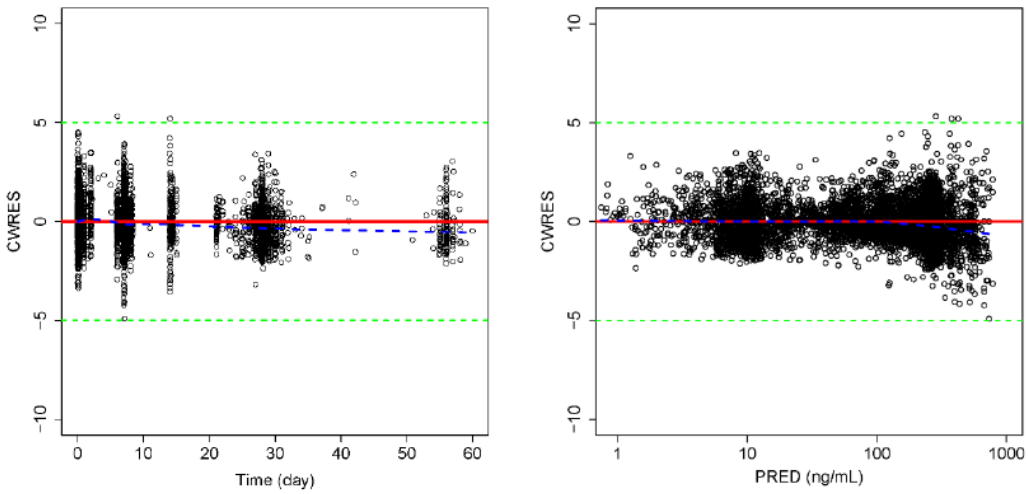
Parameter	Parameter Description	Population Estimate (%RSE)	Median (95% CI) from bootstrapping	Shrinkage (%)
	D_1	55.2 (2.18%)	55.4 (48.3, 61.5)	56.7
IOV (%RSE)	CL/F	33.7 (13.2%)	34.0 (30.8, 37.6)	44.3
	V_c/F	61.7 (0.490%)	63.3 (51.4, 79.2)	71.2

Figure 3. Predicted versus observed concentration diagnostic plots for the final PopPK model



Observed versus individual predicted concentrations (IPRED, left) and observed versus population predicted concentrations (PRED, right) for the final PK model. Red solid lines represent the unit diagonal and blue dashed lines represent the lowess smooth curves.

Figure 4. Residual diagnostic plots for the final PopPK model



Conditional weighted residuals (CWRES) versus time (left) and PRED (right). Points are individual data. Red solid lines represent the unit line at zero. Green dashed lines represent |CWRES| of 5. The blue dashed lines are smooth curves (lowess) showing the relationship between 2 variables.

Figure 5 Prediction- Corrected Visual Predictive Check for CLL/SLL

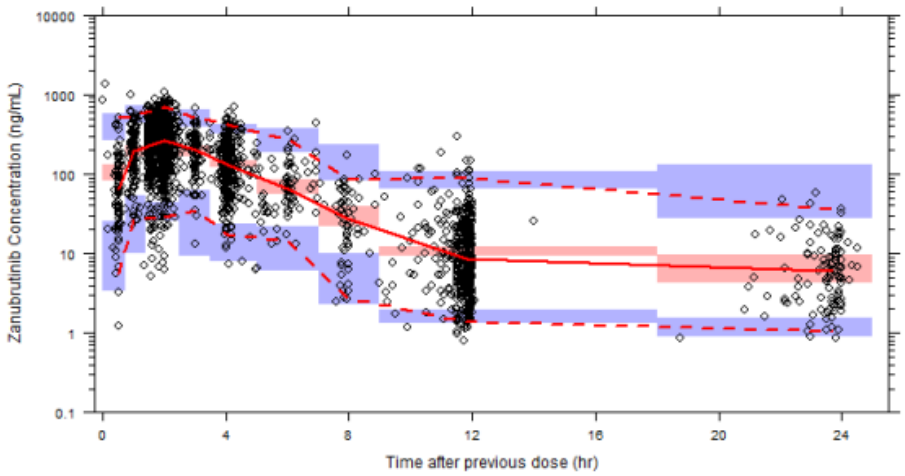
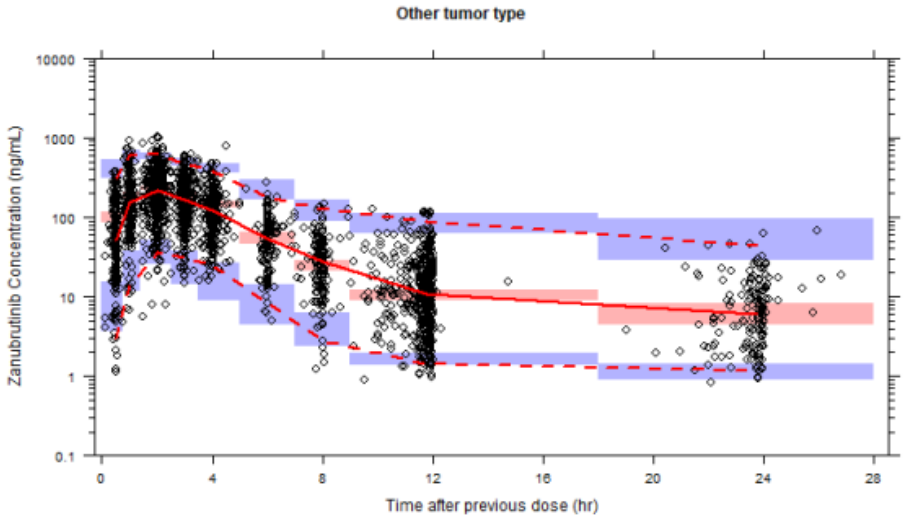


Figure 2: Prediction-Corrected Visual Predictive Check for other Tumour Types



Points are observed concentrations, solid red line represents the median observed value, and dashed red lines represent 2.5%ile and 97.5%iles of the observed values. Pink shaded area represents the spread of the median predicted values (2.5^{th} to 97.5^{th} %ile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5^{th} and 97.5^{th} predicted percentile concentrations.

Covariate effects

A summary of key population PK parameters and covariate effects is presented in Table 2. Interindividual variability (% coefficient of variation, CV) on CL/F, V_c/F, Q/F, V_p/F, and D_1 were 37.0%, 55.1%, 123%, 70.0%, and 55.2%, respectively. The geometric mean elimination half-life ($t_{½}$) was 2.52 hours with a CV of 47.6%.

Table 3: Key Population PK Parameters and Covariate Effects for Representative Subjects

PK Parameters and Baseline Covariates		Estimate	Change from Typical
Typical CL/F (L/hr, ALT=17 U/L, 67 years, patient)		155	NA
Health status	HV	96.4	-38.0%
ALT (U/L)	10th percentile (9 U/L)	168	+8.12%
	90th percentile (33 U/L)	143	-7.82%
Age (year)	10th percentile (49 years)	180	+15.6%
	90th percentile (79 years)	144	-7.34%
Typical V_c/F (L, 67 years)		73.6	NA
Age (year)	10th percentile (49 years)	94.2	+27.9%
	90th percentile (79 years)	64.7	-12.2%
Typical Q/F (L/h)		15.5	NA
Typical V_p/F (L)		472	NA
Typical k_a (hr^{-1})		0.477	NA
Typical D_1 (hr)		1.26	NA

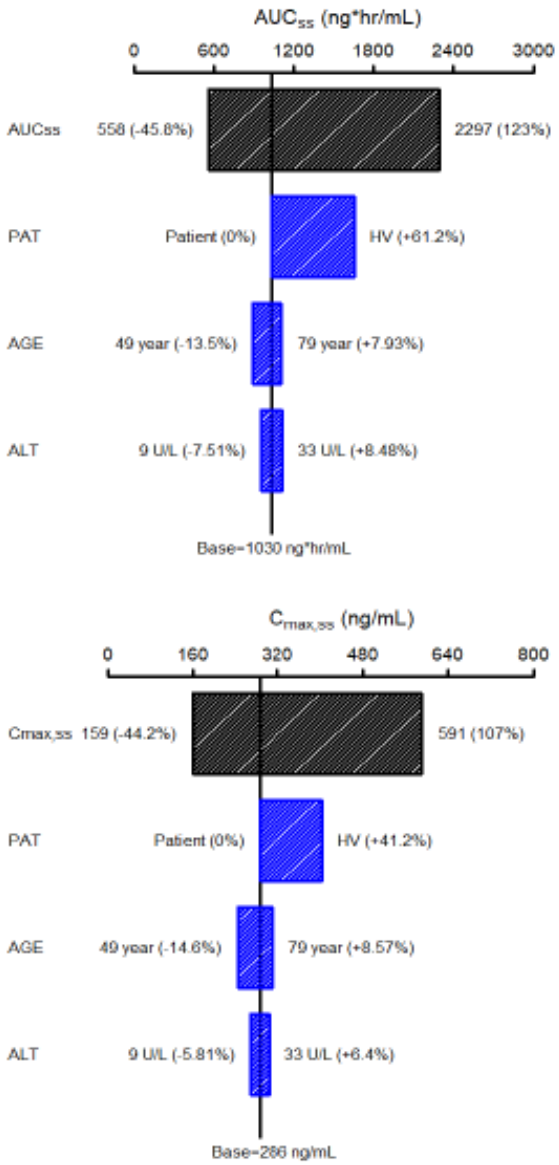
Source: Population PK Report BGB-3111-CP-010 Table 1

Abbreviations: ALT, alanine aminotransferase; CL/F, apparent oral clearance; D_1, the duration; h, hour(s); HV, healthy volunteer; k_a, absorption rate constant; NA, not applicable; PK, pharmacokinetic; Q/F, apparent clearance of distribution from the central to the peripheral compartment; V_c/F, apparent volume of the central compartment; V_p/F, apparent volume of the peripheral compartment.

Baseline body weight, sex, race, AST, bilirubin, CrCL, tumor type, and use of acid-reducing agents did not show statistically significant impact on the PK of zanubrutinib. Health status, baseline ALT, and age were found to be statistically significant covariates on CL/F. Age was identified as a significant covariate on V_c/F.

The covariate sensitivity analysis (Figure 6) showed that predicted steady-state C_{max} ($C_{max,ss}$) and AUC over the 12-hour dosing interval (AUC_{ss}) after repeated-dose administration of 160 mg were 297 ng/mL and 1110 ng•h/mL in a typical patient. This corresponds to a total daily AUCss of 2220 ng*hr/mL. The model predicted geometric mean AUCss, Cmax,ss, and Cmin,ss after repeat-dose administration of 320 mg QD were 2220 ng*hr/mL, 580 ng/mL, and 5.81 ng/mL, respectively in patients with B-Cell malignancies. This analysis also indicated that health status (patients versus HVs) was the most influential covariate on the PK of zanubrutinib. The impact of health status on zanubrutinib CL/F resulted in a 61.2% higher AUC_{ss} and a 41.2% higher $C_{max,ss}$ in HVs compared to patients with B-cell malignancies. Of note, a total of 90 HVs were included in this analysis. This result of higher exposures in HVs estimated by the population PK model is consistent with observed clinical data in healthy subjects versus patients based on cross-study comparisons. The impact of ALT and age on zanubrutinib exposure was relatively small compared with the overall variability of the population, and therefore, ALT and age are not considered to be clinically meaningful covariates.

Figure 6 ***Sensitivity Analysis Plot Comparing the Effect of Covariates on Zanubrutinib Steady-State Exposures (AUC_{ss} and $C_{max,ss}$)***



Source: Population PK Report BGB-3111-CP-010 Figure 1
Abbreviations: AGE, age; ALT, alanine aminotransferase; AUC_{ss}, steady-state area under the plasma concentration-time curve; $C_{max,ss}$, steady-state maximum observed plasma concentration; HV, healthy volunteer(s); PAT, patient.
Note: The black vertical line (Base) refers to the predicted exposure (AUC_{ss}, $C_{max,ss}$) of zanubrutinib in a typical subject after dosing at 160 mg twice daily (BID) for 10 days which serve as the reference value. All percentage values shown in each plot are the relative changes in exposure relative to the reference value. The black-shaded bar with values at each end shows the 5th to 95th percentile exposure range across the study population. Each blue-shaded bar represents the magnitude of influence of the respective covariate on the exposure. The length of each bar represents the range of predicted zanubrutinib exposure between the high/low or possible values of the covariate (indicated at each end of the bar). The covariates shown in each plot are ordered from the most influential covariate at the top to the least influential covariate at the bottom.

Exposure-response analyses

Exposure metrics:

The final population pharmacokinetic model for CLL was applied to predict zanubrutinib exposure. Zanubrutinib plasma concentration time profiles were simulated using the Bayesian post hoc individual PK parameters. Derived exposure metrics were: AUCss, Cmax,ss, and Cmin,ss.

Efficacy:

In Study BGB-3111-304, efficacy endpoints were PFS (primary) and ORR (secondary). PFS was assessed by IRC and defined as the length of time from randomization until disease progression or death. In Study BGB-3111-305, the primary endpoint was ORR (PR or higher). ORR was determined by IRC and defined as the proportion of patients who achieved a PR or CR. The ORR (PR-L or higher) was also explored as a secondary efficacy endpoint for BGB-3111-305. The E-R relationships for efficacy endpoints of ORR (PR or higher) and ORR (PR-L or higher) were explored separately and conducted based on the data from patients:

- patients without del17p (Arm A) in Study BGB-3111-304 (n=278)
- patients with del17p (Arm C) in Study BGB-3111-304 (n=110)
- patients in Study BGB-3111-305 (n=173)

Plots of Kaplan-Meier PFS curves stratified by quartiles of model-predicted AUCss, Cmax,ss, and Cmin,ss suggested that PFS was not different among zanubrutinib exposure quartiles based on the data from 388 patients in Study BGB-3111-304. There was no apparent relationship between PFS and any of the zanubrutinib exposure metrics in the zanubrutinib treated patients in Study BGB-3111-304. The probability of response plots and logistic regression models for ORR (PR or higher) or ORR (PR-L or higher) indicated none of the zanubrutinib exposure metrics had a significant effect on E-R relationship for these endpoints ($p>0.01$).

Safety:

A total of 660 patients from studies BGB-3111-304 (n=389) and BGB-311-305 (n=271) were included in the pooled exposure safety analyses. The E–R relationship was assessed between zanubrutinib exposure metrics (AUCss, Cmax,ss, and Cmin,ss) and safety endpoints, including AEs leading to treatment discontinuation and AEs of interest (grade ≥3 neutropenia, thrombocytopenia, anemia, infections/infestations, secondary primary malignancies, atrial fibrillation/flutter, major bleeding events, and any bleeding events).

The exposure ranges appeared to be similar in patients who experienced AEs of interest relative to those who were not based on 660 patients from studies BGB-3111-304 (n=389) and BGB-3111-305 (n=271). The probability of response plots and logistic regression models showed that there were no evident E–R relationships between exposure metrics (AUCss, Cmax,ss, or Cmin,ss) and the probability of occurrence of safety measures.

Absorption, distribution, metabolism, excretion

In the initial MAA (the WM indication), the ADME characteristics of zanubrutinib were documented. There is no reason to believe that the ADME characteristics should be significantly different in patients with CLL/SLL. Accordingly, the Applicant's proposed changes to SmPC section 5.2 are limited to revisions reflecting the characteristics of the 1291 subjects included in the current submission's updated PopPK analysis. This is endorsed.

Dose proportionality and time dependencies

Dose proportionality and time dependency of PK parameters were addressed in the initial WM application: Cmax and AUC0-∞ appeared to increase dose-proportionally after single-dose oral administration of zanubrutinib from 40 mg to 320 mg in patients with B-cell malignancies. The present application concerns the same proposed dose regimen (a 320 mg total daily dose administered as 160 mg twice daily or 320 mg once daily), and the dose proportionality and PK time dependency are not expected to differ from the previously approved WM indication.

Dose justification

The proposed dose regimen in patients with CLL/SLL is a 320 mg total daily dose (administered as 160 mg twice daily or 320 mg once daily). This is based on the totality of safety, efficacy, PK and pharmacodynamics (BTK occupancy data) results from studies BGB-3111-AU-003, BGB-3111-205, BGB-3111-304, and BGB-3111-305.

In Study BGB-3111-AU-003 at dose regimens of 40, 80, 160 and 320 mg once daily and 160 mg twice daily, the maximum tolerated dose was not reached, and no dose-limiting toxicities were observed during the dose-escalation part of the study. Moreover, nearly full occupancy of BTK in peripheral blood mononuclear cells (PBMC) was achieved in patients at all administered doses. The BTK occupancy in lymph node tissue was assessed at 160 mg twice daily and 320 mg once daily. At the 160 mg twice daily dose, the median BTK occupancy of 100% was observed at steady-state trough and 94% in the 320 mg once daily group. To maximize the inhibition in target tissue, the 160 mg twice daily dose has been used in studies BGB-3111-304 and BGB-3111-305, as well as other ongoing Phase 2/3 studies. The results of pivotal Phase 3 studies BGB-3111-304 and BGB-3111-305 provided the primary evidence of effectiveness in patients with CLL/SLL and supported the proposed zanubrutinib dose of 160 mg twice daily.

In study BGB-3111-AU-003, the overall response rate was 100% (N = 40/40) for the 320 mg once daily dose compared to 92.8% (N = 77/83) for the 160 mg twice daily dose. The CR rate was 22.5 % (N=9/40) for the 320 mg once daily dose compared to 13.3% (N = 11/83) for the 160 mg twice daily dose. Although the number of CLL/SLL patients treated at 320 mg once daily (N=40) is limited relative to those at 160 mg twice daily dose (N=83), the totality of data, including pharmacokinetic, pharmacodynamic, safety, efficacy, and exposure–response analyses, provided support for the recommended 320-mg total daily dose for patients with CLL/SLL. Objective responses have been observed in patients with various B-cell malignancies (including CLL/SLL, MCL, WM, MZL, and FL) at all tested dose levels from 40 mg to 320 mg. Numerically comparable overall response rates have also been observed between the once daily and twice daily regimens in patients with MCL and WM (Tam, et

al 2021). Furthermore, no remarkable difference in AEs between the 2 regimens in the safety population in study BGB-3111-AU-003 were observed (Ou et al 2021).

Additional data support a 320 mg once daily regimen as an option in addition to the 160 mg twice daily regimen for patients with CLL/SLL. Given the same total daily dose (320 mg) and linear PK, similar exposures/AUC are achieved between the 320 mg once daily and 160 mg twice daily dose. At the 320 mg once daily dose, a sustained and profound BTK inhibition in PBMC and lymph node tissue were also observed. E-R analyses indicated that there was no evident E-R relationship between exposure ($AUC_{0-24,ss}$, $C_{max,ss}$, or $C_{min,ss}$) and safety endpoints (AEs of interests) in patients with B-cell malignancies (Report BGB-3111-CP-007) and in patients with CLL/SLL (Report BGB-3111-CP-011). There were no significant relationships between zanubrutinib exposure and AEs including cytopenias, infections, and bleeding. In addition, the E-R analysis in patients with CLL/SLL (Report BGB-3111-CP-011) and other B-cell malignancies including MCL (Report BGB-3111-CP-003), WM (Report BGB-3111-CP-007), and MZL (Report BGB-3111-CP-009) indicated that efficacy (ORR) does not appear to be significantly impacted by C_{max} or C_{min}, and therefore the same total daily dose and corresponding AUC delivered by a 320 mg once daily regimen are expected to result in a similar ORR as that of the 160 mg twice daily regimen.

The totality of the data summarized here thus support the recommended dose of a 320 mg total daily dose (as 160 mg twice daily or 320 mg once daily) in adult patients with CLL/SLL. This is based on consistent and sustained BTK occupancy in PBMCs and target tissue, high rates of overall response in patients with CLL/SLL, and a favorable safety and tolerability profile.

Pharmacokinetic interaction studies

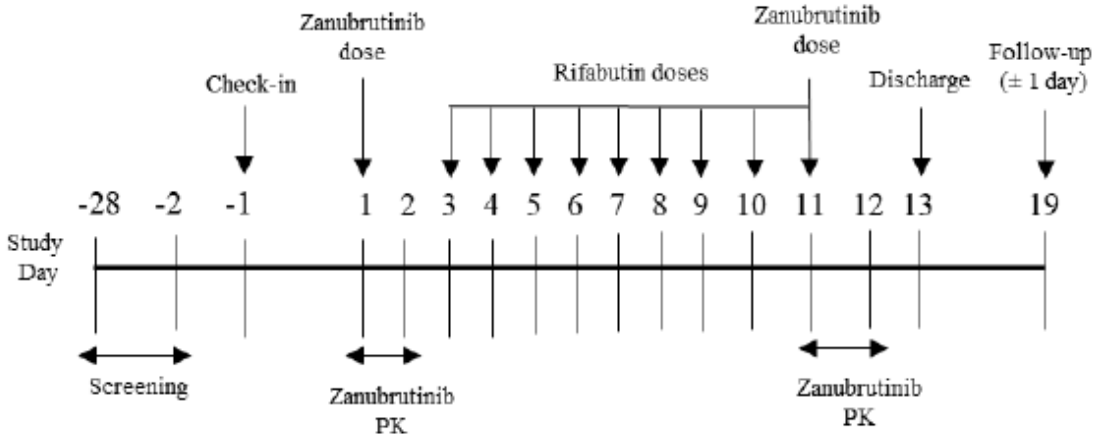
Title of Study

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

Methods

Study drug administration

Figure 7: Study Schematic



Abbreviation: PK = pharmacokinetics.

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

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

Sampling

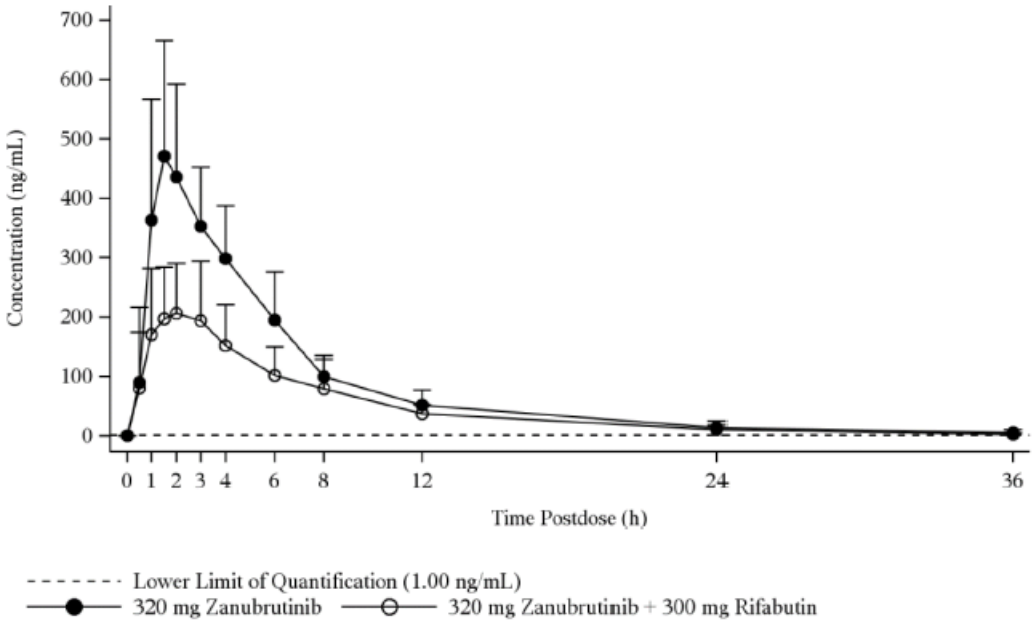
On PK sampling days (Days 1 and 11), blood samples for analysis of plasma zanubrutinib were collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours postdose. The allowed sampling windows for PK blood samples were as follows: within 15 minutes prior to dosing for the predose sample timepoint;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

Results

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

Following the administration of 320 mg zanubrutinib alone on Day 1 and the coadministration with 300 mg rifabutin on Day 11, median times of the maximum observed plasma concentration (tmax) of 1.50 and 2.00 hours postdose were observed, respectively (Figure 8). Systemic exposure to zanubrutinib was lower following the coadministration of 320 mg zanubrutinib with 300 mg rifabutin compared to the administration of 320 mg zanubrutinib alone, with a geometric mean area under the plasma concentration time curve (AUC) approximately 44% lower and maximum observed plasma concentration (C_{max}) 48% lower (Table 1). This represented a decreased exposure of 1.8-fold for AUC_{0-t} and $AUC_{0-\infty}$, and 1.9-fold for C_{max} when zanubrutinib was administered with a moderate CYP3A inducer.

Figure 8 Arithmetic Mean (+ SD) Zanubrutinib Plasma Concentration Profiles Following Administration of 320 mg Alone and Coadministration With 300 mg Rifabutin (Linear Scale)



Source: BGB-3111-112 CSR Figure 2.
Abbreviations: h, hour; mL, milliliters; ng, nanograms; SD, standard deviation.

Table 4: ***Study BGB-3111-112: Statistical Analysis of Pharmacokinetic Parameters of Zanubrutinib After Administration of 320 mg Zanubrutinib Alone and After Coadministration With 300 mg Rifabutin***

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

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

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

Pharmacodynamics

Mechanism of action

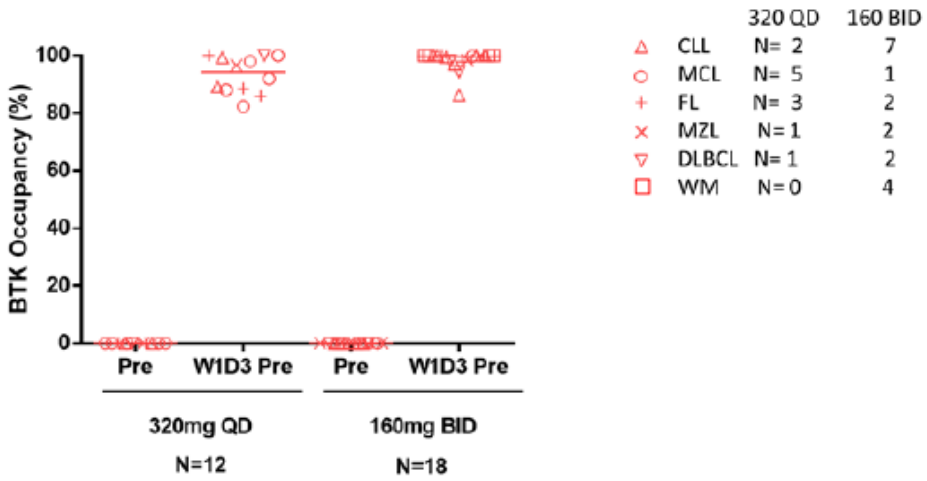
Zanubrutinib is a next-generation, potent BTK inhibitor. Like other active BTK inhibitors, zanubrutinib forms an irreversible covalent bond at Cys_{481} within the adenosine triphosphate binding pocket of the BTK protein.

Primary pharmacology

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

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

Figure 9 : BTK receptor occupancy in lymph nodes by different tumor types



PK/PD modelling

To support dose recommendations, exposure-efficacy and exposure-safety relationships were evaluated in patients with CLL/SLL receiving zanubrutinib monotherapy in studies BGB-3111-304 and BGB-3111-305. The exposure-response (E-R) analysis for efficacy was conducted separately for BGB-3111-304 in patients with TN CLL/SLL and BGB 3111 305 in patients with R/R CLL/SLL. E-R analysis also included patients with CLL/SLL for the pooled exposure-safety analysis (Report BGB-3111-CP-011, N=660).

The exposure for zanubrutinib was summarized as cumulative steady state AUC over 24 hours ($AUC_{0-24,ss}$), $C_{max,ss}$, or $C_{min,ss}$. Exposure data ($AUC_{0-24,ss}$, $C_{max,ss}$, or $C_{min,ss}$) derived from the population PK analysis (Report BGB-3111-CP-010) were used in the analysis. Analyses were performed using data from all patients who had ≥ 1 set of the estimated PK parameters. Individual PK parameters from these studies were merged with the corresponding efficacy or safety data from studies BGB-3111-304 and BGB-3111-305 (Report BGB-3111-CP-011). In both studies, zanubrutinib was administered orally as a 160 mg BID regimen.

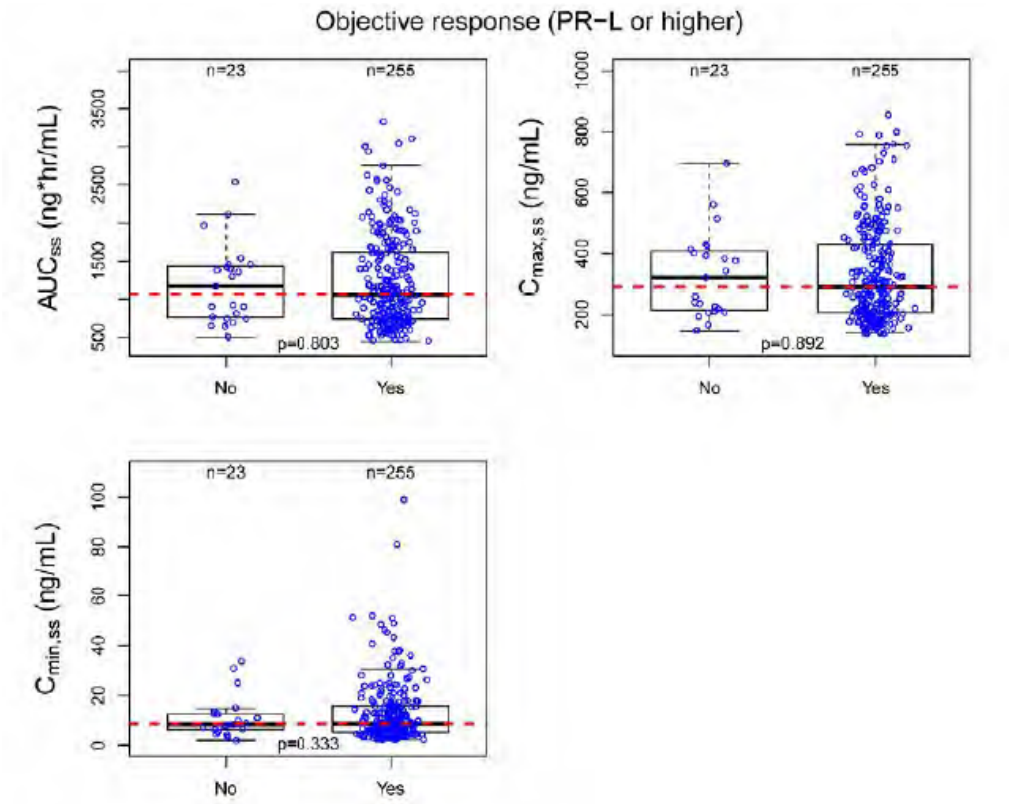
Exposure-Efficacy Relationship – Study BGB-3111-304

Data from BGB-3111-304 Arm A, in patients with CLL/SLL without del17p (N=278 with PK) and in Arm C, with del17p (N=110 with PK) were included in the E-R analysis of efficacy outcomes. The efficacy in patients with CLL/SLL was investigated with the responder group including patients with best overall response of complete response (CR), partial response (PR) or higher, and partial response with lymphocytosis (PR-L) or higher; the non-responder group included patients with best overall response of stable disease and progressive disease.

Exposure-Response Relationship for Efficacy in Patients with TN CLL/SLL (without del17p) - *ORR Assessed by IRC (PR-L or higher)*

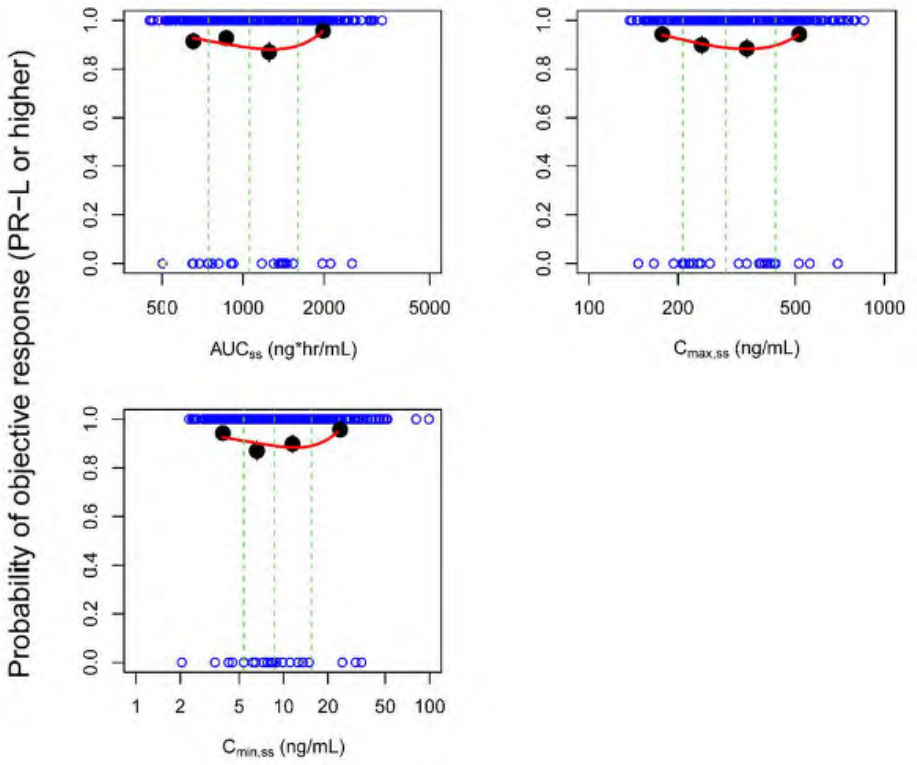
Box plots of zanubrutinib exposure by IRC-assessed objective response (PR-L or higher) of CLL/SLL patients in Arm A, without del17p, are presented in Figure 4. Although a range of exposures was observed in both responders and non-responders, the median $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{min,ss}$ values were similar in responders compared with those of non-responders. The probability of ORR (defined as the proportion of subjects who achieve CR + PR) by quantiles of zanubrutinib exposure is shown in Figure 5. Based on visual inspection of exploratory plots, the E-R logistic regression model for IRC-assessed ORR with $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$ was developed and the diagnostic plots of the model are presented in Figure 6. The results of the logistic regression model confirmed that $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$ were not associated with the probability of ORR in patients with TN CLL/SLL without del17p (p-value >0.1). Overall, there was no apparent E-R relationship for zanubrutinib based on response assessments of ORR (PR-L or higher).

Figure 10: ***Box Plots of Zanubrutinib Exposure by IRC-Assessed Objective Response of Patients With CLL/SLL in Study BGB-3111-304 (Arm A, Without del17p)***



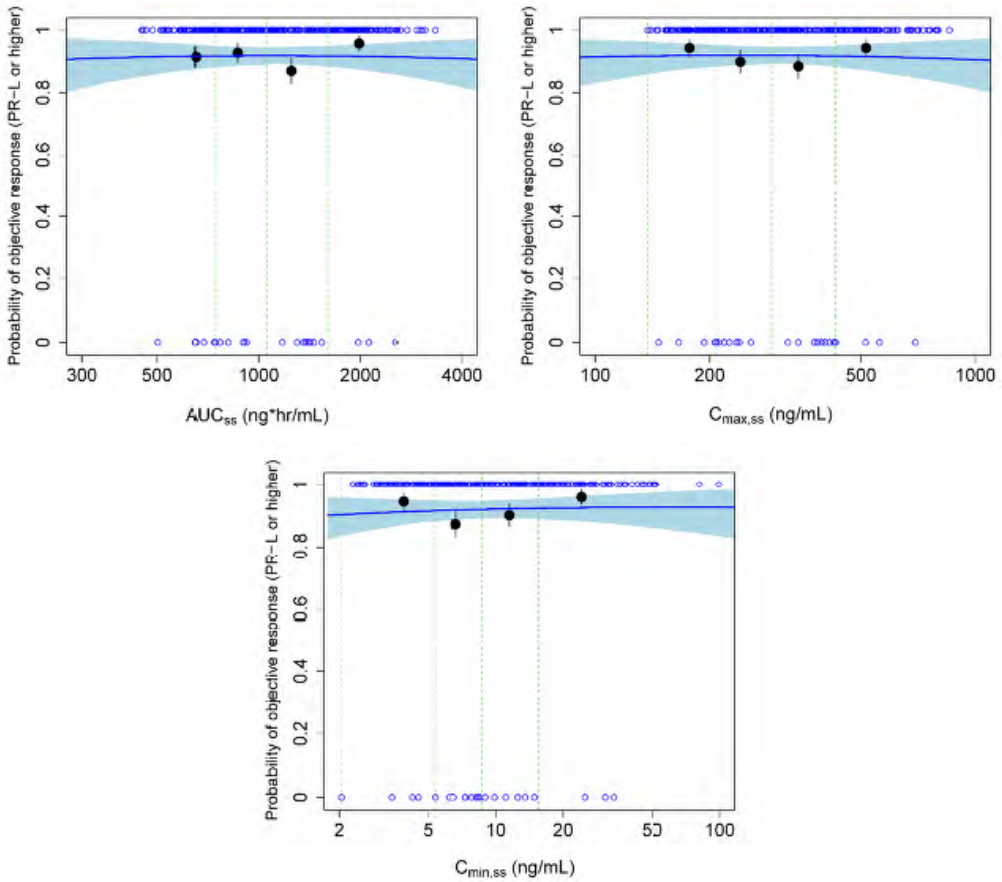
Source: Exposure-Response Analysis Report (BGB-3111-CP-011) Figure 11. Data cutoff date: 07 May 2021.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$, steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration; IQR, interquartile range.
Note: Symbols are the model predicted exposure matrices. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value of the overall population.

Figure 11 ***Probability of IRC-Assessed Objective Response Versus Exposure of Patients With CLL/SLL in Study BGB-3111-304 (Arm A, Without del17p)***



Source: Exposure-Response Report BGB-3111-CP-011 Figure 12. Data cutoff date: 07 May 2021.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration.
Note: The blue open circles reflect the observed events in zanubrutinib treated subjects. The black solid circles are the observed probability of ORs, and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of OR and N is the number of patients in each quantile bin) for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The red lines are smooth curves (loess) to show the relationship between two variables.

Figure 12 ***Logistic Regression of Probability of IRC-Assessed Objective Response Versus Exposure of Patient With CLL/SLL in Study BGB-3111-304 (Arm A, Without del17p)***



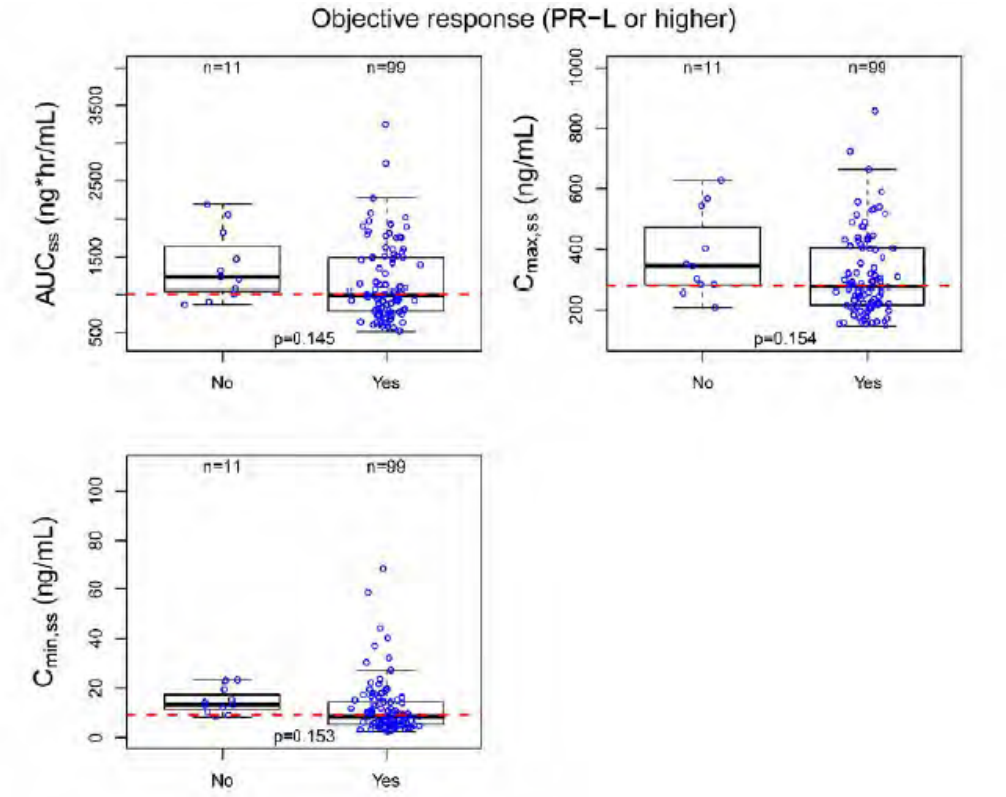
Source: Exposure-Response Report BGB-3111-CP-011 Figure 38. Data cutoff date: 07 May 2021.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration
Note: The open blue circles reflect the observed events for patients without del17p (Arm A) in study BGB-3111-304. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/N)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue line and light blue shaded area are the median and 95% prediction interval based on 1000 bootstrap samples of the model.

Exposure-Response Relationship for Efficacy in Patients with TN CLL/SLL (with del17p) – *ORR Assessed by IRC (PR-L or higher)*

Box plots of zanubrutinib exposure by IRC-assessed objective response (PR-L or higher) of CLL/SLL patients in Arm C, with del17p, are presented in Figure 7. Although a range of exposures was observed in both responders and non-responders, the median $AUC_{0\text{-}24,ss}$, $C_{max,ss}$, and $C_{min,ss}$ values were similar in responders compared with those of non-responders. The probability of ORR (defined as the proportion of subjects who achieve CR + PR) by quantiles of zanubrutinib exposure is shown in Figure 8. Based on visual inspection of exploratory plots, the E-R logistic regression model for IRC-assessed ORR with $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0\text{-}24,ss}$ was developed and the diagnostic plots of the model are presented in Figure 9. The results of the logistic regression model confirmed that $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0\text{-}24,ss}$ were not associated with the probability of ORR in patients with TN CLL/SLL with del17p (p-value>0.1).

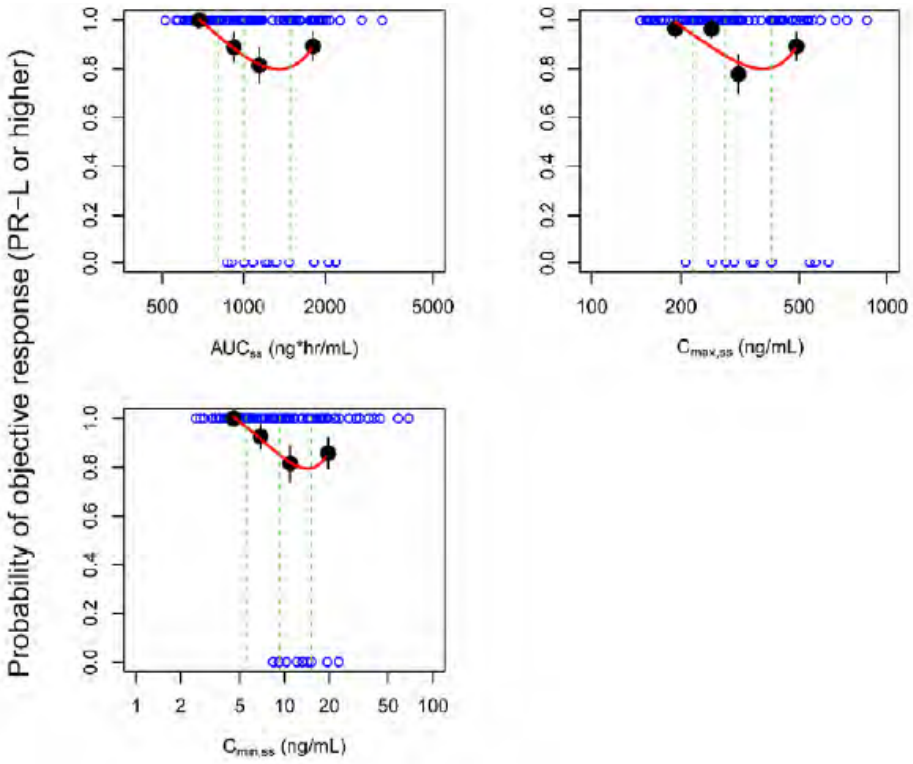
Overall, there was no apparent E-R relationship for zanubrutinib, based on response assessments of ORR (PR-L or higher).

Figure 13 ***Box Plots of Zanubrutinib Exposure by IRC-Assessed Objective Response of Patients With CLL/SLL in Study BGB-3111-304 (Arm C, With del17p)***



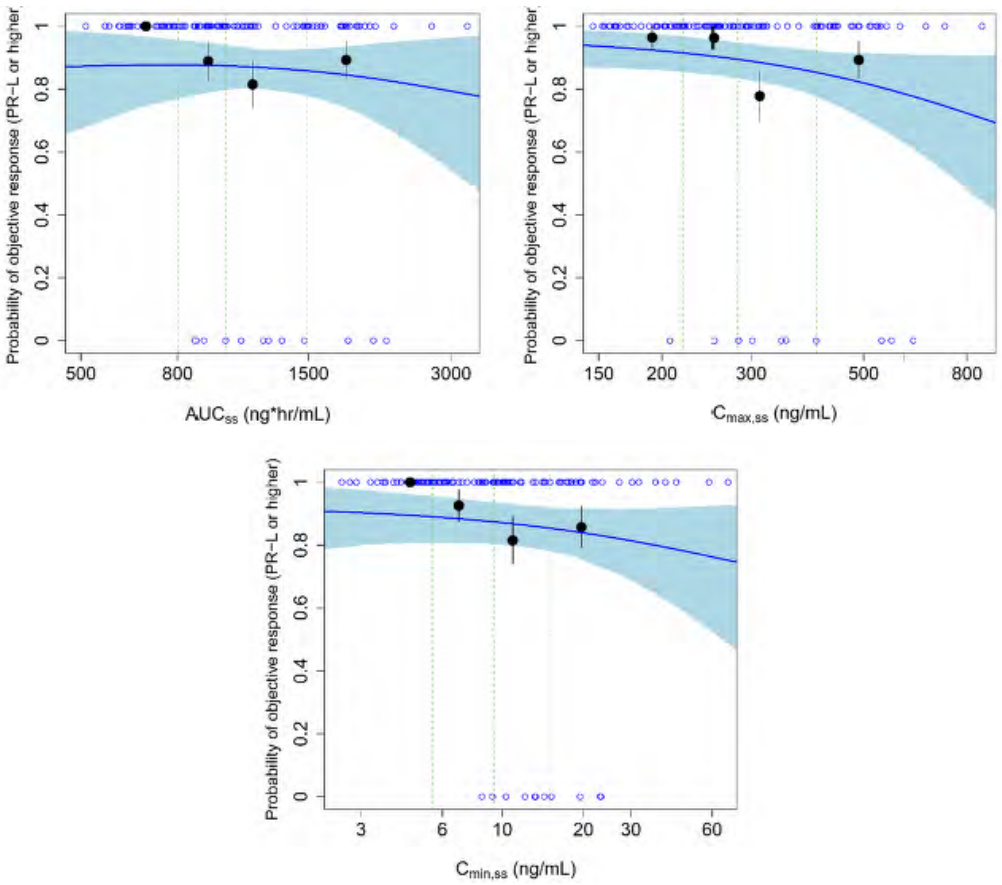
Source: Exposure-Response Analysis Report (BGB-3111-CP-011) Figure 13. Data cutoff date: 07 May 2021.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$, steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration; IQR, interquartile range.
Note: Symbols are the model predicted exposure matrices. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value of the overall population.

Figure 14 ***Probability of IRC-Assessed Objective Response Versus Exposure of Patients With CLL/SLL in Study BGB-3111-304 (Arm C, With del17p)***



Source: Exposure-Response Report BGB-3111-CP-011 Figure 14. Data cutoff date: 07 May 2021.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration.
Note: The blue open circles reflect the observed events in zanubrutinib treated subjects. The black solid circles are the observed probability of ORs, and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of OR and N is the number of patients in each quantile bin) for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The red lines are smooth curves (loess) to show the relationship between two variables.

Figure 15**: Logistic Regression of Probability of IRC-Assessed Objective Response Versus Exposure of Patient With CLL/SLL in Study BGB-3111-304 (Arm C, With del17p)**



Source: Exposure-Response Report BGB-3111-CP-011 Figure 39. Data cutoff date: 07 May 2021.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration.
Note: The open blue circles reflect the observed events for patients with del17p (Arm C) in Study BGB-3111-304. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/N)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue line and light blue shaded area are the median and 95% prediction interval based on 1000 bootstrap samples of the model.

Exposure-Efficacy Relationship

Data from study BGB-3111-305 Arm A, in patients with R/R CLL/SLL (N=173) were included in the E-R analysis of efficacy outcomes.

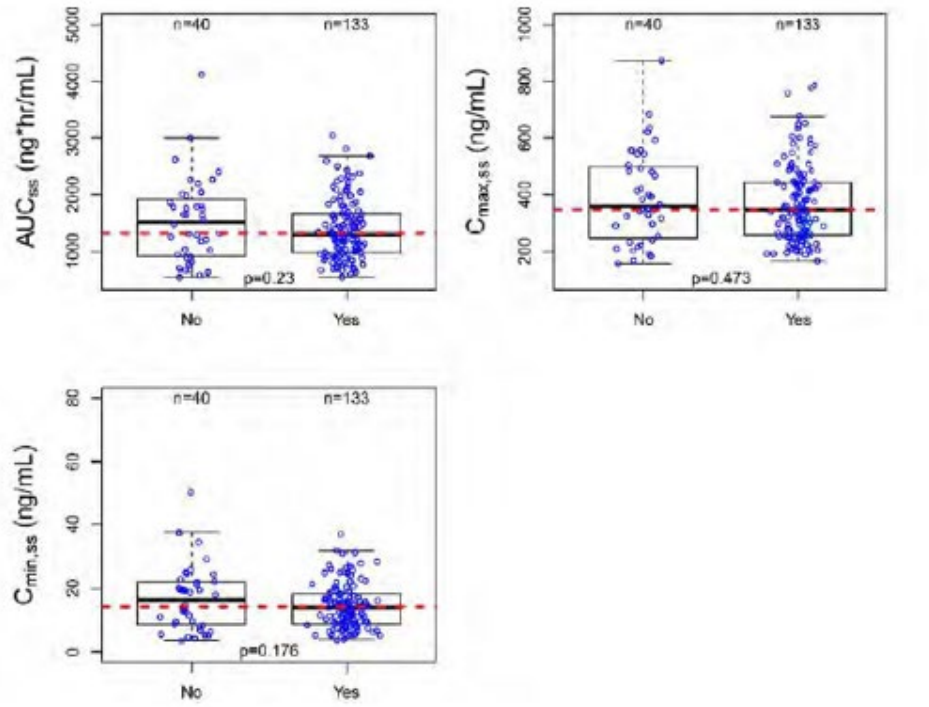
The efficacy in patients with R/R CLL/SLL was investigated with the responder group, including patients with best overall response of complete response (CR), partial response (PR) or higher, and partial response with lymphocytosis (PR-L) or higher; the non-responder group included patients with best overall response of stable disease and progressive disease.

ORR Assessed by IRC (PR or higher)

Box plots of zanubrutinib exposure by IRC-assessed objective response (PR or higher) of R/R CLL/SLL patients are presented in Figure 10. Although a range of exposures was observed in both responders and non-responders, the median $AUC_{0\text{-}24,ss}$, $C_{max,ss}$, and $C_{min,ss}$ values were similar in responders compared with those of non-responders. The probability of ORR (defined as the proportion of subjects who achieve CR + PR) by quantiles of zanubrutinib exposure is shown in Figure 11. Based on visual

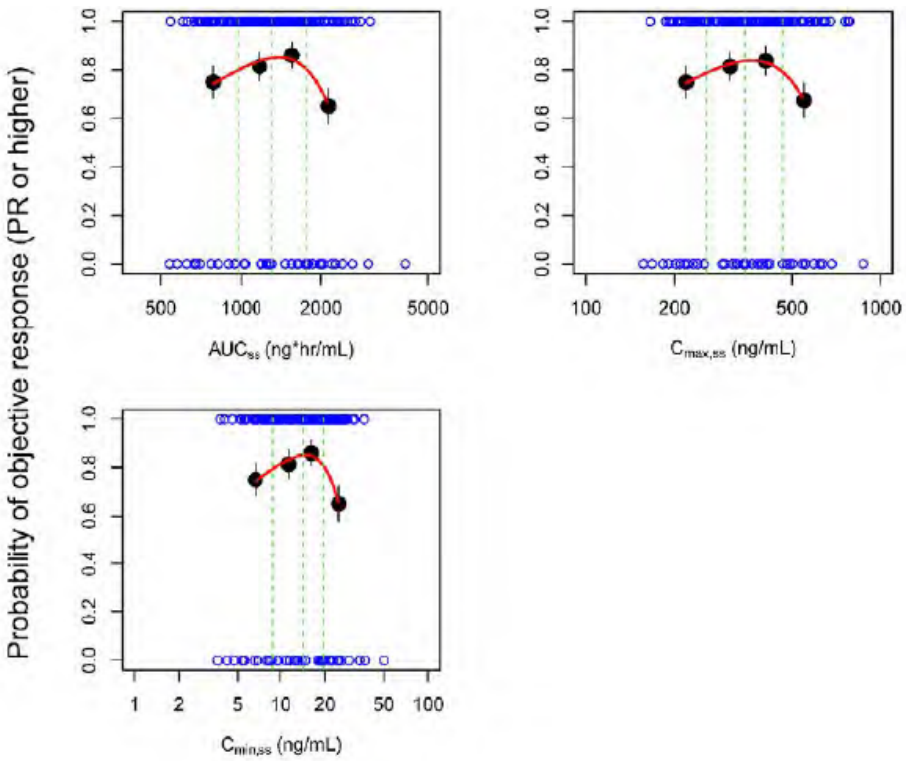
inspection of exploratory plots, the E-R logistic regression model for IRC-assessed ORR with $C_{max,ss}$, $C_{min,ss}$ and $AUC_{0-24,ss}$ was developed and the diagnostic plots of the model are presented in Figure 12. The results of the logistic regression model confirmed that $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$ were not associated with the probability of ORR in patients with RR CLL/SLL (p-value>0.1). Overall, there was no apparent E-R relationship for zanubrutinib, based on response assessments of ORR (PR or higher).

Figure 16 ***Box Plots of Zanubrutinib Exposure by IRC-Assessed Objective Response of Patients With R/R CLL/SLL in Study BGB-3111-305***



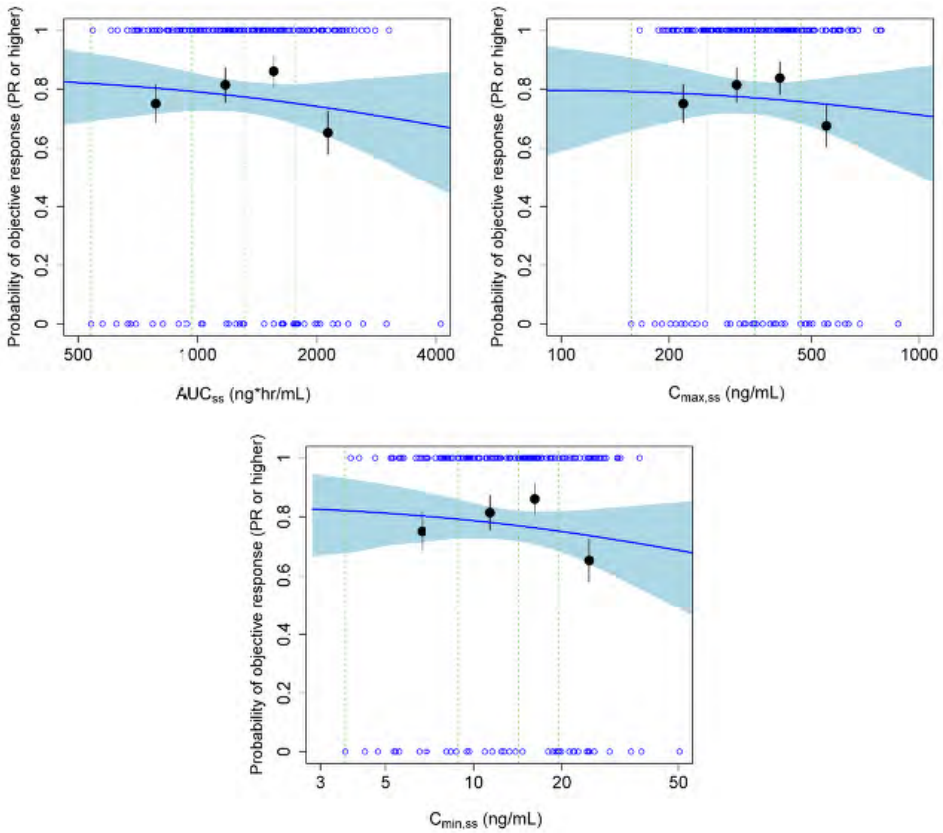
Source: Exposure-Response Analysis Report (BGB-3111-CP-011) Figure 9. Data cutoff date: 31 Dec 2020
Abbreviations: $AUC_{0-24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$, steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration; IQR, interquartile range.
Note: Symbols are the model predicted exposure matrices. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents the median value of the overall population.

Figure 17 ***Probability of IRC-Assessed Objective Response Versus Exposure of Patients With R/R CLL/SLL in Study BGB-3111-305***



Source: Exposure-Response Report BGB-3111-CP-011 Figure 10. Data cutoff date: 31 Dec 2020.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration.
Note: The blue open circles reflect the observed events in zanubrutinib treated subjects. The black solid circles are the observed probability of ORs, and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of OR and N is the number of patients in each quantile bin) for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The red lines are smooth curves (loess) to show the relationship between two variables.

Figure 18 ***Logistic Regression of Probability of IRC-Assessed Objective Response Versus Exposure of Patient With R/R CLL/SLL in Study BGB-3111-305***



Source: Exposure-Response Report BGB-3111-CP-011 Figure 37. Data cutoff date: 31 Dec 2020.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration.
Note: The open blue circles reflect the observed events for patients in study BGB-3111-305. The filled black symbols are the observed probability of events and the error bars are SE [sqrt (P*(1-P)/N)] for quantiles (at 100x(1/N)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue line and light blue-shaded area are the median and 95% prediction interval based on 1000 bootstrap samples of the model.

Exposure-Safety Relationship

Exposure-safety analyses were performed using pooled data from 2 studies (BGB-3111-304 and BGB-3111-305). A total of 660 patients were included in the exposure-safety analyses (Report BGB-3111-CP-011). E-R relationships were assessed between zanubrutinib exposure metrics (model predicted $C_{min,ss}$, $C_{max,ss}$ and $AUC_{0\text{-}24,ss}$) and adverse events (AE) of interest (Grade ≥ 3 neutropenia, Grade ≥ 3 thrombocytopenia, Grade ≥ 3 anemia, Grade ≥ 3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, any bleeding events and AEs leading to treatment discontinuation). The summary of the safety endpoints is shown below.

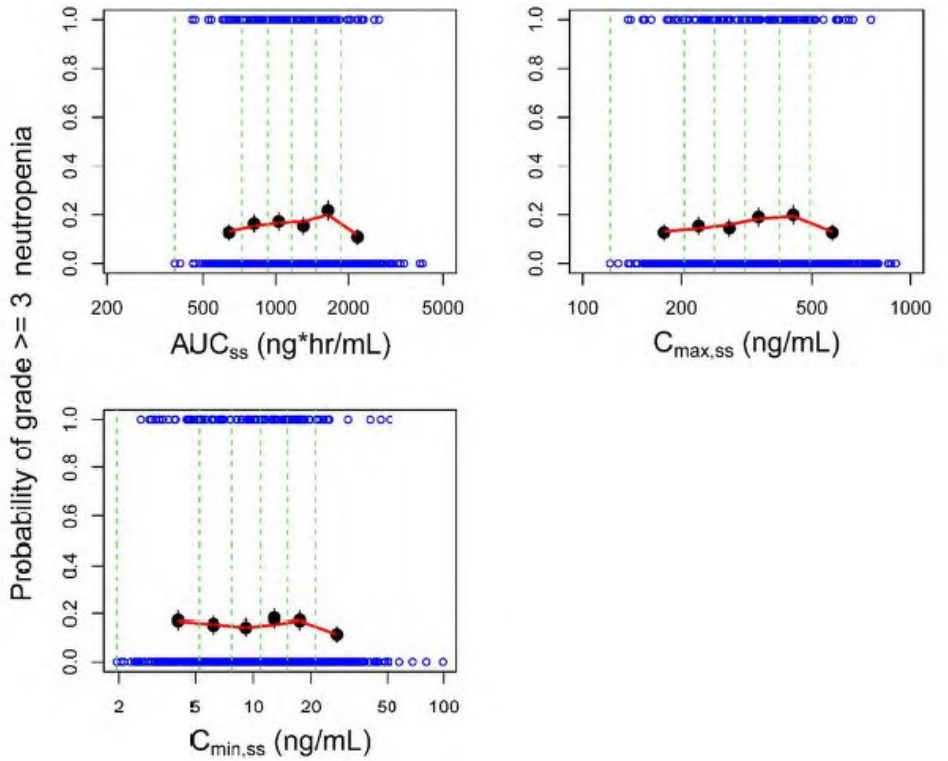
Table 5 ***Summary of safety endpoints in the exposure safety analysis dataset***

Safety Endpoints	The percentage of patients having AE [%(Yes/No)]		
	BGB-3111-304 (n=389)	BGB-3111-305 (n=271)	Total (n=660)
Grade≥3 neutropenia	17.0% (66/323)	14.0% (38/233)	15.8% (104/556)
Grade≥3 thrombocytopenia	2.57% (10/379)	4.43% (12/259)	3.33% (22/638)
Grade≥3 anemia	5.14% (20/369)	5.54% (15/256)	5.30% (35/625)
Grade≥3 infections/infestations	16.2% (63/326)	11.8% (32/239)	14.4% (95/565)
All events of secondary primary malignancies	14.1% (55/334)	5.54% (15/256)	10.6% (70/590)
All events of atrial fibrillation and flutter	3.08% (12/377)	1.11% (3/268)	2.27% (15/645)
Major bleeding events	5.66% (22/367)	2.21% (6/265)	4.24% (28/632)
Any bleeding events	46.0% (179/210)	32.1% (87/184)	40.3% (266/394)
AE leading to treatment discontinuation	7.46% (29/360)	7.38% (20/251)	7.42% (49/611)

The analysis showed that there were no evident E-R relationships between exposure ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$, or $C_{min,ss}$) and the probability to have AEs of interest examined. The exposure ranges appeared to be similar in patients experiencing AEs of interest relative to those who were not. Plots showing a probability of Grade ≥ 3 neutropenia versus steady-state exposures ($C_{max,ss}$, $AUC_{0\text{-}24,ss}$, and $C_{min,ss}$) are shown in Figure 13. Similarly, no evident E-R relationships were observed for other safety endpoints, including Grade ≥ 3 neutropenia, Grade ≥ 3 thrombocytopenia, Grade ≥ 3 anemia, Grade ≥ 3 infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, any bleeding events and AEs leading to treatment discontinuation.

Figure 19 ***Probability of Grade ≥ 3 Neutropenia vs Steady-State Exposures in Patients With CLL/SLL***

PK/PD modelling



Discussion on clinical pharmacology

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

The present application concerns approval of zanubrutinib as monotherapy for treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The current application's clinical pharmacology package includes data from a Phase 3, open-label study of zanubrutinib in patients with previously untreated CLL/SLL (Study BGB-3111-304), a Phase 3, open-label study of zanubrutinib in patients with relapsed/refractory CLL/SLL (BGB-3111-305) and a clinical DDI study (BGB-3111-112).

No new bioanalytical methods were applied for detection of zanubrutinib. A previous Pop PK model, a two-compartment model with sequential zero-order then first-order absorption and first-order elimination, was updated with data from studies 304 and 305 to characterise the PK of zanubrutinib in CLL/SLL patients.

All patients with CLL/SLL from studies BGB-3111-304 and BGB-3111-305 were exposed to an initial zanubrutinib dose of 160 mg twice daily. The justification for the dose selection relies on data submitted with the initial WM application, including analyses of PK, BTK receptor occupancy in PBMCs and lymph node biopsies, and exposure-response for safety and efficacy. Multiple cohorts of patients with various B-cell malignancies including CLL/SLL comprised the clinical populations studied in the initial WM

application; Their demographic characteristics were comparable to those expected for adult patients with CLL/SLL. The rationale of the dose selection is overall acceptable.

No relation to exposure was found for either efficacy or safety endpoints in the CLL/SLL patient population.

The ADME characteristics were described in the original WM marketing application, and the Applicant's proposed changes to SmPC section 5.2 are limited to revisions reflecting the characteristics of the 1291 subjects included in the current submission's updated PopPK analysis. Based on the efficacy, safety and PK results observed, the selected dose regimen of 320 mg total daily dose, identical to the currently approved posology for WM (administered as 160 mg twice daily or 320 mg once daily) is considered acceptable.

As part of the current MAA package, the MAH has submitted a clinical DDI study (BGB-3111-112) of zanubrutinib co-administered with the moderate CYP3A inducer rifabutin. Rifabutin was found to decrease average zanubrutinib exposure by nearly half, with a geometric mean AUC approximately 44% lower and C_{max} 48% lower. Based on these results, the MAH proposes to revise the current SmPC recommendation to avoid concomitant use of moderate CYP3A inducers, suggesting that moderate CYP3A inducers may instead "*be used with caution*" during zanubrutinib treatment. However, results of Study BGB-3111-112 became available and were assessed during the initial Brukinsa EU MAA, no new clinical efficacy data has been provided by the MAH pertaining to zanubrutinib dosing regimens starting below 320 mg daily, and data on BTK receptor occupancy in target tissues below the current recommended total daily dose of 320 mg are likewise lacking. The lack of observable exposure-response and exposure-safety relationships is also used as one argument to justify that no dose adjustments are needed in the presence of moderate CYP3A4 inducers. This argument is not fully agreed by the CHMP. While it is agreed on the basis of the plots for probability of IRC-assessed objective response vs. exposure in studies 304 + 305 that a 50% reduction in exposure in the median patient would not likely result in appreciable change in probability of response, no predictions can be made on the basis of the model for the effect of 50% exposure reduction in patients who are on the lower end of the exposure range. Hence, the concern that average decreased zanubrutinib exposure in the order of 50% may result in decreased efficacy remains. Accordingly, changes to SmPC recommendations regarding co-administration of zanubrutinib with moderate CYP3A inducers with the addition of the CLL/SLL indication were not supported; the currently approved wording to avoid concomitant use of moderate CYP3A inducers has remained in section 4.5 of the SmPC.

Conclusions on clinical pharmacology

The pharmacology package included in the current application includes data from a Phase 3, open-label study of zanubrutinib in patients with previously untreated CLL/SLL (Study BGB-3111-304), a Phase 3, open-label study of zanubrutinib in patients with relapsed/refractory CLL/SLL (BGB-3111-305) and a clinical DDI study (BGB-3111-112). Based on data submitted with the initial (WM) EU MAA, the two proposed dose regimens, 160 mg twice daily and 320 mg once daily, were found to give comparable exposure (AUC), and the same posology for the CLL/SLL indication is considered acceptable based on the efficacy, safety and PK results provided with the current application.

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

Final report from the DDI Study BGB-3111-113of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-cell Malignancies Lymphoma will be submitted by the end of 2022.

2.4 Clinical efficacy

Dose response studies

See Clinical Pharmacology

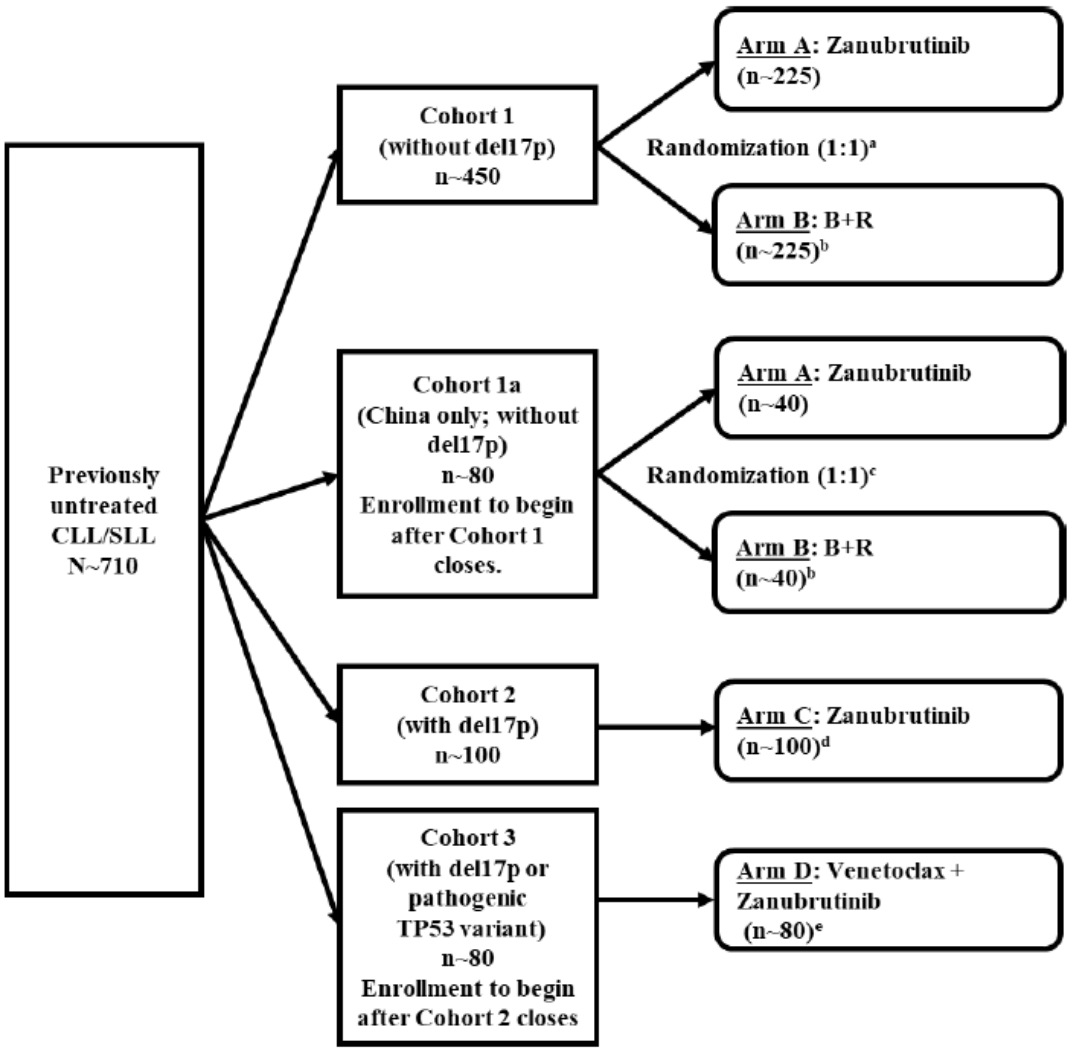
Main studies

BGB-3111-304

Study Title

An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Figure 20 Study design



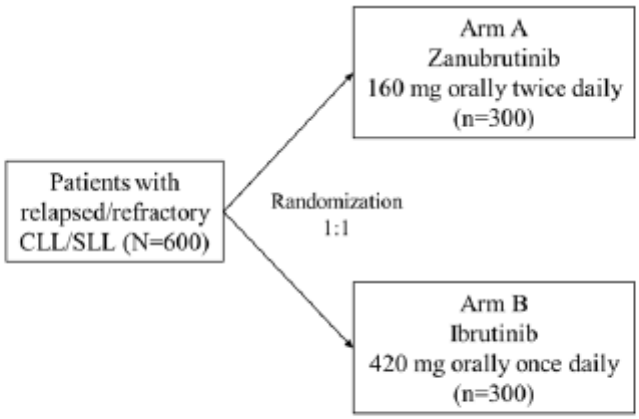
Abbreviations: B+R, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

a. Randomization for Cohort 1 will be stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), IGHV mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia Pacific).
b. Crossover for patients in Arm B to receive next-line zanubrutinib is allowed after disease progression is confirmed by independent central review.
c. The same randomization stratification factors used for Cohort 1 will be used for Cohort 1a, except for geographic region.
d. Cohort 2 (Arm C) will be closed to enrollment when the Arm C sample size (approximately 100 patients) has been reached.
e. Cohort 3 (Arm D) will be open for enrollment in selected countries/sites after Arm C closes. Arm D will be closed to enrollment when the Arm D sample size has been reached.

BGB-3111-305

Study BGB-3111-305 is an ongoing, international Phase 3, open-label, randomized study of zanubrutinib versus ibrutinib in patients with R/R CLL/SLL.

Figure 21: Schema for Study BGB-3111-305



Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Randomization will be stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/*TP53* mutation status (present versus absent).

Title of the study

A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Methods

Study participants

BGB-3111-304

Men and women ≥ 18 years of age included in this trial had a confirmed diagnosis of CD20 positive CLL or SLL requiring treatment as defined by at least one of the following: progressive marrow failure; massive, progressive or symptomatic splenomegaly; massive, progressive or symptomatic lymphadenopathy; progressive lymphocytosis with rapid doubling time; autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids; or constitutional symptoms.

Patients must have been ≥ 65 years of age at time of informed consent, or < 65 years of age and unsuitable for chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) based on 1 or more of the following factors: cumulative illness rating scale score > 6, creatinine clearance < 70 mL/min, or history of previous serious infection and/or multiple infections in the past 2 years.

Patients had measurable disease and had received no prior systemic treatment for CLL/SLL (other than 1 prior aborted regimen, < 2 weeks in duration and > 4 weeks before randomization), no history of prolymphocytic leukemia or Richter's transformation, no known central nervous system (CNS) involvement by leukemia or lymphoma, no currently active clinically significant cardiovascular disease, and no active infection requiring systemic therapy including no active hepatitis B or C or HIV. Systemic corticosteroid was to be fully tapered off/stopped ≥ 5 days before day of first study drug.

BGB-3111-305

The men and women ≥ 18 years of age included in this trial had a confirmed diagnosis of CLL or SLL that met the IWCLL criteria and required treatment as defined by at least 1 of the following:

progressive marrow failure; massive, progressive, or symptomatic splenomegaly; massive, progressive, or symptomatic lymphadenopathy; progressive lymphocytosis with rapid doubling time; or constitutional symptoms.

Patients must have been relapsed or refractory to at least 1 prior systemic therapy for CLL/SLL, with the last dose of prior therapy for CLL/SLL > 14 days before randomization and had measurable disease (defined as ≥ 1 lymph node > 1.5 cm in longest diameter, and measurable in 2 perpendicular diameters, or an extranodal lesion must measure > 10 mm in longest perpendicular diameter). A line of therapy was defined as completing at least 2 cycles of treatment of standard regimen according to current guidelines, or of an investigational regimen on a clinical trial.

Patients had no history of prolymphocytic leukemia or Richter's transformation, no known CNS involvement by leukemia or lymphoma, no currently active clinically significant cardiovascular disease, and no HIV infection or active infection with hepatitis B or C.

Treatments

BGB-3111-304

Each treatment cycle consists of approximately 28 days. Patients are treated as follows:

1. In Arm A (Cohort 1/1a) and Arm C (Cohort 2), zanubrutinib was administered orally at 160 mg twice daily.
2. In Arm B (Cohort 1/1a), bendamustine was administered IV at a dose of 90 mg/m^2/day on the first 2 days of each cycle for 6 cycles. Rituximab was administered IV at a dose of 375 mg/m^2 for Cycle 1, and at a dose of 500 mg/m^2 for Cycles 2 to 6.

Patients in Arms A, B, and C remained on study treatment (with a maximum of 6 cycles of B+R in Arm B) until unacceptable toxicity or disease progression was confirmed by independent central review.

Patients in Arm B of Cohort 1/1a may be eligible to receive crossover treatment with zanubrutinib at the time of disease progression, confirmed by independent central review. For patients who crossed over from Arm B to receive next line zanubrutinib, safety and laboratory assessments were to be performed per the zanubrutinib (Arms A and C) Schedule of Assessments and tumor response was to be evaluated by the investigator.

Arm C: Patients assigned to Cohort 2 (Arm C) received zanubrutinib monotherapy 160 mg twice a day (two 80-mg capsules twice a day) and were to remain on zanubrutinib until unacceptable toxicity or disease progression.

Table 6: Zanubrutinib Dose Reduction Levels

Toxicity occurrence	Dose level	Zanubrutinib dose[a] (Arms A, and C [zanubrutinib monotherapy run-in])
First	0 = starting dose	Restart at 160 mg twice daily
Second	-1 dose level	Restart at 80 mg twice daily
Third	-2 dose level	Restart at 80 mg once daily
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

[a.] These zanubrutinib dose modifications apply to Arms A and C during the zanubrutinib monotherapy run-in

Zanubrutinib Dose Reductions for Hematologic Toxicity

Hematologic toxicity was based on the Grading Scale for Hematologic Toxicity in CLL Studies. Dosing was to be held for individual patients under any of the following conditions, based on investigator assessment of study-drug relatedness:

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

Table 7 ***: Bendamustine Dose Reduction***

Toxicity	Action for Bendamustine[a]	Re-start Dose
≥ Grade 3 neutropenia, thrombocytopenia, or anemia on planned Day 1 of a cycle (first occurrence)	Postpone next cycle until neutropenia, thrombocytopenia, and anemia are less than Grade 3	Re-start at reduced dose of 70 mg/m^2
Signs of active infection on planned Day 1 of a cycle (first occurrence)	Postpone next cycle until all signs of active infection are resolved	Re-start at reduced dose of 70 mg/m^2
Second occurrence of ≥ Grade 3 cytopenia and/or active infection on planned Day 1 of a cycle	Postpone next cycle until neutropenia, thrombocytopenia, and anemia are less than Grade 3, and all signs of active infection are resolved.	Re-start at reduced dose of 50 mg/m^2
Third occurrence of ≥ Grade 3 cytopenia and/or active infection on planned Day 1 of a cycle	Permanently discontinue bendamustine	Not applicable
Other toxicities	Contact the medical monitor and refer to the bendamustine product label	-

[a] When bendamustine is delayed, rituximab will be delayed for same duration.

Rituximab

No dose reductions for rituximab were to be allowed. A 28-day cycle length should be maintained, if possible. If rituximab was delayed, then bendamustine should be delayed as well.

BGB-3111-305

Zanubrutinib

Zanubrutinib 160 mg was taken twice a day with or without food.

On the days of PK blood sampling, study drug administration for patients assigned to Arm A (zanubrutinib) occurred at the center under the supervision of the investigator or his/her designee after the pre-dose blood sampling had occurred. The investigator or his/her designee instructed the patient not to self-administer the study drug prior to the office visit on those days.

Ibrutinib

Patients randomized to Arm B received ibrutinib as per the Summary of Product Characteristics at a dose of 420 mg orally once daily.

Dose Interruption and Modification

Zanubrutinib and ibrutinib treatment modifications applicable to hematologic and nonhematologic toxicities are outlined in Table 8.

Table 8: Zanubrutinib and Ibrutinib Dose Reductions

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

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

Zanubrutinib Dose Modifications for Hematologic Toxicity

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

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

For the first occurrence of hematologic toxicity, zanubrutinib treatment could restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline. Dose modification for patients with ≥ Grade 3 thrombocytopenia associated with significant bleeding requiring medical intervention were discussed with the medical monitor.

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

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

Table 9 Zanubrutinib Dose Reductions for Nonhematologic Toxicity

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

Zanubrutinib Dose Modifications When Coadministered With Strong/Moderate CYP3A Inhibitors/Inducers were applied in accordance with the SmPC.

For ibrutinib dose modification, SmPC recommendations were to be followed throughout the study.

Objectives

BGB-3111-304

Study Objectives:

All efficacy and safety objectives in cohort 1 (patients without del[17p]) will compare BGB-3111 versus bendamustine plus rituximab.

Primary:

1. To compare efficacy between treatment groups in cohort 1, as measured by progression-free survival determined by independent central review

Secondary:

2. To evaluate efficacy in cohort 1, as measured by the following:
    1. Overall response rate determined by independent central review and by investigator assessment
    2. Overall survival
    3. Duration of response determined by independent central review and by investigator assessment
    4. Progression-free survival determined by investigator assessment
    5. Patient-reported outcomes
3. To compare efficacy between Arms A and B in pooled Cohort 1/1a patients from Chinese sites, as measured by the following:
    1. Progression-free survival determined by independent central review and by investigator assessment
    2. Overall response rate determined by independent central review and by investigator assessment
    3. Duration of response determined by independent central review and by investigator assessment
4. To evaluate efficacy in cohort 2 (patients with del[17p]), as measured by the following:
    1. Overall response rate determined by independent central review
    2. Overall survival
    3. Progression-free survival determined by independent central review
    4. Duration of response determined by independent central review
5. To evaluate efficacy in Cohort 3 (patients with del17p or pathogenic TP53 variant) for Arm D, as measured by the following:
    1. Overall response rate determined by investigator review
    2. Progression-free survival determined by investigator review
    3. Duration of response determined by investigator review
    4. Assess undetectable minimal residual disease at $< 10^{-4}$ sensitivity (undetectable MRD4) at various timepoints in Arm D
6. To compare safety between the treatment groups in cohort 1
7. To compare safety between the treatment groups in pooled Cohort 1/1a patients from Chinese sites
8. To summarize safety in Cohort 2 (Arm C)
9. To summarize safety in Cohort 3 (Arm D)
10. To evaluate pharmacokinetics of zanubrutinib (Arms A and C)
11. To evaluate pharmacokinetics of zanubrutinib and venetoclax (Arm D)

Exploratory:

1. To evaluate the following:
    1. Progression-free survival 2 (for Arms A, B, and C) determined by investigator assessment
    2. Candidate prognostic and predictive biomarkers and biomarkers of relapse
    3. Overall survival in pooled Cohort 1/1a patients from Chinese sites
    4. Patient-reported outcomes in pooled Cohort 1/1a patients from Chinese sites
    5. Overall survival in Cohort 2
    6. Patient-reported outcomes in Cohort 2
    7. Overall survival in Cohort 3
    8. Patient-reported outcomes in Cohort 3
    9. Time to recurrence of detectable minimum residual disease after discontinuation of zanubrutinib and/or venetoclax in Cohort 3

1. To examine the following:
    1. Medical resource utilization in Cohort 1/1a
    2. Medical resource utilization in Cohort 2
    3. Medical resource utilization in Cohort 3

BGB-3111-305

Primary Objective

The primary objective was as follows:

1. To compare the efficacy of zanubrutinib versus ibrutinib as measured by overall response rate determined by investigator assessment

Secondary Objectives

The secondary objectives were as follows:

1. To compare the efficacy of zanubrutinib versus ibrutinib as measured by:
    1. PFS determined by investigator assessment and independent central review
    2. Overall response rate determined by independent central review
    3. Duration of response as determined by independent central review
    4. Duration of response as determined by investigator assessment
    5. Time to treatment failure
    6. Rate of PR-L or higher determined by independent central review

7. Overall survival
8. Patient-reported outcomes

2. To compare the safety of zanubrutinib versus ibrutinib

Exploratory Objectives

The exploratory objectives were as follows:

1. To evaluate the correlation between clinical outcomes (eg, overall response rate, PFS, duration of response, overall survival, rate of PR) and the prognostic and predictive biomarkers, including minimal residual disease
2. To evaluate the pharmacokinetics of zanubrutinib

Outcomes/endpoints

BGB-3111-304

Primary Endpoint

The primary endpoint is progression-free survival in cohort 1 (patients without del[17p]) determined by independent central review using the IwCLL guidelines with modification for treatment-related lymphocytosis and defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first.

Secondary Endpoints

1. Overall response rate in cohort 1 defined as the proportion of patients who achieve a complete response, complete response with incomplete bone marrow recovery, partial response, or partial response with lymphocytosis, determined by independent central review and by investigator assessment
2. Overall survival in cohort 1 defined as the time from randomization to the date of death due to any reason
3. Duration of response in Cohort 1 determined by independent central review and by investigator assessment, using the iwCLL criteria with modification for treatment related lymphocytosis (in patients with CLL) and the Lugano Classification for NHL (in patients with SLL), and defined as the time from the date that criteria for response (ie, PRL or better) are first met to the date that disease progression is objectively documented or death, whichever occurs first.
4. Progression-free survival in Cohort 1 determined by investigator assessment
5. Patient-reported outcomes in cohort 1 measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
6. Progression-free survival in pooled Cohort 1/1a patients from Chinese sites determined by independent central review and by investigator assessment
7. Overall response rate in pooled Cohort 1/1a patients from Chinese sites determined by independent central review and by investigator assessment
8. Duration of response in pooled Cohort 1/1a patients from Chinese sites determined by independent central review and by investigator assessment

9. Overall response rate in cohort 2 (patients with del[17p]), Arm C, determined by independent central review and by investigator assessment
10. Progression-free survival in Cohort 2 (Arm C), determined by independent central review and investigator review
11. Duration of response in Cohort 2 (Arm C), determined by independent central review and investigator review
12. Overall response rate in Cohort 3 (patients with del17p or pathogenic TP53 variant), Arm D, determined by investigator review
13. Progression-free survival in Cohort 3 (Arm D), determined by investigator review
14. Duration of response in Cohort 3 (Arm D), determined by investigator review
15. Cohort 3 (Arm D) only: undetectable MRD4 rate
16. Safety parameters, including AEs, SAEs, clinical laboratory tests, physical examinations, and vital signs
17. Pharmacokinetic parameters of zanubrutinib such as apparent clearance of the drug from plasma (CL/F) and AUC from time 0 to 12 hours post-dose (AUC0-12) for Arms A, C, and D

Exploratory Endpoints

1. Progression-free survival 2 (PFS2) for Arms A, B, and C, determined by investigator assessment, defined as the time from randomization to the date of progression on the next line of therapy subsequent to the study treatment.
2. Clinical outcomes (eg, progression-free survival, overall response rate, duration of response, overall survival) correlated with baseline prognostic and predictive markers (eg, deletion 11q22-23, mutation status of IGHV, pathogenic TP53 variant, β-2 microglobulin level, deletion 13q14, trisomy 12)
3. Overall survival in pooled Cohort 1/1a patients from Chinese sites
4. Patient-reported outcomes in pooled Cohort 1/1a patients from Chinese sites
5. Overall survival in Cohort 2 (Arm C)
6. Patient-reported outcomes in Cohort 2 (Arm C), measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
7. Overall survival in Cohort 3 (Arm D)
8. Patient-reported outcomes in Cohort 3 (Arm D), measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires
9. Time to recurrence of detectable minimum residual disease after discontinuation of zanubrutinib and/or venetoclax in Cohort 3
10. Medical resource utilization in Cohort 1/1a as assessed by the number or hospitalizations, length of hospital stay, and supportive care in patients
11. Medical resource utilization in Cohort 2 as assessed by the number of hospitalizations, length of hospital stay, and supportive care in patients
12. Medical resource utilization in Cohort 3 as assessed by the number of hospitalizations, length of hospital stay, and supportive care in patients

13. Pharmacokinetic parameters of venetoclax such as apparent clearance of the drug from plasma (CL/F) and AUC from time 0 to 12 hours post-dose (AUC0-12) for Arm D

BGB-3111-305

Primary Endpoint

The primary endpoint was overall response rate (PR or higher, defined as CR/CRi + PR+ nodular PR) determined by investigator assessment using the "modified" 2008 IwCLL guidelines (Hallek et al 2008) with modification for treatment-related lymphocytosis (Cheson et al 2012) for patients with CLL and per the Lugano Classification for NHL (Cheson et al 2014) for patients with SLL. While the primary efficacy endpoint was per investigator assessment, overall response rate per independent central review was also analyzed to support the primary analysis.

Secondary Endpoints

Key Secondary Endpoints:

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

The key secondary endpoint of PFS was defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurred first, as determined by the investigator. While the key secondary efficacy endpoint was PFS per investigator assessment, PFS per independent central review was also analyzed to support the key secondary endpoint analysis.

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

Other Secondary Endpoints

1. Duration of response, defined as the time from the date that response criteria were first met to the date that disease progression was objectively documented or death, whichever occurs first, determined by independent central review
2. Duration of response by investigator assessment
3. Time to treatment failure, defined as the time from randomization to discontinuation of study drug due to any reason
4. Rate of PR-L or higher, defined as the proportion of patients who achieved a CR/CRi + PR + nodular PR + PR-L determined by independent central review
5. Rate of PR-L or higher determined by investigator assessment
6. Overall survival, defined as the time from randomization to the date of death due to any cause
7. PROs measuring HRQoL via the EORTC QLQ-C30 and EQ-5D-5L questionnaires
8. Safety parameters, including adverse events, serious adverse events, clinical laboratory tests, physical exams, and vital signs

Exploratory Endpoints

The exploratory endpoints were as follows:

1. Correlation between clinical outcomes (eg, overall response rate, PFS, duration of response, overall survival) and the prognostic and predictive biomarkers
2. MRD
3. PK parameters
4. Self-administered Activity and Quality of Life questionnaire

Sample size

BGB-3111-304

The sample size calculation for Cohort 1 is based on the primary efficacy analysis of PFS comparison between Arms A and B in Cohort 1. Assuming the HR (Arm A/Arm B) in Cohort 1 is 0.58, 118 events are required to achieve 83.5% power at 2-sided alpha of 0.05 to reject the null hypothesis, when 1 interim analysis is planned after 73% of the target number of events at final analysis. If 450 patients are enrolled to Cohort 1 and randomized in a 1:1 ratio to Arms A and B over a 25-month period (actual patient enrollment up to November 2018 and 28 patients per month enrollment rate after) and the hazard rate for drop-out of 0.0017/month, 118 events are expected to be accumulated at 41 months from study start. This assumes a median PFS in Arm B of 42 months and that PFS follows exponential distribution. Approximately 710 patients will be enrolled, with 450 patients without the del17p mutation in Cohort 1 available for the primary efficacy analysis, approximately 80 additional patients from Chinese sites without the del17p mutation in Cohort 1a, and approximately 100 patients with the del17p mutation in Cohort 2 and approximately 80 patients with del17p or pathogenic TP53 variant in Cohort 3. Sample size selection for Cohort 1a was to accumulate enough PFS events among patients enrolled from Chinese sites at the final analysis to support more than 80% probability of demonstrating an HR < 1 among patients enrolled from Chinese sites if the PFS HR based on the ITT Analysis Set crosses the prespecified statistical boundary at the final analysis.

Sample size selections for Cohorts 2 and 3 were driven by estimated patient availability.

BGB-3111-305

The sample size calculation was based on the primary efficacy analysis for the primary endpoint of overall response rate. Assuming a response ratio (zanubrutinib arm/ibrutinib arm) of 1.03 (72%/70%), 600 patients would provide more than 90% power to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 0.8558 (response ratio) and 1-sided alpha level of 0.025 with 1 interim analysis at 69% information fraction. The response rate for ibrutinib was approximated from published clinical data (Byrd et al 2019).

The non-inferiority margin was derived using the 95%-95% fixed margin method (FDA Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness 2016). The efficacy of ibrutinib (M1) in response ratio scale was estimated as 2.1781 from the results of RESONATE and RESONATE2 trials by a fixed-effect meta-analysis. Requiring 80% of M1 to be retained in zanubrutinib, a non-inferiority margin of 0.8558 is generated. The margin is within the clinically acceptable limit.

Assuming a hazard ratio (zanubrutinib arm/ibrutinib arm) of 0.9, 205 events would be required to achieve 80% power at a 1-sided alpha of 0.025 to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 1.3319 (hazard ratio) in PFS.

If the 600 patients were randomized in a 1:1 ratio to the 2 arms over a 24-month period including a 9-month ramp-up period before reaching the peak enrollment of 33 patients/month with a 0.0017/month hazard rate for drop-out, 205 events were expected to be accumulated in 45 months after study start. A median PFS of 47 months for ibrutinib and an exponential distribution for PFS were also assumed.

Justification of the noninferiority margin for ORR

A non-inferiority margin of 0.8558 in response ratio was derived using the 95% to 95% fixed margin approach (FDA Guidance for Industry Non-Inferiority 2016). In the RESONATE trial (Byrd et al 2014), the ibrutinib effect over ofatumumab represented by the ratio of response rate (PR or higher) was 10.43 with a 95% CI of (5.2, 21.0) based on the independent review committee assessment. Thus, M1 is 5.2, the lower bound of the 95% CI. Since the effect size of ibrutinib is versus an active control (ofatumumab), rather than placebo, the choice of M1 is conservative, and a non-inferiority margin of 0.8558 (for the response ratio) retains over 90% of M1 (on the log scale).

Justification of the noninferiority margin for PFS

A non-inferiority margin of 1.3319 was derived using the 95% to 95% fixed margin approach based on the RESONATE study. In the updated RESONATE results (Brown et al 2014), the estimated PFS HR for ibrutinib versus ofatumumab was 0.106 with a 95% CI of (0.073, 0.153). Therefore, the control arm effect (M1) is 0.153 in HR and -1.877 in log HR. A noninferiority margin of 1.3319 for the HR (zanubrutinib/ibrutinib) retains approximately 85% of M1 (on the log scale).

Randomisation

BGB-3111-304

Patients will be randomized using the IRT system for this study by permuted block stratified randomization. The stratified randomization will be produced, reviewed, and approved by an independent statistician.

Central randomization (1:1) will be used to assign patients in Cohort 1/1a to one of the following study drug treatments:

1. Arm A: zanubrutinib
2. Arm B: bendamustine + rituximab (B+R)

Randomization will be stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), immunoglobulin variable region heavy chain (IGHV) mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia-Pacific).

Because Cohort 1a enrolls only patients from Chinese sites, geographic region will not be a randomization stratification factor for Cohort 1a. Patients in Cohort 2 (Arm C) will receive treatment with zanubrutinib. Patients in Cohort 3 (Arm D) will receive treatment with venetoclax + zanubrutinib.

BGB-3111-305

Interactive Response Technology (IRT) was used to randomize patients to treatment arm and to assign study drug as applicable. Randomization will be performed as study by permuted block stratified randomization. Eligible patients were randomized in a 1:1 manner to either Arm A (zanubrutinib) or Arm B (ibrutinib). Randomization was stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present or absent).

Blinding (masking)

BGB-3111-304

Study BGB-3111-304 was open-label. The assessment of PFS for Cohort 1 was performed by an independent central review committee. Access to aggregated efficacy summary treatment results was not provided before database lock.

BGB-3111-305

Treatment with zanubrutinib or ibrutinib was open label since the safety, PK, pharmacodynamics, and antitumor effects endpoints in this study were unlikely to be biased by knowledge of the study treatment.

Treatment with zanubrutinib or treatment with ibrutinib was open label; however, the independent central review for response assessment was blinded to study treatment. The independent DMC was not blinded. However, due to the open-label nature of the study, the sponsor did not have access to aggregated data summaries by actual study treatment assignment while the study was ongoing. This was done to avoid unwanted bias due to the possibility of inconsistent queries among patients with different treatments or overinterpretation of immature accruing data. A Data Integrity Protection Plan was put in place to describe the steps taken prior to database lock for the primary analysis of efficacy to restrict data access and minimize these potential biases for the study.

Statistical methods

BGB-3111-304

Analysis Populations for Efficacy

The Intent-to-Treat (ITT) Population includes all enrolled patients who are assigned to a treatment group. The ITT population will be the primary population for efficacy analyses.

The Per-Protocol Population includes patients who received any dose of study medication and had no major protocol deviations. Criteria for exclusion from the Per-Protocol Population will be determined and documented before the database lock for the primary analysis.

Primary Efficacy Analysis: PFS

The distribution of PFS, including median PFS and PFS rate at selected timepoints such as 12, 24 and 36 months, will be summarized descriptively using the Kaplan-Meier method for each arm. The 95% confidence interval for median and other quartiles of PFS will be generated by using Brookmeyer method, whereas the 95% confidence interval for PFS rate at selected timepoints will be generated by using Greenwood formula. The primary inferential comparison of PFS

H0: Hazard ratio (HR) (Arm A/Arm B) = 1

Ha: HR (Arm A/Arm B) <1

between treatment groups will use the log-rank test stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), and IGHV mutational status (mutated vs unmutated) per IRT. The HR will be estimated using a stratified Cox proportional hazard model. Duration of follow-up for PFS will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996).

For the primary analysis of PFS, the point estimate of the hazard ratio and its 95% CI will be computed based on fixed design procedures using a Cox model. The adequacy of the proportional hazard assumption will be evaluated by examining Schoenfeld residual plot and Kaplan-Meier plot. If strong evidence of non-proportionality of the treatment effect is observed, the time axis will be partitioned using the time points suggested by the residual plot and a piecewise Cox model will be fitted as a sensitivity analysis.

Censoring rules for PFS

These conventions are based on December 2018 FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics,' and December 2012 EMA Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man, 'Methodological Consideration for using Progressive-free Survival (PFS) or Disease-free Survival (DFS) in Confirmatory Trials.'

Table 10 Date of Progression or Censoring for Progression free Survival

Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of randomization	Censored
New CLL/SLL related treatment started before documentation of PD or death	Date of last disease assessment prior to start of a new CLL/SLL related treatment	Censored[a]
Death or PD immediately after two or more missed consecutive disease assessments	Date of last disease assessment with documented non-progression[b]	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
Death before first disease assessment	Date of death	Progressed

[a] Patient with a confirmed PD within 30 days or death within 90 days of start of next line therapy will not be censored. Censoring the event from a patient at a date close to patient PD or death date will fall into informative censoring thus biases the treatment effect. Further, counting the event is unlikely to overestimate the overall PFS.
[b] For investigator disease assessment, "non-progression" includes any response assessment code other than "PD" or "Not Done."

Sensitivity analyses for PFS

1. PFS Analysis Based on the Per-Protocol Analysis Set: the Per-Protocol Analysis Set instead of the ITT analysis set will be used as the analysis population. The analysis method will be the same as that for the primary PFS analysis.
2. Initiation of Non-Protocol CLL/SLL Related Therapy Treated as a PFS Event: initiation of non-protocol CLL/SLL related therapy will be treated as a PFS event whereby PFS is broadly defined as duration from randomization to documented disease progression, initiation of non-protocol

CLL/SLL related therapy, or death, whichever occurs earlier. The data censoring rules were the same as those for the primary analysis of PFS except that the use of non-protocol CLL/SLL therapy will be treated as an event rather than a mechanism for censoring. The analysis method was the same as that for the primary PFS analysis.

3. Initiation of Non-Protocol CLL/SLL Related Therapy Treated as neither a PFS Event nor a Censoring Event: In this sensitivity analysis, the use of non-protocol CLL/SLL related therapy will be ignored. The data censoring rules are the same as those for the primary analysis of PFS except that the initiation of non-protocol CLL/SLL related therapy will be excluded as a mechanism for censoring. The analysis method will be the same as that for the primary PFS analysis.

4. Death or Disease Progression Immediately After Two or More Missed Consecutive Disease Assessments as a PFS Event: death or disease progression immediately after two or more missed consecutive disease assessments will be treated as a PFS event. The analysis method will be the same as that for the primary PFS analysis.

5. PFS Analysis under a Non-Proportional Hazard Function: If there is a substantial deviation from the proportional hazard assumption, a piecewise Cox model will be fitted to model the non-proportional hazard.

6. PFS Analysis based on all Patients Randomized to Cohort 1 and Cohort 1a: the primary PFS analysis will be repeated using all patients randomized to Cohort 1 and Cohort 1a.

7. Hospitalization due to COVID-19 was treated as a Censoring Event

8. PFS Analysis based on Interval Censoring: PD event dates were assumed as interval censored, i.e. occurred between date of disease assessment right before PD and date of disease assessment with detected PD. A non-parametric method was used to compare the 2 arms with the interval censored data (Huang 2008).

Secondary Efficacy Analyses

Overall Survival (OS) in Cohort 1

The distribution of OS, including quartiles, will be summarized descriptively using the Kaplan-Meier method per each arm. Median follow-up for OS will be estimated according to the Kaplan-Meier estimate of potential follow-up also termed "reverse Kaplan-Meier" (Schemper and Smith 1996).

The inferential comparison of OS

H0: Hazard ratio (HR) (Arm A/Arm B) = 1

Ha: HR (Arm A/Arm B) < 1

between treatment groups will use the log-rank test stratified by age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), and IGHV mutational status (mutated vs unmutated) per IRT. The HR for BGB-3111 arm over the BR arm will be estimated using a stratified Cox proportional hazards model.

The survival rate at selected landmark times (e.g., 1 year, 2 years, and 3 years from randomization) will be estimated for each treatment group by the corresponding Kaplan-Meier estimate with its 95% confidence interval using Greenwood formula.

Censoring rules for OS

Patients who are alive or lost to follow-up as of the data analysis cut-off date will be right censored at the patient's date last known to be alive.

Sensitivity analyses for OS

1. The OS result will be assessed using additional sensitivity analyses, all of which will be based on the ITT analysis set, including the followings:

2. On-Treatment Analysis: Initiation of BGB-3111 in BR Arm Patients Treated as a Censoring Event In this sensitivity analysis, initiation of BGB-3111 in BR arm patients will be treated as a censoring event. The analysis method remains the same as that for the primary analysis of OS.

3. Estimation Based on Inverse Probability of Censoring Weights (IPCW) Method (Robin and Finkelstein 2000) In this analysis, BR arm patients crossed over to receive any BGB-3111 will be artificially censored at the time of switch, and remaining BR arm patients will be weighted based upon covariate values and a model of the probability of being censored. This allows patients who have not been artificially censored to be weighted in order to reflect their similarities to patients who have been censored in an attempt to remove the selection bias caused by the censoring – patients who did not crossover and have similar characteristics to subjects who did cross-over receive higher weights. The IPCW version of Kaplan-Meier estimator, log-rank test, and Cox partial likelihood of the HR will be used for the OS analysis. The IPCW method will be only considered when more than 20% BR arm patients crossed over to receive BGB-3111.

4. Estimation Based on Iterative Parameter Estimation (IPE) Algorithm (Branson and Whitehead 2002) The IPE procedure is an extension of rank preserving structural failure time model (RPSFTM). It uses parametric methods and a counterfactual framework to estimate the causal effect of the BGB- 3111 treatment. In this analysis, a parametric accelerated failure time model is fitted to the original unadjusted ITT data to obtain an initial estimate of the treatment effect. The failure times of BR arm patients who received any BGB-3111 are then re-estimated using the model, and this iterative procedure continues until the new estimate is very close to the previous estimate, i.e. "converged." Similar to the analysis based on IPCW method, this analysis will be only considered when more than 20% BR arm patients crossed over to use BGB-3111.

Overall response rate (ORR) in Cohort 1

ORR will be estimated as the crude proportion of patients in each treatment group who achieve PR (including PR-L) or higher. Associated 95% Clopper-Pearson CI will be calculated by treatment group. The odds ratio (and 95% CI), which will be provided as a measure of the relative treatment effect, will be estimated using the stratified Cochran-Mantel-Haenszel method. The BR arm will serve as the reference treatment group in the calculations of the odds ratio. Given the high level of ORR (95%) observed in the BR arm patients in CLL10 study (Eichhorst et al 2016), the comparison between treatment groups for the ORR endpoint in cohort 1 will be descriptive. Patients with no post-baseline response assessment (due to any reason) will be considered as non-responders.

Interim analyses

Up to 2 analyses of PFS are planned: an interim analysis and the final analysis. The outcomes determined by the IRC will serve as the primary data source for the primary analysis of PFS. The monitoring boundary for early stopping in PFS will be determined using O'Brien-Fleming alpha spending function (Lan and DeMets 1983) for efficacy and Haybittle-Peto method (Haybittle 1971; Peto et al 1976) for futility so that the overall Type I error is less than or equal to 0.025 (1-sided). The interim analysis will be performed when approximately 86 events (73% of the target number of events at final analysis) from Arms A and B in Cohort 1 are observed. It is estimated that it will take approximately 33 months to observe 86 events under the assumptions described in Section 4. The

futility will be non-binding. Information is based on number of events. Monitoring boundaries will be calculated for the interim analysis based on the actual number of PFS events observed up to the data cut-off of the interim analysis. Deviation from the scheduled interim analyses will not affect overall Type I error.

The inferential comparisons for the secondary endpoints will also be performed if a stopping boundary for PFS is met at any of the analyses.

The final analysis of OS will be performed at the end of the study, approximately 5 years after first patient randomized. Two interim analyses of OS are planned at the time of the interim and final analysis of PFS. Given a 3-year 92% survival rate observed in the BR arm patients in the CLL10 study (Eichhorst et al 2016), the planned interim OS analyses are not expected to have enough power to show statistical difference between the two arms. Therefore, a one-sided 0.00005 alpha will be set for each of the two planned interim analyses.

Multiplicity considerations: Secondary Endpoint Testing Procedures

The inferential tests associated with the interim and final analyses of PFS in cohort 1 (primary efficacy endpoint) will be assessed against an overall 1-sided significance level of 0.025. Study-wide type-I error will be controlled at the level 0.025 for the testing of the primary endpoint and one secondary endpoint OS in cohort 1. All other inferences will be descriptive without multiplicity adjustment. OS is tested only if the primary endpoint, PFS, is significant.

The significance level for the OS analysis at the interim and final PFS analysis will be 0.00005, and the final OS analysis will be assigned a one-sided alpha of 0.0249. The secondary endpoint testing procedure is closed testing procedures and preserves the family-wise error rate at 0.025 in the strong sense.

SAP addendum

The purpose of this statistical analysis plan (SAP) addendum is to describe the additional analyses for overall survival to be performed per the requests from the US FDA. As specified in the protocol, the final analysis of OS for cohort 1 will be performed approximately 5 years after the first subject was randomized in Cohort 1. The first subject was randomized on October 31, 2017, and the final analysis is planned for November 2022.

BGB-3111-305

Analysis Populations for Efficacy

The Intent-to-Treat (ITT) Analysis Set included all randomized patients. The ITT Analysis Set was the primary analysis set for efficacy analyses except for the interim analysis of response endpoints including overall response rate, duration of response, and rate of PR-L or higher, which were based on the first 415 randomized patients as prespecified for the interim analysis.

The Per-protocol Analysis Set includes patients who received any dose of study drug and had no critical protocol deviation.

The Safety Analysis Set includes all patients who received any dose of study drug.

Primary Efficacy Analysis

Primary endpoint ORR

The primary hypothesis testing for the primary endpoint of ORR per investigator assessment will be to demonstrate the noninferiority of zanubrutinib to ibrutinib.

Noninferiority testing for ORR

The null and alternative hypotheses for the noninferiority test are as follows:

H0NI: Response ratio (zanubrutinib/ibrutinib) ≤ 0.8558

HaNI: Response ratio (zanubrutinib/ibrutinib) > 0.8558

The noninferiority hypothesis of ORR will be tested at each analysis using a stratified Wald test against a null response ratio of 0.8558**.**

Superiority testing for ORR

If the noninferiority in ORR per investigator assessment is statistically significant, then the superiority of zanubrutinib to ibrutinib in ORR will be tested. The null and alternative hypotheses for the superiority test are as follows:

H0SUP: Response ratio (zanubrutinib/ibrutinib) ≤ 1

HaSUP: Response ratio (zanubrutinib/ibrutinib) > 1

The superiority hypothesis of ORR will be tested using a stratified Cochran-Mantel-Haenszel test. The 95% confidence interval (CI) for the response ratio will be constructed using a normal approximation. ORR will be summarized for each treatment arm along with its corresponding 95% CI.

Response in case of intercurrent events

BOR is defined as the best response from the randomization date to the data cut-off date, disease progression or the start of new CLL/SLL therapy, whichever comes first. Patients without any postbaseline disease assessment (regardless of the reason) will be considered as non-responders.

Supportive analyses for ORR

1. While the primary efficacy endpoint is per investigator assessment, ORR per independent central review will also be analyzed to support the primary analysis. In the United States, ORR assessed by independent central review will be the basis for regulatory decisions.
2. The noninferiority of the primary endpoint of ORR will also be analyzed in the Per-protocol Analysis Set.
3. Sensitivity analysis of investigator-assessed overall response rate was performed that counted assessments of PR-L that were subsequently followed by PR or higher responses as confirmed best overall responses of PR for CLL patients.
4. To account for disease progression due to study drug interruption, ORR and BOR will be summarized based on all disease assessments through the data cut-off date, disease progression or the start of new CLL/SLL therapy, whichever comes first; however, disease progression that occurs within 6 weeks of a study drug interruption of at least 7 days will not be counted as disease progression for the purpose of this sensitivity analysis.
5. To account for the impact of COVID-19, investigator-assessed overall response rate was summarized for each treatment arm excluding patients who died due to COVID-19.

Secondary Efficacy Analyses

PFS per investigator

Noninferiority testing for PFS per Investigator Assessment

The null and alternative hypotheses for the noninferiority test are as follows:

H0NI: HR (zanubrutinib/ibrutinib) ≥ 1.3319

HaNI: HR (zanubrutinib/ibrutinib) < 1.3319

At the final analysis of PFS, hypothesis testing for the noninferiority of PFS per investigator assessment will be based on the entire ITT Analysis Set using a stratified Wald test and will have a 1-sided significance level of 0.02498.

Superiority testing for PFS per Investigator Assessment

If the noninferiority of zanubrutinib to ibrutinib in PFS per investigator assessment is statistically significant, then the superiority in PFS per investigator assessment will be tested. The null and alternative hypotheses for the superiority test are as follows:

H0SUP: HR (zanubrutinib/ibrutinib) ≥ 1

HaSUP: HR (zanubrutinib/ibrutinib) < 1

Hypothesis testing for the superiority of PFS per investigator assessment will be based on the entire ITT Analysis Set using a stratified log-rank test and will have the same 1-sided significance level of 0.02498 (equivalent to a chi-squared p-value cut-off of 0.04996) used for the noninferiority PFS testing.

Additional descriptive analysis for PFS

The HR for PFS and its 95% CI will be estimated from a stratified Cox regression model. The distribution of PFS, including the median and other quartiles, and the PFS rate at selected timepoints such as 12, 18 and 24 months, will be estimated using the Kaplan-Meier method for each treatment arm. The 95% CI for the median and the other quartiles of PFS will be estimated using the Brookmeyer-Crowley method. The duration of follow-up for PFS will be estimated using the reverse Kaplan-Meier method (Schemper and Smith 1996). Kaplan-Meier curves for PFS will be presented for each treatment arm.

Censoring rules for PFS

Table 11 Date of Progression or Censoring for Progression free Survival

Situation	Date of Progression or Censoring	Outcome
Death or PD between the planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Event
Death before the first disease assessment	Date of death	Event
No baseline/postbaseline disease assessments (and no death)	Date of randomization	Censored
Death or PD more than 6 months [1] from the last disease assessment	Date of the last disease assessment before death or PD	Censored
Alive without documentation of PD	Date of last disease assessment	Censored

[1] 12 months if a patient is on the assessment schedule of every 24 weeks.

Source: SAP

Key secondary endpoint of PFS

1. The non-inferiority of the key secondary endpoint of PFS will also be analyzed in the Per protocol Analysis Set.
2. Alternative censoring rules such as censoring for new CLL/SLL therapies will be applied as another sensitivity analysis of PFS.
3. To account for disease progression due to study drug interruption, PFS will also be summarized where disease progression that occurs within 6 weeks of a study drug interruption of at least 7 days will not be counted as disease progression for the purpose of this sensitivity analysis.
4. To account for the impact of COVID-19, PFS will be summarized for each treatment arm while additionally censoring deaths due to COVID-19.

Key secondary SAFETY endpoint: Atrial fibrillation/flutter incidence

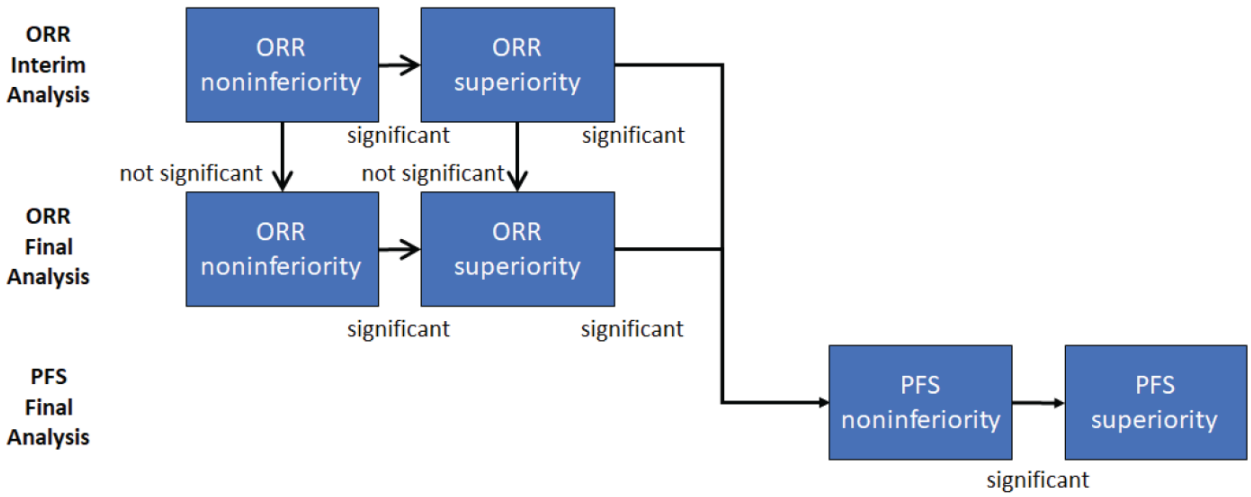
Hypothesis testing on the rate of atrial fibrillation/flutter will be performed using an unstratified chi-squared test if the expected counts in the 2 x 2 contingency table (treatment arm by atrial fibrillation/ flutter status) are at least 5 patients. If any expected count in the 2 x 2 contingency table is less than 5 patients, then hypothesis testing will be performed using Fisher's exact test.

Multiplicity Adjustment

To control the study-wide type I error, individual significance levels will be adjusted for the tests of the primary endpoint of ORR per investigator assessment (noninferiority and superiority), and the key secondary endpoint of PFS per investigator assessment (noninferiority and superiority). Multiplicity due

to multiple endpoints and multiple tests will be handled per the graphical approach by Maurer and Bretz (2013) utilizing fixed sequence hierarchical testing. Hypothesis testing will be performed according to the multiplicity adjustment as per the flowchart below

Figure 22: Flowchart for the multiplicity adjustment.



One interim analysis of ORR was planned at approximately 12 months after 415 patients have been randomized, and the final analysis of ORR will occur approximately 12 months after 600 patients have been randomized. Hypothesis testing for the noninferiority of ORR at the interim analysis will be based on the first 415 randomized patients only and will have a 1-sided significance level of 0.005. The monitoring boundaries for the noninferiority test are based on the O'Brien Fleming boundary approximated by the Lan-DeMets spending function with an overall 1-sided level of 0.025. Hypothesis testing for the noninferiority of ORR at the final analysis will be based on the entire ITT Analysis Set and will have a 1-sided significance level based on the actual information fraction (or covariance) of the interim and final test statistics. With 652 patients in the ITT Analysis Set at the final analysis, the actual information fraction is 64% (415/652), and the 1-sided significance level for the final analysis will be 0.0235.

A single analysis of PFS is performed for the purpose of inference when approximately 205 PFS events have occurred; however, a 1-sided significance level of 0.00001 will be applied to each of the two descriptive analyses of PFS for the interim and final analyses of ORR to compensate for the potential type I error increase from the descriptive analysis. From the time of the ORR analyses to the analysis of PFS after 205 events have occurred, the sponsor will continue to maintain trial integrity according to the DIPP.

If the noninferiority of zanubrutinib to ibrutinib in ORR is statistically significant, then the superiority of zanubrutinib to ibrutinib in the key secondary endpoint of atrial fibrillation/flutter will be tested but separately from the fixed sequence hierarchical testing that includes ORR and PFS. The interim analysis will be performed on the Safety Analysis Set restricted to the first 415 randomized patients and according to the actual treatment received. The final analysis will be performed on the Safety Analysis Set according to the actual treatment received. The monitoring boundaries for the superiority test are based on the O'Brien Fleming boundary approximated by the Lan-DeMets spending function with an overall 1-sided level of 0.025. If hypothesis testing for the superiority of the rate of atrial fibrillation/flutter is performed at the interim analysis, it will have a 1-sided significance level of 0.005 (equivalent to a chi-squared p-value cut-off of 0.0099). If hypothesis testing for the superiority of the

rate of atrial fibrillation/flutter is performed at the final analysis, it will have a 1-sided significance level of0.0235 (equivalent to a chi-squared p-value cutoff of 0.0469).

Changes to the SAP and planned analyses

This clinical study report reflects analyses performed on data collected through a cutoff date of 31 December 2020. After review of the interim analysis data by the independent DMC (20 April 2021), the DMC determined that the boundary was met for noninferiority of overall response rate.

Changes to the Planned Analyses

The following analyses are provided in the CSR but were not defined in the SAP or study protocols.

Patient disposition, characteristics, prior systemic therapies and study drug exposure were provided for the first 415 patients randomized.

Efficacy summaries were provided based on the first 415 patients randomized. These included analyses of PFS by investigator assessment and by independent central review as well as sensitivity analyses of PFS by investigator assessment and by independent central review that censored for new CLL/SLL therapies and overall survival. Analyses of duration of response by investigator assessment and by independent central review were also provided that include censoring for new CLL/SLL therapies. The above efficacy analyses of PFS and duration of response were performed for the subgroup of patients with del17p and the subgroup of patients with del17p and/or TP53 mutations.

Summaries of treatment-emergent adverse events among the first 415 patients randomized were provided based on the Safety Analysis Set, including treatment-emergent adverse events by System Organ Class and Preferred Term, Grade 3 or higher, serious, those leading to death or treatment discontinuation. Additionally, treatment-emergent adverse events of special interest were summarized for the first 415 patients randomized. Shift tables for comparison of baseline toxicity grade versus worst postbaseline toxicity grade were provided for laboratory parameters of interest. Box-and-whisker plots showing the mean, median, 25th and 75th percentiles, and outlier values (ie, > 1.5 times the interquartile range) were provided for laboratory parameters of interest.

Changes in Study Conduct and Planned Analyses Due to the COVID-19 Pandemic

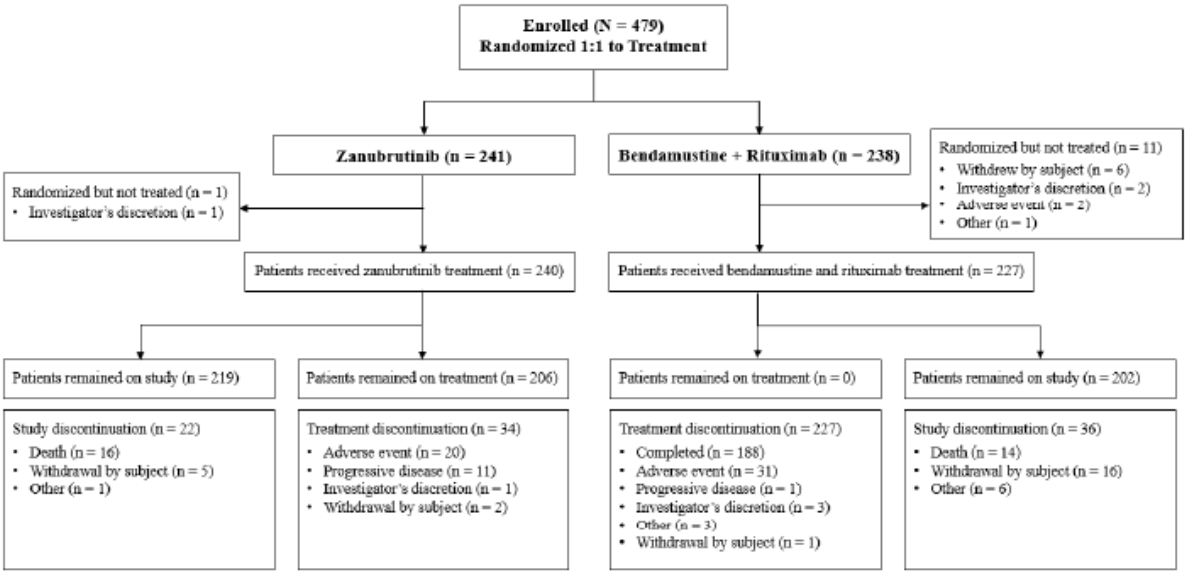
An internal committee was formed to evaluate the impact of SARS-CoV-2 (COVID-19) on BeiGene clinical studies in February 2020. This cross-functional team assessed and developed appropriate contingency measures in line with local and global regulatory guidance to maintain patient safety and study integrity. The measures were initially focused on sites in China and subsequently expanded to the global sites. Patients were prospectively informed of the specific COVID-19 responses, potential impacts on study conduction, and signed a consent addendum.

Results

Participant flow

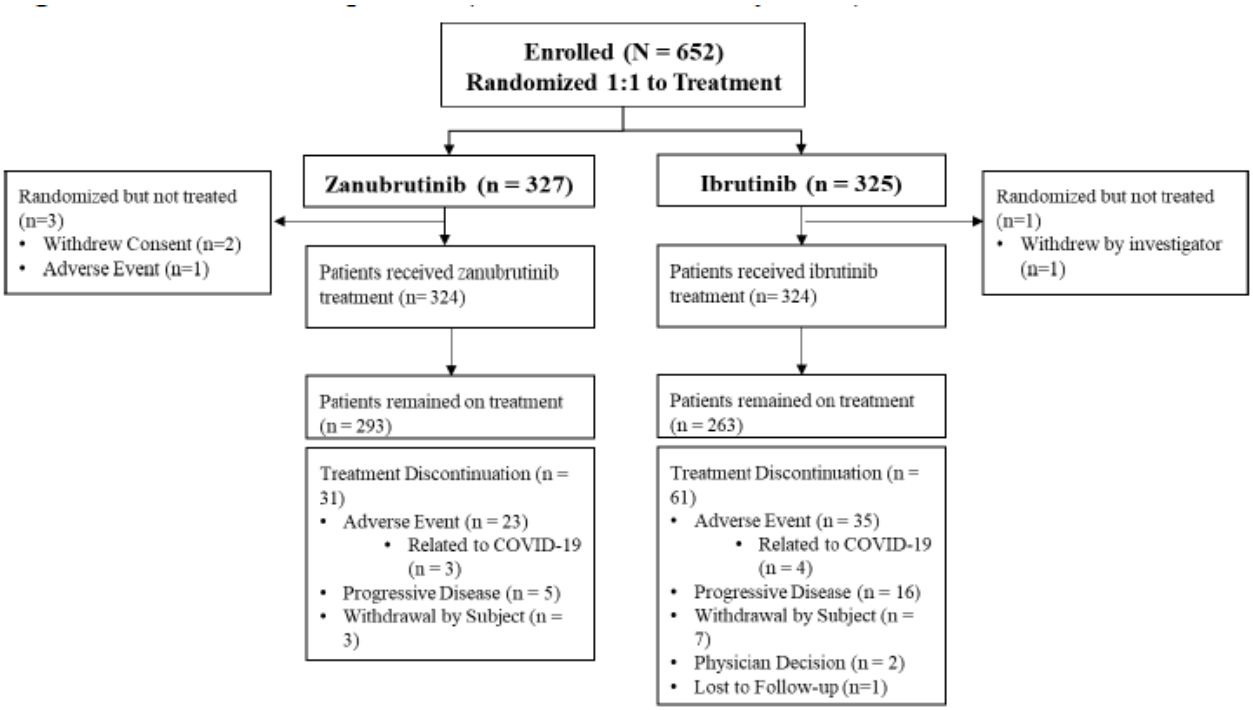
BGB-3111-304

Figure 23 Participant flow in study BGB 3111- 304



BGB-3111-305

Figure 24- Participant flow



Recruitment

BGB-3111-304

The study was conducted at 153 study centers in 14 countries and 1 region (Austria; Australia; Belgium; France; Italy; Spain; Czech Republic; Poland; Sweden; United Kingdom; Russia; United States; China; New Zealand; and Taiwan, China).

Date first patient randomized: 31 October 2017. Date last patient completed: ongoing as of data cutoff (07 May 2021).

BGB-3111-305

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

Date first patient randomized: 01 November 2018. Date last patient completed: ongoing as of data cutoff (31 December 2020).

Conduct of the study

BGB-3111-304

Protocol amendments

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

Amendment 1 (27 November 2018)
A total of 84 patients enrolled in the study under Amendment 1. Key changes to the conduct of the study implemented with Amendment 1 were as follows:

• Increased the number of patients to be randomized in Cohort 1 to increase the probability to detect a difference between Arms A and B

Notable changes include:
• Updated options at conclusion of study for patients who continue to benefit from zanubrutinib treatment to allow them to continue treatment with zanubrutinib either commercially or through a follow-up study

• Added new inclusion criterion 3 to provide a statement that disease needs to be measurable at baseline

• Modified Inclusion Criterion 10 to be in alignment with health authority for male contraception regarding use of bendamustine

• Added new second exclusion criterion regarding ongoing need for corticosteroid treatment

• Modified the exception for exclusion criterion 5 to include localized Gleason score 6 prostate cancer

Amendment 2 (01 April 2019)
A total of 590 patients enrolled before Amendment 2 of the study protocol, and a total of 63 patients enrolled in the study under Amendment 2. Key changes to the conduct of the study implemented with Amendment 2 were as follows:

• Updated throughout protocol and synopsis to add Cohort 3, Arm D, information

• Added text that 150 patients with del(17p) would enroll in Cohorts 2 and 3. The overall patient population was increased in order to allow for 50 patients to enroll in Cohort 3, Arm D

• Added a statement about the DMC reviewing data from approximately the first 6 patients in Arm D who complete at least 1 cycle of venetoclax to increase safety for Arm D patients

Notable changes include:

• Updated inclusion criterion 4 to remove autoimmune anemia and/or autoimmune thrombocytopenia that is poorly responsive to corticosteroids or other therapy

• Updated inclusion criterion 7 to require a washout of growth factor prior to ANC screening evaluations to increase patient safety

• Updated inclusion criterion 8 to match the prescribing information for intravenous powder formulation bendamustine

• Updated inclusion criterion 9 to add venetoclax contraception requirements for Arm D and to move methods of contraception to a new subsection

• Added inclusion criterion 12 to ensure it is clear throughout the protocol that FISH analysis for del(17p) is required in order to ensure patients are enrolled in the proper cohort

• Modified exclusion criterion 5 to change "superficial" to "non-muscle-invasive" regarding bladder cancer in accordance with the most current NCCN guidelines

• Modified exclusion criterion 18 to add venetoclax (for Arm D) and to ensure that patients in Arms A, B, and C would not be excluded for hypersensitivity to venetoclax (or its excipients) when they will not receive this study drug

• Added exclusion criterion 21 regarding active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia

• Added exclusion criterion 22 regarding ongoing treatment with warfarin or warfarin derivatives in Arm D only

• Moved the overall survival endpoint from secondary to exploratory

Amendment 3 (11 February 2020)
A total of 653 patients enrolled before Amendment 3 of the study protocol, and a total of 53 patients enrolled in the study under Amendment 3. Key changes to the conduct of the study implemented with Amendment 3 were as follows:

• Throughout document, updated the overall sample size to approximately 680 patients, with approximately 80 additional patients from Chinese sites without del(17p) in Cohort 1a to allow for continuing enrollment of patients from Chinese sites to support further analysis in the Chinese population

• Added secondary endpoints to allow for the comparison of PFS, overall response rate, and duration of response between Arms A and B in pooled Cohort 1/1a patients from Chinese sites

Amendment 4 (10 February 2021)
A total of 706 patients enrolled before Amendment 4 of the study protocol, and a total of 4 patients enrolled in the study under Amendment 4. Key changes to the conduct of the study implemented with Amendment 4 were as follows:

• Updated the required number of PFS events for the interim analysis in the sample size consideration and interim analysis sections to increase statistical power at the interim analysis

Notable changes include:
• Added an option to re-escalate the zanubrutinib dose after dose reduction with approval from the medical monitor based on available safety data for zanubrutinib

• Added a statement that TLS has been infrequently reported with zanubrutinib and ibrutinib treatment based on available safety data for TLS in patients administered ibrutinib and zanubrutinib

Changes to the Planned Analyses
The subgroup analyses by race were not included as most patients (89.1%) were white. Subgroup analyses for complex karyotype defined as ≥ 5 abnormalities were excluded due to the small number of patients with ≥ 5 abnormalities in karyotype at the baseline; furthermore, complex karyotype assessment was not complete at the time of the data cutoff.

There were some discrepancies in stratification by IRT versus eCRF. Thus, a sensitivity analysis using the eCRF stratification factors was conducted. The results were similar to the primary analysis using IRT stratification.

For the primary analysis and the sensitivity analyses specified in the SAP, treatment discontinuation due to adverse event (AE) was handled following the treatment policy strategy, ie, PFS was defined regardless of the occurrence of the intercurrent event (ICE). Two sensitivity analyses were conducted following two additional strategies to handle the ICE: composite strategy (ie, consider treatment discontinuation due to AE as a component event for PFS); and hypothetical strategy (ie, PFS was censored at the last adequate disease assessment prior to treatment discontinuation due to AE).

The scores and mean changes for each domain of EORTC QLQ-C30 questionnaire were summarized for each assessment timepoint. The responder analysis for GHS/QoL was not conducted because there was not a well-defined threshold to define "improved" or "worsened" and the summary of mean changes and the comparison using a restricted maximum likelihood based mixed model for repeated measures (MMRM) have provided adequate information to assess the treatment effect on the GHS/QoL. Since Cohort 1a efficacy data are preliminary, no efficacy analyses will be presented in this CSR.

Protocol deviations

The CRO identified potential protocol deviations in 2 ways: observable protocol deviations were identified by CRO monitors and other project team members, usually during site visits coincident with the source document verification process; and programmatic protocol deviations were identified via automated edit checks of the data in the clinical database. In China, these activities were conducted by BeiGene. Protocol deviations were assessed as either protocol deviation (non-important) or important and reviewed by the CRO or BeiGene's clinical operations team (China) in consultation with the medical monitor before a final determination was made. Important protocol deviations were defined as those that were likely to have had a major impact on the patient's rights, safety, well-being, and/or on the validity of the data for analysis. The final determination of important protocol deviations was made by the medical monitor, using the criteria that define important protocol deviation in the ICH E3 guidelines as follows.

• Patient randomized even though he/she did not satisfy study eligibility criteria

• Patient developed study drug withdrawal criteria but was not withdrawn

• Patient received wrong study treatment or incorrect dose

• Patient received prohibited concomitant treatment

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

Protocol Deviations – Cohort 1
Important protocol deviations (IPDs) were reported in 10 (4.1%) patients in the zanubrutinib arm and 2 (0.8%) patients in the B+R arm. Three patients in the zanubrutinib arm and 1 patient in the B+R arm reported critical protocol deviations. Important protocol deviation that related to COVID-19 were reported in 2 (0.8%) patients in the zanubrutinib arm and 0 (0.0%) patient in the B+R arm. IPDs are summarized. Study conduct, efficacy and safety conclusions were not impacted by these reported important and critical protocol deviations when considering the limited number of reported cases.

Protocol Deviations – Cohort 2
Important protocol deviations were reported in 2 (1.8%) patients in the zanubrutinib arm. One patient (0.9%) in the zanubrutinib arm reported critical protocol deviation. No important protocol deviation that related to COVID-19 was reported in the zanubrutinib arm.

Study conduct, efficacy and safety conclusions were not impacted by these reported important and critical protocol deviations when considering the limited number of reported cases.

BGB-3111-305

Protocol amendments

The protocol was amended 3 times before the data cutoff date for this clinical study report. Additional country-specific amendments for eligibility criteria or study conduct may apply based on local medical practices or input from regional health authorities. A summary of global changes to the protocol is provided below by amendment.

Amendment 1 (04 August 2018)

No patients were enrolled before Amendment 1 of the protocol, and a total of 396 patients were enrolled in the study under Amendment 1. Key changes to the conduct of the study implemented with Amendment 1 were as follows:

• Revised the inclusion criterion 9c: increased the upper limit of serum bilirubin to 3.0.

• Revised exclusion criterion 11a of HBV reactivation monitoring.

• Initial confirmation of progressive disease assessed by CT was sufficient for patients with SLL.

Amendment 2 (29 August 2019)

A total of 39 patients enrolled under Amendment 2 of the study protocol. Key changes to the conduct of the study implemented with Amendment 2 were as follows:

• Updated background information of zanubrutinib, including nonclinical data, clinical pharmacology, preliminary efficacy and safety data.

• Added "overall response rate determined by investigator assessment" as one of the secondary objectives and endpoints.

• Revised exploratory objectives and endpoints: included MRD as one of the exploratory endpoints.

• Updated study duration from 7 years to 60 months.

• Updated study drug access at study closure to clarify patients who benefit from zanubrutinib or ibrutinib may enroll in Zanubrutinib Long-Term Extension Study.

• Revision of inclusion criteria:

– Removed inclusion criterion 3 e: Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.

– Revised inclusion criterion 5: An extranodal lesion measuring > 10 mm in longest perpendicular diameter would be defined as measurable disease.

– Added note to inclusion criterion 8a: the screening hematology values confirming patient meets the ANC requirement must be dated at least 14 days following the most recent administration of peg-filgrastim and at least 7 days following the most recent administration of other myeloid growth factors (eg, G-CSF, GM-CSF).

– Revised the inclusion criterion 8b: the lower limit of platelet count was changed to 30,000/mm3 for patients with CLL.

– Added the inclusion criterion 8c: hemoglobin ≥ 7.5 g/dL (may be post-transfusion).

• Revision of exclusion criteria:

– Revised exclusion criterion 16: changed the criteria for ongoing corticosteroid use.

– Added exclusion criterion 25: Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (eg, idiopathic thrombocytopenia purpura) requiring treatment.

• Added patients must sign an informed consent form before any screening procedures are conducted.

• Revision of Safety Follow-up Visit to End-of-Treatment Visit. Clarified the separation of Long-term Follow-up and Survival follow-up. Changes were made throughout the document.

• Revised efficacy assessments including primary endpoint.

• Revised CT assessment.

• Revised bone marrow examination.

• Added new optional assessment of QOL, activity and corresponding sections to protocol.

• Added laboratory assessments may be done with either central or local laboratory; same should be used throughout the study. The contents of applicable laboratory tests were revised accordingly.

• Added HIV testing

• Added assessment of del17p and cytogenetics, MRD, *TP53* mutations and other molecular analysis.

• Added section of future research (optional).

• Updated information of ibrutinib for administration, dose reduction/modification per local labeling.

• Revised guidelines to follow for dose interruption or modification of zanubrutinib.

• Added toxicity management recommendations.

• Updated information for serious adverse events for reporting and record.

• Deleted the appendix of medication known to prolong QT interval.

Table 12 Select Protocol Modifications Noted in the 305 CSR for Amendment 2 (29 August 2019)

Section	Key Changes	Rationale for the Change
Section 2 Study Objectives; Secondary Section 9.1.2 Secondary Endpoints	Added "Overall response rate determined by investigator assessment" Added "ORR determined by investigator assessment"	Correction of omission - ORR determined by investigator has been part of the study objectives and endpoints.
Section 3.5.1 Study Drug Access at Study Closure	Updated to clarify that patients who benefited from zanubrutinib or ibrutinib may receive Zanubrutinib in the Long-Term Extension Study.	Clarifies that all patients on study will have the opportunity to take zanubrutinib as part of an extension study
Section 4.1 Inclusion Criteria (IC)	A. Deleted 3 e, Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy. B. Added to 5 "or an extranodal lesion must measure > 10 mm in longest perpendicular diameter (LPD)" C. Added bullet under 8 a clarifying ANC requirement. D. Changed 8 b platelet count to ≥ 30,000/mm3. E. Added 8 c, hemoglobin values.	For clarification of specific scenarios related to existing inclusion criteria: A. Patients with autoimmune cytopenias who require treatment are not eligible since these patients typically need ongoing treatment with corticosteroids. B. Clarifies that measurable CLL/SLL disease can be an extranodal lesion C. Clarifies that for required minimum ANC level required to maintained independent of myeloid growth factor support since both study treatments have known adverse drug reaction of neutropenia D. The minimum baseline platelet count (PC) was lowered due to input from investigators that thrombocytopenia during BTK administration is manageable, and patients with PC at baseline of 30,000/mm3 need to be represented/included in this study. E. Eligible patients need to have a baseline hemoglobin of 7.5 g/dL or above since both study treatments have known adverse drug reaction of anemia.

Section	Key Changes	Rationale for the Change
Section 4.2 Exclusion Criteria (EC)	• A. Changed EC3 superficial bladder cancer to non-muscle-invasive bladder cancer. • B. Added to EC16, ~~Prior steroid use~~ **Ongoing need for** corticosteroid use **during the trial.** Added NOTE. Deleted bullet points. • C. Added to EC24 Concurrent treatment for **CLL/SLL** outside of this participation in another therapeutic-clinical trial (includes the screening period). • D. Added new EC25, Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (eg, idiopathic thrombocytopenia purpura) requiring treatment.	A. Clarifies the specific type of bladder cancer that is not considered an excluded condition. B. Requirement for ongoing corticosteroid use while on study excludes the patient. Simplified the criteria for prior corticosteroid use. C. To facilitate accurate assessment of disease burden and baseline organ function during the screening period and avoid the confounding effects of ongoing anti-CLL therapy. D. Patients with autoimmune cytopenias who require treatment are not eligible since these patients typically need ongoing treatment with corticosteroids.
Section 5.9 Biomarkers Del(17p) and Cytogenetics Minimal residual disease Resistance mutation assay	Added that screening samples (including bone marrow) will be assessed by fluorescence in situ hybridization (FISH). Added text describing molecular assays to be performed at baseline and at time of disease progression.	Clarifies that for SLL patients central testing of del(17p) based on FISH testing is performed from the bone marrow aspirate sample. Molecular assays for TP53 mutation testing and potential additional baseline prognostic markers will be assessed, and resistance mutations will be assessed at time of disease progression.
Section 6.6 Toxicity Management Recommendations	Added new section.	To provide additional guidance in response to ethics committee from Czech Republic.

Amendment 3 (31 January 2020)

A total of 217 patients enrolled under Amendment 3 of the study protocol. Key changes to the conduct of the study implemented with Amendment 3 were as follows:

• Increased the sample size from approximately 400 patients to approximately 600 patients.

• Updated study duration to approximately 51 months.

• Clarified that the CT or MRI would be performed as specified per the Schedule of Assessments**,** independent of possible study drug hold.

• Clarified that samples taken at progression leading to permanent study drug discontinuation would be used for the assessment of relevant BTK pathway genes.

• Added information on warnings and precautions for zanubrutinib.

• Revised zanubrutinib dose reduction for nonhematologic toxicity.

• Revised the summary of tumor lysis syndrome events in clinical studies for permitted medications.

• Revised the summary for the primary endpoint (overall response rate) analysis to state that overall response rate was assessed by investigator, with assessment by independent central review performed to support the primary analysis and as the basis of regulatory decisions (in the United States).

• Revised the summary for the key secondary endpoint (PFS) analyses to state that PFS was assessed by investigator, with assessment by independent central review performed to support the key secondary endpoint analysis and as the basis of regulatory decisions (in the United States).

• Updated the noninferiority and superiority testing analysis summary for the primary endpoint (overall response rate)

• Updated analysis summary for key secondary endpoint (PFS) to remove the interim analysis and state that a single analysis would be performed.

• Deleted summary of planned sensitivity analyses for the primary efficacy endpoint (overall response rate) and the key secondary endpoint (PFS).

• Added to the note of Appendix 2 and Appendix 3 that patient may continue study treatment post first assessed PD due to drug hold if it was perceived that the patient would benefit from continued treatment.

Changes to Planned Data/Sample Collection Drop Out of the Self-Administered Quality of Life Questionnaires
Optional self-administration of a device-based quality of life questionnaire and activity tracker was planned for this study. However, this evaluation was aborted because data were obtained only from 2 zanubrutinib-treated patients. Questionnaires were completed once at baseline prior to treatment initiation without follow-up. Data for passive activity tracking and walk test data prior to treatment initiation was collected from 1 patient without follow-up. Data were not provided in this CSR.

PK Sample Collection and Informed Consent Form
Forty-seven out of 327 patients in the zanubrutinib arm were not included in the PK reporting at the data cutoff date because confirming their consent with respect to the location of the bioanalytical laboratory was in process.

Changes to the Planned Analyses
The following analyses are provided in the CSR but were not defined in the SAP or study protocols.

Patient disposition, characteristics, prior systemic therapies and study drug exposure were provided for the first 415 patients randomized. Efficacy summaries were provided based on the first 415 patients randomized. These included analyses of PFS by investigator assessment and by independent central review as well as sensitivity analyses of PFS by investigator assessment and by independent central review that censored for new CLL/SLL therapies and overall survival. Analyses of duration of response by investigator assessment and by independent central review were also provided that include censoring for new CLL/SLL therapies. The above efficacy analyses of PFS and duration of response

were performed for the subgroup of patients with del17p and the subgroup of patients with del17p and/or *TP53* mutations.

Summaries of treatment-emergent adverse events among the first 415 patients randomized were provided based on the Safety Analysis Set, including treatment-emergent adverse events by System Organ Class and Preferred Term, Grade 3 or higher, serious, those leading to death or treatment discontinuation. Additionally, treatment-emergent adverse events of special interest were summarized for the first 415 patients randomized. Shift tables for comparison of baseline toxicity grade versus worst postbaseline toxicity grade were provided for laboratory parameters of interest. Box-and-whisker plots showing the mean, median, 25th and 75th percentiles, and outlier values (ie, > 1.5 times the interquartile range) were provided for laboratory parameters of interest.

Protocol deviations

Study conduct was monitored by the CRO and the sponsor's medical monitor (BeiGene). The CRO identified potential protocol deviations in 2 ways: observable protocol deviations were identified by CRO monitors and other project team members, usually during site visits coincident with the source document verification process; and programmatic protocol deviations were identified via automated edit checks of the data in the clinical database. In China, these activities were conducted by BeiGene. Protocol deviations were assessed as either minor or important and reviewed by the CRO or BeiGene's clinical operations team (China) in consultation with the medical monitor before a final determination was made. Important protocol deviations were defined as those that were likely to have had a major impact on the patient's rights, safety, well-being, and/or on the validity of the data for analysis. The final determination of important protocol deviations was made by the medical monitor, using the criteria that define important protocol deviation in the ICH E3 guidelines as follows.

- Patient randomized even though he/she did not satisfy study eligibility criteria
- Patient developed study drug withdrawal criteria but was not withdrawn
- Patient received wrong study treatment or incorrect dose
- Patient received prohibited concomitant treatment

Critical protocol deviations are a subset of important protocol deviations that have the potential to affect the results of analyses of the primary or secondary objectives of the study. Critical protocol deviations were identified and used to define the Per-Protocol Analysis Set. Important protocol deviations were reported in 5 (1.5%) patients in the zanubrutinib arm and 2 (0.6%) patients in the ibrutinib arm. One patient (064005-004) had a critical protocol deviation (prohibitive medication or treatment) in the zanubrutinib arm. There were no important or critical protocol deviations related to COVID-19.

Study conduct, efficacy and safety conclusions were not impacted by these reported important and critical protocol deviations when considering the limited number of reported cases.

Baseline data

BGB-3111-304

Table 13 Demographics and Baseline Characteristics in Cohort 1 (Intent to Treat Analysis Set)

	BR (N = 238)	Zanubrutinib (N = 241)	Total (Cohort 1) (N = 479)
Sex, n (%)			
Male	144 (60.5)	154 (63.9)	298 (62.2)
Female	94 (39.5)	87 (36.1)	181 (37.8)
Race, n (%)			
White	206 (86.6)	221 (91.7)	427 (89.1)
Not Reported	21 (8.8)	9 (3.7)	30 (6.3)
Asian	9 (3.8)	4 (1.7)	13 (2.7)
Black or African American	1 (0.4)	4 (1.7)	5 (1.0)
Unknown	1 (0.4)	2 (0.8)	3 (0.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.2)
Age (years)			
n	238	241	479
Mean (SD)	69.35 (7.391)	69.82 (7.735)	69.58 (7.562)
Median	70.00	70.00	70.00
Q1, Q3	66.00, 74.00	66.00, 75.00	66.00, 74.00
Min, Max	35.0, 87.0	40.0, 86.0	35.0, 87.0

	BR (N = 238)	Zanubrutinib (N = 241)	Total (Cohort 1) (N = 479)
Age Group, n (%)			
< 65 years	46 (19.3)	45 (18.7)	91 (19.0)
≥ 65 years	192 (80.7)	196 (81.3)	388 (81.0)
65-75 years	139 (58.4)	133 (55.2)	272 (56.8)
≥ 75 years	53 (22.3)	63 (26.1)	116 (24.2)
Geographic Region, n (%)			
Europe	172 (72.3)	174 (72.2)	346 (72.2)
Asia Pacific [a]	38 (16.0)	33 (13.7)	71 (14.8)
North America	28 (11.8)	34 (14.1)	62 (12.9)
ECOG Performance Status, n (%)			
0	101 (42.4)	110 (45.6)	211 (44.1)
1	117 (49.2)	116 (48.1)	233 (48.6)
2	20 (8.4)	15 (6.2)	35 (7.3)
Systolic blood pressure (mmHg)			
n	238	241	479
Mean (SD)	130.84 (15.710)	132.66 (17.934)	131.76 (16.872)
Median	130.00	131.00	130.00
Q1, Q3	121.00, 140.00	120.00, 143.00	120.00, 141.00
Min, Max	95.0, 180.0	93.0, 190.0	93.0, 190.0
Diastolic blood pressure (mmHg)			
n	238	241	479
Mean (SD)	74.04 (9.666)	74.25 (10.962)	74.15 (10.328)
Median	75.00	75.00	75.00
Q1, Q3	68.00, 80.00	67.00, 80.00	67.00, 80.00
Min, Max	51.0, 100.0	40.0, 108.0	40.0, 108.0

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADBASE
Abbreviation: BR, Bendamustine and Rituximab; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; PS, performance status; Q1, first quartile; Q3, third quartile; SD, standard deviation; VAF, Variant allele frequency.
[a] Asia Pacific: Australia; New Zealand; Korea; China; and Taiwan, China.

Table 15: Demographics and Baseline Characteristics in Zanubrutinib Arm (Safety Analysis Set)

	Zanubrutinib (Arm C) (N = 111)
Sex, n (%)	
Male	79 (71.2)
Female	32 (28.8)
Race, n (%)	
White	105 (94.6)
Not Reported	4 (3.6)
Asian	1 (0.9)
Unknown	1 (0.9)
Black or African American	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
Age (years)	
n	111
Mean (SD)	69.77 (7.747)
Median	70.00
Q1, Q3	66.00, 74.00
Min, Max	42.0, 86.0
Age Group, n (%)	
< 65 years	16 (14.4)
≥ 65 years	95 (85.6)
65-75 years	68 (61.3)
≥ 75 years	27 (24.3)
Geographic Region, n (%)	

	Zanubrutinib (Arm C) (N = 111)
Europe	52 (46.8)
Asia Pacific [a]	47 (42.3)
North America	12 (10.8)
ECOG Performance Status, n (%)	
0	44 (39.6)
1	53 (47.7)
2	14 (12.6)
Systolic blood pressure (mmHg)	
n	111
Mean (SD)	128.44 (19.142)
Median	129.00
Q1, Q3	115.00, 140.00
Min, Max	76.0, 196.0
Diastolic blood pressure (mmHg)	
n	111
Mean (SD)	73.60 (11.419)
Median	74.00
Q1, Q3	67.00, 80.00
Min, Max	46.0, 105.0

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADBASE
Abbreviation: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; PS, performance status; Q1, first quartile; Q3, third quartile; SD, standard deviation.
[a] Asia Pacific: Australia; New Zealand; Korea; China; and Taiwan, China.
Programmer: yang.song, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_dm_c_i.sas
Output: t-14-1-2-1-3-dm-bsl-csafp-i.rtf (Date Generated: 07SEP2021:20:22)

Table 16: Disease History and Characteristics in Cohort 1 (Intent-to-Treat Analysis Set)

	BR (N = 238)	Zanubrutinib (N = 241)	Total (Cohort 1) (N = 479)
Cancer Type			
CLL	218 (91.6)	221 (91.7)	439 (91.6)
SLL	20 (8.4)	20 (8.3)	40 (8.4)
Time from initial diagnosis of CLL/SLL to randomization(month)			
n	238	241	479
Mean (SD)	38.64 (38.603)	47.62 (49.665)	43.16 (44.694)
Median	28.67	31.28	30.03
Q1, Q3	7.43, 54.08	8.90, 66.63	8.34, 60.98
Min, Max	0.9, 231.4	0.7, 231.9	0.7, 231.9
Bulky disease			
Any Target Lesion LDi ≥ 5cm			
Yes	73 (30.7)	69 (28.6)	142 (29.6)
No	165 (69.3)	172 (71.4)	337 (70.4)
Any Target Lesion LDi ≥ 10cm			
Yes	10 (4.2)	14 (5.8)	24 (5.0)
No	228 (95.8)	227 (94.2)	455 (95.0)
Binet Stage at study entry for CLL [a]			
A	28 (12.8)	30 (13.6)	58 (13.2)
B	124 (56.9)	126 (57.0)	250 (56.9)
C	66 (30.3)	65 (29.4)	131 (29.8)
Stage at study entry for SLL [b]			

s

	BR (N = 238)	Zanubrutinib (N = 241)	Total (Cohort 1) (N = 479)
A	3 (15.0)	3 (15.0)	6 (15.0)
B	13 (65.0)	12 (60.0)	25 (62.5)
C	4 (20.0)	5 (25.0)	9 (22.5)
Elevated LDH at baseline			
No (≤ ULN)	156 (65.5)	167 (69.3)	323 (67.4)
Yes (> ULN)	81 (34.0)	71 (29.5)	152 (31.7)
Missing	1 (0.4)	3 (1.2)	4 (0.8)
Cytopenia [c]			
Yes	109 (45.8)	102 (42.3)	211 (44.1)
No	129 (54.2)	139 (57.7)	268 (55.9)
Beta-2 Microglobulin			
n	229	234	463
Mean (SD)	4.97 (6.935)	4.49 (3.186)	4.73 (5.377)
Median	3.81	3.80	3.80
Q1, Q3	3.00, 5.15	3.10, 5.20	3.02, 5.20
Min, Max	0.0, 93.0	1.5, 38.0	0.0, 93.0
≤ 3.5 mg/L	98 (41.2)	99 (41.1)	197 (41.1)
> 3.5 mg/L	131 (55.0)	135 (56.0)	266 (55.5)
Del17p			
With Del17p	0 (0.0)	2 (0.8)*	2 (0.4)
TP53 Mutation Detected	0 (0.0)	0 (0.0)	0 (0.0)
TP53 Mutation Not Detected	0 (0.0)	2 (0.8)	2 (0.4)
Without Del17p	238 (100.0)	239 (99.2)	477 (99.6)
TP53 Mutation Detected	13 (5.5)	15 (6.2)	28 (5.8)
TP53 Mutation Not Detected	210 (88.2)	215 (89.2)	425 (88.7)
Del13q [d]			
Yes	129 (54.2)	136 (56.4)	265 (55.3)
No	109 (45.8)	105 (43.6)	214 (44.7)
Del11q			
Yes	46 (19.3)	43 (17.8)	89 (18.6)
No	192 (80.7)	198 (82.2)	390 (81.4)
Trisomy 12			
Yes	49 (20.6)	45 (18.7)	94 (19.6)
No	189 (79.4)	196 (81.3)	385 (80.4)
TP53 mutation			

	BR (N = 238)	Zanubrutinib (N = 241)	Total (Cohort 1) (N = 479)
Detected with VAF ≥ 1.0%	13 (5.5)	15 (6.2)	28 (5.8)
Not detected or VAF < 1.0%	210 (88.2)	217 (90.0)	427 (89.1)
Missing	15 (6.3)	9 (3.7)	24 (5.0)
Del17p or TP53 mutation			
Yes	13 (5.5)	17 (7.1)	30 (6.3)
No	225 (94.5)	224 (92.9)	449 (93.7)
IGHV mutational status			
Mutated	110 (46.2)	109 (45.2)	219 (45.7)
Unmutated	121 (50.8)	125 (51.9)	246 (51.4)
QNS	4 (1.7)	3 (1.2)	7 (1.5)
Missing	3 (1.3)	4 (1.7)	7 (1.5)
Complex karyotype status			
< 3 Abnormalities	78 (32.8)	84 (34.9)	162 (33.8)
≥ 3 Abnormalities	11 (4.6)	18 (7.5)	29 (6.1)
Missing [e]	149 (62.6)	139 (57.7)	288 (60.1)
Complex karyotype status			
< 5 Abnormalities	86 (36.1)	96 (39.8)	182 (38.0)
≥ 5 Abnormalities	3 (1.3)	6 (2.5)	9 (1.9)
Missing [e]	149 (62.6)	139 (57.7)	288 (60.1)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADBASE
Abbreviation: BR, Bendamustine and Rituximab; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; SD, standard deviation; Q1, first quartile; Q3, third quartile; LDH, lactate dehydrogenase; ULN, upper limit of normal; IGA, immunoglobulin A; IGG, immunoglobulin G; IGM, immunoglobulin M; TP53, tumor protein 53; IGHV, immunoglobulin heavy chain variable region; VAF, Variant allele frequency.
[a] Percentages are based on number of CLL patients.
[b] Percentages are based on number of SLL patients.
[c] Cytopenia: Patients having Anemia (hemoglobin <= 110 g/L) or Thrombocytopenia (platelet count <= 100 10^9/L) or Neutropenia (absolute neutrophil count <= 1.5 10^9/L).
[d] Based on Monosomy 13q Mutation results.
[e] Samples not yet evaluated.
* Inadvertent inclusion of these patients in Arm A.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlft/t_dh_ab_i.sas
Output: t-14-1-2-2-1-dh-c1-itt-i.rtf (Date Generated: 06SEP2021:05:58)

Table 17: Disease History and Characteristics in Zanubrutinib Arms (Safety Analysis Set)

	Zanubrutinib (Arm C) (N = 111)
Cancer Type	
CLL	100 (90.1)
SLL	11 (9.9)
Time from initial diagnosis of CLL/SLL to randomization(month)	
n	111
Mean (SD)	40.54 (55.328)
Median	21.39
Q1, Q3	6.44, 54.77
Min, Max	1.1, 323.8
Bulky disease	
Any Target Lesion LDi ≥ 5cm	
Yes	44 (39.6)
No	67 (60.4)
Any Target Lesion LDi ≥ 10cm	
Yes	12 (10.8)
No	99 (89.2)
Binet Stage at study entry for CLL [a]	
A	14 (14.0)
B	49 (49.0)
C	37 (37.0)
Stage at study entry for SLL [b]	
A	4 (36.4)
B	5 (45.5)
C	2 (18.2)
Elevated LDH at baseline	

	(Arm C) (N = 111)
No (≤ ULN)	57 (51.4)
Yes (> ULN)	54 (48.6)
Cytopenia [c]	
Yes	61 (55.0)
No	50 (45.0)
Beta-2 Microglobulin	
n	101
Mean (SD)	5.16 (2.198)
Median	4.80
Q1, Q3	3.60, 6.20
Min, Max	1.9, 13.0
≤ 3.5 mg/L	23 (20.7)
> 3.5 mg/L	78 (70.3)
Del17p	
With Del17p *	110 (99.1)
TP53 Mutation Detected	47 (42.3)
TP53 Mutation Not Detected	62 (55.9)
Without Del17p	1 (0.9)
TP53 Mutation Detected	0 (0.0)
TP53 Mutation Not Detected	0 (0.0)
Del13q [d]	
Yes	74 (66.7)
No	37 (33.3)
Del11q	
Yes	37 (33.3)
No	74 (66.7)
Trisomy 12	
Yes	20 (18.0)
No	91 (82.0)
TP53 mutation	
Detected with VAF ≥ 1.0%	47 (42.3)
Not detected or VAF < 1.0%	62 (55.9)
Missing	2 (1.8)
Del17p or TP53 mutation	
Yes	110 (99.1)
No	1 (0.9)

	Zanubrutinib (Arm C) (N = 111)
IGHV mutational status	
Mutated	36 (32.4)
Unmutated	67 (60.4)
QNS	8 (7.2)
Complex karyotype status	
< 3 Abnormalities	54 (48.6)
≥ 3 Abnormalities	32 (28.8)
Missing	25 (22.5)
Complex karyotype status	
< 5 Abnormalities	63 (56.8)
≥ 5 Abnormalities	23 (20.7)
Missing	25 (22.5)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADBASE
Abbreviation: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; SD, standard deviation; Q1, first quartile; Q3, third quartile; LDH, lactate dehydrogenase; ULN, upper limit of normal; IGA, immunoglobulin A; IGG, immunoglobulin G; IGM, immunoglobulin M; TP53, tumor protein 53; IGHV, immunoglobulin heavy chain variable region; VAF, Variant allele frequency.
[a] Percentages are based on number of CLL patients.
[b] Percentages are based on number of SLL patients.
[c] Cytopenia: Patients having anemia (hemoglobin ≤ 110 g/L) or thrombocytopenia (platelet count ≤ 100 10^9/L) or neutropenia (absolute neutrophil count ≤ 1.5 10^9/L).
[d] Based on Monosomy 13q Mutation results.
* One patient without del17p was included in this cohort due to site error. This patient was not included in the efficacy analysis.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_dh_c_i.sasOutput: t-14-1-2-2-3-dh-csafp-i.rtf (Date Generated: 06SEP2021:06:15)

BGB-3111-305

Table 13: Demographics, Baseline Characteristics and Disease History (Intent-to-Treat Analysis Set)

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

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

Source: ADSL, ADBASE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: CLL, chronic lymphocytic leukemia ; SD, standard deviation ; SLL, small lymphocytic lymphoma. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group. HBcAb, Hepatitis B Core Antibody.
Note: Baseline value was the last non-missing result before first dose of study drug (or randomization date if not dosed).

[a] Unknown = Unknown or Not Reported. Other = Other, Multiple, Black or African American, or Native Hawaiian or Other Pacific Islander.

[b] Positive HBcAb = Reactive.

[c] Complex karyotype is defined as having 3 or more abnormalities.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-dm-dh-i.sas 09AUG2021 23:08 t-4-dm-dh-i.rtf

Table 14: Prior Systemic Anticancer Therapies (Intent-to-Treat Analysis Set)

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

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

Numbers analysed

BGB-3111-304

Table 13: Analysis Sets

	BR (N = 278) n (%)	Zanubrutinib (N = 392) n (%)	Total (N = 670) n (%)
Intent-to-Treat Analysis Set [a]			
Cohort 1	238 (85.6)	241 (61.5)	479 (71.5)
Cohort 1a	40 (14.4)	40 (10.2)	80 (11.9)
Cohort 2 with del17p	0 (0.0)	110 (28.1)	110 (16.4)
Analysis Set of Patients from Chinese Sites [b]	44 (15.8)	42 (10.7)	86 (12.8)
Safety Analysis Set [c]			
Cohort 1	227 (81.7)	240 (61.2)	467 (69.7)
Cohort 1a	38 (13.7)	40 (10.2)	78 (11.6)
Cohort 2	0 (0.0)	111 (28.3)	111 (16.6)
Analysis Set of Patients from Chinese Sites [b]	42 (15.1)	42 (10.7)	84 (12.5)
Per-Protocol Analysis Set [d]			
Cohort 1	226 (81.3)	237 (60.5)	463 (69.1)
Cohort 1a	38 (13.7)	40 (10.2)	78 (11.6)
Cohort 2	0 (0.0)	110 (28.1)	110 (16.4)
Analysis Set of Patients from Chinese Sites [b]	42 (15.1)	42 (10.7)	84 (12.5)
Pharmacokinetics Analysis Set [e]			
Cohort 1	NA	239 (61.0)	239 (35.7)
Cohort 1a	NA	40 (10.2)	40 (6.0)
Cohort 2	NA	111 (28.3)	111 (16.6)
Analysis Set of Patients from Chinese Sites [b]	NA	42 (10.7)	42 (6.3)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL

Abbreviation: BR, Bendamustine and Rituximab.

[a] All Patients in the Intent-to-Treat Analysis Set was defined as patients who were randomized to a treatment group by the IRT system.

[b] All patients in the Analysis Set of Patients from China Sites was defined as Patients from Chinese Sites (Cohort 1/1a) enrolled in Cohort 1/1a and randomized to a treatment group by the IRT system.

[c] All patients in the Safety Analysis Set was defined as patients who received any dose of study drug. Percentages are based on ITT analysis set.

[d] All patients in the Per-Protocol Analysis Set was defined as patients who received any dose of study medication and had no important protocol deviations. Percentages are based on ITT analysis set.

[e] All patients in the Pharmacokinetics Analysis Set was defined as zanubrutinib treated patients for whom valid zanubrutinib PK parameters could be estimated. Percentages are based on ITT analysis set.

Programmer: yang.song, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_pop_i.sas
Output: t-14-1-1-2-pop-i.rtf (Date Generated: 07SEP2021:20:31)

Table 14 Analysis Sets (Intent to Treat Analysis Set)

	Zanubrutinib (N = 327) n (%)	Ibrutinib (N = 325) n (%)
Intent-to-Treat Analysis Set [a]	327 (100.0)	325 (100.0)
First 415 patients randomized	207 (63.3)	208 (64.0)
Safety Analysis Set [b]	324 (99.1)	324 (99.7)
Safety Analysis Set among first 415 patients randomized	204 (62.4)	207 (63.7)
Per-Protocol Analysis Set [c]	323 (98.8)	324 (99.7)
Per-Protocol Analysis Set among first 415 patients randomized	203 (62.1)	207 (63.7)

Source: ADSL. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
[a] All Patients in the Intent-to-Treat Analysis Set was defined as all randomized patients.
[b] All patients in the Safety Analysis Set was defined as all patients who received any dose of study drug.
[c] All patients in the Per-Protocol Analysis Set was defined as all patients who received any dose of study drug and had no critical protocol deviation.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-pop-i.sas 30AUG2021 19:18 t-3-pop-i.rtf

Outcomes and estimation

BGB-3111-304

Primary endpoint – PFS by IRC

Table 15 Analysis of Progression Free Survival by Independent Review Committee in Cohort 1

	BR (N = 238)	Zanubrutinib (N = 241)	Total (N = 479)
Progression-Free Survival			
Events, n (%)	71 (29.8)	36 (14.9)	107 (22.3)
Progressive disease	59 (24.8)	27 (11.2)	86 (18.0)
Death	12 (5.0)	9 (3.7)	21 (4.4)
Censored, n (%)	167 (70.2)	205 (85.1)	372 (77.7)
No documented progressive disease/death	140 (58.8)	195 (80.9)	335 (69.9)
No baseline/post-baseline assessment	16 (6.7)	2 (0.8)	18 (3.8)
No documented progressive disease/death: Withdrew consent/lost to follow-up	6 (2.5)	3 (1.2)	9 (1.9)
Progressive disease/death after missing 2 consecutive planned disease assessments	4 (1.7)	4 (1.7)	8 (1.7)
No documented progressive disease/death: Non-protocol anti-cancer therapy	1 (0.4)	1 (0.4)	2 (0.4)
Follow-up Time (Months)			
Median (95% CI) [a]	24.6 (22.8, 25.2)	25.1 (24.9, 25.4)	25.0 (24.6, 25.2)
(Min, Max)	(0.0, 36.2)	(0.0, 41.4)	(0.0, 41.4)
Hazard Ratio (95% CI) [b]		0.42 (0.28, 0.63)	
1-sided p-value (Log-Rank) [c]		<.0001 (-4.349)	
Progression-Free Survival (Months) [d]			
Median (95% CI)	33.7 (28.1, NE)	NE (NE, NE)	NE (33.7, NE)
Q1 (95% CI)	22.1 (17.5, 25.2)	NE (27.5, NE)	27.2 (22.9, 28.4)
Q3 (95% CI)	NE (33.7, NE)	NE (NE, NE)	NE (NE, NE)
Event-Free Rate at, % (95% CI) [e]			
12 Months	90.2 (85.4, 93.5)	94.5 (90.8, 96.8)	92.5 (89.7, 94.6)
18 Months	80.5 (74.4, 85.2)	91.9 (87.7, 94.8)	86.5 (83.0, 89.4)
24 Months	69.5 (62.4, 75.5)	85.5 (80.1, 89.6)	78.0 (73.6, 81.7)
30 Months	54.4 (43.8, 63.9)	81.5 (74.6, 86.6)	68.1 (61.5, 73.9)
36 Months	40.8 (17.5, 63.1)	81.5 (74.6, 86.6)	61.3 (46.0, 73.5)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADTTEIRC
Abbreviation: BR, Bendamustine and Rituximab; IRT, Interactive Response Technology; IGVH, immunoglobulin heavy-chain variable region.

Figure 25 Kaplan- Meir Plot of Progression Free Survival by Independent Review Committee in Cohort 1

Sensitivity analysis of PFS

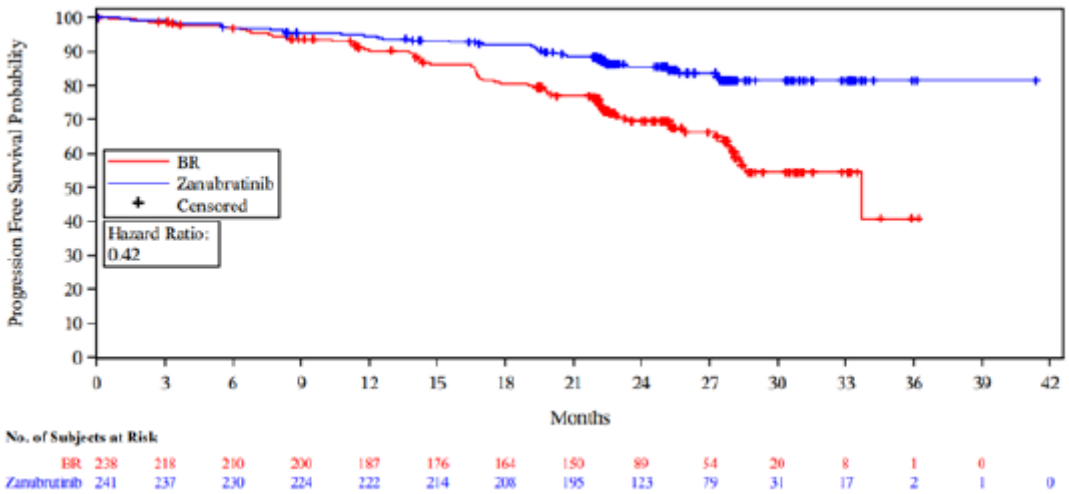


Table 14.2.1.4
Sensitivity/Supportive Analyses of Progression-Free Survival per Independent Review Committee in Cohort 1
(Intent-to-Treat Analysis Set)

	BR (N = 238)		Zanubrutinib (N = 241)			
Analysis [a]	Events/ Patients (%)	Median (months) (95% CI)	Events/ Patients (%)	Median (months) (95% CI)	Hazard Ratio (Zanu/BR) (95% CI)	P-value (1-sided) (Log-Rank)
Primary analysis	71/238 (29.8)	33.7 (28.1, NE)	36/241 (14.9)	NE (NE, NE)	0.42 (0.28, 0.63)	<.0001 (-4.349)
PFS as assessed by the investigators	57/238 (23.9)	33.7 (28.4, 33.7)	29/241 (12.0)	NE (NE, NE)	0.42 (0.27, 0.66)	<.0001 (-3.866)
Unstratified analysis	71/238 (29.8)	33.7 (28.1, NE)	36/241 (14.9)	NE (NE, NE)	0.41 (0.28, 0.62)	<.0001 (-4.460)
Based on per-protocol analysis set	71/226 (31.4)	33.7 (28.1, NE)	36/237 (15.2)	NE (NE, NE)	0.43 (0.29, 0.64)	<.0001 (-4.278)

Secondary endpoint – ORR by IRC in Cohort 1

Table 16 Analysis of Disease Response by Independent Review Committee in Cohort 1

	BR (N = 238)	Zanubrutinib (N = 241)	Total (N = 479)
Best Overall Response, n (%)			
Complete Response	36 (15.1)	16 (6.6)	52 (10.9)
Nodular Partial Response	14 (5.9)	3 (1.2)	17 (3.5)
Partial Response	153 (64.3)	206 (85.5)	359 (74.9)
Partial Response with Lymphocytosis	0 (0.0)	3 (1.2)	3 (0.6)
Stable Disease	14 (5.9)	7 (2.9)	21 (4.4)
Progressive Disease	1 (0.4)	2 (0.8)	3 (0.6)
Not Evaluable	1 (0.4)	1 (0.4)	2 (0.4)
Discontinued Prior to First Assessment	19 (8.0)	3 (1.2)	22 (4.6)
Overall Response [a] Rate, n (%)	203 (85.3)	228 (94.6)	431 (90.0)
(95% CI)	(80.1, 89.5)	(91.0, 97.1)	(86.9, 92.5)
Odds ratio (95% CI)		3.162 (1.608, 6.220)	
P-value		0.0006	

Secondary endpoints – DOR by INV and IRC in Cohort 1

Table 17 Analysis of Duration of Response by Independent Review Committee in Cohort 1

	BR (N = 238)	Zanubrutinib (N = 241)	Total (N = 479)
Duration of Response			
Number of responders, n	203	228	431
Events, n (%)	58 (28.6)	27 (11.8)	85 (19.7)
Progressive disease	53 (26.1)	21 (9.2)	74 (17.2)
Death	5 (2.5)	6 (2.6)	11 (2.6)
Censored, n (%)	145 (71.4)	201 (88.2)	346 (80.3)
No documented progressive disease/death	140 (69.0)	195 (85.5)	335 (77.7)
No documented progressive disease/death: Withdrew consent/lost to follow-up	3 (1.5)	3 (1.3)	6 (1.4)
Progressive disease/death after missing 2 consecutive planned disease assessments	2 (1.0)	3 (1.3)	5 (1.2)
Follow-up Time (Months)			
Median (95% CI) [a]	22.1 (21.2, 22.6)	22.1 (21.4, 22.3)	22.1 (21.7, 22.3)
(Min, Max)	(3.8, 32.3)	(3.3, 38.7)	(3.3, 38.7)
Duration of Response (Months) [b]			
Median (95% CI)	30.6 (25.5, NE)	NE (NE, NE)	NE (NE, NE)
Q1 (95% CI)	20.1 (17.7, 24.6)	NE (NE, NE)	24.8 (22.9, NE)
Q3 (95% CI)	NE (30.6, NE)	NE (NE, NE)	NE (NE, NE)

Table 23: Analysis of Duration of Response by Investigator in Cohort 1 (Intent-to-Treat Analysis Set)

	BR (N = 238)	Zanubrutinib (N = 241)	Total (N = 479)
Duration of Response			
Number of responders, n	211	235	446
Events, n (%)	48 (22.7)	24 (10.2)	72 (16.1)
Progressive disease	41 (19.4)	15 (6.4)	56 (12.6)
Death	7 (3.3)	9 (3.8)	16 (3.6)
Censored, n (%)	163 (77.3)	211 (89.8)	374 (83.9)
No documented progressive disease/death	158 (74.9)	208 (88.5)	366 (82.1)
No documented progressive disease/death: Withdrew consent/lost to follow-up	4 (1.9)	2 (0.9)	6 (1.3)
Progressive disease/death after missing 2 consecutive planned disease assessments	1 (0.5)	1 (0.4)	2 (0.4)
Follow-up Time (Months)			
Median (95% CI) [a]	19.8 (19.6, 20.6)	19.8 (19.6, 20.5)	19.8 (19.7, 20.3)

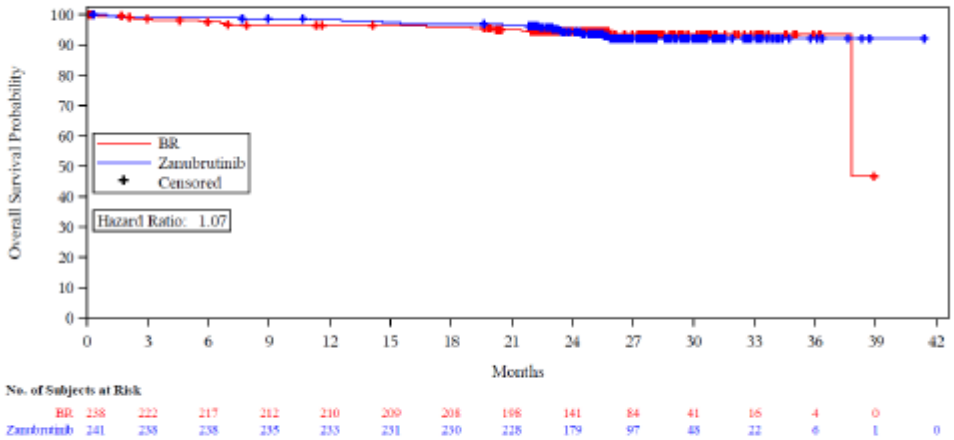
	BR (N = 238)	Zanubrutinib (N = 241)	Total (N = 479)
(Min, Max)	(0.0, 31.7)	(2.8, 35.9)	(0.0, 35.9)
Duration of Response (Months) [b]			
Median (95% CI)	30.6 (26.2, NE)	NE (NE, NE)	NE (NE, NE)
Q1 (95% CI)	24.4 (19.7, 25.3)	NE (NE, NE)	26.2 (24.6, NE)
Q3 (95% CI)	NE (30.6, NE)	NE (NE, NE)	NE (NE, NE)

Secondary endpoint – Overall Survival

Table 21: Analysis of Overall Survival in Cohort 1 (Intent-to-Treat Analysis Set)

	BR (N = 238)	Zanubrutinib (N = 241)	Total (N = 479)
Overall Survival			
Deaths, n (%)	14 (5.9)	16 (6.6)	30 (6.3)
Censored, n (%)	224 (94.1)	225 (93.4)	449 (93.7)
Not known to have died	224 (94.1)	225 (93.4)	449 (93.7)
Follow-up Time (Months)			
Median (95% CI) [a]	25.1 (24.9, 25.6)	26.5 (25.7, 27.0)	25.7 (25.2, 26.3)
(Min, Max)	(0.0, 38.9)	(0.3, 41.4)	(0.0, 41.4)
Hazard Ratio (95% CI) [b]		1.07 (0.51, 2.22)	
1-sided p-value (Log-Rank) [c]		0.5672 (0.169)	
Overall Survival (Months) [d]			
Median (95% CI)	37.8 (37.8, NE)	NE (NE, NE)	NE (37.8, NE)
Q1 (95% CI)	37.8 (37.8, NE)	NE (NE, NE)	37.8 (37.8, NE)
Q3 (95% CI)	NE (37.8, NE)	NE (NE, NE)	NE (NE, NE)

Figure 6: Kaplan-Meier Plot of Overall Survival in Cohort 1 (Intent-to-Treat Analysis Set)



Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADTTE
Abbreviation: BR, Bendamustine and Rituximab.

Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlf/f_ef_km.sas
Output: f-14-2-1-2-4-1-ef-km-os-c1-itt.pdf (Date Generated: 06SEP2021:05:56)

Secondary endpoints – ORR, DOR, PFS by IRC in Cohort 2

Table 25: Analysis of Disease Response by Independent Review Committee in Zanubrutinib Arm (Safety Analysis Set with Central Lab Del17p)

	Zanubrutinib (Arm C in Del17p+) (N = 110)
Best Overall Response, n (%)	
Complete Response	7 (6.4)
Nodular Partial Response	2 (1.8)
Partial Response	88 (80.0)
Partial Response with Lymphocytosis	2 (1.8)
Stable Disease	11 (10.0)
Overall Response [a] Rate, n (%)	99 (90.0)
(95% CI)	(82.8, 94.9)
Complete Response Rate (CR/CRi), n (%)	7 (6.4)
(95% CI)	(2.6, 12.7)
Partial Response or Higher Rate, n (%)	97 (88.2)
(95% CI)	(80.6, 93.6)
Time to Partial Response with Lymphocytosis or Higher [b] (months)	
n	99
Mean (SD)	3.76 (2.737)
Median	2.86
Q1, Q3	2.79, 3.02
Min, Max	1.9, 19.4
Time to Partial Response or Higher [b] (months)	
n	97
Mean (SD)	3.61 (2.254)
Median	2.86
Q1, Q3	2.79, 3.02
Min, Max	1.9, 13.9

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADRSIRC, ADTTEIRC
Abbreviation: CI, confidence interval; NE, not estimable; Q1, first quartile; Q3, third quartile; SD, standard deviation; CR, Complete Response; CRi, Complete Response with Incomplete Hematopoietic Recovery; nPR, Nodular Partial Response; PR, Partial Response; PR-L, Partial Response with Lymphocytosis.
Percentages are based on N.
[a] Overall response is defined as achieving a best overall response of CR, CRi, nPR, PR, or PR-L.
[b] Time to response (TTR) is summarized for responders only.
Programmer: jiapeng.he, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlft/t_eff_orr_irc_i.sas
Output: t-14-2-1-7-3-eff-orr-irc-csafp-i.rtf (Date Generated: 09SEP2021:19:29)

Table 29: Analysis of Duration of Response by Independent Review Committee in Zanubrutinib Arm (Safety Analysis Set with Central Lab Del17p)

	Zanubrutinib (Arm C in Del17p+) (N = 110)
Duration of Response	
Number of responders, n	99
Events, n (%)	10 (10.1)
Progressive disease	10 (10.1)
Death	0 (0.0)
Censored, n (%)	89 (89.9)
No documented progressive disease/death	88 (88.9)
No documented progressive disease/death: Withdrew consent/lost to follow-up	1 (1.0)
Progressive disease/death after missing 2 consecutive planned disease assessments	0 (0.0)
Follow-up Time (Months)	
Median (95% CI) [a]	25.1 (24.9, 25.6)
(Min, Max)	(2.8, 35.9)
Duration of Response (Months) [b]	
Median (95% CI)	NE (NE, NE)
Q1 (95% CI)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)
Event-Free Rate at, % (95% CI) [c]	
12 Month	94.9 (88.1, 97.8)
18 Month	93.8 (86.8, 97.2)
24 Month	91.6 (83.9, 95.7)
30 Month	88.1 (78.5, 93.6)
36 Month	NE (NE, NE)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADTTEIRC

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

[b] Medians and other quartiles of duration of response were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

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

Table 27: Analysis of Progression-Free Survival by Independent Review Committee in Zanubrutinib Arm (Safety Analysis Set with Central Lab Del17p)

	Zanubrutinib (Arm C in Del17p+) (N = 110)
Progression-Free Survival	
Events, n (%)	15 (13.6)
Progressive disease	14 (12.7)
Death	1 (0.9)
Censored, n (%)	95 (86.4)
No documented progressive disease/death	93 (84.5)
No documented progressive disease/death: Withdrew consent/lost to follow-up	1 (0.9)
Progressive disease/death after missing 2 consecutive planned disease assessments	0 (0.0)
No baseline/post-baseline assessment	0 (0.0)
No documented progressive disease/death: Non-protocol anti-cancer therapy	0 (0.0)
Progressive disease/death after new anti-cancer therapy	1 (0.9)
Follow-up Time (Months)	
Median (95% CI) [a]	27.9 (27.7, 29.2)
(Min, Max)	(1.0, 38.8)
Progression-Free Survival (Months) [b]	
Median (95% CI)	NE (NE, NE)
Q1 (95% CI)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)
Event-Free Rate at, % (95% CI) [c]	
12 Months	93.6 (87.0, 96.9)
18 Months	89.9 (82.5, 94.3)
24 Months	88.9 (81.3, 93.6)
30 Months	84.9 (76.0, 90.8)
36 Months	84.9 (76.0, 90.8)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADTTEIRC
Abbreviation: IGVH, immunoglobulin heavy-chain variable region.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles of progression-free survival were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_eff_pfs_irc_c2_i.sas
Output: t-14-2-1-2-3-eff-pfs-irc-csafp-i.rtf (Date Generated: 06SEP2021:06:17)

BGB-3111-305

Primary endpoint – ORR by INV

Table 15: Interim Analysis of Disease Response per Investigator Assessment (Intent-to-Treat Analysis Set, First 415 Patients Randomized)

Response Category	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Best Overall Response, n (%)		
Complete response	3 (1.4)	3 (1.4)
Complete response w/incomplete bone marrow recovery	1 (0.5)	0 (0.0)
Nodular partial response	1 (0.5)	0 (0.0)
Partial response	157 (75.8)	127 (61.1)
Partial response w/lymphocytosis	21 (10.1)	39 (18.8)
Stable disease	17 (8.2)	28 (13.5)
Progressive disease	1 (0.5)	2 (1.0)
Not evaluable	0 (0.0)	0 (0.0)
Discontinued prior to first assessment	6 (2.9)	8 (3.8)
Not assessed	0 (0.0)	1 (0.5)
Overall Response Rate[a], n (%)	162 (78.3)	130 (62.5)
(95% CI)[d]	(72.0, 83.7)	(55.5, 69.1)
Response ratio[b] (95% CI)		1.25 (1.10, 1.41)
		Noninferiority 1-sided p-value[c] = <.0001
		Superiority 2-sided p-value[c] = 0.0006
Time to Response (Months)		
n	162	130
Mean (SD)	5.61 (2.835)	6.34 (3.047)
Median	5.59	5.65
Q1, Q3	2.89, 8.28	3.09, 8.34
Min, Max	2.7, 14.1	2.8, 16.7
Rate of CR/CRi, n (%)	4 (1.9)	3 (1.4)
(95% CI)[d]	(0.5, 4.9)	(0.3, 4.2)
Rate of PR-L or Higher, n (%)	183 (88.4)	169 (81.3)
(95% CI)[d]	(83.2, 92.4)	(75.3, 86.3)

Source: ADSL, ADTTE, ADRS. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: CR, complete response; CRi, complete response w/incomplete bone marrow recovery; PR-L, partial response w/lymphocytosis.

[a] Responders are defined as patients with a best overall response of partial response or higher.

[b] Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.

[c] P-value is calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558 and for superiority via stratified Cochran-Mantel-Haenszel test statistic.

[d] Clopper-Pearson confidence interval.

/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eff-orrinv-i.sas 09AUG2021 23:12 t-8-eff-orrinv-i.rtf

Table 7: ORR results by investigator and by IRC at interim and final analyses in all randomised patients

	Interim Analysis (data cutoff date 31 Dec 2020)				Final Analysis (data cutoff date 01 Dec 2021)			
All randomised patients	**ITT population[1]**		**PP population[1]**		**ITT population**		**PP population**	
	Zanubrutinib (N=327)	Ibrutinib (N=325)	Zanubrutinib (N=323)	Ibrutinib (N=324)	Zanubrutinib (N=327)	Ibrutinib (N=325)	Zanubrutinib (N=323)	Ibrutinib (N=324)
ORR by investigator, n (%) (95% CI)	176 (53.8) (48.3, 59.3)	142 (43.7) (38.2, 49.3)	176 (54.5) (48.9, 60.0)	142 (43.8) (38.3, 49.4)	260 (79.5) (74.7, 83.8)	231 (71.1) (65.8, 75.9)	260 (80.5) (75.7, 84.7)	231 (71.3) (66.0, 76.2)
Response ratio (95% CI)	1.23 (1.05, 1.44)		1.24 (1.06, 1.45)		1.12 (1.02, 1.22)		1.12 (1.03, 1.23)	
ORR by IRC, n (%) (95% CI)	176 (53.8) (48.3, 59.3)	146 (44.9) (39.4, 50.5)	175 (54.2) (48.6, 59.7)	146 (45.1) (39.6, 50.7)	263 (80.4) (75.7, 84.6)	237 (72.9) (67.7, 77.7)	262 (81.1) (76.4, 85.2)	237 (73.1) (68.0, 77.9)
Response ratio (95% CI)	1.20 (1.02, 1.40)		1.20 (1.02, 1.40)		1.10 (1.01, 1.20)		1.10 (1.02, 1.20)	

Source: Table 14.2.1.1.1.1.1 for IA data in ITT by IRC, Table 14.2.1.1.1.1.2 for IA data in PP by IRC, Table 14.2.1.1.2.1.1 for IA data in ITT by INV, Table 14.2.1.1.2.1.2 for IA data in PP by INV; Table 12 and Table 14.2.1.3.2 in BGB-3111-305 FA CSR for investigator assessment using ITT and PP populations; Table 13 and Table 14.2.1.3.1 in BGB-3111-305 FA CSR for IRC assessment using ITT and PP populations.

[1] The pre-specified interim analysis was for the first 415 randomised participants. The analyses in ITT and PP population are not planned (conducted per EMA request).

Sensitivity analysis

Table 18 Sensitivity analysis of ORR per Investigator assessment

Per-protocol Analysis Set, Amongst First 415 Patients Randomized

Response Category	Zanubrutinib (N = 203)	Ibrutinib (N = 207)	Total (N = 410)
Best Overall Response, n (%)			
Complete response	3 (1.5)	3 (1.4)	6 (1.5)
Complete response w/incomplete bone marrow recovery	1 (0.5)	0 (0.0)	1 (0.2)
Nodular partial response	1 (0.5)	0 (0.0)	1 (0.2)
Partial response	157 (77.3)	127 (61.4)	284 (69.3)
Partial response w/lymphocytosis	21 (10.3)	39 (18.8)	60 (14.6)
Stable disease	16 (7.9)	28 (13.5)	44 (10.7)
Progressive disease	1 (0.5)	2 (1.0)	3 (0.7)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued prior to first assessment	3 (1.5)	7 (3.4)	10 (2.4)
Not assessed	0 (0.0)	1 (0.5)	1 (0.2)
Overall Response Rate[a], n (%)	162 (79.8)	130 (62.8)	292 (71.2)
(95% CI)[d]	(73.6, 85.1)	(55.8, 69.4)	(66.6, 75.6)
Response ratio[b] (95% CI)		1.26 (1.11, 1.43)	
		Noninferiority 1-sided p-value[c] = <.0001	
		Superiority 2-sided p-value[c] = 0.0003	

Source: ADSL, ADTTE, ADRS. Data cutoff: 31DEC2020. Data extraction: 19MAR2021

Table 19 Sensitivity analysis of ORR per Independent central review accounting for drug interruptions

Intent-to-Treat Analysis Set, First 415 Patients Randomized

Response Category	Zanubrutinib (N = 207)	Ibrutinib (N = 208)	Total (N = 415)
Overall Response Rate[a], n (%)	158 (76.3)	134 (64.4)	292 (70.4)
(95% CI)[d]	(69.9, 81.9)	(57.5, 70.9)	(65.7, 74.7)
Response ratio[b] (95% CI)		1.17 (1.04, 1.33)	
		Noninferiority 1-sided p-value[c] = <.0001	
		Superiority 2-sided p-value[c] = 0.0121	
Rate of CR/CRi, n (%)	3 (1.4)	2 (1.0)	5 (1.2)
(95% CI)[d]	(0.3, 4.2)	(0.1, 3.4)	(0.4, 2.8)
Rate of PR-L or Higher, n (%)	178 (86.0)	170 (81.7)	348 (83.9)
(95% CI)[d]	(80.5, 90.4)	(75.8, 86.7)	(80.0, 87.3)

Source: ADSL, ADRSIRC. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.

Table 20 Sensitivity analysis of ORR per Investigator assessment accounting for drug interruptions

Intent-to-Treat Analysis Set, First 415 Patients Randomized

Response Category	Zanubrutinib (N = 207)	Ibrutinib (N = 208)	Total (N = 415)
Best Overall Response, n (%)			
Complete response	3 (1.4)	3 (1.4)	6 (1.4)
Complete response w/incomplete bone marrow recovery	1 (0.5)	0 (0.0)	1 (0.2)
Nodular partial response	1 (0.5)	0 (0.0)	1 (0.2)
Partial response	158 (76.3)	128 (61.5)	286 (68.9)
Partial response w/lymphocytosis	22 (10.6)	39 (18.8)	61 (14.7)
Stable disease	15 (7.2)	27 (13.0)	42 (10.1)
Progressive disease	1 (0.5)	1 (0.5)	2 (0.5)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued prior to first assessment	6 (2.9)	9 (4.3)	15 (3.6)
Not assessed	0 (0.0)	1 (0.5)	1 (0.2)
Overall Response Rate[a], n (%)	163 (78.7)	131 (63.0)	294 (70.8)
(95% CI)[d]	(72.5, 84.1)	(56.0, 69.6)	(66.2, 75.2)
Response ratio[b] (95% CI)		1.24 (1.10, 1.41)	
		Noninferiority 1-sided p-value[c] = <.0001	
		Superiority 2-sided p-value[c] = 0.0006	

Source: ADSL, ADRS. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.

Secondary endpoints - ORR by IRC

Table 21: Interim Analysis of Disease Response per independent Central Review (Intent to Treat Analysis Set, First 415 Patients Randomized)

Response Category	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Best Overall Response, n (%)		
Complete response	3 (1.4)	2 (1.0)
Complete response w/incomplete bone marrow recovery	0 (0.0)	0 (0.0)
Nodular partial response	1 (0.5)	0 (0.0)
Partial response	154 (74.4)	132 (63.5)
Partial response w/lymphocytosis	19 (9.2)	36 (17.3)
Stable disease	21 (10.1)	25 (12.0)
Non-progressive disease	1 (0.5)	0 (0.0)
Progressive disease	1 (0.5)	4 (1.9)
Not evaluable	1 (0.5)	1 (0.5)
Discontinued prior to first assessment	6 (2.9)	7 (3.4)
Not assessed	0 (0.0)	1 (0.5)
Overall Response Rate[a], n (%)	158 (76.3)	134 (64.4)
(95% CI)[d]	(69.9, 81.9)	(57.5, 70.9)
Response ratio[b] (95% CI)		1.17 (1.04, 1.33)
		Noninferiority 1-sided p-value[c] = <.0001
		Superiority 2-sided p-value[c] = 0.0121
Time to Response (Months)		
n	158	134
Mean (SD)	5.48 (2.710)	6.30 (3.154)
Median	5.55	5.63
Q1, Q3	2.92, 8.28	3.12, 8.34
Min, Max	2.7, 14.0	2.7, 16.7
Rate of CR/CRi, n (%)	3 (1.4)	2 (1.0)
(95% CI)[d]	(0.3, 4.2)	(0.1, 3.4)

Response Category	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Rate of PR-L or Higher, n (%)	177 (85.5)	170 (81.7)
(95% CI)[d]	(80.0, 90.0)	(75.8, 86.7)

Source: ADSL, ADTTEIRC, ADRSIRC. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviations: CR, complete response; CRi, complete response w/incomplete bone marrow recovery; PR-L, partial response w/lymphocytosis.

[a] Responders are defined as patients with a best overall response of partial response or higher.

[b] Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.

[c] P-value is calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558 and for superiority via stratified Cochran-Mantel-Haenszel test statistic.

[d] Clopper-Pearson confidence interval.

/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eff-orrirc-i.sas 09AUG2021 23:11 t-7-eff-orrirc-i.rtf

Concordance between IRC and INV

Summary of Concordance of Best Overall Response per Independent Central Review versus Investigator Assessment Intent-to-Treat Analysis Set, First 415 Patients Randomized

Response Category	Zanubrutinib (N = 207)	Ibrutinib (N = 208)	Total (N = 415)
Best Overall Response, n (%)			
CR or CRi			
CR or CRi per IRC and INV	1 (0.5)	2 (1.0)	3 (0.7)
Not CR or CRi per IRC and INV	201 (97.1)	205 (98.6)	406 (97.8)
CR or CRi per IRC; Not CR or CRi per INV	2 (1.0)	0 (0.0)	2 (0.5)
Not CR or CRi per IRC; CR or CRi per INV	3 (1.4)	1 (0.5)	4 (1.0)
Partial response or higher (responder)			
Responder per IRC and INV	154 (74.4)	125 (60.1)	279 (67.2)
Non-responder per IRC and INV	41 (19.8)	69 (33.2)	110 (26.5)
Responder per IRC; Non-responder per INV	4 (1.9)	9 (4.3)	13 (3.1)
Non-responder per IRC; Responder per INV	8 (3.9)	5 (2.4)	13 (3.1)
PR-L or higher			
PR-L or higher per IRC and INV	171 (82.6)	162 (77.9)	333 (80.2)
Not PR-L or higher per IRC and INV	18 (8.7)	31 (14.9)	49 (11.8)
PR-L or higher per IRC; Not PR-L or higher per INV	6 (2.9)	8 (3.8)	14 (3.4)
Not PR-L or higher per IRC; PR-L or higher per INV	12 (5.8)	7 (3.4)	19 (4.6)

Source: ADSL, ADRS, ADRSIRC. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviations: CR, complete response; CRi, complete response w/incomplete bone marrow recovery; INV, investigator; IRC, independent central review; PR-L, partial response w/lymphocytosis.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eff-borconc.sas 09AUG2021 20:30 t-14-2-1-2-eff-borconc.rtf

Secondary endpoints - DOR by INV and IRC

Table 22 Interim Analysis of Duration of response by investigator Assessment (Intent to Treat Analysis Set first 415 Patients Randomized)

	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Duration of Response		
Number of Responders	162	130
Events, n (%)	9 (5.6)	16 (12.3)
Progressive disease	5 (3.1)	14 (10.8)
Death	4 (2.5)	2 (1.5)
Censored, n (%)	153 (94.4)	114 (87.7)
No documented PD/death	152 (93.8)	113 (86.9)
No documented PD/death: Withdrew consent/lost to follow-up	1 (0.6)	1 (0.8)
Follow-up Time (Months)		
Median (95% CI) [a]	10.1 (8.3, 11.0)	8.3 (8.3, 9.5)
(Min, Max)	(2.7, 19.2)	(2.4, 19.5)
Duration of Response (Months) [b]		
Median (95% CI)	NE (14.0, NE)	16.6 (13.7, NE)
Q1 (95% CI)	NE (12.9, NE)	13.7 (10.7, 16.6)
Q3 (95% CI)	NE (NE, NE)	NE (16.6, NE)
Event Free Rate at, % (95% CI) [c]		
6 Months	100.0 (NE, NE)	98.0 (92.3, 99.5)
12 Months	89.8 (78.1, 95.4)	77.9 (64.7, 86.7)
18 Months	77.2 (49.8, 90.8)	34.1 (1.8, 74.9)
24 Months	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
[a] Median follow-up time was estimated by the reverse Kaplan-Meier method.
[b] Medians and other quartiles of duration of response are estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Event free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eff-dorinv-i.sas 09AUG2021 23:20 t-16-eff-dorinv-i.rtf

Table 23

Table 24 Interim Analysis of Duration of Response by Independent Central Review

	Zanubrutinib (N = 207)	Ibrutinib (N = 208)
Duration of Response		
Number of Responders	158	134
Events, n (%)	14 (8.9)	18 (13.4)
Progressive disease	11 (7.0)	16 (11.9)
Death	3 (1.9)	2 (1.5)
Censored, n (%)	144 (91.1)	116 (86.6)
No documented PD/death	142 (89.9)	116 (86.6)
No documented PD/death: Withdrew consent/lost to follow-up	1 (0.6)	0 (0.0)
PD/death after >1 missing planned disease assessments	1 (0.6)	0 (0.0)
Follow-up Time (Months)		
Median (95% CI) [a]	10.1 (8.3, 10.9)	8.3 (8.3, 10.1)
(Min, Max)	(1.4, 19.2)	(2.6, 19.7)
Duration of Response (Months) [b]		
Median (95% CI)	16.7 (14.3, NE)	NE (NE, NE)
Q1 (95% CI)	14.3 (14.0, NE)	13.0 (9.9, NE)
Q3 (95% CI)	NE (16.7, NE)	NE (NE, NE)
Event Free Rate at, % (95% CI) [c]		
6 Months	97.9 (93.6, 99.3)	95.4 (89.4, 98.1)
12 Months	90.3 (82.3, 94.8)	78.0 (66.1, 86.2)
18 Months	46.3 (9.3, 77.9)	72.4 (55.6, 83.8)
24 Months	NE (NE, NE)	NE (NE, NE)

Source: ADSL, ADTTEIRC. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.

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

[b] Medians and other quartiles of duration of response are estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[c] Event free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-eff-dorirc-i.sas 09AUG2021 23:19 t-15-eff-dorirc-i.rtf

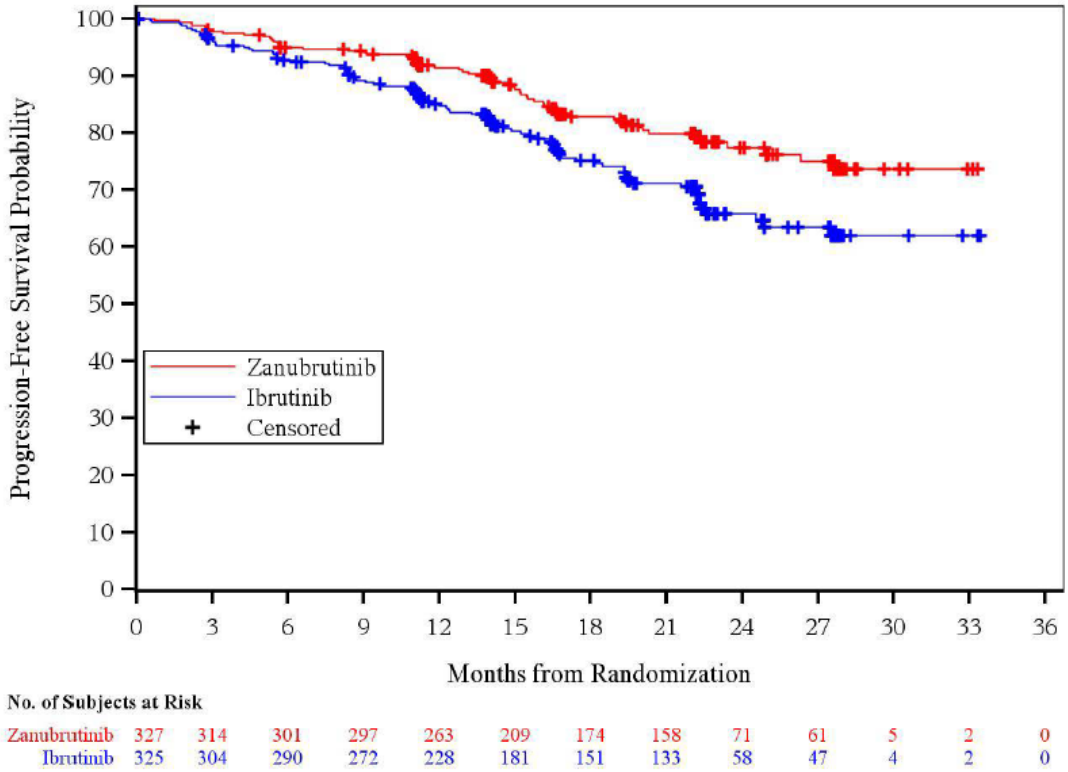
Secondary endpoints – PFS by INV and IRC

Table 25 PFS results by investigator and by IRC at interim and final analyses in all randomised patients

All randomised patients	Interim Analysis (data cutoff date 31 Dec 2020)				Final Analysis (data cutoff date 01 Dec 2021)			
	ITT population		PP population		ITT population		PP population	
	Zanubrutinib (N=327)	Ibrutinib (N=325)	Zanubrutinib (N=323)	Ibrutinib (N=324)	Zanubrutinib (N=327)	Ibrutinib (N=325)	Zanubrutinib (N=323)	Ibrutinib (N=324)
PFS by investigator assessment, n (%)								
Events, n (%)	27 (8.3)	50 (15.4)	26 (8.0)	50 (15.4)	58 (17.7)	91 (28.0)	57 (17.6)	91 (28.1)
Progressive disease	17 (5.2)	33 (10.2)	16 (5.0)	33 (10.2)	34 (10.4)	63 (19.4)	33 (10.2)	63 (19.4)
Death	10 (3.1)	17 (5.2)	10 (3.1)	17 (5.2)	24 (7.3)	28 (8.6)	24 (7.4)	28 (8.6)
Follow-up Time, Median (95% CI) [a] (Month)	11.6 (11.1, 13.8)	11.3 (11.1, 13.8)	12.9 (11.1, 13.8)	11.3 (11.1, 13.8)	22.1 (22.1, 22.2)	22.1 (22.0, 22.2)	22.1 (22.1, 22.2)	22.1 (22.0, 22.2)
PFS Median (95% CI) [b] (Month)	NE (NE, NE)	22.3 (19.4, NE)	NE (NE, NE)	22.3 (19.4, NE)	NE (29.6, NE)	NE (NE, NE)	NE (29.6, NE)	NE (NE, NE)
Hazard Ratio (95% CI) [c]	0.47 (0.29, 0.76)		0.45 (0.27, 0.73)		0.55 (0.39, 0.76)		0.54 (0.38, 0.75)	
Event-Free Rate (PFS landmark) at, % (95% CI) [d]								
12 Month	93.3 (89.3, 95.9)	83.1 (77.3, 87.6)	93.7 (89.7, 96.2)	83.1 (77.3, 87.6)	91.5 (87.8, 94.1)	84.5 (79.9, 88.1)	91.8 (88.2, 94.3)	84.5 (79.9, 88.1)
24 Month	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	78.4 (72.3, 83.4)	63.6 (56.5, 69.8)	78.7 (72.5, 83.6)	63.6 (56.5, 69.8)
PFS by IRC assessment, n (%)								
Events, n (%)	36 (11.0)	52 (16.0)	35 (10.8)	52 (16.0)	60 (18.3)	87 (26.8)	59 (18.3)	87 (26.9)
Progressive disease	25 (7.6)	37 (11.4)	24 (7.4)	37 (11.4)	37 (11.3)	63 (19.4)	36 (11.1)	63 (19.4)
Death	11 (3.4)	15 (4.6)	11 (3.4)	15 (4.6)	23 (7.0)	24 (7.4)	23 (7.1)	24 (7.4)
Follow-up Time, Median (95% CI) [a] (Month)	11.3 (11.1, 13.8)	11.3 (11.1, 13.8)	11.4 (11.1, 13.8)	11.3 (11.1, 13.8)	22.1 (22.1, 22.2)	22.1 (22.0, 22.2)	22.1 (22.1, 22.2)	22.1 (22.0, 22.2)
PFS Median (95% CI) [b] (Month)	22.1 (22.1, NE)	NE (NE, NE)	22.1 (22.1, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Hazard Ratio (95% CI) [c]	0.61 (0.39, 0.95)		0.59 (0.38, 0.92)		0.61 (0.44, 0.86)		0.60 (0.43, 0.84)	
1-sided p-value (Log-Rank)	0.0003		0.0002		<0.0001		<0.0001	
Event-Free Rate (PFS landmark) at, % (95% CI) [d]								
12 Month	90.4 (85.7, 93.6)	81.7 (75.8, 86.4)	90.8 (86.1, 93.9)	81.7 (75.8, 86.4)	91.4 (87.8, 94.1)	84.7 (80.2, 88.3)	91.7 (88.1, 94.3)	84.7 (80.2, 88.3)
24 Month	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	77.4 (71.2, 82.4)	65.8 (58.9, 71.9)	77.6 (71.4, 82.6)	65.8 (58.9, 71.9)

Source: Table 17 and Table 14.2.1.7.2.2 in BGB-3111-305 IA CSR (sequence 0014) for investigator assessment using ITT and PP populations; Table 18 and Table 14.2.1.7.1.2 in BGB-3111-305 IA CSR (sequence 0014) for IRC assessment using ITT and PP populations; Table 14 and Table 14.2.1.7.2.2 in BGB-3111-305 FA CSR for investigator assessment using ITT and PP populations; Table 15 and Table 14.2.1.7.1.2 in BGB-3111-305 FA CSR for IRC assessment using ITT and PP populations.

Figure 26 Kaplan Meier Plot of Progression free Survival by Independent Central Review

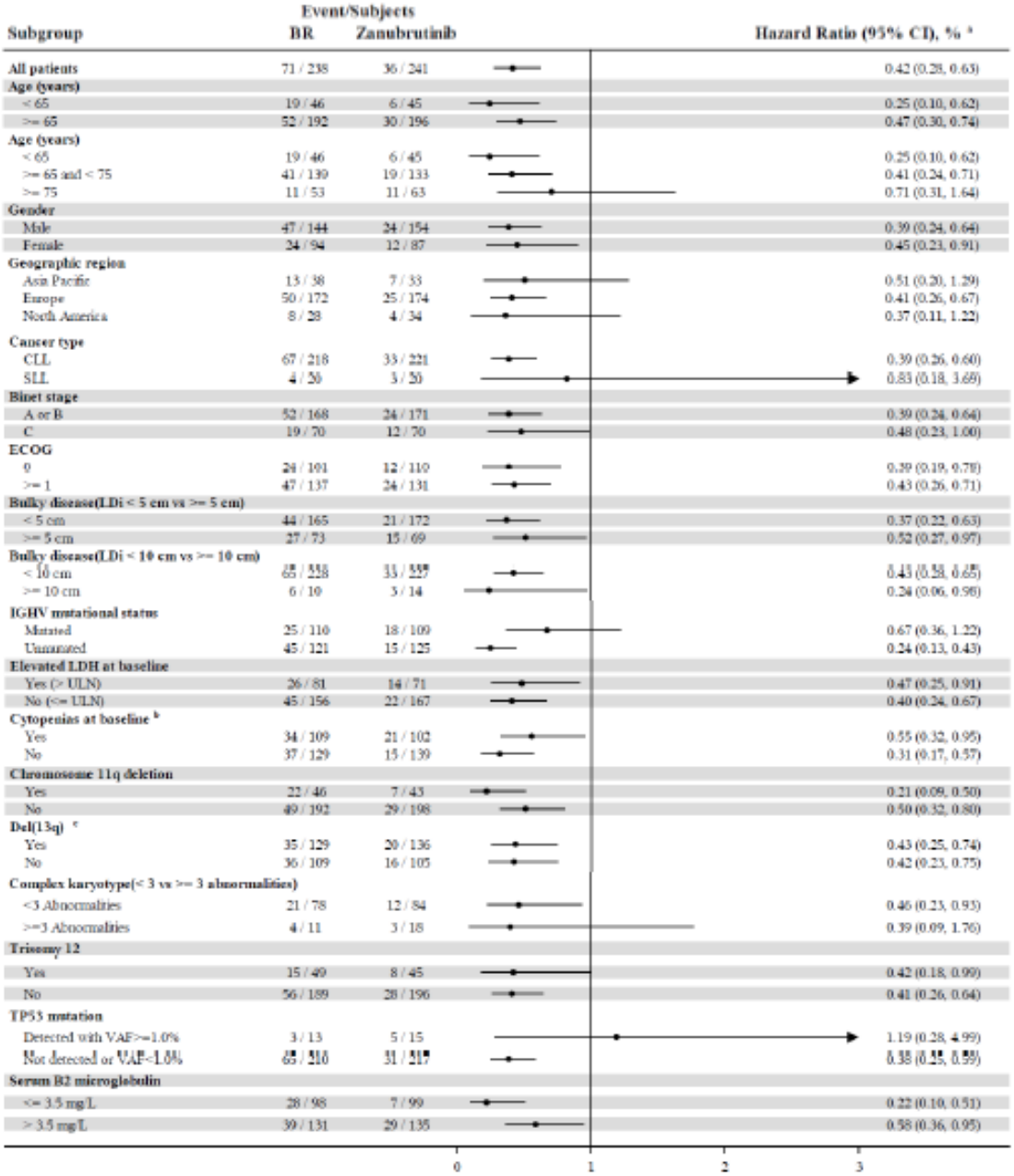


Source: ADSL, ADTTEIRC. Data cutoff: 01DEC2021. Data extraction: 04MAR2022.
/bgb_3111/bgb_3111_305/csru_orr_fa_20211201/dev/pgm/tlfs/f-eff-km-pfsirc-i.sas 26APR2022 01:17 f-70-eff-km-pfsirc-i.rtf

Ancillary analyses

BGB-3111-304

Figure 27 Forest Plot of Hazard Ratio of Progression Free Survival by Independent Review Committee in Cohort 1



Data cut-off: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADTTEIRC, ADBASE
Abbreviation: BR, Bendamustine and Rituximab; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDi, longest diameter; IGHV, immunoglobulin heavy chain variable region; LDH, lactate dehydrogenase; ULN, upper limit of normal; TP53, tumor protein 53; VAF, Variant allele frequency.

[a] Hazard ratio and 95% CI were from stratified (for all patients) or unstratified analysis (for subgroup) Cox regression model with BR arm as the reference group.

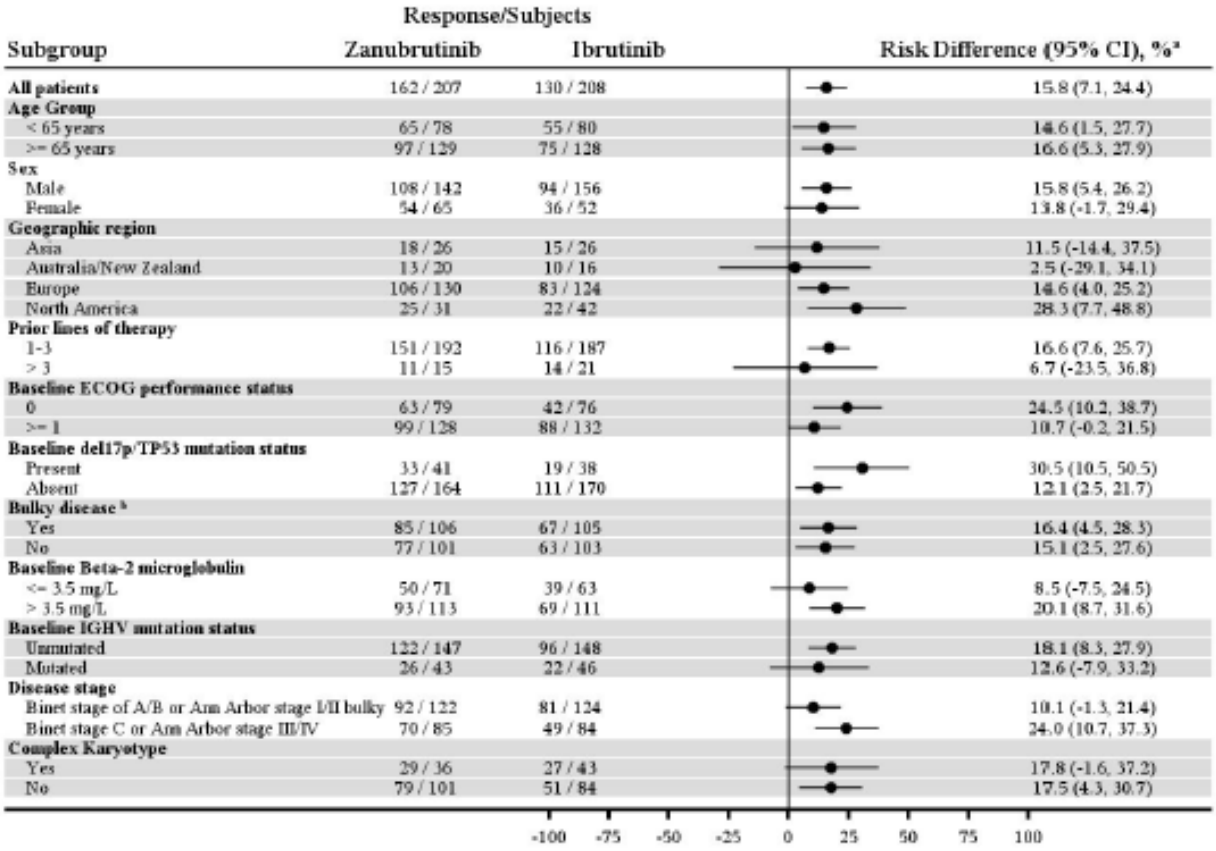
[b] Cytopenia: Patients having Anemia (hemoglobin <= 110 g/L) or Thrombocytopenia (platelet count <= 100 10^9/L) or Neutropenia (absolute neutrophil count <= 1.5 10^9/L).

[c] Based on Monosomy 13q Mutation results.

BGB-3111-305

Figure 28

Figure 29 Forest Plot of Interim Analysis of Overall Response Rate by Investigator Assessment



Source: ADSL, ADBASE, ADRS. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.

[a] Unstratified rate difference and 95% confidence interval.

[b] Bulky disease of yes is derived from any target lesion longest diameter ≥ 5 cm.

/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/f-eff-forest-i.sas 09AUG2021 23:39 f-34-eff-forestinv-i.rtf

Summary of main studies

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

*Table 26**. Summary of efficacy for trial BGB-3111-304***

Title: An International, Phase 3, Open-label, Randomized Study of BGB-3111 Compared with Bendamustine plus Rituximab in Patients with Previously Untreated Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma		
Study identifier	BGB-3111-304; EudraCT 2017-001551-31	
Design	Study BGB-3111-304 is a Phase 3, multicentre, open-label randomized study of zanubrutinib versus bendamustine plus rituximab (B+R) in patients with previously untreated chronic lymphocytic leukaemia/ small lymphocytic lymphoma (CLL/SLL) without deletion 17p (Cohort 1). This study also has a Cohort 2 of patients with deletion 17p who receive zanubrutinib treatment only since chemotherapy is not appropriate as therapy for this population. Progression-free survival will be compared between the 2 arms in Cohort 1 (patients without deletion 17p) using a stratified log-rank test based on the following 3 randomization stratification factors: age (< 65 years vs ≥ 65 years), Binet stage (C vs A or B), and IGHV mutational status (mutated vs unmutated).	
	Duration of main phase:	First patient was enrolled on 31 October 2017 and the last patient was enrolled on 22 July 2019. Study was ongoing as of the data cutoff date of 07 May 2021. The study duration is estimated to be approximately 5 years after first subject is randomized.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Hypothesis: PFS superiority of Arm A (zanubrutinib) versus Arm B (B+R) in Cohort 1. The sample size calculation for Cohort 1 is based on the hypothesis on PFS by independent central review. Assuming the PFS hazard ratio (Arm A/Arm B) in Cohort 1 is 0.58, 118 events are required to achieve 83.5% power at 2-sided alpha of 0.05 to reject the null hypothesis when 1 interim analysis is planned after 73% of the target number of events at final analysis (approximately 86 events). Based on the rate of accrual anticipated in this study, it was planned to randomize a total of approximately 450 subjects in a 1:1 ratio to the 2 treatment arms in Cohort 1.	
Treatments groups	Arm A (Cohort 1)	Zanubrutinib, 160 mg twice daily, until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination, 241 patients enrolled.
	Arm B (Cohort 1)	Bendamustine was administered intravenously at a dose of 90 mg/m2/day on the first 2 days of each cycle for 6 cycles. Rituximab was administered intravenously at a dose of 375 mg/m2 for Cycle 1 and at a dose of 500 mg/m2 for Cycles 2 to 6, 238 patients enrolled.

	Arm C (Cohort 2)		Zanubrutinib, 160 mg twice daily, until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination, 110 patients evaluable for efficacy.
Endpoints and definitions	Primary endpoint	PFS by IRC in Cohort 1	Progression free survival (PFS), defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first, as determined by independent review committee (IRC).
	Secondary Endpoints in Cohort 1	PFS by INV in Cohort 1	PFS, defined the same as above, as determined by investigator assessment (INV)
		ORR by INV and by IRC in Cohort 1	Overall response rate (ORR) (PR-L, i.e., partial response with lymphocytosis or better) determined by investigator (INV) and by IRC using the "modified" 2008 IWCLL guidelines (Hallek et al 2008) with modification for treatment related lymphocytosis (Cheson et al 2012) for patients with CLL and per Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) for patients with SLL.
		DOR by INV and by IRC in Cohort 1	Duration of response (DOR), defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first, determined by INV and by IRC.
		OS in Cohort 1	Overall survival (OS), defined as the time from randomization to the date of death due to any cause.
		PROs in Cohort 1	Patient-reported outcomes (PROs) measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires.
	Secondary Endpoints in Cohort 2	PFS by INV and by IRC in Cohort 2	Progression free survival (PFS), defined the same as for Cohort 1, as determined by INV and IRC.
		ORR by INV and by IRC in Cohort 2	Overall response rate (ORR) (PR-L, i.e., partial response with lymphocytosis or better) determined by investigator (INV) and by IRC using the same criteria as for Cohort 2.
		DOR by INV and by IRC in Cohort 2	Duration of response (DOR), defined the same as for Cohort 1, determined by INV and by IRC.
Database lock	Data cutoff date was 07 May 2021, data extracted on 28 June 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Analysis population: Cohort 1 in the Intent-to-treat population consisting of 479 patients randomized to either zanubrutinib arm (Arm A, 241 patients) or B+R arm (Arm B, 238 patients). Timepoint: at the prespecified interim analysis when approximately 86 events (73% of the target number of events at final analysis) from Arms A and B in Cohort 1 are observed.		
Descriptive statistics and estimate variability	Treatment groups	Zanubrutinib Arm A	B+R Arm B
	Number of subjects	n = 241	n=238
	Primary endpoint		
	PFS by IRC, events, n (%)	36 (14.9)	71 (29.8)
	Progressive disease	27 (11.2)	59 (24.8)
	Death	9 (3.7)	12 (5.0)
	Event Free Rate (PFS Landmark) at, % (95% CI) [a]		
	12 Month	94.5 (90.8, 96.8)	90.2 (85.4, 93.5)
	24 Month	85.5 (80.1, 89.6)	69.5 (62.4, 75.5)
	36 Month	81.5 (74.6, 86.6)	40.8 (17.5, 63.1)
Effect estimate per comparison	PFS (Month) [d], median (95% CI)	NE (NE, NE)	33.7 (28.1, NE)
	Hazard Ratio (95% CI) [b]	0.42 (0.28, 0.63)	
	1-sided p-value (Log-Rank) [c]	<.0001 (-4.349)	
Analysis description	**Secondary Analysis**		
Descriptive statistics and estimate variability	PFS by INV, events, n (%)	29 (12.0)	57 (23.9)
	Progressive disease	18 (7.5)	45 (18.9)
	Death	11 (4.6)	12 (5.0)
	Event Free Rate (PFS Landmark) at, % (95% CI) [a]		
	12 Month	95.8 (92.4, 97.7)	91.2 (86.6, 94.3)
	24 Month	87.7 (82.1, 91.6)	76.5 (69.6, 82.1)
	36 Month	84.5 (77.8, 89.3)	0.0 (NE, NE)
	PFS (Month) [d], median (95% CI)	NE (NE, NE)	33.7 (28.4, 33.7)
Notes	None		
Analysis description	Analysis population: Cohort 2 (110 patients) with centrally confirmed del(17p) who were assigned to the zanubrutinib arm (Arm C). Timepoint: data cutoff as of 07 May 2021		
Descriptive statistics and estimate variability	Treatment groups	Zanubrutinib Arm A	
	Number of subjects	n = 110	

	ORR by IRC [e], n (%)	99 (90.0)
	(95% CI)	(82.8, 94.9)
	DOR by IRC	
	Number of responders	99
	Median (95% CI) [d]	NE (NE, NE)
	Event Free Rate (still in response) at, % (95% CI) [a]	
	12 Month	94.9 (88.1, 97.8)
	24 Month	91.6 (83.9, 95.7)
	PFS by IRC, events, n (%)	15 (13.6)
	Progressive disease	14 (12.7)
	Death	1 (0.9)
	PFS (Month) [d], median (95% CI)	NE (NE, NE)
	Event Free Rate (PFS Landmark) at, % (95% CI) [a]	
	12 Month	93.6 (87.0, 96.9)
	24 Month	88.9 (81.3, 93.6)
	36 Month	84.9 (76.0, 90.8)
Notes	None	

[a] Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
[b] Hazard ratio and 95% CI were from stratified Cox regression model with B+R arm as the reference group.
[c] From stratified log-rank test.
[d] Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[e] Overall response is defined as achieving a best overall response of CR, CRi, nPR, PR, or PR-L.

Study 304:

Analysis description	**Analysis with additional follow-up (only INV assessed)**	
Analysis population and time point description	Analysis population: Cohort 1 in the Intent-to-treat population consisting of 479 patients randomized to either zanubrutinib arm (Arm A, 241 patients) or B+R arm (Arm B, 238 patients). Timepoint: Data cutoff as of 07 March 2022	
Descriptive statistics and estimate variability	PFS by INV, events, n (%)	
	Progressive disease	21 (8.7)	69 (29.0)
	Death	16 (6.6)	17 (7.1)
	Event Free Rate (PFS Landmark) at, % (95% CI) [a]	
	12 Month	95.8 (92.4, 97.7)	91.2 (86.6, 94.3)
	24 Month	89.0 (84.3, 92.4)	78.3 (72.1, 83.3)
	36 Month	83.6 (77.4, 88.2)	55.1 (46.7, 62.8)
	PFS (Month) [d], median (95% CI)	NE (NE, NE)	39.2 (33.7, NE)

	Hazard Ratio (95% CI)[b]	0.33 (0.22, 0.48)	
	OS, events, n (%)		
	Death	23 (9.5)	22 (9.2)
	OS Rate at, % (95% CI) [a]		
	12 Month	98.3 (95.6, 99.4)	96.4 (93.0, 98.2)
	24 Month	94.5 (90.7, 96.8)	94.6 (90.7, 96.9)
	36 Month	90.9 (86.3, 94.0)	89.5 (84.2, 93.1)
	OS (Month) [d], median (95% CI)	NE (NE, NE)	NE (NE, NE)
	Hazard Ratio (95% CI) [b]	0.93 (0.52, 1.67)	

Table 27 ***Summary of efficacy for trial BGB-3111-305***

Title: A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma		
Study identifier	BGB-3111-305; EudraCT 2018-001366-42	
Design	Study BGB-3111-305 is a Phase 3, multicentre, randomized, open-label study of zanubrutinib compared with ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).	
	Duration of main phase:	First patient was enrolled on 01 November 2018 and the last patient was enrolled on 15 December 2020. Study was ongoing as of the data cutoff date of 31 December 2020. The study duration is estimated to be approximately 51 months after first subject is randomized.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority followed by Superiority (sequential testing). The primary hypothesis testing for the primary endpoint of overall response rate by investigator assessment was to demonstrate the noninferiority of zanubrutinib to ibrutinib. One interim analysis occurred approximately 12 months after 415 patients had been randomized. The final analysis will occur approximately 12 months after 600 patients have been randomized. If noninferiority is demonstrated either at the interim or the final analysis, further testing for the superiority of zanubrutinib to ibrutinib will be performed. Assuming a response ratio (zanubrutinib arm/ibrutinib arm) of 1.03 (72%/70%), 600 patients will provide more than 90% power to demonstrate the non-inferiority of zanubrutinib to ibrutinib at the non-inferiority margin of 0.8558 (response ratio) and 1-sided alpha level of 0.025 when there is 1 interim analysis at 69% information fraction (415 out of 600 patients).	

Treatments groups	Zanubrutinib		Zanubrutinib, 160 mg twice daily, until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination, 327 patients enrolled.
	Ibrutinib		Ibrutinib, 420mg once daily, until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination, 325 patients enrolled.
Endpoints and definitions	Primary endpoint	ORR by INV	Overall response rate (ORR) (PR or higher, defined as CR/CRi + PR + nodular PR) determined by investigator assessment (INV) using the "modified" 2008 IWCLL guidelines (Hallek et al 2008) with modification for treatment related lymphocytosis (Cheson et al 2012) for patients with CLL and per Lugano Classification for non-Hodgkin lymphoma (NHL) (Cheson et al 2014) for patients with SLL.
	Key Secondary endpoints	PFS by INV	Progression-free survival (PFS), defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first, determined per investigator assessment.
		incidence of atrial fibrillation/flutter.	Incidence of atrial fibrillation/flutter, defined as having a treatment-emergent adverse event of "atrial fibrillation" or "atrial flutter".
	Other Secondary endpoints	ORR per independent central review	Overall response rate (ORR) (PR or higher, defined as CR/CRi + PR + nodular PR) per independent central review using the same criteria as for investigator assessment.
		PFS per independent central review	Progression-free survival (PFS), defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first, as per independent central review.
		DOR by INV	Duration of response (DOR), defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first, determined by investigator assessment.
		DOR per independent central review	DOR by independent central review defined the same as for investigator assessment except using assessments per independent central review.
		TTF	Time to treatment failure (TTF), defined as time from randomization to discontinuation of study drug due to any reason.
		OS	Overall survival (OS), defined as the time from randomization to the date of death due to any cause.

		Rate of PR-L or higher by INV	Rate of PR-L (partial response with lymphocytosis) or higher, defined as the proportion of patients who achieve a CR/CRi +PR + nodular PR + PR-L determined investigator assessment.
		Rate of PR-L or higher per independent central review	Rate of PR-L or higher by independent central review defined the same as for investigator assessment except using assessments per independent central review.
		PROs	Patient-reported outcomes (PROs) measured by the EQ-5D-5L and EORTC QLQ-C30 questionnaires.
		Safety	Safety parameters, including AEs, SAEs, clinical laboratory tests, physical exams, and vital signs.
Database lock	Data cutoff date was 31 December 2020, data extracted on 19 March 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Analysis population: First 415 randomized patients in the Intent-to-treat population at the planned interim analysis. Timepoint: Data cutoff as of 31 December 2020		
Effect estimate per comparison	Treatment group	Zanubrutinib	Ibrutinib
	Number of subjects	n = 207	n = 208
	Primary endpoint		
	ORR by INV [a], n (%)	162 (78.3)	130 (62.5)
	(95% CI) [d]	(72.0, 83.7)	(55.5, 69.1)
	Response ratio [b] (95% CI)	1.25 (1.10, 1.41)	
		Noninferiority 1-sided p-value [c] = <.0001	
		Superiority 2-sided p-value [c] = 0.0006	
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Analysis population: first 415 randomized patients in the Intent-to-treat population at the planned interim analysis. Analyses of secondary endpoints are summarized below in descriptive statistics. Timepoint: Data cutoff as of 31 December 2020.		
Descriptive statistics and estimate variability	Treatment group	Zanubrutinib	Ibrutinib
	Number of subjects	n = 207	n = 208
	ORR by IRC [a], n (%)	158 (76.3)	134 (64.4)
	(95% CI) [d]	(69.9, 81.9)	(57.5, 70.9)
	Response ratio[b] (95% CI)	1.17 (1.04, 1.33)	

		Noninferiority 1-sided p-value [c] = <.0001	
		Superiority 2-sided p-value [c] = 0.0121	
	Duration of Response (DOR) by INV		
	Treatment group	Zanubrutinib	Ibrutinib
	Number of responders	162	130
	Event Free Rate (still in response) at, % (95% CI) [f]		
	12 Months	89.8 (78.1, 95.4)	77.9 (64.7, 86.7)
	Duration of Response (DOR) by IRC		
	Treatment group	Zanubrutinib	Ibrutinib
	Number of responders	158	134
	Event Free Rate (still in response) at, % (95% CI) [f]		
	12 Months	90.3 (82.3, 94.8)	78.0 (66.1, 86.2)
Analysis population and time point description	Analysis population: the Intent-to-treat population consisting of all 652 patients randomized to either zanubrutinib arm or ibrutinib arm. Timepoint: Data cutoff as of 31 December 2020.		
Descriptive statistics and estimate variability	Treatment group	Zanubrutinib	Ibrutinib
	Number of subjects	n = 327	n = 325
	PFS by INV		
	Events, n (%)	27 (8.3)	50 (15.4)
	Progressive disease	17 (5.2)	33 (10.2)
	Death	10 (3.1)	17 (5.2)
	Hazard Ratio [e] (95% CI)	0.47 (0.29, 0.76)	
	Event Free Rate (PFS landmark) at, % (95% CI) [f]		
	12 Months	93.3 (89.3, 95.9)	83.1 (77.3, 87.6)
	24 Months	NE (NE, NE)	NE (NE, NE)
	PFS by IRC		
	Events, n (%)	36 (11.0)	52 (16.0)
	Progressive disease	25 (7.6)	37 (11.4)
	Death	11 (3.4)	15 (4.6)
	Hazard Ratio [e] (95% CI)	0.61 (0.39, 0.95)	

	Event Free Rate (PFS landmark) at, % (95% CI) [f]		
	12 Months	90.4 (85.7, 93.6)	81.7 (75.8, 86.4)
	24 Months	NE (NE, NE)	NE (NE, NE)
Notes	None		

a Responders are defined as patients with a best overall response of partial response or higher.
b Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.
c P-value is calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558 and for superiority via stratified Cochran-Mantel-Haenszel test statistic.
d Clopper-Pearson confidence interval.
e Hazard ratio is the ratio of the hazard of the zanubrutinib arm divided by that of the ibrutinib arm.
f Event free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Study 305:

Analysis description	**ORR Final Analysis**		
Analysis population and time point description	Analysis population: the Intent-to-treat population consisting of all 652 patients randomized to either zanubrutinib arm or ibrutinib arm. Timepoint: Data cutoff as of 01 December 2021		
Descriptive statistics and estimate variability	Treatment group	Zanubrutinib	Ibrutinib
	Number of subjects	n = 327	n = 325
	ORR by INV [a], n (%)	260 (79.5)	231 (71.1)
	(95% CI) [d]	(74.7, 83.8)	(65.8, 75.9)
	Response ratio [b] (95% CI)	1.12 (1.02, 1.22)	
		Noninferiority 1-sided p-value [c] = <.0001[1]	
		Superiority 2-sided p-value [c] = 0.0133	
	ORR by IRC [a], n (%)	263 (80.4)	237 (72.9)
	(95% CI) [d]	(75.7, 84.6)	(67.7, 77.7)
	Response ratio [b] (95% CI)	1.10 (1.01, 1.20)	
		Noninferiority 1-sided p-value [c] = <.0001	
		Superiority 2-sided p-value [c] = 0.0264	
	Duration of Response (DOR) by INV		
	Treatment group	Zanubrutinib	Ibrutinib
	Number of responders	260	231
	Event Free Rate (still in response) at, % (95% CI) [f]		

[1] P-value is descriptive only, since noninferiority was met for ORR by INV and IRC at interim analysis

	12 Months	92.2 (87.7, 95.1)	85.8 (79.5, 90.2)
	18 months	86.7 (80.3, 91.1)	74.2 (65.5, 81.0)
	Duration of Response (DOR) by IRC		
	Treatment group	Zanubrutinib	Ibrutinib
	Event Free Rate (still in response) at, % (95% CI) [f]		
	12 Months	91.6 (87.0, 94.6)	86.4 (80.5, 90.7)
	18 months	82.5 (75.6, 87.7)	78.1 (70.4, 84.0)
	PFS by INV		
	Events, n (%)	58 (17.7)	91 (28.0)
	Progressive disease	34 (10.4)	63 (19.4)
	Death	24 (7.3)	28 (8.6)
	Hazard Ratio [e] (95% CI)	0.55 (0.39, 0.76)	
	Event Free Rate (PFS landmark) at, % (95% CI) [f]		
	12 Months	91.5 (87.8, 94.1)	84.5 (79.9, 88.1)
	24 Months	78.4 (72.3, 83.4)	63.6 (56.5, 69.8)
	PFS by IRC		
	Events, n (%)	60 (18.3)	87 (26.8)
	Progressive disease	37 (11.3)	63 (19.4)
	Death	23 (7.0)	24 (7.4)
	Hazard Ratio [e] (95% CI)	0.61 (0.44, 0.86)	
	Event Free Rate (PFS landmark) at, % (95% CI) [f]		
	12 Months	91.4 (87.8, 94.1)	84.7 (80.2, 88.3)
	24 Months	77.4 (71.2, 82.4)	65.8 (58.9, 71.9)
Notes	None		

a Responders are defined as patients with a best overall response of partial response or higher.
b Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.
c P-value is calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558 and for superiority via stratified Cochran-Mantel-Haenszel test statistic.
d Clopper-Pearson confidence interval.
e Hazard ratio is the ratio of the hazard of the zanubrutinib arm divided by that of the ibrutinib arm.
f Event free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Supportive studies

Two studies, BGB-3111-AU-003 and BGB-3111-205, provide supportive efficacy data for this submission. They are briefly summarized below. Refer to the clinical study reports for additional details on these supportive studies.

Study BGB-3111-AU-003
Study BGB-3111-AU-003 was a Phase 1/2, open-label, multiple-dose, multicenter, international dose-escalation (Part 1) and expansion (Part 2) study designed to investigate the safety and PK of zanubrutinib in patients with B-cell malignancies. This first-in-human study for zanubrutinib has been completed. A total of 125 patients with CLL/SLL were enrolled in the study, with a median duration of treatment of 37.13 months (range: 0.8 to 71.5 months) for patients with R/R CLL/SLL, and 49.17 months (range: 3.6 to 65.3 months) for patients with TN CLL/SLL. Data for these patients are presented in Module 2.7.3 and briefly below.

The study was conducted at sites in Australia, New Zealand, Italy, South Korea, the UK, and the USA. The study was conducted in 2 parts and included patients with TN (N = 22) and R/R CLL/SLL (n = 103) who received ≥ 1 dose of study drug. This dose finding and expansion study was the first-in-human study for zanubrutinib and has a median follow-up time of 50.87 months (range: 11.1 to 65.3 months) for patients with TN CLL/SLL and a median follow-up time of 40.44 months (range: 5.3 to 71.5 months) for patients with R/R CLL/SLL. These extensive data help to support high overall response rates, long duration of response, and long PFS in patients with CLL/SLL treated with zanubrutinib. Results from Study BGB-3111-AU-003 demonstrate that zanubrutinib is safe and effective in patients with
CLL/SLL.

Efficacy results for Study BGB-3111-AU-003 are briefly described here; In patients with R/R CLL/SLL, the overall response rate (PR with lymphocytosis or better) was high at 94.2% (97 of 103 patients; 95% CI: 87.8%, 97.8%). The overall response rate was similar in patients with del(17p) mutation (92.3% [12 of 13 patients; 95% CI: 64.0%, 99.8%]). The PR or better rate overall was 90.3%, with a lower rate in patients with del(17p) mutations (84.6%). The CR/CRi rate was 15.5% overall, with a rate of 7.7% (1 patient) in patients with del(17p)+ disease. The overall response rate (PR-L or better) and the PR or better rate in patients with TN CLL/SLL was 100.0% (22 patients; 95% CI: 84.9%, 100.0% for both), with no difference in either rate according to del(17p) mutation status. The CR/CRi rate overall was 22.7%; none of the patients with del(17p) achieved a CR.
In patients with R/R CLL/SLL, the median PFS was 61.4 months (95% CI: 50.4 months, not evaluable) with a median follow-up of 39.4 months. Twenty-four (23.3%) events were observed, including 23 events of disease progression and 1 death. The median PFS was lower in patients with del(17p) (50.2 months) than in patients without del(17p) (61.4 months). Overall, PFS rates at 12, 24, and 36 months were 96.0%, 90.6%, and 82.8%, respectively. Lower rates were observed in patients with del(17p) disease (92.3%, 75.5%, and 75.5% at 12, 24, and 36 months, respectively).

Among patients with TN CLL/SLL, the median PFS was not evaluable (95% CI: 41.4 months, not evaluable) with a median follow-up of 49.4 months. Events were observed in 5 patients (22.7%), including 4 disease progression events and 1 death. Progression-free survival rates overall at 12, 24, 36, and 48 months were 95.2%, 90.5%, 81.0%, and 74.4%, respectively. With an overall median follow-up time of 48.9 months (range: 5.3 to 71.5 months), the median overall survival was not reached in either patients with R/R CLL/SLL or patients with TN disease. Overall survival rates for patients with CLL/SLL on the study were 98.4%, 95.8%, 91.1%, and 86.2% at 12, 24, 36, and 48 months, respectively. Rates were similar for patients with TN disease (100.0%, 95.2%, 90.5%, and

90.5% at 12, 24, 36, and 48 months, respectively) and R/R disease (98.0%, 95.9%, 91.2%, and 84.6% at 12, 24, 36, and 48 months, respectively).

In patients with R/R CLL/SLL, overall survival was also similar in patients with del(17p)+ and del(17p)- CLL/SLL. The median overall survival was not reached after a median follow-up time of 44.5 months (range: 9.4 to 62.6 months) for patients with del(17p)+ and 49.3 months (range: 5.8 to 71.5 months) for patients with del(17p)- CLL.

Study BGB-3111-205

Study BGB-3111-205 was a single-arm, multicenter Phase 2 study designed to evaluate the efficacy and safety of zanubrutinib in patients with CLL/SLL who had relapsed or whose disease was refractory after ≥ 1 prior treatment regimen(s). The study was conducted at sites in China. Ninety-one patients were enrolled and treated with zanubrutinib and received zanubrutinib 160 mg orally twice daily continuously in repeated 28-day cycles. Study BGB-3111-205 demonstrates that zanubrutinib is safe and effective in a population of mostly high-risk patients from China with CLL/SLL. Patients enrolled on BGB-3111-205 were of poor prognosis. At study entry, most patients had advanced clinical stage disease (Binet Stage C CLL [67.1%], Rai Stage III or IV CLL [67.1%], or Stage IV SLL [77.8%]). Over one-half of all patients (56.0%) had unmutated IGHV; approximately one-quarter of all patients had disease with ≥ 1 poor prognostic cytogenetic feature including del(17p), del(11q), and/or TP53 mutation. Approximately one-half of patients had received ≥ 2 prior lines of therapy. For most patients (79.1%), their disease was refractory to the most recent systemic therapy.

The overall response rate, defined as the proportion of patients with a best response of PR-L or better was 87.9% (95% CI: 79.40%, 93.81%; $p < 0.0001$ with respect to the null hypothesis of 32% [based on the overall response rate in the historical control as of the study start]). The median PFS for this study, as assessed by investigator assessment, has not been reached. The estimated PFS event-free rates by investigator assessment at 24 and 36 months were 80.5% (95% CI: 70.52%, 87.42%) and 68.1% (95% CI: 56.56%, 77.24%), respectively. With a median follow-up time for PFS of 34.5 months (range: 0.8 months, 41.4 months), as estimated by the reverse Kaplan-Meier method, the median PFS as assessed by independent central review, has not been reached. The estimated PFS event-free rates as assessed by independent central review at 24 and 36 months were 80.5% (95% CI: 70.52% to 87.42%) and 68.1% (95% CI: 56.56% to 77.24%), respectively.

Median overall survival (an exploratory study endpoint) has not been reached. The estimated overall survival rates at 24 and 36 months were 89.8% (95% CI: 81.27%, 94.55%) and 86.5% (95% CI: 76.62%, 92.44%), respectively, through a median follow-up time of 35.1 months.

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

N/A

Clinical studies in special populations

N/A

Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH provided two pivotal studies, 304 and 305. Both are RCTs. While study 304 investigates the use of zanubrutinib in 1L, study 305 investigated the use of zanubrutinib in R/R setting. The line agnostic indication has been sufficiently justified by including and showing efficacy in not only treatment naïve patients, but also in patients with more than 1, 2 and 3 prior therapies. Overall, the design of the studies, objectives and endpoints are endorsed. Scientific advice for study 304 has been followed by the MAH. For study 305, the MAH changed the originally proposed study design in patients with R/R CLL without further interaction with the CHMP (primary endpoint of PFS was changed to ORR).

In study 305 the primary endpoint was ORR (investigator-based) and PFS (investigator-based) is the only efficacy secondary endpoint considered in the testing strategy. The safety secondary endpoint of rate of atrial fibrillation/flutter was partially included in the testing strategy. The type I error due to multiple endpoints is controlled using a hierarchical approach.

One interim analysis was planned for ORR to be performed after the first 415 randomized patients had the opportunity to receive treatment for at least 12 months. The monitoring boundaries for the noninferiority test were based on the O'Brien Fleming boundary approximated by the Lan-DeMets spending function with an overall 1-sided level of 0.025.

A single analysis of PFS for the purpose of inference was planned when approximately 205 PFS events have occurred. However, two descriptive analyses of PFS for the interim and final analyses of ORR were to be performed. A 1-sided significance level of 0.00001 was to be applied to each of the analyses to compensate for the potential type I error increase from the descriptive analyses.

The secondary safety endpoint rate of atrial fibrillation/flutter would only be tested if the non-inferiority hypothesis for ORR is rejected, but outside the testing strategy for PFS. The monitoring boundaries for the superiority test are based on the O'Brien Fleming boundary approximated by the Lan-DeMets spending function with an overall 1-sided level of 0.025.

To summarize, the testing strategy is based on a hierarchical testing combined with alpha spending functions to control the type I error due to interim analyses. One interim (64 % of information fraction) and one final analysis are planned for ORR. First, non-inferiority will be tested, and if the null hypothesis is rejected, superiority will be tested. If superiority for ORR is shown, PFS was to be tested, first for non-inferiority and then for superiority. Two descriptive and one final analysis for PFS were planned to take place at the interim analysis for ORR, at the final analysis of ORR, and after 205 events for PFS have occurred. For the descriptive analyses, an alpha of 0.00001 was assigned. The secondary safety endpoint rate of atrial fibrillation/flutter was to be tested for superiority if non-inferiority for ORR was shown. To control the type I error due to multiple looks, the O'Brien Fleming boundary approximated by the Lan-DeMets spending function was implemented for ORR and atrial fibrillation rate.

It is not considered appropriate to label the PFS interim analyses as descriptive since alpha is allocated and the "descriptive" analysis occurs before the inferential analysis. The consequences of making the PFS interim results public may compromise the interpretation of the "final" PFS results. Of note, the

currently available PFS results are considered "descriptive" by the MAH. Updated results were requested (see Result section).

The MAH clarified that the atrial fibrillation endpoint is not controlled for type I error inflation in the strong sense. It is reassuring that a lower occurrence of atrial fibrillation in the zanubrutinib arm was reported in two head-to-head studies. However, this does not compensate for the lack of strong control of the family-wise type I error in the 305 study for the endpoint frequency of atrial fibrillation.

The current version of the SAP is version 1.0 dated March 12th, 2021. The data cut-off date was 31st December 2020.

Efficacy data and additional analyses

Study 304 met its primary endpoint showing statistically significant and clinically meaningful improvement of PFS. Median PFS is 33.7 months in the BR arm, while it is not reached in the zanubrutinib arm. The MAH performed a number of sensitivity analyses – all are in line with the primary endpoint/objective of the study. Data are immature. Therefore, the MAH is asked to commit to providing the final PFS analysis as well as OS analysis post-approval (REC). In general, the secondary endpoints seem to support the primary endpoint, however, due to lack of control for multiplicity, no firm conclusions can be drawn. The ORR by IRC is 90% in Cohort 2. The median duration of follow up was 27.9 (range: 1.0 to 38.8) and the event-free rate at 24 months 88.9% (95% CI 81.3, 93.6). These data clearly show that zanubrutinib lead to clinically meaningful results in CLL patients with del17p.

The DMC determined on the 20 April 2021 that the boundary for non-inferiority of ORR (investigator-based) was crossed and thus the study primary endpoint was met. In the CSR, several supplementary tables and descriptive analyse were presented. Those analyses do not affect the interpretation of the results of the trial.

Study 305 also met its primary objective showing non-inferiority with 1-sided p-value. The ORR rate was 78.3% vs. 62.5% in zanubrutinib and ibrutinib arms respectively. The response ratio is 1.25 (1.10 – 1.41). Superiority was met when applying a 2-sided p-value. However, for the interim analysis, only the first 415 randomized patients were included. The MAH was requested to present ORR, PFS results (investigator- and IRC assessed) and OS results for all randomized participants regardless of their treatment duration using the ITT and PP-populations: With a median follow-up time of 22 months at the Final analysis (+11 months) the ORR by INV (and IRC) in the ITT population was of the same magnitude as at the Interim analysis. A number of sensitivity analyses were planned and conducted. All are in line with the primary endpoint, showing at least non-inferiority to ibrutinib.

Despite inclusion exclusion criteria of study 304 in the frontline setting clearly indicate that patients should have been unsuitable for treatment chemoimmunotherapy (FCR), study 305 showed non-inferiority and superiority (based on INV assessment) against ibrutinib in the R/R setting. Having in mind that ibrutinib is also approved in 1L, and recommended in both fit and unfit patients, it seems justified to extrapolate the use of zanubrutinib to 1L fit patients. Thus, despite the limitations of study 304 and the comparison against BR in an elderly and unfit population, the totality of evidence supports the use of zanubrutinib in both fit and unfit patients. There are no scientific arguments to require a non-inferiority study in 1st line against ibrutinib. In conclusion, a restriction of zanubrutinib to unfit patients in 1L is not scientifically nor clinically justified and the MAH's proposal for 4.1 of the SmPC is supported. As SLL is not considered a distinct entity to CLL, the final indication only refers to CLL as follows:

"BRUKINSA as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)".

Conclusions on the clinical efficacy

The MAH has provided two RCTs to support the claimed indication for CLL. Both studies met their primary objective, and are overall considered reasonably well-designed and well-conducted. Study BGB-3111-305 is the pivotal clinical study on which basis the CHMP issued a positive opinion on the treatment of patients with R/R CLL. The study is ongoing. The MAH accepted a recommendation from the CHMP to submit the final study report upon completion of the clinical study, which is expected in March 2023.

2.5 Clinical safety

Introduction

The zanubrutinib safety profile is derived from 1550 patients with CLL/SLL and other B-cell malignancies enrolled into 9 clinical studies (2 Phase 1 studies, 4 Phase 2 studies, and 3 Phase 3 studies, including 2 pivotal Phase 3 studies), as described below. All of these studies have completed enrollment; 5 studies are complete, and 4 studies are ongoing.

Comparative safety data on the use of zanubrutinib in patients with CLL/SLL are derived from the 2 Phase 3 studies, Study BGB-3111-304 (versus B+R) and Study BGB-3111-305 (versus ibrutinib).

Table 28 key design features of Clinical Studies

Table 29 Key design features of Clinical Studies

Study Location	Study Design	Population	Zanubrutinib Starting Dose	Number of Treated Patients			First Patient First Dose/ Data Cutoff Date/ Study Status
				Zanubrutinib		Comparator	
				CLL/SLL	All		
Pivotal studies							
BGB-3111-304 (AU, China, EU [AT, BE, CZ, ES, FR, IT, PO, SW], NZ, UK, RUS, US	Phase 3, randomized, open-label, multicenter study	Patients with TN CLL/SLL	160 mg BID	240 in Cohort 1/ 40 in Cohort 1a/ 111 in Cohort 2	240 in Cohort 1/ 40 in Cohort 1a/ 111 in Cohort 2	227 in Cohort 1/ 38 in Cohort 1a (B + R)	02 November 2021 / 07 May 2021 / Ongoing
BGB-3111-305 (AU, China, EU [BE, CZ, ES, FR, GE IT, NL, PO, SW,], TR, NZ, UK, US)	Phase 3, randomized, open-label, multicenter study	Patients with R/R CLL/SLL	160 mg BID	324	324	324 (Ibrutinib)	05 November 2018 31 December 2020/ Ongoing
Supportive studies							
BGB-3111-AU-003 (AU, NZ, SK, US, IT, UK)	Phase 1/2, single-arm, dose escalation and cohort expansion	Patients with R/R or TN CLL/SLL, DLBCL, FL, HCL, MALT, MCL, MZL, NHL, RT, or WM	160 mg BID 320 mg QD	123 (101 R/R, 22 TN)	373	NA	16 September 2014/ 03 May 2021/ Closed
BGB-3111-205 China	Phase 2, single-arm	Patients with R/R CLL/SLL	160 mg BID	91	91	NA	09 March 2017/ 11 September 2020/ Closed
BGB-3111-1002 China	Phase 1, single-arm	Patients with R/R CLL/SLL, MCL, WM/LPL, FL, MZL, HCL or nGCB DLBCL	160 mg BID 320 mg QD	9	44	NA	05 July 2016/ 30 August 2020/ Closed
BGB-3111-206 China	Phase 2, single-arm	Patients with R/R MCL	160 mg BID	NA	86	NA	02 March 2017/ 10 November 2020/ Closed
BGB-3111-210 China	Phase 2, single-arm	Patients with R/R WM	160 mg BID	NA	44	NA	31 August 2017/ 04 February 2021/ Closed
BGB-3111-214 (AU, China, EU [CZ, FR, IT], NZ, SK, UK US)	Phase 2, open-label, single-arm study	Patients with R/R MZL	160 mg BID	NA	68	NA	19 February 2019/ 18 April 2021/ Ongoing
BGB-3111-302 (AU, UK, US, EU [CZ, ES, GE, FR, GR, IT, NL, PO, SW])	Phase 3, randomized, open-label, multicenter study	Patients with R/R or TN WM	160 mg BID	NA	129	98 (Ibrutinib)	25 January 2017/ 01 February 2021/ Ongoing
BGB-3111-LTE1[a]	Long-term extension	Patients with B-cell malignancies who were previously enrolled in a BeiGene parent study	Initial dosing regimen of 160 mg BID or 320 mg QD in parent study	BGB-3111-AU-003 n = 82 BGB-3111-1002 n = 3 BGB-3111-205 n = 60	337 BGB-3111-AU-003 n = 201 BGB-3111-1002 n = 11 BGB-3111-205 n = 60 BGB-3111-206 n = 40 BGB-3111-210 n = 25	NA	Ongoing
Total Patients in the Integrated Safety Population				**938**	**1550**	NA	NA

Patient exposure

Table 30 Summary of treatment exposure (SAS)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Starting Dose Regimen, n (%)					
160 mg BID	391 (100.0)	324 (100.0)	500 (95.2)	894 (95.3)	1445 (93.2)
320 mg QD	0 (0.0)	0 (0.0)	25 (4.8)	44 (4.7)	105 (6.8)
Duration of Exposure (months) [a]					
n	391	324	525	938	1550
Mean (SD)	24.76 (8.282)	11.29 (6.227)	20.95 (16.671)	23.15 (14.385)	23.88 (15.777)
Median	26.58	13.50	15.77	22.93	22.95
Q1, Q3	22.90, 30.06	5.08, 16.36	6.97, 35.29	13.34, 31.15	10.61, 35.38
Min, Max	0.5, 42.2	0.4, 23.0	0.2, 71.2	0.2, 71.2	0.1, 71.2
Total exposure (patient-months)	9681.94	3658.18	10999.72	21718.21	37019.66
Duration of Exposure, n (%)					
<3 months	5 (1.3)	39 (12.0)	48 (9.1)	53 (5.7)	134 (8.6)
3 - < 6 months	9 (2.3)	59 (18.2)	64 (12.2)	74 (7.9)	128 (8.3)
6 - < 9 months	23 (5.9)	29 (9.0)	36 (6.9)	59 (6.3)	94 (6.1)
9 - < 12 months	13 (3.3)	7 (2.2)	12 (2.3)	25 (2.7)	53 (3.4)
12 - < 18 months	22 (5.6)	150 (46.3)	158 (30.1)	181 (19.3)	236 (15.2)
18 - < 24 months	54 (13.8)	40 (12.3)	52 (9.9)	106 (11.3)	161 (10.4)
24 - < 30 months	162 (41.4)	0 (0.0)	9 (1.7)	173 (18.4)	203 (13.1)
30 - < 36 months	94 (24.0)	0 (0.0)	16 (3.0)	111 (11.8)	176 (11.4)
36 - < 48 months	9 (2.3)	0 (0.0)	94 (17.9)	104 (11.1)	261 (16.8)
48+ months	0 (0.0)	0 (0.0)	36 (6.9)	52 (5.5)	104 (6.7)
Cumulative Dose Administered (g)					
n	391	324	525	938	1550
Mean (SD)	228.81 (79.563)	104.69 (58.940)	192.80 (157.242)	213.82 (136.507)	220.46 (149.898)
Median	245.28	128.32	147.04	208.04	204.76
Q1, Q3	208.00, 284.00	48.04, 153.76	62.40, 295.44	116.72, 288.64	90.40, 321.92
Min, Max	4.5, 392.3	2.9, 224.0	1.1, 687.5	1.1, 687.5	1.0, 687.5
Actual Dose Intensity (mg/day) [b]					
n	391	324	525	938	1550
Mean (SD)	303.46 (29.086)	307.14 (30.697)	304.22 (39.495)	304.08 (35.046)	303.91 (35.670)
Median	313.54	319.11	318.44	316.27	316.56
Q1, Q3	303.54, 318.90	310.36, 320.00	310.32, 320.00	306.78, 320.00	306.75, 319.84

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Min, Max	126.1, 335.3	143.6, 321.4	46.7, 330.9	46.7, 335.3	46.7, 335.3
Relative Dose Intensity (%) [c]					
n	391	324	525	938	1550
Mean (SD)	94.83 (9.089)	95.98 (9.593)	95.07 (12.343)	95.03 (10.953)	94.97 (11.146)
Median	97.98	99.72	99.47	98.84	98.92
Q1, Q3	94.85, 99.66	96.99, 100.00	96.98, 100.00	95.88, 100.00	95.87, 99.95
Min, Max	39.4, 104.8	44.9, 100.4	14.6, 103.4	14.6, 104.8	14.6, 104.8
Patients with Dose Reduction, n (%)	55 (14.1)	33 (10.2)	59 (11.2)	114 (12.2)	166 (10.7)
Reason for dose reduction [d]					
Adverse Event	34 (8.7)	25 (7.7)	43 (8.2)	77 (8.2)	120 (7.7)
Number of Dose Reductions Per Patient					
n	55	33	59	114	166
Mean (SD)	1.2 (0.58)	1.2 (0.50)	1.4 (0.81)	1.3 (0.71)	1.3 (0.71)
Median	1.0	1.0	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 2.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 4	1, 3	1, 5	1, 5	1, 5
Number of Dose Reductions Per Patient, n (%)					
1	45 (11.5)	26 (8.0)	43 (8.2)	88 (9.4)	127 (8.2)
2	8 (2.0)	6 (1.9)	11 (2.1)	19 (2.0)	30 (1.9)
3	1 (0.3)	1 (0.3)	3 (0.6)	4 (0.4)	5 (0.3)
4	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	2 (0.1)
5	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
≥ 6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients With Dose Interruptions due to Adverse Event, n (%) [e]	135 (34.5)	84 (25.9)	175 (33.3)	321 (34.2)	557 (35.9)
Patients With Dose Modification (Reduction or Interruption) due to Adverse Event, n (%)	150 (38.4)	91 (28.1)	184 (35.0)	345 (36.8)	584 (37.7)

Source: ADSL, ADEXSUM. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; eCRF, electronic case report form; QD, once daily; R/R, relapsed/refractory.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.

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

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

Demographics

Table 31 Demographics and baseline characteristics (SAS)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Age (years)					
n	391	324	525	938	1550
Mean (SD)	69.1 (8.34)	66.7 (10.21)	65.0 (10.60)	66.8 (9.87)	66.2 (10.71)
Median	70.0	67.0	66.0	68.0	67.0
Q1, Q3	66.0, 74.0	60.0, 74.0	58.0, 73.0	61.0, 73.0	60.0, 73.0
Min, Max	32, 86	35, 90	24, 90	24, 90	20, 95
Age Group, n (%)					
< 65 years	77 (19.7)	126 (38.9)	239 (45.5)	322 (34.3)	600 (38.7)
≥ 65 years	314 (80.3)	198 (61.1)	286 (54.5)	616 (65.7)	950 (61.3)
Sex, n (%)					
Male	260 (66.5)	212 (65.4)	345 (65.7)	623 (66.4)	1027 (66.3)
Female	131 (33.5)	112 (34.6)	180 (34.3)	315 (33.6)	523 (33.7)
Race, n (%)					
Asian	45 (11.5)	45 (13.9)	149 (28.4)	194 (20.7)	424 (27.4)
White	325 (83.1)	261 (80.6)	349 (66.5)	696 (74.2)	1033 (66.6)
Black or African American	4 (1.0)	4 (1.2)	7 (1.3)	11 (1.2)	13 (0.8)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Native Hawaiian or Other Pacific Islander	1 (0.3)	3 (0.9)	4 (0.8)	5 (0.5)	6 (0.4)
Multiple [a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Other	0 (0.0)	2 (0.6)	7 (1.3)	7 (0.7)	23 (1.5)
Not Reported	13 (3.3)	6 (1.9)	6 (1.1)	19 (2.0)	39 (2.5)
Unknown	3 (0.8)	3 (0.9)	3 (0.6)	6 (0.6)	8 (0.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Geographic Region, n (%) [b]					
Asia	44 (11.3)	45 (13.9)	148 (28.2)	192 (20.5)	406 (26.2)
European Union	225 (57.5)	199 (61.4)	201 (38.3)	426 (45.4)	551 (35.5)
North America	46 (11.8)	52 (16.0)	70 (13.3)	117 (12.5)	179 (11.5)
Oceania	76 (19.4)	28 (8.6)	106 (20.2)	203 (21.6)	414 (26.7)
HBcAb, n (%) [c]					
Positive	51 (13.0)	37 (11.4)	77 (14.7)	128 (13.6)	244 (15.7)
Negative	340 (87.0)	285 (88.0)	435 (82.9)	794 (84.6)	1273 (82.1)
Equivocal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Missing	0 (0.0)	2 (0.6)	13 (2.5)	16 (1.7)	31 (2.0)
HCV antibody, n (%) [c]					
Positive	2 (0.5)	1 (0.3)	2 (0.4)	4 (0.4)	5 (0.3)
Negative	389 (99.5)	323 (99.7)	523 (99.6)	934 (99.6)	1544 (99.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
ECOG Performance Status, n (%)					
0	168 (43.0)	126 (38.9)	222 (42.3)	399 (42.5)	690 (44.5)
1	188 (48.1)	191 (59.0)	290 (55.2)	489 (52.1)	765 (49.4)
2	35 (9.0)	7 (2.2)	13 (2.5)	50 (5.3)	95 (6.1)
Height (cm)					
n	383	320	519	924	1533
Mean (SD)	169.16 (8.772)	169.21 (10.095)	169.32 (9.793)	169.34 (9.402)	169.00 (9.525)
Median	170.00	169.25	170.00	170.00	170.00
Q1, Q3	163.00, 175.00	162.00, 177.00	162.00, 176.00	162.00, 176.00	162.00, 176.00
Min, Max	147.0, 191.0	140.0, 197.0	140.0, 197.0	140.0, 197.0	140.0, 197.0
Weight (kg)					
n	391	323	524	937	1549
Mean (SD)	76.53 (16.393)	78.35 (17.670)	77.05 (17.942)	76.96 (17.265)	75.25 (16.998)
Median	74.60	76.30	75.00	75.00	73.00
Q1, Q3	65.00, 86.00	66.00, 89.00	65.00, 87.80	65.00, 87.00	63.00, 85.00
Min, Max	42.5, 147.0	42.5, 149.0	42.5, 149.0	42.5, 149.0	36.0, 149.0
BMI (kg/m^2)					
n	383	319	518	923	1532
Mean (SD)	26.73 (5.169)	27.24 (4.946)	26.74 (5.135)	26.75 (5.158)	26.23 (4.970)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Median	25.86	26.72	25.92	25.92	25.46
Q1, Q3	23.26, 29.36	23.56, 30.56	23.15, 29.72	23.22, 29.48	22.79, 28.91
Min, Max	16.5, 50.6	15.9, 53.1	15.9, 54.6	15.9, 54.6	15.2, 54.6

Source: ADSL, ADBASE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; R/R, Relapsed/Refractory; HBcAb, Hepatitis B core antibody; HCV, Hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BMI, Body Mass Index.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.

[a] Patient BGB-3111-AU-003-S2215-2-366, BGB-3111-214-039022-005 and BGB-3111-214-061005-002 reported two races: American Indian or Alaska Native and White.

[b] Asia includes China (Mainland and Taiwan) and South Korea; European Union includes Austria, Belgium, Czech, France, Germany, Greece, Italy, Netherlands, Russian Federation, Poland, Spain, Sweden, Turkey, and United Kingdom; North America includes United States; Oceania includes Australia and New Zealand.

[c] For 305 study, central lab data was used with 'Non-Reactive' mapped to 'Negative' and 'Reactive' mapped to 'Positive'.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-dm-bsl-i.sas 24AUG2021 01:20 t-3-dm-bsl-i.rtf

Table 32 ***Disease Characteristics (SAS)***

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Diagnosis, n (%)					
CLL/SLL	391 (100.0)	324 (100.0)	525 (100.0)	938 (100.0)	938 (60.5)
WM					249 (16.1)
MCL					140 (9.0)
MZL					93 (6.0)
FL					59 (3.8)
DLBCL					45 (2.9)
OTHER [a]					26 (1.7)
Time From Initial Diagnosis to First Study Dose (years)					
n	391	324	525	938	1550
Mean (SD)	3.59 (4.213)	7.48 (4.613)	7.22 (4.716)	5.69 (4.901)	5.39 (4.936)
Median	2.20	6.95	6.43	4.50	4.05
Q1, Q3	0.48, 4.90	3.99, 10.19	3.56, 9.85	1.88, 8.48	1.57, 7.82
Min, Max	0.1, 27.0	0.1, 28.8	0.1, 28.8	0.1, 28.8	0.0, 29.5
Baseline Absolute Lymphocyte Count (10^9/L)					
n	391	324	525	938	1549
Mean (SD)	78.21 (79.583)	59.48 (70.602)	52.86 (66.399)	64.22 (73.507)	40.40 (65.416)
Median	56.95	36.54	27.67	40.12	7.59
Q1, Q3	18.14, 106.30	8.56, 82.77	6.55, 73.80	9.94, 91.98	1.51, 56.60
Min, Max	0.9, 715.8	0.5, 392.0	0.4, 392.0	0.4, 715.8	0.0, 715.8

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Baseline Hemoglobin (g/L)					
n	391	324	525	938	1550
Mean (SD)	118.90 (19.676)	121.61 (21.889)	120.48 (22.122)	119.85 (21.051)	117.88 (21.590)
Median	120.00	122.50	122.00	122.00	120.00
Q1, Q3	106.00, 132.00	105.00, 138.00	105.00, 137.00	105.00, 135.00	103.00, 133.00
Min, Max	61.0, 181.0	57.0, 183.0	53.0, 183.0	53.0, 183.0	53.0, 212.0
Baseline Hemoglobin, n (%)					
≤ 110 g/L	134 (34.3)	103 (31.8)	170 (32.4)	309 (32.9)	575 (37.1)
>110 g/L	257 (65.7)	221 (68.2)	355 (67.6)	629 (67.1)	975 (62.9)
Baseline Platelet (10^9/L)					
n	391	324	525	938	1550
Mean (SD)	153.38 (65.651)	139.06 (65.489)	136.32 (64.794)	143.39 (65.362)	164.55 (83.812)
Median	148.00	126.00	123.00	133.50	148.00
Q1, Q3	102.00, 193.00	92.00, 177.00	91.00, 172.00	94.00, 181.00	101.00, 211.00
Min, Max	23.0, 577.0	21.0, 413.0	21.0, 413.0	21.0, 577.0	1.0, 577.0
Baseline Platelet, n (%)					
≤ 100 x 10^9/L	96 (24.6)	101 (31.2)	177 (33.7)	280 (29.9)	380 (24.5)
>100 x 10^9/L	295 (75.4)	223 (68.8)	348 (66.3)	658 (70.1)	1170 (75.5)
Baseline Absolute Neutrophil Counts (10^9/L)					
n	391	324	525	938	1548
Mean (SD)	5.05 (3.400)	4.12 (2.429)	3.84 (2.669)	4.35 (3.034)	4.03 (2.745)
Median	4.41	3.59	3.22	3.66	3.40
Q1, Q3	2.85, 6.23	2.37, 5.21	2.11, 4.77	2.41, 5.51	2.30, 5.02
Min, Max	0.2, 30.8	0.5, 13.7	0.0, 24.9	0.0, 30.8	0.0, 30.8
Baseline Absolute Neutrophil Counts, n (%)					
≤ 1.5 x 10^9/L	25 (6.4)	28 (8.6)	64 (12.2)	89 (9.5)	150 (9.7)
>1.5 x 10^9/L	366 (93.6)	296 (91.4)	461 (87.8)	849 (90.5)	1398 (90.2)
Cytopenia, n (%) [b]					
Yes	188 (48.1)	172 (53.1)	296 (56.4)	495 (52.8)	811 (52.3)
No	203 (51.9)	152 (46.9)	229 (43.6)	443 (47.2)	739 (47.7)

Table 33 Prior Anti-cancer therapies (SAS)

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With any Prior Anticancer Drug Therapy, n (%)	NA	324 (100.0)	525 (100.0)	525 (56.0)	1068 (68.9)
Prior Treatment Status, n (%)					
Treatment Naive	391 (100.0)	0 (0.0)	0 (0.0)	413 (44.0)	482 (31.1)
Relapsed/Refractory	0 (0.0)	324 (100.0)	525 (100.0)	525 (56.0)	1068 (68.9)
Number of Prior Lines of Therapy/Regimens [a]					
n		324	525	525	1068
Mean (SD)		1.7 (1.01)	1.8 (1.32)	1.8 (1.32)	2.1 (1.44)
Median		1.0	1.0	1.0	2.0
Q1, Q3		1.0, 2.0	1.0, 2.0	1.0, 2.0	1.0, 3.0
Min, Max		1, 6	1, 10	1, 10	1, 12
Number of Prior Lines of Therapy/Regimens, n (%) [a, b]					
1		190 (58.6)	286 (54.5)	286 (54.5)	496 (46.4)
2		86 (26.5)	139 (26.5)	139 (26.5)	276 (25.8)
3		26 (8.0)	53 (10.1)	53 (10.1)	151 (14.1)
4		13 (4.0)	21 (4.0)	21 (4.0)	73 (6.8)
5		7 (2.2)	13 (2.5)	13 (2.5)	37 (3.5)
≥ 6		2 (0.6)	13 (2.5)	13 (2.5)	35 (3.3)
Time From End of Last Therapy to First Study Dose (Months)					
n		324	519	519	1051
Mean (SD)		34.77 (34.292)	29.84 (31.823)	29.84 (31.823)	24.37 (29.278)
Median		25.45	21.09	21.09	12.91
Q1, Q3		8.57, 49.17	5.36, 43.01	5.36, 43.01	3.29, 36.11
Min, Max		0.6, 245.7	0.0, 245.7	0.0, 245.7	0.0, 245.7
Patients with any Prior Transplant, n (%)					
Yes	0 (0.0)	1 (0.3)	8 (1.5)	8 (0.9)	43 (2.8)
No	391 (100.0)	323 (99.7)	516 (98.3)	929 (99.0)	1506 (97.2)
Unknown	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Patients with any Prior Anticancer Radiotherapy, n (%)					
Yes	1 (0.3)	3 (0.9)	10 (1.9)	13 (1.4)	87 (5.6)
No	390 (99.7)	321 (99.1)	515 (98.1)	925 (98.6)	1463 (94.4)

Adverse events

Study 304:

A treatment-emergent adverse event was defined as an adverse event that had an onset date or was worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 30 days for Arms A and C patients and 90 days for Arm B patients following study drug discontinuation or the start of new anticancer therapy for CLL/SLL, whichever comes first. Worsening of a treatment-emergent adverse event to Grade 5 beyond 30 days after the last dose of zanubrutinib, or beyond 90 days after the last dose of rituximab or bendamustine, was also considered a treatment-emergent adverse event. Two sets of summary tables were provided: Treatment-emergent adverse events and combined treatment-emergent adverse events plus adverse events/serious adverse events reported during the Post-treatment Follow-up phase (termed "Treatment-Emergent + Post-Treatment" in the safety tables). All adverse events, treatment-emergent or otherwise, were presented in patient data listings.

The incidence of treatment-emergent adverse event plus post-treatment phase adverse events were reported as the number (and percentage) of patients with treatment-emergent adverse events plus post-treatment phase adverse events by system organ class and preferred term. A patient was counted only once by the highest severity grade according to CTCAE v4.03 within a system organ class and preferred term, even if the patient experienced more than 1 treatment-emergent adverse event or post-treatment phase adverse event within a specific system organ class and preferred term.

Table 34 Overall Summary of Treatment-Emergent + Post-Treatment AEs (SAS)

	Cohort 1		Cohort 2
	B+R (N = 227)	Zanubrutinib (N = 240)	Zanubrutinib (N = 111)
	n (%)	n (%)	n (%)
Patients With at Least One AE	218 (96.0)	224 (93.3)	109 (98.2)
Grade 3 or Higher AE	181 (79.7)	126 (52.5)	61 (55.0)
Serious AE	113 (49.8)	88 (36.7)	45 (40.5)
TEAE Leading to Dose Modification	159 (70.0)	115 (47.9)	57 (51.4)
TEAE Leading to Dose Interruption	NA	111 (46.3)	56 (50.5)
TEAE Leading to Dose Delay/Held	154 (67.8)	NA	NA
TEAE Leading to Dose Reduction	84 (37.0)	18 (7.5)	6 (5.4)
TEAE Leading to Treatment Discontinuation	31 (13.7)	20 (8.3)	6 (5.4)
TEAE or Post-Treatment AE Leading to Death	12 (5.3)	11 (4.6)	3 (2.7)
Treatment Related TEAE	202 (89.0)	168 (70.0)	79 (71.2)
Treatment Related Grade 3 or Higher TEAE	148 (65.2)	58 (24.2)	25 (22.5)
Treatment Related Serious TEAE	66 (29.1)	23 (9.6)	10 (9.0)

Study 305:

A treatment-emergent adverse event was defined as an adverse event that had an onset date on or after the first dose of study drug up to 30 days following study drug discontinuation or the day prior to initiation of a new CLL/SLL therapy, whichever occurred first. If a treatment-emergent adverse event worsened to Grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the Grade 5 AE was considered treatment-emergent. Only treatment-emergent adverse events

were included in the summary tables. All adverse events, treatment-emergent or otherwise, were included in patient data listings.

The incidence of treatment-emergent adverse events was reported as the number (and percentage) of patients with treatment-emergent adverse events by System Organ Class and Preferred Term. A patient was counted only once by the highest severity grade according to NCI-CTCAE v4.03 within a System Organ Class and Preferred Term, even if the patient experienced more than 1 treatment-emergent adverse events within a specific System Organ Class and Preferred Term.

Table 35 Overall Summary of TEAEs (SAS)

	Zanubrutinib (N = 324) n (%)	**Ibrutinib (N = 324) n (%)**
Patients with at Least One TEAE	291 (89.8)	309 (95.4)
Grade 3 or Higher	143 (44.1)	144 (44.4)
Serious	70 (21.6)	82 (25.3)
Leading to Death	13 (4.0)	15 (4.6)
Leading to Treatment Discontinuation	21 (6.5)	34 (10.5)
Leading to Dose Modification	103 (31.8)	122 (37.7)
Leading to Dose Interruption	98 (30.2)	114 (35.2)
Leading to Dose Reduction	24 (7.4)	31 (9.6)
Treatment-Related	216 (66.7)	243 (75.0)
Treatment-Related Grade 3 or Higher	82 (25.3)	89 (27.5)

Integrated safety summary (ISS)

Safety data are displayed for zanubrutinib-treated patients for 5 data groupings side by side as follows:

- **Study BGB-3111-304** (n = 391)
- **Study BGB-3111-305** (n = 324)
- The **All R/R CLL/SLL** group (n = 525), comprising all patients with CLL/SLL treated with zanubrutinib from Studies BGB-3111-305 (n = 324), BGB-3111-AU-003 (CLL/SLL patients, n = 101), BGB-3111-205 (CLL/SLL patients, n = 91), and BGB-3111-1002 (CLL/SLL patients, n = 9)
- The **All CLL/SLL** group (n = 938), comprising all patients with CLL/SLL treated with zanubrutinib from Studies BGB-3111-304 (n = 391), BGB-3111-305 (n = 324), BGB3111-AU-003 (CLL/SLL patients, n = 123), BGB-3111-205 (CLL/SLL patients, n = 91), and BGB-3111-1002 (CLL/SLL patients, n = 9)
- The **All Zanubrutinib** group (n = 1550), comprising data from all patients who were initially treated with zanubrutinib monotherapy at 160 mg twice a day (n = 1445) or 320 mg once a day (n = 105) from all 9 aforementioned studies. Crossover patients were not included in this analysis.

Table 36 Overall Summary of Treatment Emergent Adverse Events

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE	371 (94.9)	291 (89.8)	492 (93.7)	885 (94.3)	1483 (95.7)
Grade 3 or Higher	202 (51.7)	143 (44.1)	300 (57.1)	516 (55.0)	897 (57.9)
Serious	145 (37.1)	70 (21.6)	185 (35.2)	341 (36.4)	623 (40.2)
Leading to Death	14 (3.6)	13 (4.0)	21 (4.0)	36 (3.8)	76 (4.9)
Leading to Treatment Discontinuation	27 (6.9)	21 (6.5)	46 (8.8)	75 (8.0)	144 (9.3)
Leading to Dose Reduction	25 (6.4)	24 (7.4)	45 (8.6)	70 (7.5)	116 (7.5)
Leading to Dose Interruption	175 (44.8)	98 (30.2)	199 (37.9)	388 (41.4)	649 (41.9)
Treatment-Related	282 (72.1)	216 (66.7)	399 (76.0)	701 (74.7)	1181 (76.2)
Treatment-Related Grade 3 or Higher	93 (23.8)	82 (25.3)	191 (36.4)	292 (31.1)	485 (31.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-i.sas 24AUG2021 01:21 t-8-teae-i.rtf

Common Treatment-Emergent Adverse Events

Study 304:

The most commonly reported adverse events (those occurring in ≥ 10% of patients) with a percentage difference between arms of ≥ 5% were as follows:

Higher by ≥ 5% in B+R compared with zanubrutinib

– Nausea: B+R 32.6% versus zanubrutinib 10.0%

– Vomiting: B+R 14.5% versus zanubrutinib 7.1%

– Constipation: B+R 18.9% versus zanubrutinib 10.0%

– Rash: B+R 19.4% versus zanubrutinib 10.8%

– Pyrexia: B+R 26.4% versus zanubrutinib 7.1%

– Infusion related reaction: B+R 18.9% versus zanubrutinib 0.4%

– Neutropenia: B+R 45.8% versus zanubrutinib 12.9%

– Neutrophil count decreased: B+R 12.3% versus zanubrutinib 2.5%

– Anemia: B+R 18.9% versus zanubrutinib 4.6%

– Thrombocytopenia: B+R 13.7% versus zanubrutinib 3.8%

Higher by ≥ 5% in zanubrutinib compared with B+R

– Contusion: zanubrutinib 19.2% versus B+R 3.5%

– Upper respiratory tract infection: zanubrutinib 17.1% versus B+R 11.9%

Study 305:

The incidences of adverse events were generally comparable between the zanubrutinib arm and ibrutinib arm (Table 14.3.1.2.2.1 and Table 14.3.1.2.3.1). The following adverse events occurred at an incidence difference of ≥ 5% between the 2 arms (Table 25):

• Diarrhoea: zanubrutinib 11.7% versus ibrutinib 18.8%

• Muscle spasms: zanubrutinib 2.5% versus ibrutinib 9.6%

• Atrial fibrillation: zanubrutinib 1.5% versus ibrutinib 7.4%

Integrated safety summary (ISS)

Table 37 TEAEs in > 10% of patients in any patient group by SOC and PT (SAS)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE	371 (94.9)	291 (89.8)	492 (93.7)	885 (94.3)	1483 (95.7)
Infections and infestations	247 (63.2)	152 (46.9)	331 (63.0)	595 (63.4)	1019 (65.7)
Upper respiratory tract infection	73 (18.7)	48 (14.8)	152 (29.0)	236 (25.2)	432 (27.9)
Pneumonia	28 (7.2)	20 (6.2)	80 (15.2)	110 (11.7)	184 (11.9)
Urinary tract infection	28 (7.2)	24 (7.4)	63 (12.0)	97 (10.3)	179 (11.5)
Gastrointestinal disorders	194 (49.6)	116 (35.8)	256 (48.8)	464 (49.5)	809 (52.2)
Diarrhoea	55 (14.1)	38 (11.7)	98 (18.7)	158 (16.8)	292 (18.8)
Constipation	43 (11.0)	14 (4.3)	50 (9.5)	98 (10.4)	191 (12.3)
Nausea	43 (11.0)	24 (7.4)	49 (9.3)	96 (10.2)	164 (10.6)
Skin and subcutaneous tissue disorders	178 (45.5)	105 (32.4)	223 (42.5)	416 (44.3)	730 (47.1)
Rash	46 (11.8)	22 (6.8)	62 (11.8)	112 (11.9)	233 (15.0)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Respiratory, thoracic and mediastinal disorders	136 (34.8)	77 (23.8)	196 (37.3)	343 (36.6)	599 (38.6)
Cough	43 (11.0)	28 (8.6)	94 (17.9)	144 (15.4)	251 (16.2)
Musculoskeletal and connective tissue disorders	160 (40.9)	70 (21.6)	143 (27.2)	318 (33.9)	565 (36.5)
Arthralgia	56 (14.3)	28 (8.6)	55 (10.5)	115 (12.3)	199 (12.8)
General disorders and administration site conditions	122 (31.2)	74 (22.8)	158 (30.1)	292 (31.1)	557 (35.9)
Fatigue	38 (9.7)	20 (6.2)	46 (8.8)	90 (9.6)	185 (11.9)
Investigations	73 (18.7)	64 (19.8)	186 (35.4)	269 (28.7)	518 (33.4)
Neutrophil count decreased	19 (4.9)	21 (6.5)	103 (19.6)	123 (13.1)	235 (15.2)
Platelet count decreased	13 (3.3)	10 (3.1)	54 (10.3)	68 (7.2)	144 (9.3)
Injury, poisoning and procedural complications	134 (34.3)	64 (19.8)	145 (27.6)	296 (31.6)	503 (32.5)
Contusion	68 (17.4)	36 (11.1)	87 (16.6)	168 (17.9)	281 (18.1)
Blood and lymphatic system disorders	94 (24.0)	103 (31.8)	178 (33.9)	275 (29.3)	497 (32.1)
Anaemia	25 (6.4)	38 (11.7)	86 (16.4)	111 (11.8)	211 (13.6)
Neutropenia	46 (11.8)	48 (14.8)	75 (14.3)	122 (13.0)	206 (13.3)
Nervous system disorders	102 (26.1)	68 (21.0)	146 (27.8)	258 (27.5)	454 (29.3)
Headache	40 (10.2)	17 (5.2)	51 (9.7)	96 (10.2)	161 (10.4)
Vascular disorders	92 (23.5)	55 (17.0)	95 (18.1)	194 (20.7)	325 (21.0)
Hypertension	43 (11.0)	40 (12.3)	70 (13.3)	117 (12.5)	187 (12.1)
Renal and urinary disorders	59 (15.1)	22 (6.8)	101 (19.2)	169 (18.0)	287 (18.5)
Haematuria	24 (6.1)	7 (2.2)	63 (12.0)	95 (10.1)	148 (9.5)

Adverse events related to COVID-19

Overall, across all groups, a small proportion of patients reported adverse events related to COVID-19. Death is considered COVID-19 related when death is reported as due to an adverse event and the adverse event is considered to be related to COVID-19.

Table 38 ***Overall summary of treatment – emergent Adverse events related to COVID-19 (SAS)***

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE	27 (6.9)	18 (5.6)	20 (3.8)	47 (5.0)	56 (3.6)
Grade 3 or Higher	16 (4.1)	11 (3.4)	12 (2.3)	28 (3.0)	35 (2.3)
Serious	15 (3.8)	9 (2.8)	11 (2.1)	26 (2.8)	32 (2.1)
Leading to Death	5 (1.3)	3 (0.9)	4 (0.8)	9 (1.0)	12 (0.8)
Leading to Treatment Discontinuation	5 (1.3)	3 (0.9)	4 (0.8)	9 (1.0)	12 (0.8)
Leading to Dose Reduction	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Leading to Dose Interruption	17 (4.3)	11 (3.4)	13 (2.5)	30 (3.2)	35 (2.3)
Treatment-Related	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Treatment-Related Grade 3 or Higher	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)

Grade 3 and higher adverse events

Study 304:

Table 39 grade 3 or higher TEAEs in ≥ 2% of patients

Preferred Term in Cohort 1 and Cohort 2 (Safety Analysis Set)

	Cohort 1		Cohort 2
	BR (N = 227)	Zanubrutinib (N = 240)	Zanubrutinib (N = 111)
Preferred Term	n (%)	n (%)	n (%)
Patients With at Least One AE of Grade 3 or Higher	181 (79.7)	126 (52.5)	61 (55.0)
Neutropenia	94 (41.4)	22 (9.2)	12 (10.8)
Hypertension	11 (4.8)	15 (6.3)	5 (4.5)
COVID-19	2 (0.9)	11 (4.6)	1 (0.9)
COVID-19 pneumonia	0 (0.0)	7 (2.9)	2 (1.8)
Neutrophil count decreased	24 (10.6)	5 (2.1)	5 (4.5)
Pneumonia	10 (4.4)	4 (1.7)	6 (5.4)
Thrombocytopenia	16 (7.0)	4 (1.7)	1 (0.9)
Febrile neutropenia	17 (7.5)	2 (0.8)	1 (0.9)
Sepsis	6 (2.6)	2 (0.8)	0 (0.0)
Urinary tract infection	6 (2.6)	2 (0.8)	2 (1.8)
Atrial fibrillation	3 (1.3)	1 (0.4)	4 (3.6)
Fall	2 (0.9)	1 (0.4)	3 (2.7)
Hypotension	5 (2.2)	1 (0.4)	2 (1.8)
Infusion related reaction	6 (2.6)	0 (0.0)	0 (0.0)
Leukopenia	5 (2.2)	0 (0.0)	0 (0.0)
Pyrexia	8 (3.5)	0 (0.0)	1 (0.9)
Rash	6 (2.6)	0 (0.0)	0 (0.0)

Study 305:

Table 40 Grade 3 or Higher Treatment Emergent Adverse Events by System Organ Class and Preferred Term ≥1% in Either Arm (Safety Analysis Set)

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One Grade 3 or Higher TEAE	143 (44.1)	144 (44.4)
Blood and lymphatic system disorders		
Neutropenia	33 (10.2)	28 (8.6)
Anaemia	7 (2.2)	8 (2.5)
Thrombocytopenia	7 (2.2)	6 (1.9)
Cardiac disorders		
Atrial fibrillation	2 (0.6)	4 (1.2)
Gastrointestinal disorders		
Diarrhoea	4 (1.2)	1 (0.3)
Infections and infestations		
Pneumonia	11 (3.4)	15 (4.6)
COVID-19	8 (2.5)	3 (0.9)
COVID-19 pneumonia	3 (0.9)	5 (1.5)
Investigations		
Neutrophil count decreased	12 (3.7)	12 (3.7)
Blood pressure increased	2 (0.6)	7 (2.2)
Nervous system disorders		
Syncope	7 (2.2)	4 (1.2)
Vascular disorders		
Hypertension	26 (8.0)	17 (5.2)

Source: ADSL, ADAE. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviation: TEAE, treatment-emergent adverse event.
TEAE is defined as an AE that has an onset date on or after the first dose of study drug up to 30 days after the last dose of study drug or the day prior to initiation of a new CLL/SLL therapy, whichever occurs first. If a TEAE worsens to grade 5 more than 30 days after last dose of study drug and prior to initiation of a new CLL/SLL therapy, the grade 5 AE will be treatment-emergent.
Notes: Adverse events were classified based on MedDRA Version 23.0.
Adverse event grades were evaluated based on NCI-CTCAE Version 4.03.
Patients with multiple events for a given preferred term and system organ class were counted only once for each preferred term and system organ class, respectively.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-ae-socpt-cut-i.sas 09AUG2021 23:26 t-22-ae-socpt-gr3plus-i.rtf

Integrated safety summary (ISS)

Table 41 ***Grade 3 or Higher Treatment Emergent Adverse Events Reported in ≥3% of Patients in Any Patient Group by System Organ Class and Preferred Term***

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One Grade 3 or Higher TEAE	202 (51.7)	143 (44.1)	300 (57.1)	516 (55.0)	897 (57.9)
Infections and infestations	64 (16.4)	37 (11.4)	119 (22.7)	190 (20.3)	338 (21.8)
Pneumonia	13 (3.3)	11 (3.4)	45 (8.6)	59 (6.3)	109 (7.0)
Blood and lymphatic system disorders	46 (11.8)	44 (13.6)	85 (16.2)	132 (14.1)	258 (16.6)
Neutropenia	34 (8.7)	33 (10.2)	54 (10.3)	89 (9.5)	151 (9.7)
Anaemia	1 (0.3)	7 (2.2)	24 (4.6)	25 (2.7)	80 (5.2)
Thrombocytopenia	7 (1.8)	7 (2.2)	17 (3.2)	24 (2.6)	47 (3.0)
Investigations	23 (5.9)	18 (5.6)	75 (14.3)	102 (10.9)	188 (12.1)
Neutrophil count decreased	12 (3.1)	12 (3.7)	65 (12.4)	78 (8.3)	135 (8.7)
Vascular disorders	30 (7.7)	28 (8.6)	41 (7.8)	75 (8.0)	122 (7.9)
Hypertension	21 (5.4)	26 (8.0)	36 (6.9)	60 (6.4)	97 (6.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given Preferred Term and with multiple Preferred Terms within a System Organ Class are counted only once at the Preferred Term and System Organ Class levels, respectively. Events are sorted by decreasing frequency first by System Organ Class and then by Preferred Term within each System Organ Class in the 'All Zanubrutinib' column.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-12-teae-soc-pt-grd3-3-i.rtf

Adverse events of special interest (AESI)

Table 42 ***Adverse Events of Special Interest***

Adverse Event of Special Interest Category	Search Criteria
Hemorrhage (including minor bleeding such as contusion and petechiae)	Hemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major hemorrhage - defined as serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade	Major hemorrhage: • All subdural haematoma PT, Subdural haemorrhage PT • All haemorrhage PTs if adverse event SOC is "Nervous system disorders" or • Serious or ≥ Grade 3 haemorrhage PT if adverse event SOC is not "Nervous system disorders"

Adverse Event of Special Interest Category	Search Criteria
Atrial fibrillation and flutter	Atrial fibrillation PT, Atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Second primary malignancies Skin cancers	Malignant tumours (SMQ) Narrow Subcategory - Skin malignant tumours (SMQ) narrow
Tumor lysis syndrome	Tumour lysis syndrome (SMQ) Narrow
Infections Opportunistic infections	Infections: Infections and Infestations SOC Subcategory - Opportunistic infections: Opportunistic infections (SMQ) Narrow
Cytopenia	
Neutropenia	Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, Platelet count decreased PT
Anemia	Anaemia PT, Haemoglobin decreased PT

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SMQ, Standardized MedDRA Query; SOC, System Organ Class.

Study 304:

Table 43 ***Treatment Emergent + Post Treatment Adverse Events of Special Interest Reported in ≥ 2% of Patients by Category and Preferred Term in Cohort 1 and Cohort 2***

	Cohort 1		Cohort 2
Category Preferred Term	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Patients With at Least One AE of Special Interest	202 (89.0)	199 (82.9)	101 (91.0)
Anemia	44 (19.4)	11 (4.6)	6 (5.4)
Anaemia	43 (18.9)	11 (4.6)	6 (5.4)
Atrial fibrillation and flutter	6 (2.6)	8 (3.3)	5 (4.5)
Atrial fibrillation	6 (2.6)	8 (3.3)	5 (4.5)
Hemorrhage	25 (11.0)	108 (45.0)	57 (51.4)
Contusion	8 (3.5)	46 (19.2)	22 (19.8)
Petechiae	0 (0.0)	18 (7.5)	5 (4.5)
Haematoma	1 (0.4)	13 (5.4)	6 (5.4)
Haematuria	5 (2.2)	13 (5.4)	10 (9.0)
Epistaxis	1 (0.4)	12 (5.0)	8 (7.2)
Ecchymosis	1 (0.4)	7 (2.9)	6 (5.4)
Purpura	0 (0.0)	5 (2.1)	4 (3.6)
Major hemorrhage	4 (1.8)	12 (5.0)	8 (7.2)
Haematuria	1 (0.4)	4 (1.7)	3 (2.7)
Hypertension	24 (10.6)	34 (14.2)	12 (10.8)
Hypertension	20 (8.8)	29 (12.1)	10 (9.0)
Infections	127 (55.9)	149 (62.1)	79 (71.2)
Upper respiratory tract infection	27 (11.9)	41 (17.1)	23 (20.7)

Category Preferred Term	Cohort 1 BR (N = 227) n (%)	Cohort 1 Zanubrutinib (N = 240) n (%)	Cohort 2 Zanubrutinib (N = 111) n (%)
COVID-19	8 (3.5)	21 (8.8)	3 (2.7)
Urinary tract infection	19 (8.4)	17 (7.1)	9 (8.1)
Nasopharyngitis	12 (5.3)	16 (6.7)	11 (9.9)
Cellulitis	2 (0.9)	12 (5.0)	2 (1.8)
Pneumonia	19 (8.4)	12 (5.0)	13 (11.7)
Sinusitis	10 (4.4)	12 (5.0)	6 (5.4)
Lower respiratory tract infection	4 (1.8)	9 (3.8)	6 (5.4)
COVID-19 pneumonia	0 (0.0)	8 (3.3)	2 (1.8)
Bronchitis	15 (6.6)	7 (2.9)	3 (2.7)
Respiratory tract infection	9 (4.0)	7 (2.9)	5 (4.5)
Skin infection	1 (0.4)	6 (2.5)	2 (1.8)
Herpes zoster	9 (4.0)	5 (2.1)	1 (0.9)
Conjunctivitis	6 (2.6)	4 (1.7)	4 (3.6)
Oral herpes	7 (3.1)	3 (1.3)	2 (1.8)
Sepsis	6 (2.6)	2 (0.8)	0 (0.0)
Infection	7 (3.1)	1 (0.4)	2 (1.8)
Pharyngitis	0 (0.0)	1 (0.4)	4 (3.6)
Ear infection	4 (1.8)	0 (0.0)	3 (2.7)
Neutropenia	129 (56.8)	38 (15.8)	21 (18.9)
Neutropenia	104 (45.8)	31 (12.9)	13 (11.7)
Neutrophil count decreased	28 (12.3)	6 (2.5)	7 (6.3)

Category Preferred Term	Cohort 1 BR (N = 227) n (%)	Cohort 1 Zanubrutinib (N = 240) n (%)	Cohort 2 Zanubrutinib (N = 111) n (%)
Febrile neutropenia	17 (7.5)	2 (0.8)	1 (0.9)
Second primary malignancies	20 (8.8)	31 (12.9)	24 (21.6)
Basal cell carcinoma	3 (1.3)	11 (4.6)	12 (10.8)
Squamous cell carcinoma of skin	5 (2.2)	5 (2.1)	4 (3.6)
Skin cancers	10 (4.4)	16 (6.7)	17 (15.3)
Basal cell carcinoma	3 (1.3)	11 (4.6)	12 (10.8)
Squamous cell carcinoma of skin	5 (2.2)	5 (2.1)	4 (3.6)
Thrombocytopenia	40 (17.6)	11 (4.6)	8 (7.2)
Thrombocytopenia	31 (13.7)	9 (3.8)	4 (3.6)
Platelet count decreased	11 (4.8)	2 (0.8)	4 (3.6)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADAE
Abbreviation: B, Bendamustine; R, Rituximab; BR, Bendamustine and Rituximab; TEAE, treatment-emergent adverse event; AE, adverse event.
Notes: Adverse events were classified based on MedDRA Version 24.0
Patients with multiple events for a given preferred term were counted only once for each preferred term.
Events were sorted by descending order within category, and by preferred term within category in the Treatment-Emergent and Post-treatment Cohort 1 Zanubrutinib column.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_aesi_postteae_ab_i.sas
Output: t-14-3-1-2-10-1-1-teae-aesi-c1-saf-i.rtf (Date Generated: 17SEP2021:23:42)
Source: Table 14.3.1.2.10.1.1

Source: CSR 304

Study 305:

Table 44 Treatment Emergent Adverse Events of Special Interest by Category

	Zanubrutinib (N = 324) n (%)		Ibrutinib (N = 324) n (%)	
Category Preferred Term	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Patients With ≥ 1 AESI	240 (74.1)	117 (36.1)	245 (75.6)	109 (33.6)
Anemia	39 (12.0)	7 (2.2)	47 (14.5)	8 (2.5)
Atrial fibrillation and flutter	6 (1.9)	3 (0.9)	26 (8.0)	5 (1.5)
Hemorrhage	108 (33.3)	6 (1.9)	104 (32.1)	7 (2.2)
Major hemorrhage	6 (1.9)	6 (1.9)	10 (3.1)	7 (2.2)
Hypertension	42 (13.0)	27 (8.3)	40 (12.3)	24 (7.4)
Infections	152 (46.9)	37 (11.4)	166 (51.2)	45 (13.9)
Opportunistic infections	2 (0.6)	2 (0.6)	3 (0.9)	2 (0.6)
Neutropenia	69 (21.3)	45 (13.9)	56 (17.3)	41 (12.7)
Second primary malignancies	19 (5.9)	10 (3.1)	16 (4.9)	5 (1.5)
Skin cancers	8 (2.5)	3 (0.9)	12 (3.7)	2 (0.6)
Thrombocytopenia	30 (9.3)	9 (2.8)	35 (10.8)	9 (2.8)
Tumor lysis syndrome	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)

Integrated safety summary (ISS)

Table 45 TEAEs of Special Interest by category (SAS)

AESI Category	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE of Special Interest	332 (84.9)	240 (74.1)	438 (83.4)	792 (84.4)	1333 (86.0)
Anemia	25 (6.4)	39 (12.0)	92 (17.5)	117 (12.5)	218 (14.1)
Atrial fibrillation and flutter	13 (3.3)	6 (1.9)	13 (2.5)	26 (2.8)	49 (3.2)
Hemorrhage	179 (45.8)	108 (33.3)	253 (48.2)	447 (47.7)	746 (48.1)
Major hemorrhage	22 (5.6)	6 (1.9)	12 (2.3)	34 (3.6)	70 (4.5)
Hypertension	50 (12.8)	42 (13.0)	74 (14.1)	128 (13.6)	201 (13.0)
Infections	247 (63.2)	152 (46.9)	331 (63.0)	595 (63.4)	1019 (65.7)
Opportunistic infections	2 (0.5)	2 (0.6)	11 (2.1)	15 (1.6)	31 (2.0)
Neutropenia	67 (17.1)	69 (21.3)	172 (32.8)	241 (25.7)	427 (27.5)
Second primary malignancies	55 (14.1)	19 (5.9)	47 (9.0)	109 (11.6)	192 (12.4)
Skin cancers	33 (8.4)	8 (2.5)	23 (4.4)	62 (6.6)	115 (7.4)
Thrombocytopenia	29 (7.4)	30 (9.3)	92 (17.5)	122 (13.0)	247 (15.9)
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	5 (0.3)

Infections

Table 46 Infections reported in ≥5% of Patients in Any Patient Group by Preferred Term

Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One Infections	247 (63.2)	152 (46.9)	331 (63.0)	595 (63.4)	1019 (65.7)
Upper respiratory tract infection	73 (18.7)	48 (14.8)	152 (29.0)	236 (25.2)	432 (27.9)
Pneumonia	28 (7.2)	20 (6.2)	80 (15.2)	110 (11.7)	184 (11.9)
Urinary tract infection	28 (7.2)	24 (7.4)	63 (12.0)	97 (10.3)	179 (11.5)
Nasopharyngitis	26 (6.6)	4 (1.2)	16 (3.0)	43 (4.6)	94 (6.1)
Sinusitis	19 (4.9)	9 (2.8)	38 (7.2)	57 (6.1)	84 (5.4)
Lower respiratory tract infection	15 (3.8)	8 (2.5)	28 (5.3)	43 (4.6)	70 (4.5)
COVID-19	23 (5.9)	14 (4.3)	16 (3.0)	39 (4.2)	43 (2.8)

Table 47 Exposure Adjusted Incidence Rate for TEAE of Special Interest Infections

AESI Category	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Infections					
Number of patients experiencing the event, n (%)	247 (63.2)	152 (46.9)	331 (63.0)	595 (63.4)	1019 (65.7)
Total exposure time (months)	5129.4	2316.6	3911.2	9443.5	14888.8
EAIR (person per 100 person-months)	4.82	6.56	8.46	6.30	6.84
Opportunistic infections					

AESI Category	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Number of patients experiencing the event, n (%)	2 (0.5)	2 (0.6)	11 (2.1)	15 (1.6)	31 (2.0)
Total exposure time (months)	9671.1	3674.0	10868.3	21524.9	36845.0
EAIR (person per 100 person-months)	0.02	0.05	0.10	0.07	0.08

Source: ADSL, ADTTEAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: AESI, TEAE of special interest; BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; EAIR, exposure adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD. Percentages are based on N, unless otherwise specified.
Exposure adjusted incidence rate was calculated as the number of patients experiencing the event of interest divided by the total exposure time, which was calculated as the total time of all patients from the first dose date to the first event date, or from first dose date to the treatment-emergent period end date if there was no event.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-aesi-eair-i.sas 28OCT2021 19:30 t-27-teae-aesi-eair-infe-i.rtf

Hepatitis B reactivation

Twenty-seven (1.7%) patients within the All Zanubrutinib group reported infectious hepatic events. These included hepatitis B reactivation (14 patients, 0.9%), hepatitis B (7 patients, 0.5%), and hepatitis B DNA increased (2 patients, 0.1%).

Cytopenias

Table 48 Exposure Adjusted Incidence Rate for TEAE of Special Interest Cytopenias

AESI Category	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Anemia					
Number of patients experiencing the event, n (%)	25 (6.4)	39 (12.0)	92 (17.5)	117 (12.5)	218 (14.1)
Total exposure time (months)	9367.9	3330.9	9447.0	19856.0	34156.8
EAIR (person per 100 person-months)	0.27	1.17	0.97	0.59	0.64
Neutropenia					
Number of patients experiencing the event, n (%)	67 (17.1)	69 (21.3)	172 (32.8)	241 (25.7)	427 (27.5)
Total exposure time (months)	8444.3	2928.1	7224.5	16629.1	27785.2
EAIR (person per 100 person-months)	0.79	2.36	2.38	1.45	1.54
Thrombocytopenia					
Number of patients experiencing the event, n (%)	29 (7.4)	30 (9.3)	92 (17.5)	122 (13.0)	247 (15.9)
Total exposure time (months)	9247.0	3440.0	9309.3	19578.3	32946.5
EAIR (person per 100 person-months)	0.31	0.87	0.99	0.62	0.75

Haemorrhage

Table 49 Exposure Adjusted Incidence Rate for TEAE of Special Interest- Hemorrhage

AESI Category	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Hemorrhage					
Number of patients experiencing the event, n (%)	179 (45.8)	108 (33.3)	253 (48.2)	447 (47.7)	746 (48.1)
Total exposure time (months)	5695.5	2569.1	5076.2	11070.8	19368.4
EAIR (person per 100 person-months)	3.14	4.20	4.98	4.04	3.85

Source: ADSL, ADTTEAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; EAIR, exposure adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
Exposure adjusted incidence rate was calculated as the number of patients experiencing the event of interest divided by the total exposure time, which was calculated as the total time of all patients from the first dose date to the first event date, or from first dose date to the treatment-emergent period end date if there was no event.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-aesi-eair-i.sas 28OCT2021 19:30 t-21-teae-aesi-eair-hemo-i.rtf

Serious adverse event/deaths/other significant events

Deaths

Study 304

Table 50 Summary of all deaths in Cohort 1

	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Total (N = 467) n (%)
Total Number of Deaths, n (%)	15 (6.6) [a]	16 (6.7)	31 (6.6)
Cause of Death			
AE	11 (4.8)	11 (4.6)	22 (4.7)
Progressive Disease	0 (0.0)	2 (0.8)	2 (0.4)
Other	0 (0.0)	1 (0.4)	1 (0.2)
Patient Died of Septic Shock after the Protocol Reporting Period	0 (0.0)	1 (0.4)	1 (0.2)
Unknown	3 (1.3)	2 (0.8)	5 (1.1)
Death During Palliative Care/Hospice	2 (0.9)	0 (0.0)	2 (0.4)
Specific Cause of Death not Available	1 (0.4)	2 (0.8)	3 (0.6)
Deaths Within 30 Days of Last Zanubrutinib Dose Date or 90 Days of Last B or R Dose Date, n (%)	7 (3.1)	8 (3.3)	15 (3.2)
Cause of Death			
AE	6 (2.6)	8 (3.3)	14 (3.0)
Unknown	1 (0.4)	0 (0.0)	1 (0.2)
Specific Cause of Death not Available	1 (0.4)	0 (0.0)	1 (0.2)
Death > 30 Days of Last Zanubrutinib Dose Date or > 90 Days of Last B or R Dose Date, n (%)	7 (3.1)	8 (3.3)	15 (3.2)
Cause of Death			
AE	5 (2.2)	3 (1.3)	8 (1.7)
Progressive Disease	0 (0.0)	2 (0.8)	2 (0.4)
Other	0 (0.0)	1 (0.4)	1 (0.2)
Patient Died of Septic Shock after the Protocol Reporting Period [b]	0 (0.0)	1 (0.4)	1 (0.2)
Unknown	2 (0.9)	2 (0.8)	4 (0.9)
Death During Palliative Care/Hospice	2 (0.9)	0 (0.0)	2 (0.4)
Specific Cause of Death not Available	0 (0.0)	2 (0.8)	2 (0.4)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL
Abbreviation: BR, Bendamustine and Rituximab.
[a] One of these 15 patients died due an adverse event of confusional state after the data cutoff date.
[b] The patient died after disease progression and start of other anticancer therapy; therefore, the death was out of the adverse event reporting period.
Programmer: jinling.li, Location: /bgb_3111/bgb_3111_304/csr_2021/dev/pgm/tlfs/t_dth_sum_c12_i.sas
Output: t-14-3-1-2-8-1-1-dth-sum-c1-saf-i.rtf (Date Generated: 06SEP2021:06:07)
Source: Table 14.3.1.2.8.1.1

Study 305*Table 51 Summary of all deaths*

Death Summary	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Total Number of Deaths	15 (4.6)	23 (7.1)
Cause of Death		
Adverse Event	8 (2.5)	11 (3.4)
COVID-19	3 (0.9)	6 (1.9)
Disease Under Study	6 (1.9)	11 (3.4)
Indeterminate	1 (0.3)	1 (0.3)
Deaths Within 30 Days of Last Dose Date	11 (3.4)	16 (4.9)
Cause of Death		
Adverse Event	7 (2.2)	9 (2.8)
COVID-19	3 (0.9)	5 (1.5)
Disease Under Study	4 (1.2)	6 (1.9)
Indeterminate	0 (0.0)	1 (0.3)
Deaths > 30 Days of Last Dose Date	4 (1.2)	7 (2.2)
Cause of Death		
Adverse Event	1 (0.3)	2 (0.6)
COVID-19	0 (0.0)	1 (0.3)
Disease Under Study	2 (0.6)	5 (1.5)
Indeterminate	1 (0.3)	0 (0.0)

Source: ADSL. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-death-sum-i.sas 09AUG2021 23:32 t-27-death-sum-i.rtf

Table 52 Summary of all deaths (SAS)

Integrated safety summary

Death Summary	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Total Number of Deaths	25 (6.4)	15 (4.6)	42 (8.0)	69 (7.4)	207 (13.4)
Cause of death					
Progressive disease [a]	7 (1.8)	6 (1.9)	18 (3.4)	26 (2.8)	98 (6.3)
Adverse event	14 (3.6)	8 (2.5)	15 (2.9)	30 (3.2)	66 (4.3)
Related to COVID-19	5 (1.3)	3 (0.9)	4 (0.8)	9 (1.0)	12 (0.8)
Other	2 (0.5)	0 (0.0)	7 (1.3)	9 (1.0)	24 (1.5)
Unknown [b]	2 (0.5)	1 (0.3)	2 (0.4)	4 (0.4)	19 (1.2)
Deaths Within 30 Days of Last Dose Date	11 (2.8)	11 (3.4)	20 (3.8)	32 (3.4)	81 (5.2)
Cause of death					
Adverse event	11 (2.8)	7 (2.2)	13 (2.5)	25 (2.7)	53 (3.4)
Related to COVID-19	4 (1.0)	3 (0.9)	4 (0.8)	8 (0.9)	10 (0.6)
Progressive disease [a]	0 (0.0)	4 (1.2)	6 (1.1)	6 (0.6)	23 (1.5)
Other	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.2)
Unknown [b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Deaths > 30 Days of Last Dose Date	14 (3.6)	4 (1.2)	22 (4.2)	37 (3.9)	126 (8.1)
Cause of death					
Progressive disease [a]	7 (1.8)	2 (0.6)	12 (2.3)	20 (2.1)	75 (4.8)
Other	2 (0.5)	0 (0.0)	6 (1.1)	8 (0.9)	21 (1.4)
Unknown [b]	2 (0.5)	1 (0.3)	2 (0.4)	4 (0.4)	17 (1.1)
Adverse event	3 (0.8)	1 (0.3)	2 (0.4)	5 (0.5)	13 (0.8)
Related to COVID-19	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)

Table 53 TEAEs leading to death by SOC and PT (SAS)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Death	14 (3.6)	13 (4.0)	21 (4.0)	36 (3.8)	76 (4.9)
Infections and infestations	7 (1.8)	11 (3.4)	16 (3.0)	23 (2.5)	39 (2.5)
Pneumonia	1 (0.3)	3 (0.9)	6 (1.1)	7 (0.7)	11 (0.7)
COVID-19	4 (1.0)	3 (0.9)	4 (0.8)	8 (0.9)	9 (0.6)
COVID-19 pneumonia	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)
Pneumonia fungal	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Sepsis	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Acute hepatitis B	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Arthritis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Endocarditis	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Escherichia sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Infection	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Pneumonia cryptococcal	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Pneumonia influenza	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Pneumonia staphylococcal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory tract infection	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Scedosporium infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	0 (0.0)	2 (0.6)	4 (0.8)	4 (0.4)	11 (0.7)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	5 (0.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
Malaise	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Cardiac disorders	3 (0.8)	0 (0.0)	2 (0.4)	5 (0.5)	10 (0.6)
Acute myocardial infarction	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Cardiac arrest	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Cardiac failure	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiogenic shock	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Cardiomegaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Pulseless electrical activity	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.8)	0 (0.0)	0 (0.0)	4 (0.4)	8 (0.5)
Acute myeloid leukaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Adenocarcinoma gastric	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Lung neoplasm malignant	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Lung squamous cell carcinoma recurrent	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Lymphoma transformation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Metastatic squamous cell carcinoma	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Skin squamous cell carcinoma recurrent	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Nervous system disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.3)
Central nervous system lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cerebral infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Haemorrhagic transformation stroke	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.2)
Brain herniation	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Subdural haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.3)	2 (0.4)	2 (0.2)	3 (0.2)
Acute respiratory failure	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Bronchiectasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory failure	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)
Renal and urinary disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Renal failure	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bone marrow necrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Colitis	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Hepatobiliary disorders	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Jaundice	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Mobility decreased	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Toxic epidermal necrolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Aortic dissection	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

Serious adverse events

Study 304:

Table 54 Serious Treatment Emergent+ Post Treatment Adverse Events Reported in ≥2% of Patients by System Organ Class and Preferred Term in Cohort 1 and Cohort 2

	Cohort 1		Cohort 2
System Organ Class Preferred Term	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Zanubrutinib (N = 111) n (%)
Patients With at Least One Serious AE	113 (49.8)	88 (36.7)	45 (40.5)
Infections and infestations	36 (15.9)	41 (17.1)	19 (17.1)
COVID-19	1 (0.4)	8 (3.3)	1 (0.9)
COVID-19 pneumonia	0 (0.0)	7 (2.9)	1 (0.9)
Pneumonia	7 (3.1)	4 (1.7)	6 (5.4)
Sepsis	6 (2.6)	2 (0.8)	0 (0.0)
Urinary tract infection	5 (2.2)	1 (0.4)	2 (1.8)
Cardiac disorders	10 (4.4)	17 (7.1)	3 (2.7)
Atrial fibrillation	1 (0.4)	4 (1.7)	3 (2.7)
Injury, poisoning and procedural complications	13 (5.7)	9 (3.8)	7 (6.3)
Fall	2 (0.9)	0 (0.0)	3 (2.7)
Infusion related reaction	7 (3.1)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	20 (8.8)	7 (2.9)	2 (1.8)
Anaemia	5 (2.2)	2 (0.8)	1 (0.9)
Febrile neutropenia	11 (4.8)	1 (0.4)	1 (0.9)
Gastrointestinal disorders	15 (6.6)	5 (2.1)	3 (2.7)
Diarrhoea	5 (2.2)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	18 (7.9)	5 (2.1)	2 (1.8)
Pyrexia	17 (7.5)	2 (0.8)	2 (1.8)

Study 305:

Table 55 Serious Adverse Events by System Organ Class and Preferred Term Reported in ≥ 2 Patients in Either Arm

System Organ Class Preferred Term	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Patients With at Least One Serious TEAE	70 (21.6)	82 (25.3)
Blood and lymphatic system disorders		
Anaemia	3 (0.9)	3 (0.9)
Hypoglobulinaemia	1 (0.3)	2 (0.6)
Haemolytic anaemia	0 (0.0)	2 (0.6)
Cardiac disorders		
Atrial fibrillation	0 (0.0)	4 (1.2)
Cardiac arrest	0 (0.0)	2 (0.6)
Myocardial infarction	0 (0.0)	2 (0.6)
Ventricular fibrillation	0 (0.0)	2 (0.6)
General disorders and administration site conditions		
Pyrexia	2 (0.6)	3 (0.9)
Malaise	2 (0.6)	0 (0.0)
Infections and infestations		
Pneumonia	10 (3.1)	15 (4.6)
COVID-19	7 (2.2)	3 (0.9)
Urinary tract infection	3 (0.9)	5 (1.5)
COVID-19 pneumonia	2 (0.6)	5 (1.5)
Sepsis	3 (0.9)	1 (0.3)
Upper respiratory tract infection	0 (0.0)	2 (0.6)
Investigations		
Platelet count decreased	2 (0.6)	1 (0.3)
Musculoskeletal and connective tissue disorders		
Haemarthrosis	2 (0.6)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder transitional cell carcinoma	2 (0.6)	0 (0.0)
Nervous system disorders		
Cerebrovascular accident	3 (0.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	1 (0.3)	2 (0.6)
Respiratory failure	0 (0.0)	2 (0.6)

Table 56 Integrated safety summary (ISS)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One Serious TEAE	145 (37.1)	70 (21.6)	185 (35.2)	341 (36.4)	623 (40.2)
Infections and infestations	63 (16.1)	35 (10.8)	110 (21.0)	179 (19.1)	307 (19.8)
Pneumonia	12 (3.1)	10 (3.1)	44 (8.4)	57 (6.1)	106 (6.8)
Urinary tract infection	3 (0.8)	3 (0.9)	8 (1.5)	11 (1.2)	20 (1.3)
Cellulitis	3 (0.8)	1 (0.3)	5 (1.0)	8 (0.9)	19 (1.2)
COVID-19	8 (2.0)	7 (2.2)	9 (1.7)	17 (1.8)	18 (1.2)
COVID-19 pneumonia	8 (2.0)	2 (0.6)	2 (0.4)	10 (1.1)	14 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25 (6.4)	10 (3.1)	23 (4.4)	49 (5.2)	80 (5.2)
Lung adenocarcinoma	4 (1.0)	0 (0.0)	0 (0.0)	4 (0.4)	4 (0.3)
Blood and lymphatic system disorders	13 (3.3)	9 (2.8)	16 (3.0)	29 (3.1)	61 (3.9)
Anaemia	4 (1.0)	3 (0.9)	5 (1.0)	9 (1.0)	21 (1.4)
Cardiac disorders	20 (5.1)	2 (0.6)	13 (2.5)	33 (3.5)	60 (3.9)
Atrial fibrillation	7 (1.8)	0 (0.0)	2 (0.4)	9 (1.0)	15 (1.0)
Respiratory, thoracic and mediastinal disorders	8 (2.0)	5 (1.5)	12 (2.3)	20 (2.1)	54 (3.5)
Pleural effusion	4 (1.0)	1 (0.3)	2 (0.4)	6 (0.6)	17 (1.1)
General disorders and administration site conditions	8 (2.0)	5 (1.5)	8 (1.5)	18 (1.9)	52 (3.4)
Pyrexia	4 (1.0)	2 (0.6)	3 (0.6)	8 (0.9)	26 (1.7)
Reproductive system and breast disorders	5 (1.3)	0 (0.0)	1 (0.2)	6 (0.6)	9 (0.6)
Benign prostatic hyperplasia	4 (1.0)	0 (0.0)	1 (0.2)	5 (0.5)	5 (0.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Patients with multiple events for a given Preferred Term and with multiple Preferred Terms within a System Organ Class are counted only once at the Preferred Term and System Organ Class levels, respectively. Events are sorted by decreasing frequency first by System Organ Class and then by Preferred Term within each System Organ Class in the 'All Zanubrutinib' column.
MedDRA Version: 24.0.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-soc-pt-i.sas 24AUG2021 02:10 t-15-ser-teae-soc-pt-1-i.rtf

Laboratory findings

Haematology

Study 304:

Table 57 worsening shifts of ≥ 2 CTCAE toxicity grades compared with baseline

	BR (N = 227) n (%)	Zanubrutinib (N = 240) n (%)	Total (N = 467) n (%)
Absolute Lymphocytes Count(10^9/L) (Low)	202 (89.0)	2 (0.8)	204 (43.7)
Absolute Lymphocytes Count(10^9/L) (High)	0 (0.0)	11 (4.6) [a]	11 (2.4)
Absolute Lymphocytes Count-Selected(10^9/L) (Low) [b]	210 (92.5)	8 (3.3)	218 (46.7)
Absolute Lymphocytes Count-Selected(10^9/L) (High) [b]	0 (0.0)	11 (4.6) [a]	11 (2.4)
Absolute Neutrophil Count-Selected(10^9/L) (Low) [b]	165 (72.7)	52 (21.7)	217 (46.5)
Hemoglobin(g/L) (Low)	22 (9.7)	6 (2.5)	28 (6.0)
Hemoglobin(g/L) (High)	0 (0.0)	1 (0.4)	1 (0.2)
Leukocytes(10^9/L) (Low)	174 (76.7)	5 (2.1)	179 (38.3)
Leukocytes(10^9/L) (High)	1 (0.4)	49 (20.4) [a]	50 (10.7)
Platelets(10^9/L) (Low)	36 (15.9)	4 (1.7)	40 (8.6)
Prothrombin Intl. Normalized Ratio(RATIO) (High)	0 (0.0)	1 (0.4)	1 (0.2)

Data cutoff: 07May2021; Data extraction: 28Jun2021; Data Source: ADSL, ADLB

Study 305:

Table 58 Worsening shifts of ≥ CTCAE Toxicity Grades Compared with Baseline: Hematology Parameters

Parameter (Directional Change)	Zanubrutinib (N = 324) n (%)	Ibrutinib (N = 324) n (%)
Absolute Lymphocytes Count (Derived) (Low)	5 (1.5)	13 (4.0)
Absolute Lymphocytes Count (Derived) (High)	22 (6.8)	29 (9.0)
Absolute Neutrophils Count (Derived) (Low)	10 (3.1)	11 (3.4)
Hemoglobin (Low)	6 (1.9)	10 (3.1)
Lymphocytes (Low)	5 (1.5)	13 (4.0)
Lymphocytes (High)	20 (6.2)	29 (9.0)
Neutrophils (Low)	68 (21.0)	51 (15.7)
Platelets (Low)	3 (0.9)	6 (1.9)
Leukocytes (Low)	15 (4.6)	9 (2.8)
Leukocytes (High)	68 (21.0)	68 (21.0)

Source: ADSL, ADLB. Data cutoff: 31DEC2020. Data extraction: 19MAR2021.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.
Laboratory results were graded using NCI-CTCAE Version 4.03.
/bgb_3111/bgb_3111_305/csru_dev_20201231/dev/pgm/tlfs/t-lab-hem-shift-i.sas 09AUG2021 23:33 t-28-lab-hem-shift1-i.rtf

Integrated safety summary (ISS)

Table 59 Shifts of ≥ 2 Toxicity Grades from Baseline to the Worst Postbaseline Grade for Selected Hematology Parameters

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Hemoglobin (g/L)					
n	391	324	525	938	1550
Low directionality	11 (2.8)	6 (1.9)	19 (3.6)	30 (3.2)	67 (4.3)
High directionality	1 (0.3)	0 (0.0)	3 (0.6)	4 (0.4)	6 (0.4)
Platelets (10^9/L)					
n	391	324	525	938	1550
Low directionality	10 (2.6)	3 (0.9)	13 (2.5)	23 (2.5)	91 (5.9)
Neutrophils (10^9/L)					
n	391	324	525	938	1550
Low directionality	90 (23.0)	10 (3.1)	107 (20.4)	207 (22.1)	391 (25.2)
Lymphocytes (10^9/L)					
n	391	324	525	938	1550
Low directionality	14 (3.6)	5 (1.5)	43 (8.2)	61 (6.5)	166 (10.7)
High directionality	18 (4.6)	22 (6.8)	46 (8.8)	65 (6.9)	175 (11.3)

Source: ADSL, ADLB. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on n, the number of patients with at least one assessment at baseline or any time postbaseline, respectively.
Postbaseline laboratory results were summarized up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever comes first.
Laboratory results are graded using CTCAE v4.03.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-hem-abn-shift2-i.sas 24AUG2021 01:23 t-36-hem-abn-shift2-i.rtf

Clinical chemistry

Integrated safety summary (ISS)

Table 60 Shifts of ≥ 2 Toxicity Grades from Baseline to the Worst Postbaseline Grade for Selected Chemistry Parameters

	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Alanine Aminotransferase (U/L)					
n	391	324	525	938	1550
High directionality	10 (2.6)	3 (0.9)	13 (2.5)	24 (2.6)	41 (2.6)
Aspartate Aminotransferase (U/L)					
n	391	324	525	938	1550
High directionality	8 (2.0)	0 (0.0)	4 (0.8)	13 (1.4)	25 (1.6)

Source: ADSL, ADLB. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory.
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on n, number of patients with at least one assessment at baseline or any time postbaseline.
Postbaseline laboratory results were summarized up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever comes first.
Laboratory results are graded using CTCAE v4.03.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-chem-abn-shift2-i.sas 24AUG2021 01:23 t-37-chem-abn-shift2-i.rtf

Safety in special populations

Intrinsic factors:

Age

Table 61

	All R/R CLL/SLL Zanubrutinib (N = 525)		All CLL/SLL Zanubrutinib (N = 938)		All Zanubrutinib (N = 1550)	
	< 65 years (N = 239) n (%)	≥ 65 years (N = 286) n (%)	< 65 years (N = 322) n (%)	≥ 65 years (N = 616) n (%)	< 65 years (N = 600) n (%)	≥ 65 years (N = 950) n (%)
Patients With at Least One TEAE	222 (92.9)	270 (94.4)	296 (91.9)	589 (95.6)	567 (94.5)	916 (96.4)
Grade 3 or Higher	132 (55.2)	168 (58.7)	166 (51.6)	350 (56.8)	324 (54.0)	573 (60.3)
Serious	82 (34.3)	103 (36.0)	104 (32.3)	237 (38.5)	199 (33.2)	424 (44.6)
Leading to Death	3 (1.3)	18 (6.3)	5 (1.6)	31 (5.0)	16 (2.7)	60 (6.3)
Leading to Treatment Discontinuation	12 (5.0)	34 (11.9)	17 (5.3)	58 (9.4)	36 (6.0)	108 (11.4)
Leading to Dose Reduction	16 (6.7)	29 (10.1)	19 (5.9)	51 (8.3)	33 (5.5)	83 (8.7)
Leading to Dose Interruption	91 (38.1)	108 (37.8)	118 (36.6)	270 (43.8)	212 (35.3)	437 (46.0)
Treatment-Related	184 (77.0)	215 (75.2)	243 (75.5)	458 (74.4)	457 (76.2)	724 (76.2)
Treatment-Related Grade 3 or Higher	99 (41.4)	92 (32.2)	114 (35.4)	178 (28.9)	194 (32.3)	291 (30.6)
Patients With at Least One AESI	197 (82.4)	241 (84.3)	262 (81.4)	530 (86.0)	501 (83.5)	832 (87.6)
Grade 3 or Higher AESI	116 (48.5)	140 (49.0)	140 (43.5)	275 (44.6)	268 (44.7)	450 (47.4)
Serious AESI	65 (27.2)	80 (28.0)	81 (25.2)	169 (27.4)	146 (24.3)	294 (30.9)

Sex

Table 62

	All R/R CLL/SLL Zanubrutinib (N = 525)		All CLL/SLL Zanubrutinib (N = 938)		All Zanubrutinib (N = 1550)	
	Male (N = 345) n (%)	Female (N = 180) n (%)	Male (N = 623) n (%)	Female (N = 315) n (%)	Male (N = 1027) n (%)	Female (N = 523) n (%)
Patients With at Least One TEAE	320 (92.8)	172 (95.6)	586 (94.1)	299 (94.9)	980 (95.4)	503 (96.2)
Grade 3 or Higher	196 (56.8)	104 (57.8)	342 (54.9)	174 (55.2)	594 (57.8)	303 (57.9)
Serious	122 (35.4)	63 (35.0)	226 (36.3)	115 (36.5)	420 (40.9)	203 (38.8)
Leading to Death	15 (4.3)	6 (3.3)	27 (4.3)	9 (2.9)	59 (5.7)	17 (3.3)
Leading to Treatment Discontinuation	30 (8.7)	16 (8.9)	51 (8.2)	24 (7.6)	98 (9.5)	46 (8.8)
Leading to Dose Reduction	29 (8.4)	16 (8.9)	43 (6.9)	27 (8.6)	74 (7.2)	42 (8.0)
Leading to Dose Interruption	131 (38.0)	68 (37.8)	262 (42.1)	126 (40.0)	437 (42.6)	212 (40.5)
Treatment-Related	254 (73.6)	145 (80.6)	454 (72.9)	247 (78.4)	771 (75.1)	410 (78.4)
Treatment-Related Grade 3 or Higher	120 (34.8)	71 (39.4)	191 (30.7)	101 (32.1)	312 (30.4)	173 (33.1)
Patients With at Least One AESI	280 (81.2)	158 (87.8)	517 (83.0)	275 (87.3)	873 (85.0)	460 (88.0)
Grade 3 or Higher AESI	163 (47.2)	93 (51.7)	272 (43.7)	143 (45.4)	469 (45.7)	249 (47.6)
Serious AESI	94 (27.2)	51 (28.3)	165 (26.5)	85 (27.0)	298 (29.0)	142 (27.2)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).
Abbreviations: AESI, TEAE of special interest; BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event
N = number of patients who received zanubrutinib at the initial dose of 160 mg BID or 320 mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.
/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-sum-sub-i.sas 24AUG2021 02:44 t-40-teae-sum-sex-i.rtf

Weight

Table 63

	All R/R CLL/SLL Zanubrutinib (N = 525)		All CLL/SLL Zanubrutinib (N = 938)		All Zanubrutinib (N = 1550)	
	< Median Weight (N = 239) n (%)	≥ Median Weight (N = 285) n (%)	< Median Weight (N = 419) n (%)	≥ Median Weight (N = 518) n (%)	< Median Weight (N = 765) n (%)	≥ Median Weight (N = 784) n (%)
Patients With at Least One TEAE	226 (94.6)	265 (93.0)	398 (95.0)	486 (93.8)	736 (96.2)	746 (95.2)
Grade 3 or Higher	145 (60.7)	154 (54.0)	235 (56.1)	280 (54.1)	456 (59.6)	440 (56.1)
Serious	85 (35.6)	100 (35.1)	150 (35.8)	191 (36.9)	314 (41.0)	309 (39.4)
Leading to Death	14 (5.9)	7 (2.5)	18 (4.3)	18 (3.5)	44 (5.8)	32 (4.1)
Leading to Treatment Discontinuation	25 (10.5)	21 (7.4)	35 (8.4)	40 (7.7)	79 (10.3)	65 (8.3)
Leading to Dose Reduction	20 (8.4)	25 (8.8)	31 (7.4)	39 (7.5)	56 (7.3)	60 (7.7)
Leading to Dose Interruption	92 (38.5)	106 (37.2)	163 (38.9)	224 (43.2)	303 (39.6)	345 (44.0)
Treatment-Related	190 (79.5)	208 (73.0)	333 (79.5)	367 (70.8)	614 (80.3)	566 (72.2)
Treatment-Related Grade 3 or Higher	104 (43.5)	86 (30.2)	149 (35.6)	142 (27.4)	269 (35.2)	215 (27.4)
Patients With at Least One AESI	208 (87.0)	229 (80.4)	364 (86.9)	427 (82.4)	668 (87.3)	664 (84.7)
Grade 3 or Higher AESI	131 (54.8)	124 (43.5)	199 (47.5)	215 (41.5)	372 (48.6)	345 (44.0)
Serious AESI	67 (28.0)	78 (27.4)	109 (26.0)	141 (27.2)	220 (28.8)	220 (28.1)

Source: ADSL, ADAE, ADBASE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: AESI, TEAE of special interest; BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

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

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

Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.

Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

The median baseline weight (73.0kg) is based on patients included in the 'All Zanubrutinib' column. Those patients with no baseline weight are excluded.

/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-sum-sub-i.sas 24AUG2021 02:44 t-42-teae-sum-wgt-i.rtf

Race

Table 64

	All R/R CLL/SLL Zanubrutinib (N = 525)			All CLL/SLL Zanubrutinib (N = 938)			All Zanubrutinib (N = 1550)		
	White (N = 349) n (%)	Asian (N = 149) n (%)	Other (N = 27) n (%)	White (N = 696) n (%)	Asian (N = 194) n (%)	Other (N = 48) n (%)	White (N = 1033) n (%)	Asian (N = 424) n (%)	Other (N = 92) n (%)
Patients With at Least One TEAE	323 (92.6)	144 (96.6)	25 (92.6)	652 (93.7)	187 (96.4)	46 (95.8)	983 (95.2)	409 (96.5)	90 (97.8)
Grade 3 or Higher	184 (52.7)	100 (67.1)	16 (59.3)	372 (53.4)	118 (60.8)	26 (54.2)	584 (56.5)	257 (60.6)	55 (59.8)
Serious	110 (31.5)	63 (42.3)	12 (44.4)	248 (35.6)	77 (39.7)	16 (33.3)	413 (40.0)	167 (39.4)	42 (45.7)
Leading to Death	12 (3.4)	8 (5.4)	1 (3.7)	26 (3.7)	8 (4.1)	2 (4.2)	50 (4.8)	19 (4.5)	7 (7.6)
Leading to Treatment Discontinuation	29 (8.3)	16 (10.7)	1 (3.7)	56 (8.0)	17 (8.8)	2 (4.2)	98 (9.5)	37 (8.7)	8 (8.7)
Leading to Dose Reduction	31 (8.9)	12 (8.1)	2 (7.4)	54 (7.8)	13 (6.7)	3 (6.3)	90 (8.7)	22 (5.2)	4 (4.3)
Leading to Dose Interruption	133 (38.1)	56 (37.6)	10 (37.0)	307 (44.1)	64 (33.0)	17 (35.4)	477 (46.2)	134 (31.6)	38 (41.3)
Treatment-Related	241 (69.1)	138 (92.6)	20 (74.1)	490 (70.4)	176 (90.7)	35 (72.9)	743 (71.9)	372 (87.7)	65 (70.7)
Treatment-Related Grade 3 or Higher	101 (28.9)	84 (56.4)	6 (22.2)	186 (26.7)	95 (49.0)	11 (22.9)	282 (27.3)	176 (41.5)	26 (28.3)
Patients With at Least One AESI	281 (80.5)	134 (89.9)	23 (85.2)	581 (83.5)	171 (88.1)	40 (83.3)	885 (85.7)	370 (87.3)	77 (83.7)
Grade 3 or Higher AESI	155 (44.4)	91 (61.1)	10 (37.0)	293 (42.1)	105 (54.1)	17 (35.4)	462 (44.7)	218 (51.4)	37 (40.2)
Serious AESI	85 (24.4)	52 (34.9)	8 (29.6)	178 (25.6)	62 (32.0)	10 (20.8)	287 (27.8)	125 (29.5)	27 (29.3)

Source: ADSL, ADAE. Data cutoff: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304).

Abbreviations: AESI, TEAE of special interest; BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event

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

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

Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.

Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.

/bgb_3111/filing_cll_2021/iss/dev/pgm/tlfs/t-teae-sum-sub-i.sas 24AUG2021 02:44 t-44-teae-sum-race-i.rtf

Extrinsic factors: Region

Table 65

	All Relapsed/Refractory CLL/SLL Zanubrutinib		All CLL/SLL Zanubrutinib		All Zanubrutinib	
	China (N = 145) n (%)	Non-China (N = 380) n (%)	China (N = 187) n (%)	Non-China (N = 751) n (%)	China (N = 363) n (%)	Non-China (N = 1187) n (%)
Patients With at Least One TEAE	140 (96.6)	352 (92.6)	180 (96.3)	705 (93.9)	351 (96.7)	1132 (95.4)
Grade 3 or Higher	97 (66.9)	203 (53.4)	114 (61.0)	402 (53.5)	216 (59.5)	681 (57.4)
Serious	61 (42.1)	124 (32.6)	75 (40.1)	266 (35.4)	138 (38.0)	485 (40.9)
Leading to Death	8 (5.5)	13 (3.4)	8 (4.3)	28 (3.7)	19 (5.2)	57 (4.8)
Leading to Treatment Discontinuation	15 (10.3)	31 (8.2)	16 (8.6)	59 (7.9)	32 (8.8)	112 (9.4)
Leading to Dose Reduction	11 (7.6)	34 (8.9)	12 (6.4)	58 (7.7)	17 (4.7)	99 (8.3)
Leading to Dose Interruption	53 (36.6)	146 (38.4)	61 (32.6)	327 (43.5)	102 (28.1)	547 (46.1)
Patients With at Least One AESI	131 (90.3)	307 (80.8)	165 (88.2)	627 (83.5)	323 (89.0)	1010 (85.1)
Grade 3 or Higher AESI	89 (61.4)	167 (43.9)	103 (55.1)	312 (41.5)	189 (52.1)	529 (44.6)
Serious AESI	52 (35.9)	93 (24.5)	62 (33.2)	188 (25.0)	108 (29.8)	332 (28.0)

Data Source: ADSL, ADAE. Data cut-off: 30AUG2020(1002), 31MAR2021(AU-003), 11SEP2020(205), 08SEP2020(206), 11JAN2021(210), 16APR2021(214), 01FEB2021(302), 24MAR2021(LTE1), 31DEC2020(305), 07MAY2021(304);
Abbreviations: AESI, TEAE of special interest; BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IWCLL, International Workshop on Chronic Lymphocytic Leukemia; LTE, long-term extension; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; TEAE, treatment-emergent adverse event;
N = number of patients who received zanubrutinib at the initial dose of 160mg BID or 320mg QD. Percentages are based on N, unless otherwise specified.
TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Worsening of an event to Grade 5 beyond 30 days after last dose of study drug and prior to initiation of new anticancer therapy is also considered as treatment-emergent.
Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for hematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale was used.
Treatment-related TEAEs include those events considered by the investigator to be related, probably or possibly related, or with missing assessment of the causal relationship.
Location: /bgb_3111/filing_cll_2021/iss_eu/dev/pgm/tlfs/t_teae.sas Output: t-2-7-4-2- 14-5-teae.rtf (Date Generated: 22NOV2021:01:41)

Safety related to drug-drug interactions and other interactions

No new information on drug interactions has been submitted with the current variation application, this is endorsed.

Discontinuation due to adverse events

Table 66 TEAEs leading to dose reduction reported in ≥ 2 patients in any patient group

Group by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Dose Reduction	25 (6.4)	24 (7.4)	45 (8.6)	70 (7.5)	116 (7.5)
Infections and infestations	2 (0.5)	3 (0.9)	11 (2.1)	13 (1.4)	21 (1.4)
Pneumonia	0 (0.0)	2 (0.6)	6 (1.1)	6 (0.6)	9 (0.6)
Hepatitis B reactivation	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.3)	3 (0.2)
Pneumonia cryptococcal	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	2 (0.1)
Gastrointestinal disorders	2 (0.5)	1 (0.3)	6 (1.1)	8 (0.9)	16 (1.0)
Diarrhoea	1 (0.3)	1 (0.3)	3 (0.6)	4 (0.4)	10 (0.6)
Vomiting	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	3 (0.2)
Nausea	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Blood and lymphatic system disorders	2 (0.5)	3 (0.9)	5 (1.0)	7 (0.7)	14 (0.9)
Neutropenia	1 (0.3)	2 (0.6)	4 (0.8)	5 (0.5)	9 (0.6)
Thrombocytopenia	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	3 (0.2)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Febrile neutropenia	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Skin and subcutaneous tissue disorders	1 (0.3)	4 (1.2)	5 (1.0)	6 (0.6)	12 (0.8)
Purpura	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.2)
Petechiae	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Cardiac disorders	5 (1.3)	2 (0.6)	3 (0.6)	8 (0.9)	11 (0.7)
Atrial fibrillation	5 (1.3)	2 (0.6)	3 (0.6)	8 (0.9)	9 (0.6)
Musculoskeletal and connective tissue disorders	5 (1.3)	3 (0.9)	3 (0.6)	8 (0.9)	10 (0.6)
Arthralgia	3 (0.8)	0 (0.0)	0 (0.0)	3 (0.3)	5 (0.3)
Muscle spasms	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Myalgia	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Injury, poisoning and procedural complications	3 (0.8)	1 (0.3)	2 (0.4)	5 (0.5)	9 (0.6)
Contusion	2 (0.5)	1 (0.3)	2 (0.4)	4 (0.4)	7 (0.5)
Investigations	2 (0.5)	1 (0.3)	3 (0.6)	5 (0.5)	9 (0.6)
Neutrophil count decreased	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	5 (0.3)
General disorders and administration site conditions	1 (0.3)	2 (0.6)	3 (0.6)	4 (0.4)	8 (0.5)
Fatigue	1 (0.3)	0 (0.0)	1 (0.2)	2 (0.2)	3 (0.2)
Pain	0 (0.0)	1 (0.3)	1 (0.2)	1 (0.1)	2 (0.1)
Vascular disorders	0 (0.0)	6 (1.9)	6 (1.1)	6 (0.6)	7 (0.5)
Hypertension	0 (0.0)	4 (1.2)	4 (0.8)	4 (0.4)	4 (0.3)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Haematoma	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Nervous system disorders	3 (0.8)	2 (0.6)	2 (0.4)	5 (0.5)	6 (0.4)
Dizziness	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)
Headache	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	6 (0.4)
Epistaxis	0 (0.0)	2 (0.6)	2 (0.4)	2 (0.2)	2 (0.1)
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Metabolism and nutrition disorders	1 (0.3)	1 (0.3)	3 (0.6)	4 (0.4)	4 (0.3)
Tumour lysis syndrome	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.1)

Table 67 TEAEs Leading to Dose Interruption Reported in ≥1% Patients in Any Patient Group by System Organ Class and Preferred Term

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Patients With at Least One TEAE Leading to Dose Interruption	175 (44.8)	98 (30.2)	199 (37.9)	388 (41.4)	649 (41.9)
Infections and infestations	57 (14.6)	39 (12.0)	85 (16.2)	148 (15.8)	258 (16.6)
Pneumonia	10 (2.6)	8 (2.5)	30 (5.7)	40 (4.3)	69 (4.5)
COVID-19	11 (2.8)	8 (2.5)	10 (1.9)	21 (2.2)	23 (1.5)
Cellulitis	3 (0.8)	0 (0.0)	1 (0.2)	4 (0.4)	16 (1.0)
Urinary tract infection	3 (0.8)	3 (0.9)	5 (1.0)	8 (0.9)	16 (1.0)
Upper respiratory tract infection	4 (1.0)	2 (0.6)	4 (0.8)	10 (1.1)	15 (1.0)
COVID-19 pneumonia	8 (2.0)	2 (0.6)	2 (0.4)	10 (1.1)	14 (0.9)
Lower respiratory tract infection	4 (1.0)	1 (0.3)	1 (0.2)	5 (0.5)	10 (0.6)
Hepatitis B reactivation	1 (0.3)	2 (0.6)	5 (1.0)	6 (0.6)	9 (0.6)
Gastrointestinal disorders	40 (10.2)	6 (1.9)	26 (5.0)	66 (7.0)	121 (7.8)
Diarrhoea	16 (4.1)	3 (0.9)	8 (1.5)	24 (2.6)	35 (2.3)
Vomiting	12 (3.1)	0 (0.0)	2 (0.4)	14 (1.5)	27 (1.7)
Nausea	8 (2.0)	1 (0.3)	2 (0.4)	10 (1.1)	19 (1.2)
Abdominal pain	5 (1.3)	1 (0.3)	1 (0.2)	6 (0.6)	6 (0.4)
Blood and lymphatic system disorders	22 (5.6)	18 (5.6)	32 (6.1)	55 (5.9)	107 (6.9)
Neutropenia	13 (3.3)	14 (4.3)	26 (5.0)	40 (4.3)	74 (4.8)
Thrombocytopenia	4 (1.0)	2 (0.6)	3 (0.6)	7 (0.7)	16 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (4.1)	11 (3.4)	26 (5.0)	45 (4.8)	76 (4.9)
Basal cell carcinoma	4 (1.0)	1 (0.3)	3 (0.6)	7 (0.7)	16 (1.0)
Investigations	12 (3.1)	5 (1.5)	17 (3.2)	31 (3.3)	55 (3.5)

System Organ Class Preferred Term	304 Zanubrutinib (N = 391) n (%)	305 Zanubrutinib (N = 324) n (%)	All R/R CLL/SLL Zanubrutinib (N = 525) n (%)	All CLL/SLL Zanubrutinib (N = 938) n (%)	All Zanubrutinib (N = 1550) n (%)
Neutrophil count decreased	4 (1.0)	2 (0.6)	9 (1.7)	13 (1.4)	24 (1.5)
Cardiac disorders	17 (4.3)	1 (0.3)	10 (1.9)	27 (2.9)	48 (3.1)
Atrial fibrillation	8 (2.0)	1 (0.3)	4 (0.8)	12 (1.3)	16 (1.0)
General disorders and administration site conditions	7 (1.8)	6 (1.9)	8 (1.5)	15 (1.6)	44 (2.8)
Pyrexia	2 (0.5)	3 (0.9)	3 (0.6)	5 (0.5)	20 (1.3)
Nervous system disorders	11 (2.8)	5 (1.5)	9 (1.7)	21 (2.2)	34 (2.2)
Headache	4 (1.0)	0 (0.0)	1 (0.2)	5 (0.5)	7 (0.5)
Dizziness	4 (1.0)	0 (0.0)	0 (0.0)	4 (0.4)	6 (0.4)
Renal and urinary disorders	13 (3.3)	3 (0.9)	6 (1.1)	20 (2.1)	32 (2.1)
Haematuria	5 (1.3)	0 (0.0)	1 (0.2)	7 (0.7)	13 (0.8)
Vascular disorders	7 (1.8)	9 (2.8)	10 (1.9)	17 (1.8)	29 (1.9)
Hypertension	0 (0.0)	6 (1.9)	6 (1.1)	6 (0.6)	10 (0.6)
Musculoskeletal and connective tissue disorders	8 (2.0)	3 (0.9)	6 (1.1)	15 (1.6)	27 (1.7)
Arthralgia	4 (1.0)	0 (0.0)	2 (0.4)	6 (0.6)	9 (0.6)
Ear and labyrinth disorders	6 (1.5)	0 (0.0)	1 (0.2)	7 (0.7)	10 (0.6)
Vertigo	5 (1.3)	0 (0.0)	0 (0.0)	5 (0.5)	6 (0.4)

Post marketing experience

Cumulatively, as of 24 July 2021, approximately 7,576,866 capsules of zanubrutinib have been supplied to the market in Canada, China and the USA (equivalent to 1,894,217 daily doses; approximately 62,309.8 person-months; 5192.5 person-years. No regulatory actions concerning safety have been taken since the International Birth Date of 14 November 2019.

Discussion on clinical safety

The safety pool for this application consists of 938 patients with CLL/SLL and a total of 1550 with B-cell malignancies (the All Zanubrutinib pool), which is the safety pool presented in the SmPC (updated from 779 patients for the initial application for WM). The All Zanubrutinib pool all received either the recommended dose of 160 mg BID (93.2%) or 320 mg QD (6.2%) as monotherapy. The median duration of exposure for this safety pool is 23 months. In line with the Scientific advice by the CHMP; "With respect to safety, taking into account the increasing experience with BTK inhibitors and the preclinical data suggesting that BGB-3111 is more selective than ibrutinib (which should result in higher tolerability), the proposed safety database (more than 1000 patients exposed, 500 patients with CLL/SLL) were considered overall adequate for the assessment in the claimed indication"- this is considered an adequate safety pool.

Two randomized Phase 3 studies (BGB-3111-304 and BGB-3111-305) support the safety in the applied indication for CLL:

Study BGB-3111-304:

Patients with treatment naïve CLL/SLL treated with zanubrutinib monotherapy were randomised against bendamustine + rituximab (BR) in patients not deemed fit to receive FCR. Furthermore, there was a non-randomised arm of patients with del17/ tp53 mutation receiving zanubrutinib monotherapy; these patients were also included in the safety population. Zanubrutinib had lower rates of neutropenia and gastrointestinal adverse events (particularly nausea and vomiting) compared with B+R. Higher rates of treatment discontinuation due to adverse events was seen with B+R compared with zanubrutinib (B+R 13.7%; zanubrutinib 8.3%;); the same concerns treatment modification (B+R 70.0%; zanubrutinib 47.9%).

Study BGB-3111-305:

Patients with R/R CLL/SLL treated with zanubrutinib monotherapy were randomised against the first-generation BTK-inhibitor ibrutinib. Diarrhoea and atrial fibrillation/flutter appeared lower among zanubrutinib-treated patients than in patients treated with ibrutinib.

Generally, the safety profiles of the zanubrutinib treatment arms in studies 304 and 305 were consistent with results in the approved prescribing information and no new adverse events were observed.

Integrated Safety Analysis Set

In the Integrated Safety Analysis Set (N=1550), the overall zanubrutinib safety profile also appeared consistent with the known safety profile. No new signals for zanubrutinib were identified when safety findings were evaluated in the larger pooled All Zanubrutinib group.

Across all groups, neutropenia and hypertension were the most commonly (> 5% of patients) reported ≥Grade 3 adverse events. The lower frequencies of pneumonia and neutrophil count decreased could well be explained by the treatment-naïve patients in study 304 and the shorter follow-up in study 305.

In Study 304 SAEs reported in >1% of patients were pneumonia (3.1%), COVID-19 (2.0%), COVID-19 pneumonia (2.0%), and atrial fibrillation (1.8%).

In Study 305 SAEs reported in > 1% of patients were pneumonia (3.1%) and COVID-19 (2.2%)

In the ISS pneumonia was the most common SAE in every group studied reported in 6.8% of the population.

Adverse events were the most common cause of death in both studies and comparable between arms.

The safety database has been doubled in size with this application and thus allows for better characterization of the safety profile of Brukinsa. The ADRs Table under section 4.8 of the SmPC was updated and justification as to why some of the common ADRs should not be included was provided (see SmPC section 4.8).

The safety pool for this application consists of 938 patients with CLL/SLL and a total of 1550 with B-cell malignancies (the All Zanubrutinib pool), which is the safety pool presented in the SmPC (updated from 779 patients for the initial application for WM). The All Zanubrutinib pool all received either the recommended dose of 160 mg BID (93.2%) or 320 mg QD (6.2%) as monotherapy. The median duration of exposure for this safety pool is 23 months.

Two randomized Phase 3 studies (BGB-3111-304 and BGB-3111-305) support the safety in the applied indication for CLL:

Study BGB-3111-304:

Patients with treatment naïve CLL/SLL treated with zanubrutinib monotherapy were randomised against bendamustine + rituximab (BR) in patients not deemed fit to receive FCR. Furthermore, there was a non-randomised arm of patients with del17/ tp53 mutation receiving zanubrutinib monotherapy; these patients were also included in the safety population. Zanubrutinib had lower rates of neutropenia and gastrointestinal adverse events (particularly nausea and vomiting) compared with B+R. Higher rates of treatment discontinuation due to adverse events was seen with B+R compared with zanubrutinib (B+R 13.7%; zanubrutinib 8.3%;); the same concerns treatment modification (B+R 70.0%; zanubrutinib 47.9%).

Study BGB-3111-305:

Patients with R/R CLL/SLL treated with zanubrutinib monotherapy were randomised against the first-generation BTK-inhibitor ibrutinib. Diarrhoea and atrial fibrillation/flutter appeared lower among zanubrutinib-treated patients than in patients treated with ibrutinib.

Generally, the safety profiles of the zanubrutinib treatment arms in studies 304 and 305 were consistent with results in the approved prescribing information and no new adverse events were observed.

Integrated Safety Analysis Set

In the Integrated Safety Analysis Set (N=1550), the overall zanubrutinib safety profile also appeared consistent with the known safety profile. No new signals for zanubrutinib were identified when safety findings were evaluated in the larger pooled All Zanubrutinib group.

Tumour lysis syndrome has been infrequently reported with zanubrutinib therapy, particularly in patients who were treated for CLL. A relevant warning has been included in the SmPC section 4.4 advising to assess relevant risks (e.g., high tumour burden or blood uric acid level) and take appropriate precautions (see SmPC section 4.4).

The safety database has been doubled in size with this application and thus allows for better characterization of the safety profile of Brukinsa. The MAH is asked to update the Table 3 in the SmPC; atrial fibrillation and flutter were included. In addition, hypertension, TLS, Hyperuricemia, pruritus, purpura and Peripheral oedema were also added on the list of ADR in Table 3 of Section 4.8 these ADRs were added in the PL as well (see PI).

Additional expert consultations

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable.

Conclusions on clinical safety

Zanubrutinib treatment was generally well tolerated, and the safety profile was consistent across patient groups. The spectrum of adverse events observed across all patient groups is consistent with the known toxicity profile for the BTK inhibitor class as well as those intrinsic to B-cell malignancy patient populations and were generally manageable, and for the most part, were reversible.

No new safety concerns were observed.

PSUR cycle

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

2.6 Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Table 68 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 (DDI) with CYP3A inhibitors and inducers Teratogenicity
Missing information	Safety in patients with severe hepatic impairment Safety in patients with severe renal impairment/on dialysis Long-term safety (> 2 years)

Pharmacovigilance plan

Table 69 Ongoing and Planned 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				

Table 69 Ongoing and Planned Additional Pharmacovigilance Activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
BGB-3111-113 A Drug-Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-cell Malignancies Lymphoma Ongoing	To assess the DDI between zanubrutinib and moderate (fluconazole, diltiazem) and strong (voriconazole, clarithromycin) CYP3A inhibitors in patients with B-cell malignancies.	DDI	Study completion (database lock): Final report submission:	2nd Quarter 2022 3rd Quarter 2022
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)	Annual Development Safety Update Report: Interim reports submission: Estimated study completion date: Final report submission:	3rd Quarter annually until study completion December 2024 and December 2025 December 2026 Planned June 2027

Risk minimisation measures

Table 70 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	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:

Table 70 Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription	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 Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
Second primary malignancies (other than non-melanoma skin cancer)	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: None
Second primary non-melanoma skin cancer	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities

Table 70 Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: medical prescription	Additional pharmacovigilance activities: None
DDI with CYP3A inhibitors and inducers	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction SmPC Section 5.2 Pharmacokinetic properties Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities Additional pharmacovigilance activities: BGB-3111-113 A Drug-Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B cell Malignancies Lymphoma Final study report 3rd Quarter 2022
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
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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation through routine pharmacovigilance and aggregate analysis in the PSUR Safety signal detection activities

Table 70 Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None Legal status: medical prescription	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 Interim report submission: December 2024 and 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.

2.7 Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to tumour lysis syndrome has been added to the product information. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3 Benefit-Risk Balance

3.1 Therapeutic Context

Disease or condition

BRUKINSA as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL).

Available therapies and unmet medical need

Treatment options for CLL/SLL patients include multiagent chemoimmunotherapy, such as fludarabine/cyclophosphamide/rituximab (FCR), bendamustine/rituximab(B+R), and chlorambucil/ obinutuzumab (Cl+O). Such treatments, however, are less effective in patients with high-risk disease; furthermore, many patients cannot tolerate multiagent chemoimmunotherapy due to age and comorbidities. Recent treatment options include BTK inhibitors such as ibrutinib or acalabrutinib.
PI3K inhibitors such as idelalisib have also been approved however, these treatments have significant toxicities, which limit tolerability and may lead to treatment discontinuation. Front-line treatment recommendations as per European Society for Medical Oncology (ESMO) guidelines are summarized below.

- Patients without TP53 mutation or del(17p)
    - IGVH unmutated
        - Fit: ibrutinib or FCR (or BR in patients above 65 years)
        - Unfit: venetoclax + obinutuzumab or ibrutinib or acalabrutinib or chemoimmunotherapy (if contraindicated to targeted therapy or if they are not available) or chlorambucil + obinutuzumab
    - IGVH mutated
        - Fit: FCR (or BR in patients above 65 years) or ibrutinib
        - Unfit: venetoclax + obinutuzumab or chlorambucil + obinutuzumab or ibrutinib or acalabrutinib
- All patients WITH TP53 mutation or del(17p): ibrutinib or acalabrutinib or venetoclax +/- obinutuzumab or idelalisib + rituximab

Main clinical studies

Study BGB-3111-304 is an ongoing, international, Phase 3, open-label, randomised study designed to evaluate the efficacy of zanubrutinib versus B+R in patients with previously untreated CLL/SLL. Approximately 710 patients will be enrolled in the study.

The study included approximately 450 patients in Cohort 1 and approximately 80 additional patients from Chinese sites in Cohort 1a to support further analysis in the Chinese population. Cohort 1a was opened to enrollment in China when the Cohort 1 sample size was reached. Patients in Cohort 1 and Cohort 1a were randomised 1:1 to receive zanubrutinib (Arm A) or B+R (Arm B).

There are 2 additional cohorts in the study which were not randomised: Cohort 2/Arm C, with approximately 100 planned patients with CLL/SLL with del(17p), and Cohort 3/Arm D, with approximately 80 planned patients with del(17p). Patients in Cohort 2 (Arm C) received zanubrutinib monotherapy in a non-randomized fashion since chemoimmunotherapy is not indicated as treatment

for patients with del(17p) due to poor response reported in this patient population. Patients in Cohort 3 (Arm D) received zanubrutinib in combination with venetoclax and are not included in this application.

Study BGB-3111-305 is an ongoing, international Phase 3, open-label, randomised study of zanubrutinib versus ibrutinib in 652 patients (600 planned) with R/R CLL/SLL. Patients were randomised in a 1:1 manner to one of the following treatment arms:

- Arm A: Zanubrutinib 160 mg orally twice daily
- Arm B: Ibrutinib 420 mg orally once daily

3.2 Favourable effects

Study 304met its primary endpoint by showing a median PFS of 33.7 months in the BR arm, while it is not reached in the zanubrutinib arm; the hazard ratio (95% CI) being 0.42 (0.28, 0.63). The MAH performed a number of sensitivity analyses – all are in line with the primary endpoint/objective of the study.

The ORR by IRC is 90% in Cohort 2. The median duration of follow up was 27.9 months (range: 1.0 to 38.8) and the event-free rate at 24 months 88.9% (95% CI 81.3, 93.6).

Study 305 also met its primary objective showing non-inferiority with 1-sided p-value. The ORR rate was 78.3% vs. 62.5% in zanubrutinib and ibrutinib arms respectively. The response ratio is 1.25 (1.10 – 1.41). Superiority was met when applying a 2-sided p-value.

3.3 Uncertainties and limitations about favourable effects

The IRC-assessed PFS results for study 304 with a DCO date of 07 May 2021 was considered as the final inferential analysis of PFS. The MAH has provided updated INV-PFS with a DCO date of 07 March 2022 (+10 months) remaining consistent with the primary analysis with a HR of 0.33 (95% CI: 0.22 to 0.48, descriptive P<0.0001). The MAH will provide the final OS analysis from Study 304 expected in Q2 2023.

Despite inclusion /exclusion criteria of study 304 in the frontline setting clearly indicating that patients should have been unsuitable for treatment chemoimmunotherapy (FCR), thus covering also 1st line patients, study 305 showed non-inferiority against ibrutinib in the R/R setting. Having in mind that ibrutinib is also approved in 1L, and recommended in both fit and unfit patients, it seems justified to extrapolate the use of zanubrutinib to 1L fit patients. Thus, despite the limitations of study 304 and the comparison against BR in an elderly and unfit population, the totality of evidence supports the use of zanubrutinib in both fit and unfit patients.

The MAH will provide the final CSR from Study 305.

3.4 Unfavourable effects

Study BGB-3111-304:

Patients with treatment naïve CLL/SLL treated with zanubrutinib monotherapy were randomised against bendamustine + rituximab (BR) in patients not deemed fit to receive FCR. Furthermore, there was a non-randomised arm of patients with del17/ tp53 mutation receiving zanubrutinib monotherapy; these patients were also included in the safety population. Zanubrutinib had lower rates of neutropenia and gastrointestinal adverse events (particularly nausea and vomiting) compared with B+R. Higher rates of treatment discontinuation due to adverse events was seen with B+R compared with zanubrutinib (B+R 13.7%; zanubrutinib 8.3%;) or treatment modification (B+R 70.0%; zanubrutinib 47.9%;).

Study BGB-3111-305:

Patients with R/R CLL/SLL treated with zanubrutinib monotherapy were randomised against the first-generation BTK-inhibitor ibrutinib. Diarrhoea and atrial fibrillation/flutter appeared lower among zanubrutinib-treated patients than in patients treated with ibrutinib.

Generally, the safety profiles of the zanubrutinib treatment arms in studies 304 and 305 were consistent with results in the approved prescribing information and no new adverse events were observed.

Integrated Safety Analysis Set

In the Integrated Safety Analysis Set (N=1550), the overall zanubrutinib safety profile also appeared consistent with the known safety profile. No new signals for zanubrutinib were identified when safety findings were evaluated in the larger pooled All Zanubrutinib group.

The profile of adverse events of special interest was similar in the All Zanubrutinib, All R/R CLL/SLL, and All CLL/SLL groups. In the All Zanubrutinib group, events within the categories of infections (65.7%), hemorrhage (48.1%), and neutropenia (27.5%) were the most frequently reported. Across all groups, neutropenia and hypertension were the most commonly (> 5% of patients) reported ≥Grade 3 adverse events.

3.5 Uncertainties and limitations about unfavourable effects

Long term safety data are still needed to be evaluated, more information will be expected from ongoing studies such as BGB-3111-LTE1; an Open-label, Multicenter, Long-term Extension Study of Zanubrutinib (BGB-3111) Regimens in Patients with B-cell Malignancies aiming to evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies who participated in a parent study for zanubrutinib (see RMP). Further data will also be provided from the final study report from study 305.

3.6 Effects Table

Table 71 Effects Table for Brukinsa as monotherapy for the treatment of adult patients with chronic lymphocytic leukemia (CLL). Data cut-off: 07 May 2021 (304) and 31 December 2020 (305).

Effect	Short description	Unit	Treatment Brukinsa	Control	Uncertainties / Strength of evidence	References
Favourable Effects 304 (TN CLL)			**Brukinsa (n = 241)**	**B+R (n=238)**		

Effect	Short description	Unit	Treatment Brukinsa	Control	Uncertainties / Strength of evidence	References
Primary endpoint (Cohort 1)	PFS by IRC: Events PD Death Median [b] (95% CI)	n (%)	 36 (14.9) 27 (11.2) 9 (3.7) NE (NE, NE)	 71 (29.8) 59 (24.8) 12 (5.0) 33.7 (28.1, NE)	 Hazard Ratio [a] (95% CI): 0.42 (0.28, 0.63)	
Secondary endpoints	Overall Response Rate (ORR)	% (95% CI)	94.6% (91.0, 97.1)	85.3% (80.1, 89.5)		
Median Follow-up		Months	22.6	22.8		
Cohort 2* -del(17p) patients	ORR by IRC (95% CI)	n (%)	**(n = 110)** 99 (90.0) (82.8, 94.9)	Not applicable		
Median Follow-up		Months	27.7	-		
Favourable Effects 305 (R/R CLL)			**Brukinsa (n=207)**	**Ibrutinib (n=208)**		
Primary endpoint	ORR by INV (95% CI) [c]	n (%)	162 (78.3) (72.0, 83.7)	130 (62.5) (55.5, 69.1)	Investigator assessed Response ratio [d] (95% CI); 1.25 (1.10, 1.41)	
Secondary endpoints	ORR by IRC (95% CI)	n (%)	158 (76.3) (69.9, 81.9)	134 (64.4) (57.5, 70.9)	Response ratio [d] (95% CI); 1.17 (1.04, 1.33)	
	DOR by INV Event free rate [e] at 12 months (95% CI)	 n (%)	N=162 89.8 (78.1, 95.4)	N=130 77.9 (64.7, 86.7)		
Median Follow-up		Months	13.60	13.47		
Unfavourable Effects: ISS; 1550 patients with B-cell malignancies (938 with CLL/SLL)						
Infections by SOC Pneumonia	All ≥Grade 3 ≥Grade 3	n (%)	1019 (65.7) 338 (21.8) 109 (7.0)	-		
Neutropenia (AESI)	All ≥Grade 3	n (%)	427 (27.5) 286 (18.5)	-		
Haemorrhage (AESI)	All Major	n (%)	746 (48.1) 70 (4.5)	-		
Non-melanoma skin cancer	All	n (%)	115 (7.4)	-		
Diarrhoea, PT	All ≥Grade 3	n (%)	292 (18.8) 24 (1.5)	-		
Discontinuation due to AE		n (%)	144 (9.3)	-		

Abbreviations: AESI; Adverse event of special interest, B+R; Bendamustine + rituximab, CI; Confidence interval, INV; Investigator, IRC; Independent review committee, ORR; Overall response rate, PFS; Progression-free survival, PT; preferred term, R/R; relapsed or refractory CLL, TN; Treatment-naïve,

Notes: *Cohort 2: Patients with centrally confirmed del(17p)

[a] Hazard ratio and 95% CI were from stratified Cox regression model with B+R arm as the reference group.
[b] Medians and other quartiles were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.
[c] Clopper-Pearson confidence interval.
[d] Response ratio is the estimated ratio of the overall response rate of the zanubrutinib arm divided by that of the ibrutinib arm.
[e] (Still in response). Event free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

3.7 Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Second-line CLL/SLL treatment is guided by the duration of the first remission for relapsed disease. Refractory disease is defined as having either no response to treatment or relapse within 6 months after the last treatment. ESMO guidelines recommend a change of therapeutic regimen in case of symptomatic relapse within 3 years, or refractory disease, in which case treatment with venetoclax (+/- rituximab), ibrutinib, acalabrutinib, or other BTKi monotherapy should be considered. Patients with remissions of more than 3 years may be re-exposed to the same time-limited regimen; however, repetition of the FCR regimen is not recommended. Other treatment options include acalabrutinib, ibrutinib, venetoclax + rituximab, or idelalisib + rituximab. For patients with TP53 mutation or del(17p), allogenic stem-cell transplantation should be considered for fit patients. The US NCCN guidelines' list of preferred regimens for RR CLL/SLL patients are the same as for frontline treatment except venetoclax monotherapy is recommended only for patients with TP53 mutation or del(17p).
Since study 305 showed non-inferiority against ibrutinib in the R/R setting and having in mind that ibrutinib is also approved in 1L, and recommended in both fit and unfit patients, it seems justified to extrapolate the use of zanubrutinib to 1L fit patients. Thus, despite the limitations of study 304 and the comparison against BR in an elderly and unfit population, the totality of evidence supports the use of zanubrutinib in both fit and unfit patients. There are no scientific arguments to require a non-inferiority study in 1L against ibrutinib.

The integrated safety pool has doubled since the initial approval for Waldenström's MB; from 779 to 1550 patients. Zanubrutinib treatment was generally well tolerated, and the safety profile was consistent across patient groups. The spectrum of adverse events observed across all patient groups is consistent with the known toxicity profile for the BTK inhibitor class as well as those intrinsic to B-cell malignancy patient populations and were generally manageable, and for the most part, were reversible. No new safety concerns were observed.

Balance of benefits and risks

Collectively results from Studies BGB-3111-304 and BGB-3111-305, including favourable PFS and ORR,

durable responses, and improvements in important safety and tolerability assessments such as events leading to discontinuation or interruption of treatment, provide substantial evidence of a positive benefit-risk assessment for zanubrutinib in the treatment of patients with CLL/SLL. In study 305 zanubrutinib demonstrated efficacy across risk groups.

Additional considerations on the benefit-risk balance

In addition, as part of the application the MAH requested a 1-year extension of the market protection. However, since 1-year extension has been already granted by the CHMP as part of the procedure II-02 in marginal zone lymphoma (MZL), an assessment as part of this procedure would be considered redundant and was not performed.

3.8 Conclusions

The overall B/R of Brukinsa is positive.

4 Recommendations

Outcome

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

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

Extension of indication to include treatment of adult patients with chronic lymphocytic leukaemia (CLL) for Brukinsa; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.3 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Brukinsa is not similar to Gazyvaro within the meaning

of Article 3 of Commission Regulation (EC) No. 847/200.

5 EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Brukinsa- EMEA/H/C/004978/II/0003