16 September 2021
EMA/627600/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Brukinsa

International non-proprietary name: zanubrutinib

Procedure No. EMEA/H/C/004978/0000

Note

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

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Table of contents

List of abbreviations

AS	active substance
BCS	biopharmaceutical classification system
CEP	Certificate of Suitability of the EP
CMA	Critical material attribute
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DoE	design of experiment
DSC	Differential scanning Calorimetry
DVS	Dynamic vapor sorption
EP	European Pharmacopoeia
FP	finished product
FT-IR	Fourrier transmission infra red (spectroscopy)
HDPE	High-density polyethylene
HPLC	High performance liquid chromatography
ICP-MS	inductively coupled plasma-mass-spectrometry
IPC	In-process control test
GC	Gas chromatography
ICH	International conference on harmonisation
ICP-MS	inductively coupled plasma-mass-spectrometry
IR	Infra-red spectroscopy
KF	Karl Fischer titration
LDPE	Low-density polyethylene
LOD	Loss on Drying
LoD	Limit of detection
LoQ	Limit of Quantitation
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MO	major objection
MS	Mass spectroscopy
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PAR	Proven acceptable range
PDA	Photo diode array
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
PLM	polarized light microscopy
PP	Polypropylene
QbD	quality by design
QC	Quality Control
QTPP	Quality Target Product Profile
RH	Relative Humidity
RRT	Relative retention time
Rt	Retention time
RT	Room temperature
SEM	scanning electron microscopy

SLS Sodium Lauryl Sulphate
SmPC Summary of Product Characteristics
TGA Thermo-Gravimetric Analysis
TSE/BSE Transmissible spongiform encephalopathy/ Bovine Spongiform Encephalopathy
TTC Threshold of toxicological concern
USP United States Pharmacopeia
UV Ultra violet spectrometry
XRPD X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BeiGene Ireland Ltd submitted on 28 May 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Brukinsa, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2018.

Brukinsa, was designated as an orphan medicinal product EU/3/19/2167 on 29 May 2019 in the following condition: lymphoplasmatic lymphoma.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 4 October 2021 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website ema.europa.eu/en/medicines/human/EPAR/brukinsa .

The applicant applied for the following indication "treatment of adult patients with Waldenström's macroglobulinaemia (WM), who have received at least 1 prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0398/2019 on the granting of a (product-specific) waiver.

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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3

of the Regulation (EC) No. 141/2000; the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

New active Substance status

The applicant requested the active substance zanubrutinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
13/10/2016	EMEA/H/SA/3376/2/2016/II	Dr Jan Sjöberg, Dr Odoardo Olimpieri
25/07/2019	EMEA/H/SA/3376/5/2019/PA/I	Prof. Markku Pasanen, Dr Paolo Foggi

The Protocol assistance pertained to the following quality and clinical aspects:

- The proposed designated starting material (BG-10) in the drug substance manufacturing process for zanubrutinib; the dissolution method used to test zanubrutinib drug product for release and stability testing;
- The Clinical Pharmacology package and QT requirements to support an MAA;
- The design of the phase 3 pivotal study BGB-3111-302 to support a MAA, including the choice of patient population; the primary endpoint of major response rate, supported by secondary endpoints including the proportion of patients achieving either very good partial response (VGPR) or complete response; the definition of VGPR.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Johanna Lähteenvuo

The application was received by the EMA on	28 May 2020
The procedure started on	18 June 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	8 September 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	7 September 2020

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	15 September 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 October 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 March 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 April 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 April 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 June 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Brukinsa on	16 September 2021
The CHMP adopted a report on similarity of Brukinsa with Imbruvica on (Appendix 1)	16 September 2021
The CHMP adopted a report on derogations applicable to similar orphan products for Brukinsa on (Appendix 2)	16 September 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication is for the treatment of adult patients with Waldenström's macroglobulinaemia (WM), who have received at least 1 prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

2.1.2. Epidemiology and risk factors, screening tools/prevention

The median age in WM is 70-years, and the age-adjusted incidence rate for males/females is 0.92 and 0.3 per 100.000 respectively, with 60% being males. A higher male predominance has been reported in Asia (Jeong et al, Blood 2018). WM is extremely rare in children, and the incidence increases with age (Brandefors et al, Br J Haematol 2018). WM represents 1-2% of all hematologic malignancies, and in the USA, there are 1000 to 1500 new cases / year (1/260.000). A similar epidemiology and a prevalence of 1/102.220, is noted in Europe as in all 7.200 persons are living with WM (Kaeb et al, StatPearls 2020; Orphanet 2020). WM is reported with a higher incidence (RR 1.5) in Caucasians than among African-American and Asian-Pacific subjects (Teras et al, CA Can J Clin 2016).

The epidemiology indicates that sex, race and age *per se* are risk factors. Clustering of B-cell neoplasia and familial predisposition in the role of genomics have been described (Treon et al, Ann Oncol 2006; Kapoor et al, Curr Treat Options Oncol 2016). No specific exogenously risk factors have been identified in *progressive* lymphoplasmacytic proliferations, and hepatitis have not consistently been related to WM (Sanjose et al, Clin Gastroenterol Hepatol 2014; WHO_2016). There is no rational in screening for IgM monoclonality, but observation of an IgM isotype in blood-samples in 10-20% of the 3% of persons older than 50-years, who have MGUS is a reasonable cause for a careful diagnostic work-up due to the risk of the underlying conditions, associated with IgM gammopathy (Grunenberg & Buske, Dtsch Ârztebl 2017)

2.1.3. Biologic features, Aetiology and pathogenesis

WM originates in the bone marrow, which is infiltrated by a heterogeneous population of post-germinal center, hyper-mutated, monoclonal, low-proliferating cells, from small B-lymphocytes (CD19+,20+,22+,25+,79a+) to differentiated plasma cells (CD138+), producing a monoclonal IgM (Braggio et al, Haematologica 2012; Wang & Lin, Pathology 2020).

Several genetic abnormalities are associated with WM, including structural aberrant cytogenetic, gene mutations and possibly epigenetic mechanisms, no one is disease specific. Genes involved like the MYD88 (Myeloid differentiation primary response 88) gene, mutated in position L265P, and CXCR4 (C-X-C chemokine receptor type 4), which shows a more variable mutational pattern and may involve WHIM (-like) mutations (Xu et al, Br J Hameatol 2016) in WM, are also associated with solid and other haematological malignancies and other disorders. The WHIM syndrome is a rare combined primary immunodeficiency disorder caused by autosomal dominant gain-of-function mutations in the chemokine receptor, causing warts, hypo-gammaglobulinaemia, recurrent infections, and myelokathexi

(bone marrow retention) (Heusinkveld et al, Exp Op Orphan Drugs 2017), but in WM it is an acquired mutation.

Genomic abnormalities at diagnosis include del(6q) (50%), hyper-mutation in IGHV, t(9;14) (50%), CXCR4 (WHIM-like) mutations (30%) and MYD88L265P mutations (90-95%). Deletions involving chromosome 6q are common in MYD88MUT patients and include genes that modulate NFķβ, BCL2, Bruton Tyrosine Kinase (BTK), and apoptosis. CXCR4 mutational status in combinations with MYD88 also influences the sensitivity of BTK inhibitor (BTKi) in the signalling pathways in WM. MYD88 mutations are detectable in 50% to 80% of IgM MGUS cases, suggesting an early oncogenic role for WM pathogenesis. Unrevealing the BTK pathophysiology has a rational impact on treatment strategies in WM with ibrutinib and zanubrutinib (Hunter et al, J Clin Oncol 2017;Sacco et al, Oncotarget 2017; Treon et al, J Clin Oncol 2020). Zanubrutinib is developed in B-cell malignancies due to the ubiquitous importance of BTK in the pathophysiology of these disorders (Hendriks et al, Nat Rev Cancer 2014).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

WM presents as indolent cases (for many years), to IgM-induced hyperviscosity (normally >40 g/L in blood, 30%) causing bleeding and visual disturbances, night-sweats, weight loss, and bone marrow-infiltration induced anaemia and neutropenia. Tissue deposition of the M-component and autoimmunity nay present as peripheral neuropathy (25-50%), thermo-proteins, amyloid (heart) involvement and haemolysis (Vijay & Gertz Blood 2007). The diagnosis of WM requires confirmation of bone marrow infiltration by monoclonal LPL cells and serum IgM of any amount, by immunofixation, and a complete clinical status (Kastritis Et al, ESMO guideline Ann Oncol 2018).

Patients with wild-type MYD88 show lower bone marrow disease burden, lowest in combination with $CXCR4^{wild\text{-}type}$, and serum immunoglobulin M levels, and an increased risk of death due to transformation to aggressive lymphoma. Patients with CXCR4 mutations have higher bone marrow disease burden, and those with nonsense CXCR4 mutations have higher serum immunoglobulin M levels and incidence of symptomatic hyperviscosity (Treon et al, Blood 2014; Hunter et al, J Clin Oncol 2017).

Patients with WM is staged by a risk score for overall survival, based on age (>65 years), B-haemoglobin ≤11.5 g/dL, platelets ≤100 x109/L, β2-microglobulin >3 mg/L, and serum-monoclonal protein concentration > 70 g/L. The five covariates separate patients in low-risk (27%), intermediate-risk (38%), and high-risk patients (35%), age being the dominant factor. The five-year survival rates were 87%, 68%, and 36%, respectively (Morel et al, Blood 2009). Patients under the age of 70-years, in previous retrospective studies have a median survival in excess of 10 years; those older than 70-years less than 7-years and age-dependent (Castillo et al, Br J Haematol 2015). Despite the survival has improved, the prognosis, relapsing disease and debilitating symptoms provide an unmet need.

2.1.5. Management

The applied indication reflects that patients with Waldenström's macrglobulinaemia (WM) have a relapsing course on medical treatment. Therapeutic strategies in WM is based on individual patient (fit, unfit / co-morbidity) and disease characteristics (indolent or endurable). WM is very chemo-sensitive, with overall response rate of 90% in first line. Autologous and allogeneic stem cell transplantation has a role in (some) younger patients, often with early relapses.

Treatment is indicated only to reduce symptoms and subsequent organ damage, due to rheological and autoimmune manifestations, bone marrow-insufficiency and bulky disease (Dimopoulus et al, Blood 2014). Algorithms in first line in most patients include 4-6 cycles of chemo-immuno-therapy combinations with rituximab, alkylators, glucocorticoid, and proteasome inhibitor. Durable responses provided by drugs often used in B-cell malignancies, and maintenance with anti-CD20 antibody (rituximab) is recommended. All patients, treatment naïve (TN) or relapsed / refractory (RR) are candidates to be included in clinical trials, to further improve efficacy and / or reduce adverse events. These SOC may be repeated in later lines, depending on time to relapse and an individual re-assessment.

The approval of the BTKi Imbruvica (ibrutinib) in WM in 2015 in EU, represents a novel, effective and oral treatment option for both TN and RR patients, continued daily until progression or intolerance, and without the potential risk of secondary malignancy, by SOC combinations (Leblond et al, Blood 2016; ESMO guideline, Ann Oncol 2018). Responses are evaluated by internationally accepted criteria, reflecting reductions in objective clinical and para-clinical parameters (Owen et al, Br J Haematol 2013), added the major response (MR, partial response or better) in the ibrutinib development. By these criteria, ibrutinib monotherapy in RR patients gave a very good partial response (VGPR) and MR of 15.9% and 77.7%, respectively. Complete responses (CR) are unusual, which supports CR + VGPR as a primary endpoint. With a median follow-up of 47.1 months, median PFS for all patients was not reached. Median PFS has also not been reached for $MYD88^{MUT}CXCR4^{wild\text{-}type}$ patients. For $MYD88^{L265P}CXCR4^{MUT}$ patients, the median PFS was 45 and 21 months for $MYD88^{wild\text{-}type}CXCR4^{wild\text{-}type}$ patients. Adverse events of grade 2 or higher included neutropenia (22%) and thrombocytopenia (14%). Comparable results have been presented in treatment naïve (TN) WM (Treon et al, NEJM 2015; Treon et al, J Clin Oncol 2018; Papanota et al, J Blood Med 2019). The comparable results in TN and RR WM likely reflects that BTK dependent pathways are not the only important drivers in WM.

About the product

Zanubrutinib, (Brukinsa), is a FIH, oral, second generation BTK inhibitor (BTKi) an inhibitor of Bruton's tyrosine kinase (BTK). Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion (see SmPC section 5.1).

It is intended as monotherapy for the indication "treatment of adult patients with WM, who have received at least 1 prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy" (see SmPC section 4.1).

Zanubrutinib is formulated as oral capsules of 80mg. The recommended total daily dose of zanubrutinib is 320 mg. The daily dose may be taken either once daily (four 80 mg capsules) or divided into two doses of 160 mg twice daily (two 80 mg capsules) (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as hard capsules containing 80 mg of zanubrutinib as active substance (AS).

Other ingredients are:

- in capsule content: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate (E487), colloidal silicon dioxide, magnesium stearate;

- in capsule shell: gelatin, titanium dioxide (E171);

- in printing ink: shellac glaze (E904), iron oxide black (E172), polypropylene glycol (E1520).

The product is available in HDPE bottles with PP child-resistant screw cap as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of zanubrutinib is (7S)-2-(4-phenoxyphenyl)-7-[1-(prop-2-enoyl)piperidin-4-yl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide. It corresponds to the molecular formula $C_{27}H_{29}N_5O_3$. Its relative molecular mass is 471.55 and it has the chemical structure shown below.

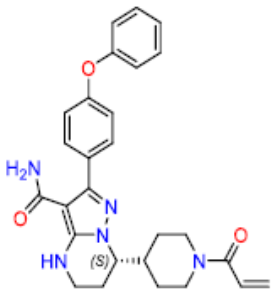


Figure 1.Chemical structure of zanubrutinib.

The structure of the active substance (AS) was adequately elucidated by a combination of mass spectrometry (LC-MS), elemental analysis, ultraviolet (UV) spectroscopy, FTIR, ^{1}H-NMR, ^{13}C-NMR, and X-Ray Powder Diffraction (XRPD). Physicochemical properties were investigated by optical rotation, single crystal X-ray, polymorph screening (salt screening), Dynamic vapor sorption (DVS), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), particle size distribution, microscopic image by polarized light microscopy (PLM) and scanning electron microscopy (SEM). Data and spectra with interpretations have been presented.

Zanubrutinib appears as white to off-white, slightly hygroscopic, crystalline powder. It is freely soluble in methanol, soluble in ethanol and acetone, slightly soluble in pH 1.2 hydrochloric acid buffer, very slightly soluble or practically insoluble in aqueous buffers (pH range 2.0 - 8.0). The AS pKa is 3.33 and its partition coefficient LogP was found to be 4.21.

Zanubrutinib is an optically active compound having the *(S)*-configuration at the single stereocentre. The configuration of this chiral centre cannot interconvert to form the *(R)*-enantiomer.

The AS exhibits polymorphism. Only one crystal form (Form A) was observed in polymorph screening and routine process. XRPD showed zanubrutinib to be crystalline with distinctive diffraction peaks.

Manufacture, characterisation and process controls

The active substance is synthesised from two regulatory starting materials with appropriate specifications. The synthetic process consists of six process stages including micronisation. Reaction schemes for the starting materials, including information on the reagents/solvents used, as well as adequate details on manufacturers have been provided. The information provided on the two starting materials has been found satisfactory and they are considered acceptable.

Critical steps/process parameters have been identified and justified. The in-process controls are described in detail. Normal operating range (NOR) and proven acceptable range (PAR) for each indexed parameter are presented. Assignment and justification of critical process parameters (CPPs) was accomplished using a combination of quality risk assessment (QRA), accumulated process knowledge and experimental process characterization. Although some quality by design (QbD) elements have been utilized to develop the zanubrutinib manufacturing process, no design space is being claimed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Discussion on impurities is in general adequate (specified and unspecified organic impurities, genotoxic impurities, and elemental impurities). The Applicant has provided a detailed overview of organic impurities with indication of origin and fate for each impurity. Control and carry-over of potential impurities from the starting materials to the final active substance have been discussed. Fate of impurities as well as intermediates through processing seems well understood and supported by purge studies. Solvents applied in synthesis of starting materials are controlled in the relevant starting material specification with limits according to EU/ICH Q3C. The catalyst is used in the synthesis of one of the intermediates and was evaluated both in the concerned intermediate and in the AS; the catalyst is controlled in the active substance specification.

The Applicant has satisfactorily accounted for changes in the process during development. Bridging between early and later synthetic processes has been satisfactorily ensured and the synthesis proposed is supported by data in the dossier. Considering all the presented information the proposed synthesis is acceptable.

The packaging material for the AS has been described and compliance of the primary packaging material with requirements of Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with foods was presented.

Specification

The AS specification, includes appropriate tests and limits for appearance (visual), identification (HPLC, IR), assay (HPLC), related substances (HPLC), chiral purity (chiral HPLC), residual solvents (GC), water content (KF), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.), elemental impurities (ICP-MS), polymorphic form (XRPD) and particle size distribution (Ph. Eur.).
The proposed specifications are considered acceptable. The limits for impurities are justified based on batch data, stability data and toxicology qualification results. All impurities were negative within *in vitro* mutagenicity evaluation. The limit of chiral purity is justified based on toxicology qualification, batch release data and stability data. The limits are based on current permitted daily exposure (PDE). The catalyst used in the synthesis is controlled in the active substance specification with an acceptable limit. Residual solvent limits are according to the ICH guidelines. Benzene was found below the detection limit of 0.25 ppm, which is less than 30% of the acceptable limit for benzene (2 ppm) in 7 tested commercial-size batches of AS (unmilled). Therefore it is acceptable that benzene is not controlled in the AS but instead tested in the only solvent where it may be present. Due to the low risk

of microbial contamination and the low water activity of zanubrutinib, microbial limits testing is not conducted; this is considered acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Zanubrutinib has been manufactured at three different manufacturing sites during development. The batch history consisting of 26 representative batches of zanubrutinib manufactured by all three manufacturers over a period of 5 years is presented. Nine of these batches are manufactured by the proposed manufacturing site and 7 were of commercial scale.

All batches were produced using the proposed route of synthesis and can be considered representative for the proposed commercial manufacturing process. Data for the different batches show that there are no significant changes on impurity levels, assay or chiral purity, which means that the process optimization and up scaling had no impact on impurity levels. Level of impurities is stable and low in the commercial batches. The results are within the specifications and consistent from batch to batch.

Stability

Stability data has been provided for three commercial scale batches manufactured at the proposed manufacturing site. These stability batches were packaged in the proposed container closure system. Stability data were provided for up to 24 months stored under long term conditions (30°C / 65% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines.

The parameters studied were appearance, assay, related substances, chiral purity, water content, loss on drying, polymorphic form and particle size distribution. No changes in product quality or trends have been observed for any of the evaluated parameters at any of the storage conditions.

Supportive stability data were also presented on 15 batches of AS for up to 48 months at 30°C / 65% RH and 6 months at 40°C / 75% RH. These batches were used in various stages of development and manufactured at different scales (~ 10 kg to ~ 100 kg), by different manufacturers. The same manufacturing process has been used with minor differences as detailed and justified in manufacturing process development. The samples were tested using methods and acceptance criteria that were in place at the time of testing. The same acceptance criteria used on release were applied on stability. No changes in product quality or trends were observed for any of the evaluated parameters at any of the storage conditions.

A photostability study was conducted as per ICH Q1B on two pilot batches; no changes were observed in any of the measured attributes. Zanubrutinib is stable under photolytic degradation conditions and it does not need to be protected from light.

A forced degradation study was performed on a pilot batch. Samples were subjected to a variety of stress conditions including acid, base, oxidation, simulated sunlight, thermal and humidity. The results indicate that zanubrutinib is sensitive to acidic, alkaline and oxidative stress conditions, while it is stable with respect to heat, moisture and light. It was also confirmed that the method for related substance is stability-indicating.

Based on the available stability data, the proposed retest period of 24 months without any specific storage restrictions when the active substance is stored in the proposed container closure system, is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as white to off-white opaque hard capsules, printed with "ZANU 80" in black ink and containing white to off-white powder containing 80 mg of zanubrutinib as active substance. The capsules are size 0 and have a length of 22 mm. The qualitative composition of Brukinsa 80 mg capsules and of the printing ink are shown in section 2.2.1 of this report and in SmPC section 6.1.

Formulation development
The finished product is a conventional immediate release hard gelatin capsule for oral administration. The FP formulation for the 80 mg capsule was introduced in Phase 1 clinical trials and has remained unchanged throughout development. The choice of pharmaceutical form/ strength adequately addresses the proposed dosing regime, i.e. 320 mg zanubrutinib daily, taken either as four 80 mg capsules once daily or two 80 mg capsules twice daily. According to the applicant the feasibility of an optimised dosage form with higher strength and/or smaller size is currently under evaluation; this is acknowledged.

The Quality Target Product Profile (QTPP) of zanubrutinib capsules,80 mg, was developed in accordance with ICH Q8 guidance and is provided below.

Table 1. Quality Target Product Profile of Brukinsa capsules

QTPP Elements		**Target**	**Justification**
Dosage form		Oral Solid Hard Capsule	Melting point of drug substance is < 150°C, which is not preferred in tableting process.
Dose		Immediate-release capsule	Suitable for the intended therapeutic use of the product.
Route of administration		Oral	Suitable for the intended therapeutic use of the product.
Dosage strength		80 mg	To provide dose of 160 mg, p.o., b.i.d, (320 mg/day) for the intended therapeutic use of the product.
Pharmacokinetics		Immediate release with sufficient drug exposure	Ensure efficacy of the product.
Stability		Minimum 24-month shelf-life at proposed storage condition in the foreseen packaging	Ensure drug product quality standards are met.
Drug Product Quality Attributes	Physical attributes	Meet 21 CFR 206 and ICH Q6A requirements and appearance requirements	A visual identification of the product.
	Assay	95.0%-105.0%	Ensure efficacy of the product.
	Content Uniformity	Meet compendial requirements	Ensure efficacy and safety of the product.
	Chiral Purity	Meet safety and efficacy requirements	Ensure product efficacy and safety.
	Impurities (related substances,	Meet safety and compendial requirements	Ensure product safety over the shelf-life.

QTPP Elements		Target	Justification
	residual solvents, heavy metal)		
	Microbial limits	Meet compendial requirements	Meet GMP requirements and ensure patient safety.
	Dissolution	Immediate release with the dissolution plateau reached in 45-60 minutes	Ensure product efficacy and safety.
Container closure system		Qualified as suitable	Maintain product integrity during shipping and over the shelf-life.

Note: GMP = Good Manufacturing Practice; p.o. = per os (by mouth); b.i.d. = bis in die (twice a day); QTPP = quality target product profile

Based on the QTPP, assay, related substances, content uniformity and dissolution were identified as Critical Quality Attributes (CQAs) and their justification is provided.

During development the following characteristics of the zanubrutinib active substance was considered: Zanubrutinib is a BCS Class 2 drug with poor aqueous solubility (high lipophilicity) and high permeability, it exhibits irregularly shaped, cohesive, crystalline particles with poor flow characteristics and a tendency to agglomerate, and it is anhydrous and relatively stable when exposed to humidity.

The excipients were selected and evaluated in different grades and/or ranges. Medium to high risk formulation factors were investigated and mitigation strategies evaluated. Potential formulation risks were then reassessed. With the selected excipient grade, concentration, AS control, and process controls, all the risk levels specified have subsequently been deemed low.

The chosen excipients are commonly used in immediate release hard capsules and are described in Ph. Eur. except the gelatin capsule shell, which consist of pharmacopeial ingredients. The selection of each excipient in the proposed level have been adequately discussed and justified.

The dissolution method selected for QC testing is Apparatus I, Basket at 100 rpm with 900 ml of medium consisting of 0.1N HCl with 0.3% SLS. The development of the dissolution method proposed for QC testing is acceptable. The discriminatory properties of the method regarding particle size of the AS are demonstrated. Since it has been demonstrated that particle size is the only critical material attribute for zanubrutinib capsules and that the formulation and manufacturing process have wide ranges of operation the discriminative properties of the proposed dissolution method is considered sufficient.

Manufacturing process development
The proposed manufacturing process is a standard direct blending and encapsulation process. The AS physicochemical properties were taken into account in the selection of the finished product manufacturing process. A process risk assessment, in accordance with ICH Q9, was conducted to identify which variables and unit operations/steps could impact product quality. The process variables identified as medium or high risk from the initial risk assessment were evaluated in further studies. Appropriate control strategies were put in place to mitigate risks and ensure the commercial manufacturing process is capable of producing zanubrutinib capsules, 80 mg, per pre-defined specification. The development of the manufacturing process and establishment of the operation conditions have been adequately discussed considering the influence on CQAs. The operational ranges for the critical process parameters have been evaluated using principles of Quality by Design. However, no design spaces were claimed for the manufacturing process of the finished product. The same process of direct blending and encapsulation remained unchanged from clinical to the proposed commercial scale.

Zanubrutinib 80 mg capsules used in clinical trials were manufactured by 5 different sites. A comparability assessment of finished product from these 5 manufacturing sites was conducted. Release data, blend uniformity and dissolution profiles were compared. In addition, stability data from the different sites are presented. The proposed commercial formulation and manufacturing process has remained unchanged from early development and has been used for all clinical trials and PK-studies. All results evaluated showed that the finished products manufactured by different sites are comparable.

Container closure system
The finished product will be packed in standard HDPE bottles with polypropylene (PP) child-resistant screw cap. The proposed packaging is found suitable for packaging of the finished product as it has been demonstrated to provided adequate protection, safety, integrity and compatibility. The suitability of the packaging has been confirmed through the stability studies.

The proposed container closure system is common for this type of dosage form. Brukinsa capsules are packaged in 150 mL (60 ct) or in 200 mL (120 ct) white high-density polyethylene (HDPE) wide-mouth round bottle with a 38/400 polypropylene white child resistant screw cap with a heat-induction sealed liner. The inner cap and outer cap are comprised of the same resins and colorants, are commonly utilized in the pharmaceutical industry, and compliant with relevant indirect food additive regulations. The liner is comprised of various layers, including a PET film and heat seal; the liner is complaint with indirect food additive regulations. Both bottles are compliant the relevant Commission Regulation for material in contact with food The primary packaging materials also comply with Ph. Eur. requirements.

Manufacture of the product and process controls

The manufacturing process is a standard direct blending and encapsulation process comprising eight main steps. The commercial batch size range has been clearly stated.

The critical steps for the manufacture of the finished product have been evaluated in DoE studies and are clearly defined. Appropriate ranges for the critical process parameters have been established and sufficient in-process controls are applied during the process. The overall control strategy including process parameters and in-process controls are adequately set to control the process leading to consistent quality. Hold time studies have been performed for the final blend and finished bulk capsules and respective hold time have been established.

No design space for the manufacture of the finished product has been claimed.

The manufacturing process has been validated using three batches in the proposed commercial scale. The validation confirmed the consistency of the manufacturing process.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (HPLC, chiral-HPLC), assay (HPLC), impurities (HPLC), dissolution (Ph. Eur., HPLC), content uniformity (Ph. Eur., HPLC), water content (KF), chiral purity (chiral-HPLC) and microbial limits (Ph. Eur.).

The specification has been justified according to relevant EU/ICH Q6A. The parameters included in the finished product specification are acceptable and adequate justification for the parameters omitted from the specification is provided.

No degradation products are found in the finished product. Two synthesis impurities can be carried forward from the active substance and are specified to the same limits in the finished product as in the

active substance. An additional synthesis impurity was controlled in the finished product during the development, but is included as unspecified impurity for the control of the commercial product. The limit for impurities are justified and where needed toxicologically qualified by appropriate studies.

The dissolution limit is justified based on batch analysis and stability testing of the clinical batches. Polymorphic form is not tested since there is only one crystalline form and no change of crystalline form has been observed in during formal stability studies.

An elemental risk assessment has been conducted for zanubrutinib capsules based on principles of ICH Q3D. Elemental impurities including Cd, Pb, As, Hg, Co, V, Ni and Pd were considered in the risk assessment. The assessment examined potential sources of elemental impurities including manufacturing equipment, container closure system, water, AS, and excipients. The assessment on zanubrutinib capsules was conducted using both the component approach (Option 2b) and the FP approach. The outcomes of both approaches suggest that adequate controls are in place, as the potential elemental impurity levels were less than 30% of the PDE. Therefore, it is not necessary to control elemental impurities in zanubrutinib capsules at release.

In response to a Major Objection (MO) raised by the CHMP, a risk evaluation concerning the potential presence of nitrosamine impurities in the finished product was submitted considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, no risk was identified and no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The finished product is released onto the market based on the above release specifications, through traditional final product release testing.

Batch analysis results are presented for 3 primary stability batches manufactured in the proposed commercial scale at the proposed manufacturing site. In addition, batch analysis of numerous clinical batches manufactured at 5 different manufacturing sites were presented. The results showed that the finished product meet the specifications proposed and confirmed batch-to-batch consistency.

Stability of the product

Stability data from three commercial scale batches, stored for up to 24 months under long term conditions (25°C / 60% RH), for up to 24 months under intermediate conditions at 30°C /65% RH and for up to 6 months under accelerated conditions (40°C / 75% RH), according to the ICH guidelines, were provided. These primary stability batches were manufactured at the proposed manufacturing site and were packaged in the proposed commercial container closure system.

Additional supportive stability studies have been carried out on clinical batches manufactured at the proposed commercial site and at 4 other sites. The total of 36 supportive stability batches were of the same formulation and manufacturing process as the commercial batches. The batches were packaged in HDPE bottles of various number of capsules and stored at 25°C / 60% RH for up to 36 months, at 30°C /65% RH for up to 36 months and at 40°C / 75% RH for 6 months.

Stability samples were tested for appearance, assay, impurities dissolution, water content, chiral purity, microbial limits and polymorphic form. No significant changes or trends were observed in any of the parameters tested. All results were well within the proposed specifications at all times and conditions.

A photostability study has been carried out in accordance with the ICH Q1B guideline on one primary stability batch. The exposed and protected samples were examined for appearance, assay, impurities, water content, chiral purity and dissolution. No significant changes in any of the parameters were observed after exposure to light. The results were similar for the exposed and dark control samples, indicating that the finished product is not sensitive to light.

Additional stress studies under high temperature (40°C and 60°C), high humidity (75% RH and 92.5% RH), and light exposure, have been carried out. At the high heat conditions the water content decreased, whereas at the high humidity conditions the water content increased. No other trends were observed under the stress conditions. The high-water content has been demonstrated not to affect other quality attributes of the FP.

An open-dish study has been performed. Capsules were stored in open petri dishes at 25 °C /60% RH for 3 months. A slight increase in water content, still well within the specification limit was observed. No other trends were observed; therefore, an in-use shelf-life for zanubrutinib capsules is not necessary.

Based on the overall available data, the proposed shelf life of 3 years without special storage conditions as stated in SmPC 6.3 and 6.4, is acceptable.

Adventitious agents

With the exception of the capsule shell, no animal or human derived raw materials are used in the manufacturing process of Brukinsa. The gelatin capsule shells are made with pharmaceutical grade gelatin obtained from bovine sources and are free of TSE/BSE. To this effect valid TSE CEP from the suppliers of the gelatine used in the manufacture were provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The MO in relation to the potential formation and presence of nitrosamines in the finished product has been resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal studies were conducted in accordance with current testing guidelines and in compliance with Good Laboratory Practice (GLP) regulations issued by US FDA, OECD and CFDA. No deviations were noted to have any impact on the quality and integrity of those studies. As the test facility where the pivotal toxicity studies has been performed, has been part of an inspection programme of a GLP monitoring authority (the Belgian GLP Compliance monitoring Authority) the studies included in the present MAA, can be considered GLP compliant

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro Pharmacology

BGB-3111 is a novel irreversible BTK inhibitor, designed to form a covalent bond with a cysteine residue at the BTK active site, leading to inactive BTK enzymatic activity in vitro. Upon BCR activation, BTK is initially trans-phosphorylated at Tyr-551 residue by Syk and Lyn kinases and physiologically activated by autophosphorylation at Tyr-223, then resulting in phosphorylation of phospholipase C gamma 2 (PLCγ2) and activation of transcription factors essential for B-cell proliferation and differentiation. These downstream reactions are then blocked by BGB-3111.

Covalent binding of BGB-3111 to BTK was demonstrated in an assay with BGB-3111 in solution with excess BTK enzyme and subsequent protein precipitation (R01-BIOL-145). Full binding of BGB-3111 was shown by precipitation with acetonitrile in which BGB-3111 is highly soluble. This method is referring to a publication by Copeland, 2000.

Functional activity of BGB-3111 was evaluated in a panel of haematological cancer cell lines (R01-BIOL-142). Among the 23 haematological cancer cell lines tested, BGB-3111 potently inhibited the cell proliferation.BGB-3111 inhibited BTK pY223 with an IC50 of 1.8 nM in a cellular assay. As an irreversible inhibitor, BGB-3111 formed covalent bond with a cysteine residue at BTK active site and occupied the protein. In the BTK occupation assay, BGB-3111 occupied intracellular BTK with an IC50 of 2.2 nM. (R01-BIOL-141). Potency values for ibrutinib from study R01-BIOL-141,are similar to BGB-3111.

The lack of ex vivo studies on haematological lymphoma cells was justified by the applicant, as such specimens was not available commercially, and since the pharmacological effect in patients in the clinical trials is considered relevant, this issue will not be pursued further.

It is commonly reported in the literature that for ibrutinib the presence of primary or acquired resistance mainly due to mutations in cysteine 481 binding site of BTK or its substrate CXCR4, but also by numerous other mechanisms is common and often leads to poor therapeutic outcome. To study resistant mechanisms ibrutinib-resistant cell lines have been established following long-term exposure to the substance. However, the applicant has not conducted any resistance studies in WM resistant and wild-type WM cells but studies are ongoing in other cancer cell lines including IMD-8 and Ramos. Results from these studies are expected to be published once available.

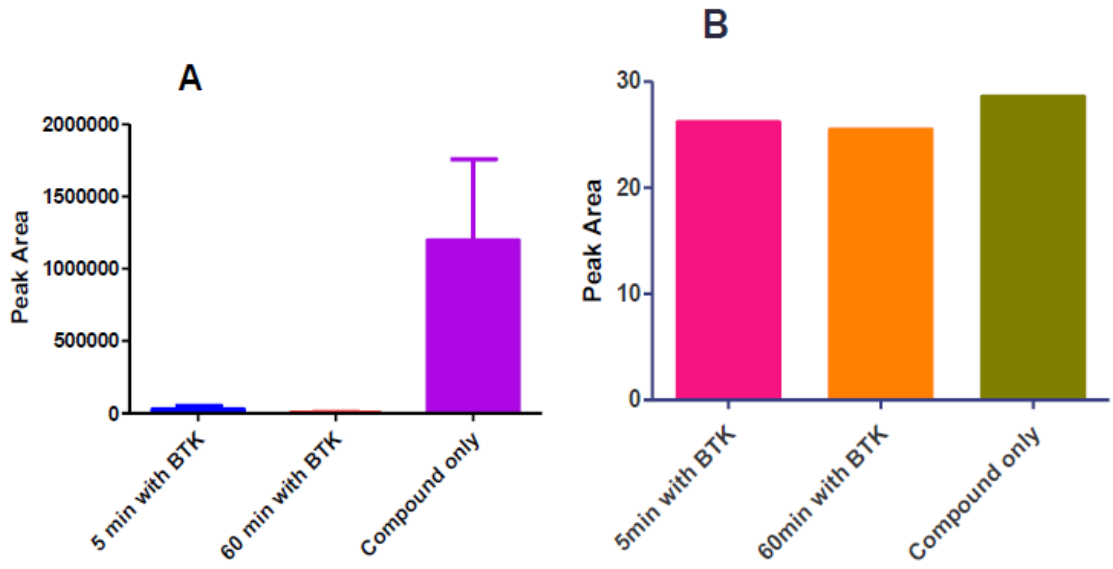
Table 1 In Vitro Primary Pharmacology Studies

Report number	Title	Test system	Noteworthy findings		
R01-BIOL-145	Inhibition of Enzymatic Activity of BTK by BGB-3111	Biochemical assay	Ibrutinib IC_{50}=0.18 nM BGB-3111 IC_{50}=0.30 nM BGB-3111 is a covalent inhibitor of BTK		
R01-BIOL-141	Inhibition of Cellular BTK Activation and BTK Occupancy by BGB-3111	Cellular mechanistic assay	Ibrutinib pY223 IC_{50}=3.5 nM BGB-3111 pY223 IC_{50}=1.8 nM Ibrutinib occupancy IC_{50}=2.3 nM BGB-3111 occupancy IC_{50}=2.2 nM		
R01-BIOL-142	Effects of BGB-3111 on Tumor Cell Proliferation in a Panel of Haematological Cancer Lines	Cellular functional assay	BCR signalling pathway dependent cell lines: REC-1 (MCL) IC_{50}=0.36 nM Mino (MCL) IC_{50}=3.8 nM JeKo-1 (MCL) IC_{50}=20 nM TMD8 (DLBCL(ABC)) IC_{50}=0.54 nM		
R01-BIOL-155	In vitro Biochemical and Cellular Characterization of BGB-3111 and its Metabolites	Biochemical assay	BGB-3111 IC_{50}=0.21 nM BGB-7941 IC_{50}=0.76 nM M417 IC50=3879 nM Acrylic Acid IC_{50}>10000 nM		
		Cellular mechanistic and functional assay	IC_{50}	BGB-3111	BGB-7941
		No activity for both M417 and Acrylic acid in the cellular assay	REC-1 proliferation assay	0.52 nM	5.9 nM
			BTK pY233 assay	2.8 nM	5.2 nM
			BTK occupation assay	1.5 nM	3.6 nM

In Vitro Biochemical Characterization

Biochemical potency of BGB-3111 for inhibition of BTK enzyme activity was determined. BGB-3111 was confirmed to be a covalent/irreversible inhibitor of BTK via the following experiment (Copeland, 2000). BTK protein was pre-incubated with BGB-3111 or BGB-1903 (a reversible BTK inhibitor) to form BTK/compound complexes (with BTK enzyme in excess to ensure complete binding of compounds by BTK protein). The BTK protein was then denatured and precipitated by centrifugation. The supernatants were analyzed for quantity of the original compounds. BGB-1903 remained in the supernatant regardless of presence or absence of BTK protein during pre-incubation, consistent with the reversible nature of its BTK binding. In contrast, BGB-3111 completely disappeared from the supernatant after incubation with precipitated BTK protein. The data also showed that the covalent bond formation between BTK and BGB-3111was largely completed within 5 minutes (Study R01-BIOL-145).

***Figure 2* Residual BGB-3111 (A) and BGB-1903 (B) in the Supernatant after BTK was Denatured and Precipitated from BTK/Compound Complexes**



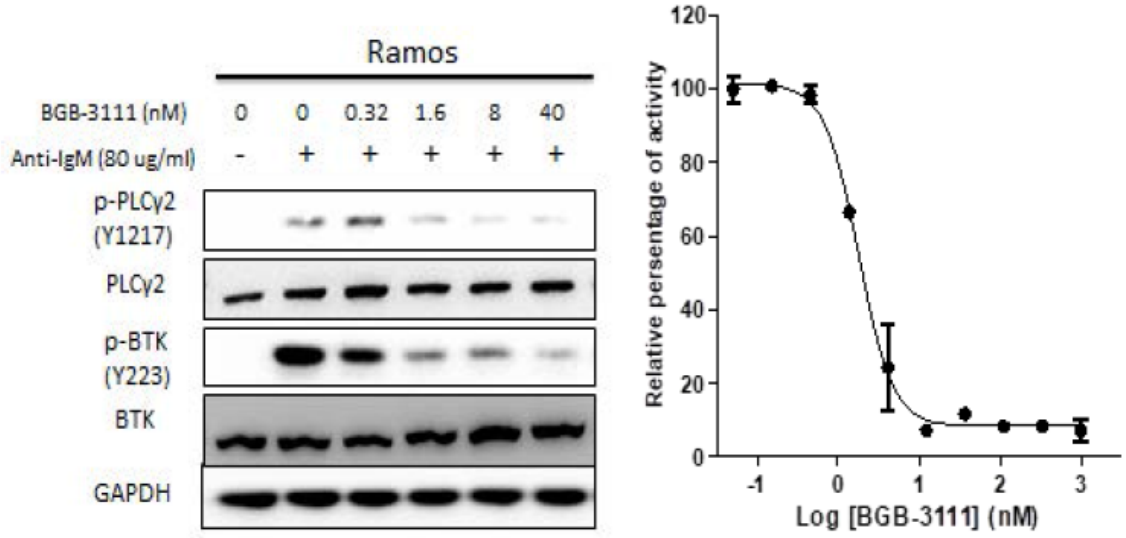
The first two bars in panels A and B show the residual compound after pre-incubation with BTK for 5 min and 60 min, respectively; the third bar in panels A and B is compound control without BTK.

Western-blot analysis demonstrated that BGB-3111, after 2-hr incubation, dose-dependently inhibited BCR aggregation-triggered BTK autophosphorylation, and blocked downstream PLCγ2 signaling. BGB-3111 had an IC50 of 1.8 ± 0.2 nM (n=3) in an HTRF based BTKpY223 assay.

BGB-3111 can form a covalent bond with BTK on the Cys-481 residue, which blocks its kinase activity and keeps other molecules from forming covalent bonds in the same manner (Honigberg et al., 2010; Wu et al., 2014). In a study that measured occupancy of BTK by an irreversible probe, BGB-3111 showed dose-dependent BTK occupancy in Z-138 cells. The IC50 of BGB-3111 in the occupancy assay was 2.2 ± 1.0 nM (n=3).

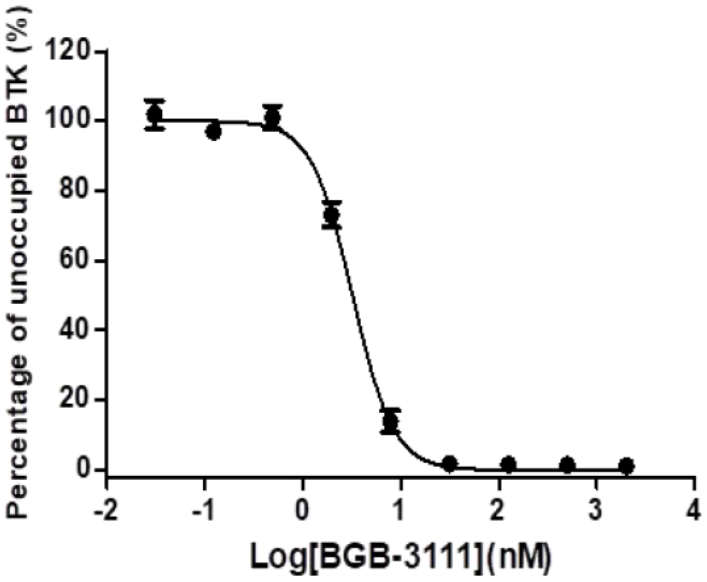
To further evaluate antitumor activity and specificity of BGB-3111, the anti-proliferative IC50 of BGB-3111 was determined in a panel of 23 hematologic cancer cell lines.

Figure 3 ***Inhibition of BTK Tyr223 Phosphorylation by BGB-3111 in Ramos Cells (R01-BIOL-141)***



In all panels, Ramos cells were treated with the indicated concentration of compounds for 2 hours. before lysis. BGB-3111 inhibited BTK Tyr223 and PLCγ2 Tyr1217 phosphorylation in Ramos cells (left panel). The inhibitory potency of BGB-3111 to BTKpY223 was measured with a HTRF based assay (right panel).

Figure 4 ***Evaluation of BTK Occupation by BGB-3111 in Z-138 Cells***



Z-138 mantle cell lymphoma cells were incubated with the indicated concentration of BGB-3111 at 37°C for 2 hours. After incubation, cells were washed twice with PBS and lysed with lysis buffer. Cell lysates were incubated within probe-coated 96-well assay plate at 4°C overnight. Unoccupied BTK protein was determined with specific BTK antibodies.

In vivo Pharmacology

The anti-tumor activity of BGB-3111 was evaluated in female NOD/SCID mice. Daily oral administration of BGB-3111 for 20 days demonstrated dose-dependent anti-tumour activity in this model. Body weight was stable throughout the study. This study was supported by exposure measurement. Drug exposure (both C_{max} and $AUC_{0\text{-}8h}$) at steady state increased proportionally with the dose. At the comparable drug dose level, BGB-3111 (24.9 mg/kg, BID) induced better tumour growth inhibition than ibrutinib (48.9 mg/kg, QD), which correlates with higher drug exposure of BGB-3111 compared to that of ibrutinib. At this dose, C_{max} was approximately 6 µM corresponding to 2.8 mg/mL. At C_{max} of 2 µM, the effect (survival at dose 7.4 mg/kg BID) was similar to ibrutinib. For comparison to relevant exposure in patients: At the highest recommended dose in patients, mean steady state C_{max} is 300 to 500 ng/mL (SmPC). A dedicated PKPD study is discussed below (R01-VIVO-121).

In another study in the same animal model, this time with tail-vein injection of the tumour cells, similar dose-dependent survival was shown, (R01-VIVO-119). The dosing went on for 78 days, however between day 40 and day 50, animals began to deteriorate as observed from the decrease in body weight. Only the highest dose levels for BGB-3111 and ibrutinib appeared to differentiate somewhat from vehicle on this parameter at the end of study.

The REC-1 systemic xenograft model was used for further evaluation of the in vivo anti-tumor activity of BGB-3111. Treatment with either ibrutinib (48.9 mg/kg qd or bid) or BGB-3111 (7.4 mg/kg bid or 24.7 mg/kg bid) significantly prolonged animal survival compared to the vehicle group ($P < 0.01$). The median survival of the treatment group receiving BGB-3111 at 7.4 mg/kg bid was similar to that of the ibrutinib treatment group at 48.9 mg/kg qd, which is its clinically relevant dose. There was no benefit on animal survival when the ibrutinib dose was increased from 48.9 mg/kg qd to 48.9 mg/kg bid. BGB-3111 at 24.7 mg/kg bid demonstrated significantly better efficacy than the other three treatment groups ($P < 0.01$). Initially, BGB-3111 and ibrutinib were both well-tolerated at the doses administered (data not shown). Most body weight loss at later study stage was caused by disease progression. However, around day 40, significant body weight loss was noted in several animals in the ibrutinib 48.9 mg/kg bid group, which was considered to be potentially treatment related.

Table 2 Efficacy and PK Parameters of BGB-3111 and Ibrutinib in Human REC-1 Xenograft Model (R01-VIVO-118)

Compound	Dose (mpk)	N	Mean Tumor Volume (mm^3±SEM)	Mean Tumor Weight (mg±SEM)	PK Parameters (Day 19)	
			(Day 20)	(Day 20)	C_{max} (μM)	AUC_{0-8h} (μM·h)
Vehicle		10	2981.4±382.2	1157.8±240.1		
Ibrutinib	14.7 qd	10	1526.0±281.0	428.2±128.5	0.85±0.09	0.7
	48.9 qd	10	959.1±126.4	308.4±53	1.28±0.19	2.5
BGB-3111	2.5 bid	10	1100.4±179.6	302.8±63.6	0.36±0.16	0.2
	7.5 bid	10	527.1±137.6	174.0±43.2	1.93±0.26	0.9
	24.9 bid	10	392.3±95.5	90.1±17.9	5.93±0.49	5.7

On Day 20 of treatment, tumor diameter was measured to estimate volume. Tumors were then surgically removed and weighed. For PK analysis, plasma drug level on Day 19 was measured and PK parameters were calculated.

In vivo efficacy of BGB-3111 and ibrutinib was also examined in TMD-8 DLBCL xenografts grown subcutaneously in NOD/SCID mice (R01-VIVO124). Following daily oral administration at well tolerated doses of 2.4, 7.2, 24.1 or 48.3 mg/kg bid, BGB-3111 induced dose-dependent anti-tumor effects. Ibrutinib at 48.9 mg/kg bid was more effective than ibrutinib at 48.9 mg/kg qd. BGB-3111 was more effective than ibrutinib in this model.

Study R01-VIVO-121 was undertaken to evaluate the pharmacokinetic (PK) and pharmacodynamics (PD) relationship of BGB-3111 and compare it with ibrutinib in ICR mice. BGB-3111 was quickly absorbed and eliminated in ICR mice. It achieved rapid BTK inhibition in both PBMC and spleen in a dose-dependent manner. Consistent with its irreversible nature, BGB-3111 induced BTK occupancy in both target organs was more sustained than its plasma drug levels with rebound appearing earlier in spleen than in PBMC. The increase in the unoccupied fraction of BTK protein at later time point is likely due to new BTK protein synthesis. These data suggested that BTK might have different protein synthesis rate in PBMC and spleen and its synthesis might be faster in spleen than in PBMC. BGB-3111 was about 3-fold more potent than ibrutinib in mouse determined as % unoccupied BTK in PBMC and spleen versus dose. Exposure determination indicate that the difference in potency is due to higher bioavailability of BGB-3111 compared to ibrutinib.

At a cellular level it was shown that, to achieve above 70% target inhibition in PBMC and spleen, plasma C_{max} values greater than 0.11 and 0.32 μM for BGB-3111 are needed. These concentration values are considered clinically relevant (1 μM = 472 ng/mL, similar to clinical steady state C_{max}).

Active metabolite BGB-7941

Three identified metabolites of BGB-3111 were evaluated for pharmacological activity. Only the mon-oxygenated BGB-7941 was shown to have effect. BGB-7941 showed slightly weaker effect than BGB-3111 also on functional endpoints (cell growth, R01-BIOL-155). This metabolite comprised of approximately 6% of BGB-3111 related radioactivity AUC in human plasma. Hence, is not considered to contribute significantly to the effects of BGB-3111.

Secondary pharmacodynamic studies

Biochemical selectivity

BGB-3111 selectivity was evaluated on the majority of known human kinases (342 out of 481). Only a fraction of those have a cysteine in the binding pocket similar to BTK. These were evaluated more closely (R01-BIOL-147). BGB-3111 was more selective than ibrutinib for inhibition of BTK vs. EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC.

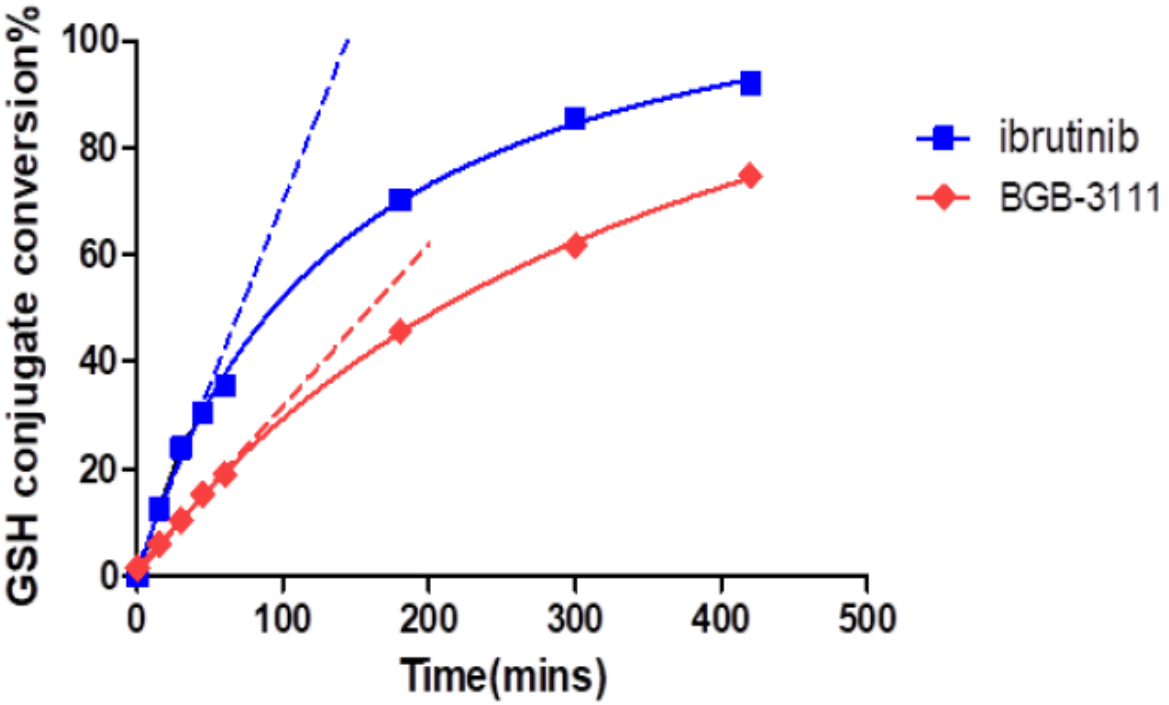
BGB-3111 was designed to bind covalently with cysteine 481 near the ATP binding site of BTK. Among 491 kinases in the human kinome, only BTK and nine other kinases have the cysteine at this position, including ITK, TEC, JAK3, EGFR, HER2, BMX, TXK, HER4 and BLK (Singh et al., 2010). The irreversible mechanism of inhibition affords BGB-3111 selectivity against kinases that does not harbor the specific cysteine. Among the ten kinases that have the specific cysteine, selectivity could also be achieved through improved specific binding to BTK vs. the other nine kinases.

Selectivity of BGB-3111 was profiled against a panel of 342 kinases at 1 μM at Reaction Biology Corp. BGB-3111 displayed less than 70% inhibition against 329 kinases, and greater than 70% inhibition against 12 kinases besides BTK. IC50 of BGB-3111 for these 13 kinases and other kinases that harbour the specific cysteine residue, were determined. BGB-3111 was more selective than ibrutinib for inhibition of BTK vs. EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC.

However, the difference from ibrutinib was marginal on ERBB4/HER4. BGB-3111 was similar to ibrutinib on BMX/ETK, BLK and TXK. The potential clinical implication of inhibition of ERBB4/HER4, BMX/ETK, BLK and TXK was discussed in light of the clinical experience with ibrutinib and BGB-3111 (zanubrutinib) and observed adverse effects.

The below figure shows the reaction curves of GSH with BGB-3111 and ibrutinib, respectively. The initial reaction rates were derived from the linear range of the reaction curves. The relative GSH reaction rate of BGB-3111 was 0.03 μM/min, about half of that of ibrutinib (0.07 μM/min).

Figure 5 ***Reaction Curves of GSH with BGB-3111 and Ibrutinib (R01-BIOL-148)***



Cellular selectivity

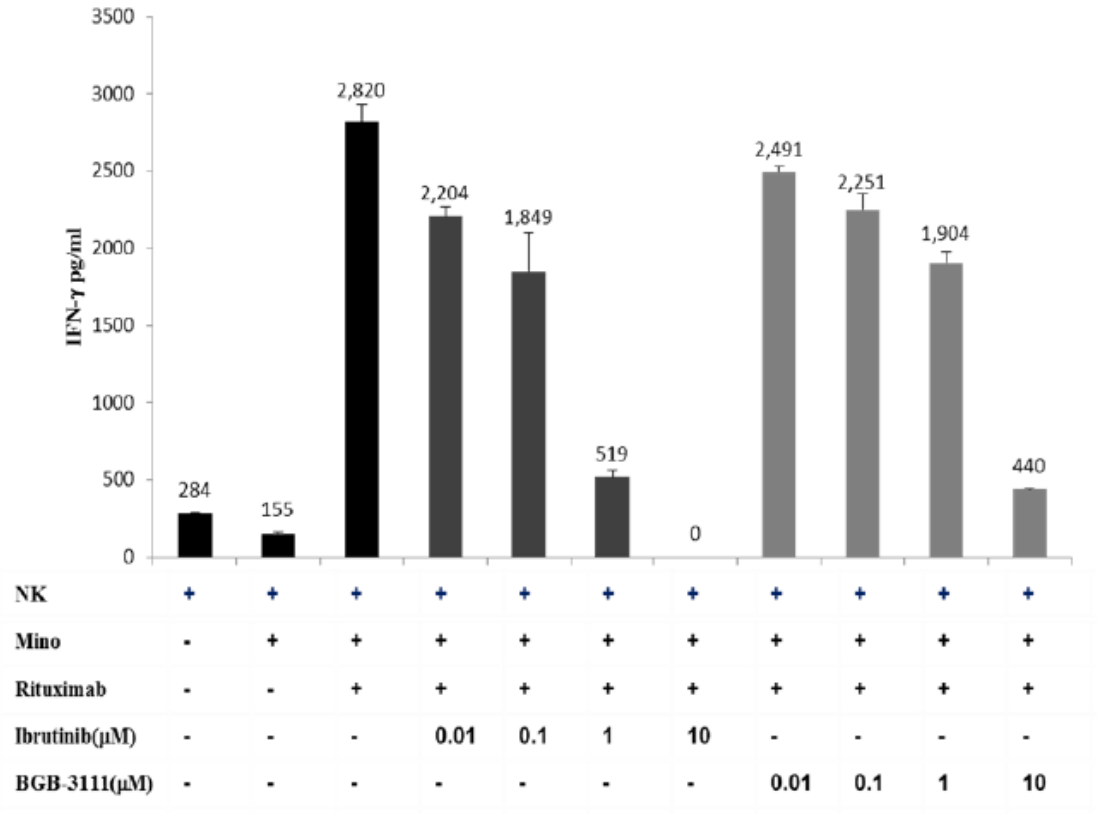
BGB-3111 showed better selectivity over ITK and EGFR than ibrutinib in biochemical assays. The selectivity of BGB-3111 in ITK and EGFR inhibition was confirmed at the cellular level (Report No. R01-BIOL-143). The investigator stated the following in the conclusion of this report: *"Although BGB-3111 showed some ITK and EGFR inhibitory activity, the potency is very low. We speculate that the cellular IC50s of BGB-3111 on ITK and EGFR are higher than its physiological reachable concentration. On the contrary, ibrutinib inhibited ITK and EGFR in physiological relevant concentration, which is consistent with its clinical observations."*

IL2-inducible T-cell kinase (ITK), a member of the Tec family tyrosine kinases, is the predominant Tec kinase in T cells and natural killer (NK) cells mediating T cell receptor (TCR) and Fc receptor (Fc R) initiated signal transduction. ITK deficiency results in impaired T and NK cell functions.

Table 3 Summary of Cellular Selectivity

Targets	Assays	IC_{50} (nM)		
		Ibrutinib	BGB-3111	BGB-3111/Ibrutinib
BTK	BTKpY223 assay	3.5±1.9 (n=3)	1.8±0.2 (n=3)	0.5
	REC-1 proliferation	0.34±0.2 (n=3)	0.36±0.03 (n=3)	1.1
	BTK occupation assay	2.3 (n=1)	2.2 ±1.0 (n=3)	1.0
EGFR	p-EGFR HTRF assay	101±38 (n=2)	606±49 (n=2)	6.0
	A431 proliferation	323±100 (n=2)	3210±606 (n=2)	9.9
ITK	p-PLCγ_1 assay	76.9±3.3 (n=2)	3433±217.8 (n=2)	44.6
	IL-2 production assay	259.7 (n=1)	2536 (n=1)	9.8

Figure 6 ***Effect of BGB-3111 and Ibrutinib on Rituximab-Mediated IFN-γ Release***

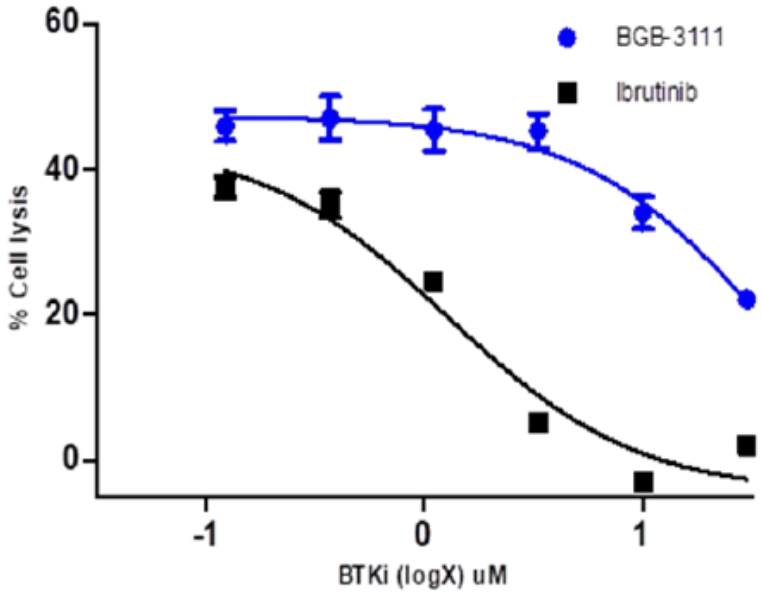


Mino cells and NK92MI cells were co-seeded and treated. IFN-γ level in the conditioned medium was measured and presented as mean of IFN-γ ± standard deviation (SD). The mean IFN-γ level (pg/mL) is presented above each bar on the graph.

Effects of these BTK inhibitors on rituximab-induced ADCC were further confirmed by cytotoxicity assays. Both ibrutinib and BGB-3111 induced dose-dependent inhibition of NK cell specific lysis of rituximab-coated Mino cells, but at different potency. The IC50 of ibrutinib (0.85 μM) was almost 30-fold lower than that of BGB-3111 (25 μM).

Figure 7 ***Effect of BGB-3111 and Ibrutinib on Rituximab-Mediated In Vitro Cytotoxicity***

(A)



(B)

Compound	IC_{50} (μM)
Ibrutinib	0.85
BGB-3111	25

Mino cells and NK92MI cells were co-seeded and treated. IC_{50} of both compounds was calculated and listed in the table.

In this context, the effect of BGB-3111 and ibrutinib on rituximab induced antibody-dependent cellular cytotoxicity (ADCC) was evaluated. Ibrutinib significantly inhibited rituximab-induced NK cell IFN-γ secretion and in vitro cytotoxicity of mantle cell lymphoma cells in a dose-dependent manner. In comparison, BGB-3111 was at least 10-fold weaker than ibrutinib in inhibiting rituximab induced ADCC, consistent with its weak ITK inhibition activity.

Safety pharmacology programme

Table 4 Summary of Safety Pharmacology Studies

Study Number	GLP	Study Title	Test System	Noteworthy Findings
ICE-BGB-hERG-004	No	hERG Test for BGB-000003111-000-035	Transfected HEK 293 cells	IC_{50} = 3.8 µM
180-0190-EP	Yes	BGB-3111: Effects on Electric Current Passing through Cloned hERG Potassium Channels Stably Expressed in Chinese Hamster Ovary (CHO) Cells using Manual Patch-Clamp Technique	Transfected CHO cells	IC_{50} = 9.11 µM
180-0084-SP	Yes	BGB-3111: Effects of Oral Administration (Oral Gavage) on Central Nervous System Function in Rats	Sprague Dawley rats	No effects on central nervous system function were noted following oral administration at single doses of 30, 100, or 300 mg/kg up to 24 hours
180-0085-SP	Yes	BGB-3111: Effects of Oral Administration (Oral Gavage) on Respiratory Functions in Rats	Sprague Dawley rats	No effects on respiratory function were noted following oral administration at single doses of 30, 100, or 300 mg/kg up to 24 hours
180-0067-SP	Yes	Cardiovascular Safety Pharmacology Evaluation of BGB-3111 Administered by Oral Gavage to Telemetry-Instrumented Conscious Beagle dogs	Beagle dogs	No effects on blood pressure, heart rate or ECG were noted in the telemetry-instrumented conscious dogs following oral administration at single doses of 10, 30, or 100 mg/kg up to 24 hours. Specifically, no QT prolongation was noted.

Cardiovascular safety

The effect of BGB-3111 on potassium ion channels was evaluated via hERG (human ether à go-go-related gene) assay using manual patch-clamp technique, which is a cell-based assay using a CHO cell line expressing hERG channels stably. In the GLP-study (2017), IC50 for BGB-3111 was determined to be 9.11 µM and 50 nM for the positive control terfenadine. Based on this study, the risk of hERG inhibition is low considering the C_{max} at steady state being approximately 1 µM. In an earlier non-GLP study (2014), IC50 was determined to be lower (1.9 µM).

Cardiovascular safety was evaluated in vivo in the telemetry instrumented conscious dog after oral administration of single doses of BGB-3111 (0, 10, 30 or 100 mg/kg). No difference from vehicle were observed on endpoints of heart rate (from both the blood pressure and ECG waveforms), systemic blood pressure (systolic, diastolic, mean, and pulse pressures), or electrocardiograms (PR, RR, QRS, QT intervals, and QTc).

The study was not supported by exposure determination. However, one case of vomiting in the high dose group, indicates exposure, since this finding was in correlation with the 28-days repeat-dose toxicity study. Moreover, formulation analysis was within specifications of ±15%.

ECG tracings of a minimum 30 seconds duration were obtained from all dogs twice prior to each dose (at least 30 minutes apart) and at 6 post dose timepoints (1, 2, 4, 8, 12, and 24 hours). These tracings were evaluated by a veterinary cardiologist for waveform abnormalities and arrhythmias.

CNS

Male and female (40/sex) rats were assigned to 4 groups with 10/sex/group and received vehicle (0.5% (w/v) methylcellulose in purified water), 30, 100, or 300 mg/kg of BGB-3111 in vehicle via oral gavage. FOB observations were conducted once at pre-test and then once each at approximately 0.5, 2, and 24 hours post dose. No test article related changes were noted in the FOB test which included motor activity, behaviour changes, coordination, sensory/motor reflex responses and body temperature assessments. The study appeared to be GLP compliant with a comprehensive audit program. No difference from vehicle group was found in the FOB assay (180-0084-SP).

Respiratory function

BGB-3111 was administered once to Sprague Dawley rats by oral gavage to evaluate the effects of BGB-3111 on the respiratory system functions. A total of 40 male and female (20/sex) Sprague Dawley rats were assigned to 4 groups, with 5/sex/group. Each group received a single dose of 30, 100, or 300 mg/kg of BGB-3111 or control vehicle (180-0085-SP).

Animals preconditioned to restraint-tubes were placed in 'head-out' plethysmographs and allowed to acclimate to environmental conditions for at least 5 minutes prior to each data collection period. Immediately following the acclimation period, ventilatory parameters (tidal volume, respiratory rate, and derived minute volume) were measured for an approximate 15-minute period pre-dose, and then for approximate 15 minutes at 0.5 hours (±10 min), 2 hours (±10 min), and 24 hours post dose.

The formulations of BGB-3111 were analysed at each dose level and found within specification. No mortality was noted during the study. No significant changes in the respiration rate, tidal volume, or derived minute volume were noted by the investigator at any dose levels at 0.5, 2, and 24 hours after dosing. This is supported.

The core battery of safety pharmacology testing of BGB-3111 including CNS and respiratory function, as assessed in the rat at single doses up to 300 mg/kg, did not indicate any specific concern.

Pharmacodynamic drug interactions

2.3.3. Pharmacokinetics

Methods of Analysis

Bioanalysis for all toxicology studies were performed using a state-of-the-art LC-MS/MS method. The method was validated in compliance with GLP for the three matrices of rat, dog and rabbit as documented in the submitted validation reports. The sample preparation technique appeared simple and robust by using protein precipitation and subsequent dilution in mobile phase. For some reason, the internal standard was verapamil and not as usual a stable label form of the analyte, e.g. ^{13}C. Nevertheless, it appeared to provide sufficient robustness of the method as run summaries in the validation reports also show. In some studies, stability under room temperature had to be re-assayed (rabbit and rat including the metabolite). The dynamic range was suitable (5-5000 ng/mL) and extended by including dilution QCs. Stability under storage was documented for approximately 3 months for each species. Incurred sample reproducibility was excellent for the three matrices of BGB-3111 alone, however, more on the limit when the method also included the metabolite BGB-7941, although still within acceptance criteria. For most toxicity studies, the same version of the bioanalytical method was used in the validation and the study (V2.0), however in the case of the rabbit study 180-0167-TX, there was a discrepancy as version 1 of the method was validated and version 2 of the method was used in rabbit study. The difference was due to an update of stability data summary; hence this discrepancy is acceptable.

In conclusion, the bioanalytical testing program is considered appropriate for documenting exposure in the pivotal GLP repeat-dose toxicity studies and providing data for toxicokinetic reporting.

Absorption

BGB-3111 is a highly permeable compound without P-gp inhibition potential, in the Caco-2 cell system. BGB-3111 might have marginal efflux potential at low concentrations but not at high concentrations. (Study 3D-rn016116).

Pharmacokinetics of BGB-3111 were determined after multiple oral dosing once daily for seven days for rats at 30 mg/kg and dogs at 7.5 mg/kg (Report No. 3D_RN016119 and 3D_RN016120). There was no significant difference in $AUC_{0\text{-}inf}$ of the 7^{th} dose over the 1^{st} dose in both rats and dogs, suggesting no accumulation of BGB-3111 following multiple oral dosing in both rats and dogs. After single dose, bioavailability appeared similar even though doses increased 10-fold (from 10 to 100 mg/kg in the rat and from 2.5 to 25 mg/kg in the dog), hence BGB-3111 show linear pharmacokinetics.

After intravenous administration to rat and dog at 3 and 2 mg/kg, respectively, clearance was 43 to 61 mL/kg/min in rat and 23-24 mL/kg/min in the dog roughly adhering to allometric scaling based on body surface area. Volume of distribution was similar in the two species (1.4 to 2 L/kg) indicating some distribution to tissues.

Female rats showed higher exposure than males. This was evident from bioavailability and AUC at all three doses (10, 30 or 100 mg/kg), but not clearly on half-life and clearance. Bioavailability ranged from 9 to 20% in male rats and 31 to 41% in female rats.

Time for maximal plasma concentration was 0.5 to 1 hour after oral administration. Half-life was in the range of approximately 0.5 hours after intravenous administration and 1.2 to 2.6 hours after oral administration, indicating absorption rate limited elimination in the rat.

In dog, there were no sex-differences in the pharmacokinetics of BGB-3111. Bioavailability was 45 to 50 % across the dose range of 2.5 to 25 mg/kg. Time for maximal plasma concentration was around

0.5 hour after oral administration. Half-life was in the range of approximately 1 hour after intravenous administration and 1.4 to 3.9 hours after oral administration, indicating absorption rate limited elimination also in the dog.

However, a study of the pharmacokinetics of ^{14}C-BGB-3111 in rat showed that t1/2 values were 31.6 - 34.8 hours in blood and 7.75 -10.5 hours in plasma, indicating slower elimination of BGB-3111 related radioactivity in blood than in plasma (RTC00782). This may correlate to concentration dependent preference of BGB-3111 for red blood cells in the rat. A similar evaluation was performed in humans (BGB-3111-105 CSR). This study showed similar half-life of BGB-3111 related radioactivity in plasma and blood (44.4 hours in blood and 46.7 hours in plasma).

Distribution

The plasma protein binding (PPB) properties of BGB-3111 were evaluated in plasma from human, Cynomolgus monkey, Beagle dog, Sprague-Dawley rat, and ICR mouse, using an equilibrium dialysis method at drug concentrations ranging from 0.5 to 15 μM (3D_RN016124). The PPB of BGB-3111 appeared to be concentration-independent in all 5 species tested. The mean bound fractions of BGB-3111 were similar among species with 94.2%, 93.9%, 93.3%, 96.7%, and 94.9% in human, monkey, dog, rat, and mouse plasma, respectively.

The blood-to-plasma concentration ratios of BGB-3111 were investigated in blood from human, Beagle dog, and Sprague Dawley rat (3D_RN016123). The mean blood-to-plasma concentration ratios of BGB-3111 were 0.804 and 0.752 in humans and dogs, respectively, suggesting that BGB-3111 has a partitioning preference for plasma in the whole blood of humans and dogs at 0.3-30 μM. In rats, the blood-to-plasma concentration ratios of BGB-3111 was 0.766, 1.03, and 1.39 at 0.3, 3, and 30 μM, respectively, suggesting a concentration-dependent red blood cells/plasma partition preference in rats, which change to a preference for red blood cells at higher concentrations in the rat. Since this was only observed in rat, this is probably not of clinical relevance, however may correlate to the long half-life of BGB-3111 related radioactivity in whole blood as opposed to plasma in the rat study (RTC00782).

Tissue distribution of BGB-3111 was determined in the rat after an oral dose of 30 mg/kg non-labelled material to rats (3D-RN016121). Tissue concentration was determined after 0.25, 2 or 8 hours post dose in selected organs. BGB-3111 showed preference for stomach, small intestine and liver. Very low concentration was found in brain and testes, however elimination from testes appeared to be slower than for other tissues. Other tissues than GI tract and liver showed slightly higher concentration than plasma at 0.25 and 2 hours after dosing, namely heart, kidney and ovary.

A conventional QWBA study was conducted using 10 male Long-Evans rats and 3 Sprague Dawley rats in order to compare potential melanin binding (RPT04060). There was no difference in binding to melanin containing tissues between the two rat strains. Quite a busy sampling schedule (0.5, 2, 4, 8, 24, 48, 72, 168, and 336 hours post-dose) was used. This allowed for PK parameters for all analysed tissues to be calculated. As observed in a previous study, t½ of BGB-3111 related radioactivity in blood was much longer than in plasma (69 vs. 8 hours). This should be compared to the half-life of BGB-3111 in the rat of 1-2 hours. In the adrenal gland, cortex and medulla, a similarly long t½ correlated with high tissue to plasma ratios (21 to 24 times higher AUC in adrenal compared to plasma). Half-life was also similar to blood in bone marrow, spleen, pituitary gland, stomach wall and lung. However, the tissue:plasma ratios indicated similar overall exposure (AUC) as in plasma. Tissues showing high tissue to plasma exposure ratios despite shorter t½ was small intestine wall (t½ 6.4 h) and liver (t½ 37.2 h). These two tissues showed the highest tissue to plasma exposure ratios of 47 and 26, respectively. The majority of these tissues are associated with very common adverse effects (Table 3 in SmPC), such as neutropenia, anaemia, upper respiratory tract infections, cough and diarrhoea.

Metabolism

In vitro metabolism

Interspecies comparison of in vitro metabolism in liver microsomes showed a moderate to high turnover with the lowest clearance in dog liver microsomes.

BGB-3111 was extensively metabolised with a total of 11 metabolites (M1 to M11, the corresponding ID of in vivo metabolites are shown in Table 4) were found. Of these, 10 metabolites, were found in human and monkey liver microsomes, while 8 metabolites in dog liver microsomes, and 9 metabolites were found in rat and mouse liver microsomes with considerable overlap in identity. BGB-3111 was metabolised by oxidative deamination, hydroxylation, N-dealkylation and dehydration in liver microsomes. De-acrylated metabolites were not identified in vitro.

Metabolites in plasma of human and rat

Acrylic acid was identified as the major component in plasma in humans in the human AME study. This metabolite was not identified in the non-clinical species, hence cannot be considered qualified by exposure. A considerable effort was made in order to assess the impact of this potential safety issue in patients. The presence of acrylic acid in plasma of the healthy volunteers in the human AME study could partly be due to acrylic acid being present in the administered ^{14}C-BGB-3111 in amounts above 7%, as confirmed in a radiochromatogram of the dosing material. Acrylic acid was stated to account for a maximum of 2.83% of the dose based on the radioactivity of two unknown metabolites in urine in the human AME study. On this basis, applicant presented the following safety assessment: *Following 320 mg daily dose to human, only approximately 9 mg of BGB-3111 (MW=471) was hydrolyzed and converted to 1.38 mg of acrylic acid (MW=72) in the body, corresponding to ~0.02 mg/kg/day for a 60 kg human. This is significantly less than the NOAEL (53 mg/kg/day) for systemic and developmental toxicity in rats (Hellwig et al. 1997).* This is in principle agreed. However, since the exposure in circulation was so much higher than parent compound, the safety assessment of acrylic acid as a human metabolite with no documented non-clinical exposure was not considered convincing. In the next round of assessment, the applicant further clarified the positive safety assessment of acrylic acid as a metabolite in human plasma by mainly referring to the fact that acrylic acid was present in the dosing material of BGB-3111 in the human AME study (radio-chromatogram submitted) and not in the ADME study in rat. Moreover, deacrylated metabolites were present in both rat, dog and human in very low amounts indicating very low amounts of acrylic acid would be produced. Hence, the importance of this clearance pathway is minimal. The request for bioanalytical comparison of presence of acrylic acid in plasma from rat, dog and human cannot be carried out, since non-radiolabelled acrylic acid is not detectable using either LC-MS or LC-UV, not even after derivatisation.

After a single dose of ^{14}C-BGB-3111 to rat, parent compound was the major circulating component (45-65%) with BGB-7941 (M487a, hydroxylated phenyl) being the major metabolite (14%). BGB-7941 is pharmacologically active and is also present in human plasma although at lower percentage of total radioactivity in plasma (5.73%). It was stated that no acrylic acid related peaks were identified in rat plasma or dosing material (XBLC14646N_RTC00568). However, de-acrylated BGB-3111 (M417/1) was identified after 30 mg/kg dose in rat and dog toxicology studies (RTC01128), indicating the formation of de-acrylated metabolites and acrylic acid via acrylamide hydrolysis pathways in these species. De-acrylated metabolites would not be detected in the human and rat AME studies, since this is the site of labelling in both studies. The study report on study XBLC14646N_RTC00568 was located in the next round of assessment and a radio-chromatogram was found in Appendix A confirming the high purity of the dosing material used in the rat ADME study.

Based on metabolite identification in the human AME study, it is considered unlikely that all BGB-3111 will degraded to acrylic acid. However, to put the issue into perspective the following calculation is made:

Worst case scenario: In case all BGB-3111 will degraded to acrylic acid. NOAEL of acrylic acid in rat = 53 mg/kg/day (Hellwig, 1997). Human equivalent dose (HED) of NOAEL of acrylic acid = 0.16*53 mg/kg/day = 8.48 mg/kg/day. Maximum daily dose is 320 mg/day/50 kg = 6.4 mg/kg/day BGB-3111 corresponding to (72 g/mol for acrylic acid/471 g/mol for BGB-3111)*6.4 = 1 mg acrylic acid/kg/day. This dose is almost an order of magnitude lower than the HED of the NOAEL in the rat and the potential exposure to acrylic acid may be considered safe. The reactivity of acrylic acid (Michael addition) is low at pH 7.4 as outlined by Frederick et al, 1989. However, it should be kept in mind that the mechanism of action is by irreversible covalent binding to a protein.

In this context, it should also be mentioned that in study RTC01116, it was found that some ^{14}C-containing material, accounting for 24.99% and 21.73% of the TRA in 0-24-h male and female rat plasma samples could not be extracted and remained in the plasma post-extraction pellets, possibly due to covalent binding to plasma proteins. Since the mechanism of action is irreversible inhibition of Bruton's kinase by covalent binding, very high selectivity is warranted. However, the applicant elaborated that, the selectivity of zanubrutinib is lower in rat as compared to human, since the covalent-bound radioactivity was high in rat plasma (22-25%) and lower in human plasma (5.5 to 6%). Comparing with ibrutinib, covalent binding in human plasma is much lower for zanubrutinib (38-51% vs 5.5 to 6%) indicating higher selectivity of zanubrutinib versus ibrutinib, which is reassuring.

Metabolites in excreta

In both human and rat, faeces was by far the major route of excretion of BGB-3111 related radioactivity with 86% in humans and 94-97% in rat. In humans, parent compound comprised of 38% of the radioactive dose. The hydroxylated metabolite of phenyl, BGB-7941 (M487a) was the primary metabolite in faeces, representing 37.12% of the dose in male rat faecal samples, and 41.20% of the dose in female rat faecal samples, whereas BGB-3111 comprised of 6% in the rat faeces. In humans, urine comprised 7.4% of the dose with Unknown 1 and 2 identified as acrylic acid and being the most abundant metabolites (0.78 and 1.95%, respectively). Parent compound was found in 0.11% of the radioactive dose. Many metabolites were identified in both urine and faecal samples from rat and humans and reflected the Phase 1 metabolites identified in vitro supplemented secondary metabolites and a range of Phase 2 conjugates as such cysteine, N-acetylcysteine, glucuronic acid and sulphate.

CYP and UGT Phenotyping

BGB-3111 was found to be primarily metabolised by CYP3A4 (3D_RN016193). In humans, UGT plays a minor role in the clearance of BGB-3111 in vivo. In vitro, no conjugation to glucuronic acid could be detected (3D_RN016192).

Excretion

The majority of BGB-3111 related radioactivity was excreted with faeces in both rat and human with 96% in the rat and 87 % in human. Very little was excreted in urine with 2% in rat and 7.6% in human. In the bile-duct cannulated rat, bile accounted for 40% of the excreted radioactive dose. In both rat and human, BGB-3111 comprised very small amounts of the radioactivity in urine, bile or faeces, hence the major clearance pathway for BGB-3111 is via metabolism. From this, it can also be concluded that BGB-3111 is well absorbed. Excretion was also evaluated in the rat after multiple dosing. No remarkable difference to single dose was observed. Excretion and in vivo metabolism were

not studied in the non-rodent nonclinical species; the dog. The omission of conducting ADME study of BGB-3111 in dog was justified in the next round of assessment by the following points: i) In vitro metabolic profiles (liver microsomes) were similar between rat, dog and humans. ii) The majority of BGB-3111 related radioactivity was excreted through feces in both rat and human. iii) Similar pattern of low amounts of de-acrylated metabolites was found in both rat, dog and human plasma. iiii) Sufficient safety margins to human exposure were obtained from non-clinical safety studies. The justification was accepted and requesting a new in vivo ADME study in a non-rodent at this stage of development is not considered necessary.

Pharmacokinetic drug interactions

BGB-3111 as a substrate of CYPs

BGB-3111 is a substrate of CYP3A4. This was shown by profiling against 7 major CYP450 isoforms using human liver microsomes and recombinant CYPs (3D_RN016193) and further confirmed in vivo in a clinical study (BGB-3111-104 CSR) that showed a 3.8-fold increase in $AUC_{0\text{-}inf}$ of BGB-3111 when co-administered with a strong CYP3A inhibitor (itraconazole), and a 13.5-fold decrease in $AUC_{0\text{-}inf}$ when co-administered with multiple-dose of a strong CYP3A inducer (rifampin). This is adequately described in SmPC section 4.5.

BGB-3111 as an inducer of CYPs

BGB-3111 appears to be a pan CYP-inducer as shown in experiments of human hepatocytes (3D-RN016127 and C19047) at 0.3, 3 and 30 µM. Fold induction of enzyme activity and mRNA was generally highest at 3 µM, which may be considered highly clinically relevant as C_{max} is approximately 0.6 µM (299 ng/mL) and the concentration in the liver can be expected to be considerably higher. Only CYP2B6 is mentioned in this context in SmPC. This issue is discussed under Clinical Pharmacology OCs.

BGB-3111 as an inhibitor of CYPs

In an in vitro CYP inhibition study (3D-RN016125), IC50 values was determined for BGB-3111 on 6 major CYPs. IC50 was >50 µM on CYP1A2, 2B6, 2D6 and 3A4 using testosterone as substrate. Potentially clinically relevant IC50s were observed for 2C8 (**4.03 µM**), 2C9 (5.69 µM) and 3A4 using midazolam as substrate (14.3 µM). Using FDAs guidance, only CYP2C8 fell out as potentially clinically relevant in terms of inhibition of CYPs in the liver and both substrates of CYP3A4 when taking intestinal CYP3A4 into consideration. Inhibition potential by BGB-3111 of CYP3A, 2C8, 2C9 and 2C19 was followed up by clinical in vivo drug-drug interaction studies or in the case of CYP2C8 by PBPK modelling. The outcomes are described in SmPC, however the impact of BGB-3111 was only modest.

BGB-3111 as a Substrate of Transporters

BGB-3111 was not a substrate of BCRP, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 (RD-S1503-02-02 and RD-S1503-02-04). In vitro data indicate that BGB-3111 was likely to be a substrate of human P-gp efflux transporter (3D-RN016116 and BGB-3111-DMPK-PK-DDI-0001). However, since BGB-3111 is well absorbed with high permeability in humans, this is not considered of clinical relevance.

BGB-3111 as an Inhibitor of Transporters

BGB-3111 was neither an inhibitor of P-gp at concentrations up to 10.0 µM (3D_RN016116) nor an inhibitor of BCRP or hepatic uptake transporters OATP1B1, OATP1B3, or renal uptake transporters OCT2, OAT1, and OAT3 at concentrations up to 5.0 µM.

Due to predicted high concentrations in the GI associated with p.o. administration, potential inhibition of BCRP and P-gp could not be outruled by the in vitro study.

This was followed up by a clinical drug drug interaction study with digoxin as a P-gp substrate and rosuvastatin as BCRP substrate. However, only marginal increase in digoxin exposure was observed and no difference with rosuvastatin as also described in SmPC section 4.5.

2.3.4. Toxicology

Single dose toxicity

Single dose studies were conducted in rats and dogs with doses up to 1000 mg/kg. The dog study was conducted with escalating doses of 100, 300 and 1000 mg/kg administered with four days apart in the same animals.

No mortalities were observed in any of the studies. In both studies the maximum tolerated dose (MTD) was determined to be ≥ 1000 mg/kg/day.

In the 14-day toxicity study in rats, measured concentrations of zanubrutinib drug substance in dose formulations were between 62.5% and 100.5% of nominal concentrations. For example, at nominal concentration 25 mg/mL the analysed concentration was only 15.625 mg/mL. The applicant was therefore asked to explain the reason for such a variability in concentrations of dose formulations, and its impact on the study results including TK. However, the applicant was not able to provide a consistent explanation for the variation in measured concentrations of zanubrutinib in dose formulation. Regardless, since there was no impact on the GLP toxicology studies, in which data consistency in toxicity and TKL profiles was shown, the issue will not be further pursued.

Beside a shortened APTT in both male and female rats receiving 1000 mg/kg, no significant changes were observed in the single-dose rat study (18-0062-TX).

In the single dose toxicity study in Beagle dogs (180-0063-TX) vomitus was observed post dosing in one female at 100 mg/kg and two males at 1000 mg/kg. As BGB-3111 was administered by oral route, vomiting could potentially affect the dose of BGB-3111 received by the dogs. Since no toxicokinetic data was presented and no registration of the time of vomiting post dosing could be found, it was unclear if vomiting potentially could have affected the dose of BGB-3111 received by the dogs and hence the reliability of the data in these dogs.

Beside an increase in WBC and neutrophils in one female dog at 100 mg/kg and in fibrinogen in a male dog at 1000 mg/kg, no other changes were observed. The potential reasons for the increases are not sufficiently discussed by the applicant but they are not considered to be of great importance for the interpretation of the study.

Repeat-dose toxicity

Two non-GLP 14-days explorative dose studies were conducted in rats and dogs prior to initiation of the pivotal studies. Pivotal repeat dose studies of 28-days and 13-weeks in rat and dog as well as a 6-months study in rats and a 9-months study in dogs, were conducted in accordance with relevant ICH guidelines.

Rats

Three pivotal repeat-dose toxicity studies were conducted in Sprague Dawley rats with zanubrutinib administration for respectively 28 days with doses of 50, 150 and 500 mg/kg/day, 13 weeks with doses of 30, 100 and 300 mg/kg/day and 6 months with doses of 30, 100, 300 and 1000 mg/kg/day. In all studies zanubrutinib was administered orally by gavage, which corresponded to the intended

clinical route of administration in human patients. Toxicokinetic evaluation were conducted for all the pivotal repeat-dose studies at all dose levels.

Zanubrutinib-related mortality was observed at repeated doses of 1000 mg/kg/day by Day 6-9 as part of the 6-month study. Systemic exposures at this dose level corresponded to 62-71 times the clinically relevant exposure. Due to the high mortality (16 out of 20 animals), the remaining animals of the 1000 mg/kg/day treatment group was terminated at Day 8-9. Mortality was likely caused by the severe gastrointestinal lesions of erosion/necrosis/ulceration, atrophy and neutrophilic infiltration. No test article-related mortality was noted at dose up to 500 mg/kg/day in the 28-day study and at 300 mg/kg/day in the 13-week and 26-week studies.

In the 28-day repeat-dose study, clinical observations included scab/swelling around nose/mouth/lip/ eyes from doses of 50 mg/kg/day in females (5 times clinical exposure), and salivation, soft stool and decrease in body weight (males only) at high doses of 500 mg/kg/day. Changes in hematological parameters were observed as increases in WBCs, NEUTs and RETs and decreases in RBCs, HGB and HCT. Additionally, abnormal changes in urine analysis were noted at 500 mg/kg/day in both sexes. None of the changes persisted after the recovery period. Histopathological changes were detected in the pancreas, skin, spleen, prostate, liver, ovary, uterus, adrenal glands and thymus. Although some microscopic changes persisted in the pancreas and spleen, most of the findings were reversible during the recovery phase.

Findings in the 13-week and 26-week repeat-dose studies were to a large degree consistent with the findings of the 28-day study with a few exceptions. Clinical observations of a time-dependent decrease in body weight were noted at all doses in the 26-week study. Findings of scab/swelling around nose/mouth/lip/eyes were also seen in the 13-week study, again with lesion debuting at lower dose in females (30 mg/kg/day, 3 times clinical exposure) than in males (300 mg/kg/day, 19 times clinical exposure).

Changes were seen in hematology (increases of WBC, NEUT, MONO, EOS), serum chemistry (increasing ALT, A/G and TCHO and decreasing TP, GLB, K and CK) and urinanalysis parameters (urine glucose, occult blood, urobilinogen, and higher incidence of turbid urine) in both the 13-week and 26-week study. Even though, the increases/decreases often were small in magnitude, many of them were significantly changed compared to the control but most of them still within historical reference data.

Lymphocyte immunophenotyping was conducted in both the 13-week study and the 26-week study, revealing increases in T-cells and T-helper cell and decreasing B-cells, which was considered to be within the expected pharmacological effect of zanubrutinib.

Test article-related statistically significant absolute and relative organ weight alterations occurred at 300 mg/kg/day in the 13-week repeated-dose study in rats, including increased adrenal gland weights for males and females, and increased heart, liver, kidney, spleen and thymus weights for females. However, no correlating histopathologic findings were noted in these organs with the exception that hypertrophy or cortical angiectasis in the adrenal glands and follicular cell hypertrophy in the thyroid glands.

Pancreatic lesion was noted, primarily in male rats, as a consistent finding at all dose levels in all three studies. Lesion furthermore persisted after recovery although the frequency and severity of the lesions were reduced over time. This reflected an increased toxic effect of zanubrutinib on pancreas of rats, which according to the applicant did not correspond to the clinical findings. In an article by Bhaskaran *et al.* (2018), the effect of BTK-inhibitors on pancreas was shown to be species specific in rats with higher sensitivity in Sprague Dawley rats compared to other strains and the lack of clinical relevance of these findings are therefore acceptable.

NOAELs were determined as 300 mg/kg/day, corresponding to the highest dose tested without mortally in all three rat studies. The NOAEL of 300 mg/kg/day in rats are, however, not accepted. For the rat studies, a NOAEL of 100 mg/kg/day is considered appropriate.

Dogs

Three pivotal repeat-dose toxicity studies were conducted in Beagle dogs for 28 days, 13 weeks and 9 months respectively with doses of 10, 30 and 100 mg/kg/day. Additionally, a non-GLP 14-day explorative study were conducted in dogs prior to the pivotal studies. Zanubrutinib was administered orally in all the studies, which corresponded to the intended clinical route in human patients. Toxicokinetic evaluation were conducted for all the pivotal repeat-dose studies at all dose levels.

In the 28-day and 13-week repeat-dose studies similar findings were detected. Evidence of an adverse gastrointestinal effect was noted, as incidences of diarrhoea (soft/watery/mucoid stool) occurring already at low doses ≥ 10 mg/kg/day in both studies (2 times clinical exposure). Since gastrointestinal (GI) disturbances and diarrhoea appeared to be a consistent finding in many of the repeat-dose studies in both rats and dogs, the applicant was asked to discuss the potential mechanisms behind the GI findings and compare the occurrence of GI related changes in the rats and dogs with respect to safety margins to human exposure and clinical relevance. In the next round of assessment, the applicant sufficiently addressed the occurrence of GI disturbances in rats and dogs and provided exposure margins to human clinical exposure as requested. The GI changes was considered to be clinically relevant and comparable to reported clinical symptoms of diarrhea, constipation, nausea, vomiting and abdominal pain in human patients. The effect on the GI tract is potentially related to inhibition of EGFR in the intestine. The findings were transient in rats at 300 mg/kg/day but more pronounced in dogs, with a change into watery/mucoid diarrhoea in 50% of the male dogs at doses of ≥10 mg/kg/day and in 100% of the female dogs at high doses of 100 mg/kg/day.

Vomiting was seen in the dogs at high dose of 100 mg/kg/day in the 28-day study. In the 13-week study, a dose-dependent decrease in body weight was noted in male dogs already at dose ≥ 10 mg/kg/day with the highest decrease of 7,4%. Pathological lesions were limited to lymphoid depletion in the spleen in the 28-day study and in the spleen and lymph nodes in the 13-week study. Changes in an increasing number of clinical pathological parameters were noted in the 13-week study compared to the 28-day study with some of the changes being consistent between the studies (e.g. fibrinogen).

In general, an increasing incidence and severity of findings were seen in the 9-month long-term repeat-dose study compared to the two other repeat-dose studies in dogs. As for the other pivotal studies, evidence of gastrointestinal disturbances was seen as diarrhoea in all animals at all doses ≥ 10 mg/kg/day (2 times clinical exposure) along with a dose-dependent decrease in body weight in both males (8.6-18%) and females (7.8-10.9%). Additionally, salivation was observed at low doses.

Clinical signs of skin lesion (scab, skin discoloration, swelling, rash and thickening) appeared at ≥ 10 mg/kg/day (2 times clinical exposure). Oddly enough, the changes are not registered at macroscopically examination and not microscopically examined. Since skin lesion also occurred in the 28-day and 13-week repeat-dose studies in rats, the applicant was asked to discuss the underlying reason for the changes further, compare the lesion between the studies and discuss the clinical relevance according to safety margins and lesions detected in human patients. In response to the question, the applicant provided a sufficient discussion of the clinical and non-clinical presentation of skin changes with estimation of exposure margins to human systemic exposure for the different doses as requested. It is agreed that the skin changes are of clinical relevance, potential caused by inhibition of EGFR in the skin and occur at doses of 300 mg/kg/day in rat and 10 mg/kg/day in dogs.

Changes were observed in clinical pathological parameter (haematology, clinical chemistry and urinanalysis) with a tendency of a dose-dependent increase in magnitude and number of changed

parameters over time. Moreover, some parameters even increased/decreased consistently between species (ex. WBC, NEUT etc.). In the next round of assessment, the applicant provided tables summarising and better visualizing changes in haematological parameters, leukocytes and serum chemistry in the conducted rat and dog studies. Historical reference range were furthermore included in the tables. According to the applicant, changes in hematological parameters were considered related to BTK inhibition, since BTK is not solely restricted to B cells. This could be a plausible explanation for the observed changes in hematological parameters (i.e. RBC, HGB, HCT and RET). However, increasing levels of neutrophils and related increases in WBC, cannot be explained by BTK inhibition, as this supposedly should lead to decreasing neutrophil values. The dose-dependent increase in neutrophils across species appeared to be caused by inflammatory cell infiltration in e.g. skin, gastrointestinal tract, and/or pancreas. However, the relevance was considered to be limited, as the finding differed from the clinical setting, where neutropenia was observed to a larger degree.

In dogs, a significant dose-dependent increase in fibrinogen levels were seen compare to control animals at doses ≥ 30 mg/kg/day. It is acknowledged that the increase is within the historical control range, however, the finding is still considered potential clinically relevant, as it could be an initial indication of haemorrhages. For the serum chemistry parameters, electrolytes and the occurrence of proteinuria and/or occult blood in rats, most of the data were within the historical normal range, except for a decrease or increase in parameters at the highest dose levels in rats (300 or 500 mg/kg/day) and/or dogs (100 mg/kg/day). Since no strong correlation were seen with histopathological changes in e.g. liver or kidney, the clinical relevance of the findings are unknown. However, in the light of NOAEL determination, this further substantiates the need for redefining the NOAELs.

Lymphoid depletion observed at all three dog studies were suspected to be within the expected pharmacological effect.

Generally, mortality was low in all three repeat-dose studies in dog. However, one unscheduled mortality was observed in a male dog in the 100 mg/kg/day treatment group in the 9-month repeat-dose study. The animal died due to torsion of the jejunum. The applicant stated that the dead was not treatment related, however, this is not endorsed by the assessor. High incidences of diarrhea were a general clinical sign in all animals at all dose levels in the 9-month dog study and occurrence of irritating condition in the gastrointestinal system, as evidenced by diarrhea in this case, often leads to changes in intestinal motility which could be associated with torsion of the intestines. It can therefore not be excluded, that the observed mortality could be treatment-related.

The NOAEL were in all three repeat-dose studies in dog determined to 100 mg/kg/day corresponding to the highest dose tested. The NOAEL of 100 mg/kg/day in dogs are not endorsed based on the following. Clinically relevant GI changes with a switch to more watery/mucoid diarrhoea were seen in a high percentage of male and female dogs at doses of 100 mg/kg/day and in males ≥10 mg/kg/day. Among other changes that could be mentioned at 100 mg/kg/day in dogs, are increased incidences of clinically relevant skin changes (red discoloration and thickened skin) and decrease in body weight gain. For the dog studies, a NOAEL of 10 mg/kg/day is considered appropriate.

Toxicokinetics and interspecies comparison

The systemic exposure of zanubrutinib (BGB-3111) increased dose proportionally without apparent accumulation. No sex difference where noted in the dogs but a higher exposure was detected in female rats compared to male rats. The applicant has revised the Cmax ratio (animal to human) and the AUC ratio (animal to human) in the interspecies comparison as requested by using the geometric mean of Cmax (299 ng/ml) and AUC0-24h (2099 h*ng/mL) of zanubrutinib following multiple oral doses to patients with B-cell malignancies in Study BGB-3111-AU-003 for comparison. The interspecies comparison table will be updated accordingly. The systemic exposure (AUC) at the redefined NOAEL of

100 mg/kg/day in rats and 10 mg/kg/day in dogs was approximately 13 and 3-fold human systemic exposure.

The systemic exposure of the metabolite BGB-7941 was evaluated in the 26-week repeat-dose study in rats. BGB-7941 appeared to increase less than dose proportionally without apparent drug accumulation, however, female rats appeared to have a higher systemic exposure than males.

Genotoxicity

Zanubrutinib did not induce mutations when adequately tested in histidine-requiring strains of Salmonella typhimurium (TA98, TA100, TA1535 and TA1537) and Escherichia coli (WP2 uvrA) at concentrations up to 5000 µg/plate in the absence and presence of a rat liver metabolic activation system (±S9).

In an in vitro mammalian chromosome aberration tests in Chinese hamster ovary cells, Zanubrutinib was negative at the presence and absence of metabolic activation. However, a deviation was noted in the S9 activated 3 h treatment group at 60 µg/mL but since no changes were noted at other dose groups at this or higher dose-levels, the study director's discussion of lack of biological relevance was accepted.

In an in vivo chromosomal aberration test (micronucleus) in rats, zanubrutinib was not clastogenic when administered at doses up to 2000 mg/kg/day. Although a dose-dependent increase of MN-PCE frequency ($p \leq 0.05$, Cochran-Armitage) was identified by statistical analysis at 24 h in male, this were still within the range of negative controls. By comparison to toxicokinetic data from the repeat-dose studies, sufficient exposure to clinical safety margins were obtained at all doses tested (safety margin of 2-5-fold at the lowest doses of 50 mg/kg). No mortality was observed in any of the treatment groups.

Carcinogenicity

Carcinogenicity studies have not been performed (see discussion on non-clinical aspects).

Reproduction and developmental toxicity

Fertility and early embryonic development

A fertility and early embryonic development study were conducted in male and female rats with dose of 30, 100 and 300 mg/kg administered daily by oral gavage. No test article-related effect on male and female fertility parameters were noted at doses up to 300 mg/kg/day. However, 12% post-implantation loss (compared to 6% in the control group) and abnormal sperm morphology were detected at dose of 300 mg/kg. Despite of these changes, the applicant determined the overall NOAEL = 300 mg/kg, which is not endorsed. The implantation finding has been taken into consideration and the NOAEL reduced to 100 mg/kg/day with a revised safety margin of 3-fold.

Clinical signs of soft stool and nasal discharge observed at high doses which corresponded to findings in the repeat-dose studies.

Embryo-foetal development

Embryo-foetal developmental studies were conducted in both rats (doses of 30, 75 and 150 mg/kg/day) and rabbits (doses of 30, 70 and 150 mg/kg/day) according to guideline. In rat foetuses, a higher incidence of two or three chamber hearts were observed at all doses and should be considered a teratogenic effect and addressed sufficiently in the SmPC 4.6 and 5.3 with safety margin specifications. The heart malformations were detected from doses 3-4 times clinical systemic exposure in patients and occurred with a dose-dependent increase in incidence from 0.3% to 1.5% at the highest dose of 150 mg/kg/day. Additionally, a selection of three different kidney variations (i.e. dilated renal pelvis,

convoluted ureters and dilated ureters) were observed in the rat foetuses. In response to a question, the applicant has provided requested historical control data and MARTA data, showing that the observed kidney variations are within the maximum span of these reference data. Furthermore, as no kidney-related adverse effects were observed in the clinical setting, the issue will not be further pursued. No NOAELs were determined for the F1 generation but the NOAEL estimated by the assessor was less than 30 mg/kg/day (F1: NOAEL < 30 mg/kg/day).

Except a transient decrease in body weight in the high dose group in the first days of the study, no significant changes were noted in the maternal rats in the embryo-developmental study (F0: NOAEL = 150 mg/kg/day).

In the embryo-foetal developmental study in rabbits, a slight but statistically significant increased post-implantation loss (9.3% compared to 3.1% in control) was observed at the 150 mg/kg/day.

When closely inspecting the study report (180-0167-TX), a slight increase in the number of skeletal malformations were noted in the rabbit fetuses with a potential dose-dependent occurrence in supernumerary sternebra in addition to more individual occurring malformation of the ribs, vertebra and sternebra. The occurrence of supernumerary sternebra were according to the applicant within historical control data, however, the article by Ema M from 2012 were not submitted for assessment. The article by Ema et al. 2012 was provided on request and the observed malformations of the ribs, vertebra and sternebra appeared to be within the maximum range reported and the malformations were considered to represent expected variability and not related to zanubrutinib treatment. In maternal rabbits, a 3.2% decrease in body weight were observed in the high dose group of 150 mg/kg/day and corresponding to general findings of inappetence and periodically decrease food consumption in all groups. Abortions were additionally seen with a slightly increasing trend in the treated animals but without a clear dose-dependent occurrence. However, according to the applicant no obvious changes in body weight, food consumption or macroscopic findings preceded the abortions and a direct treatment-related effect could not be established.

The overall NOAEL in rabbits was determined to 150 mg/kg/day by the applicant, which is not endorsed due to findings of e.g. post-implantation loss (F1) and decreasing body weight (F0) among other issues at this dose. The implantation finding has been taken into consideration and the NOAEL reduced to 70 mg/kg/day with a revised safety margin of 25-fold.

Additionally, in TK analysis of the rabbit study, the systemic exposure of dams was considerably lower on GD18 than on GD6. In the next round of assessment, the applicant provided supporting individual systemic exposure data in pregnant rabbits. The systemic exposure of dams was lower on GD18 than GD6 at high dose group, but not at low or middle dose groups. Based on individual data, plasma concentrations were lower at the 1- and 8-hour time points. It is agreed that reason may be an endogenous animal variation in exposure due to pregnancy and the low animal number (n=4) per group.

Pre- and postnatal development and maternal function

Pre- and postnatal development toxicity studies were conducted in pregnant female rats (F0) and their offspring (F1) with dose of 30, 75 and 150 mg/kg/day zanubrutinib. The most significant finding was ophthalmic lesions in the F1 animals at dose ≥ 30 mg/kg/day, with a dose-dependent increase in severity and occurence from 26-46% (compared to 26% in control). Clinical observations of eye abnormalities (protuding eyes, big eyes and white eyes) were noted in addition to ophthalmological findings of pupil dilation post-mydriatics, cataract, corneal opacity, invisible intraocular structure, and unclear fundus. The abnormalities occured at safety margins of 3-4 times human clinical exposure (AUC) and should be sufficiently adressed in the SmPC section 4.6 and 5.3. The clinical relevance of

the findings is however uncertain since ophthalmic lesions were observed in the control group and they are also a common background finding in young Sprague Dawley rats as reported in the literature.

Additionally, 5-7% decrease in body weight of the F1 animals were detected from laction to termination at doses ≥ 75 mg/kg/day (13 times human AUC). No effect was detected on fertility and reproduction parameters of the F1 animals. The NOAEL for F1 animal was estimated by the assessor to < 30 mg/kg/day.

Beside clinical signs similar to the findings in the repeat-dose studies (transient salivation, decrease food intake, swelling of the lip and perinasal discharge), no significant changes with relevance to peri- and post-development toxicity were observed in the mother animals of F0. The NOAEL for F0 animals were therefore estimated to 150 mg/kg/day, in accordance with the suggestion made by the applicant.

A study evaluating transfer of zanubrutinib into milk was not located. Since the intended patient population are elderly, additionally animal studies are not supported from a 3R perspective. However, the lack of excretion data should be sufficiently addressed in the SmPC section 4.6 along with a recommendation to discontinue breast-feeding.

Juvenile studies

No juvenile studies were conducted for zanubrutinib, which is acceptable as the intended patient population with Waldenström's macroglobulinaemia has a median age of 63 to 68 years.

Other toxicity studies

Metabolites

The toxicokinetics of BGB-7941 was evaluated in the 6-month repeat-dose study in rats. BGB-7941 composed a higher systemic exposure in rats compared to humans (only present at 5.37% of radioactivity in plasma) and are therefore considered sufficiently characterized. Additionally, no further studies are required for metabolites present at less than 10% in human plasma.

Acrylic acid was thoroughly discussed in the pharmacokinetics section and was therefore not further addressed in this part.

Impurities

The mutagenic potential of 46 impurities were assessed by *in-silico* analysis using CASE Ultra software with two complementary methodologies (expert rule-based and statistical). A mutagenic-alert in structure were identified for six of the impurities and a mini-Ames test were conducted. All Ames-test were negative. All 46 impurities were therefore considered non-mutagenic in accordance with ICH M7 guideline.

Phototoxicity

Light absorption of BGB-3111 was only noted between 290 and 320 nm (UVB) with MEC higher than 1000 L mol^{-1} cm^{-1}, and no absorption above 320 nm. BGB-3111 was photostable when tested under light (4500Ix) in a stress condition. It has a favorable PK profile with short half-life and no tissue accumulation.

Based on the information from ICH S10, UV absorption only noted at UVB is rarely considered a problem for pharmaceuticals with systemic exposure, since UVB minimally penetrates beyond the epidermis; for compounds that only absorb light below 400 nm, such wavelengths do not reach the retina of the adult human eye due to limited penetration of the cornea, lens, and vitreous body. Additionally, there were no adverse effects noted in the eyes upon ophthalmology examination in repeat-dose toxicity studies of BGB-3111 up to 6-month or 9-month duration in both rats and dogs.

Based on its photochemical properties and available nonclinical data and general information, the potential risk of phototoxicity of BGB-3111 is considered low.

2.3.5. Ecotoxicity/environmental risk assessment

The pKa for zanubrutinib was calculated to be 3.33 and therefore this compound will be in its neutral form at environmentally relevant pH's (5 to 9). The log Kow was determined in a GLP study at 3 pH's. At pH 5, the log Kow was determined using the slow stirring method (OECD 123); at pH 7 and 9, the partition coefficient was determined with the shake flask method (OECD 107). The log Kow values were 3.2 at pH 5, 3.6 at pH 7 and 3.7 at pH 9. As all values were below the trigger of 4.5, a further PBT/vPvB assessment was not required.

Table 5: Summary of main study results of the provided ERA

Substance (INN/Invented Name): zanubrutinib/Brukinsa			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	LogK_{ow} < 4.5 (i.e. 3.2 at pH 5, 3.6 at pH 7 and 3.7 at pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	< 4.5	not B
	BCF		not B
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0,022	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II studies: not completed			

An Fpen default value of 0.01 (1%) is proposed in the guideline EMEA/CHMP/SWP/4447/00 corr 2 assuming that 100% of the patient population is daily taking the medicinal product. For zanubrutinib, the dosing regimen includes an oral dose of 160 mg taken twice daily (320 mg daily) over the whole year and thus refinement of Fpen based on treatment regimen is not possible. The prevalence indicated in the orphan designation was 1.4 per 10,000 (or 0.00014) which was used in the calculation of $PEC_{SURFACEWATER}$. The calculated $PEC_{SURFACEWATER}$ of 0.022 µg/L for WM indication exceeded 0.01 µg/mL and thus a Phase II environmental fate and effects assessment was triggered.

GLP-compliant Algal growth inhibition test (OECD 201), Daphnia sp. reproduction test (OECD 211) and Fish, Early Life Stage Toxicity Test (OECD 210) recommended in Phase II Tier A have been completed. Based on screening data set in algae, Daphnia and fish, the ratio $PEC_{surfacewater}/PNEC_{surfacewater}$ for the drug substance is below 1. Based on obtained effect parameters (NOEC), the fish is the most sensitive species for $PNEC_{water}$ prediction. However, in OECD 210 study effects greater than 10% was observed for the end-point body weight in all test concentrations. Hence, the lowest concentration tested has to

be considered as LOEC and a reliable NOEC cannot be determined. According to the guideline EMEA/CHMP/SWP/4447/00 corr 2, $PNEC_{water}$ calculation should be based on the lowest NOEC results from the base set long-term toxicity tests in three trophic levels. Based on obtained effect parameters (NOEC), the fish is the most sensitive species for $PNEC_{water}$ prediction. Zanubrutinib had a significant effect on the growth of the exposed larvae. Both body length and body weight end-points, being indicative of larval growth, were significantly affected at mean measured concentrations of 0.017 mg/L and higher. The NOEC was below the lowest concentration tested (i.e. <0.017 mg/L) for both endpoints and thus, reliable NOEC could not be determined for these parameters.

The CHMP further recommends a new OECD 210 study on the environmental risk assessment of zanubrutinib according to EMEA/ CHMP/SWP/4447/00 corr 2, 01 June 2006.

Adsorption and desorption parameters were determined using the batch equilibrium method (OECD 106) with three soils and two sludges as recommended in EMEA/ CHMP/SWP/4447/00 corr 2.

Additionally, the experimentally determined log Kow 3.2 at pH 5, 3.6 at pH 7 and 3.7 at pH 9 triggers a need of performing a bioaccumulation study in fish. The substance is not readily biodegradable and if the results from the water sediment study (OECD 308) demonstrate significant shifting of the drug to the sediment, effects on sediment organism should be investigated in Tier B. The GLP-compliant Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308) study, Sediment organism study *Chironomus sp* (OECD 218) and bioaccumulation study in fish (OECD 305) are presumably ongoing.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

- Phase II of the ERA is still ongoing. A standard Phase II Tier A assessment is ongoing and the results triggered Tier B assessment including sediment organism study in *Chironomus sp*. and bioaccumulation study in fish. These studies have been initiated. The full package will be completed by 4th Quarter 2022, and the applicant commits to submitting the final ERA report in December 2022.

2.3.6. Discussion on non-clinical aspects

GLP compliance

Initially GLP compliance was questioned, as the full non-clinical programme was performed in a non-MAD OECD country. However as the test facility has been included in the Belgian GLP compliance monitoring Authority, during the period studies with zanubrutinib was performed at the test facility, and no major scientific reasons for triggering a study specific GLP inspection was identified the studies included in the present MAA were considered GLP compliant; no GLP inspections will be triggered in the current MAA. This position is based on the fact that GLP and related inspections are harmonized across all OECD MAD countries and therefore the outcome of inspections carried out by the GLP CMA of a EU MS part of the OECD MAD (in this case Belgium) ensure in principle the same standards of inspections carried out by any other OECD MAD country acknowledging that the site was included in the Belgian GLP Monitoring program, inspected every two years and found GLP compliant during these inspections, including in the period in which the studies considered for assessment were conducted.

Pharmacology

BGB-3111 is designed to form a covalent bond at the BTK active site. This was shown in vitro both by inhibition of downstream reactions and precipitation experiments. Functional activity was demonstrated in cancer cell lines. BGB-3111 appeared to be selective for mantle dell lines, TMD8 and ABC-DBCL cell lines. BGB-3111 occupied intracellular BTK at similar potency to ibrutinib. While BGB-3111 was shown to be functional in relevant cancer cell lines, ex vivo studies in primary lymphoma cells from patients was not conducted, as such specimens are not available commercially.

BGB-3111 was consistently more potent and efficient than ibrutinib in NOD/SCID disease models of subcutaneous lymphoma tumours. This is most likely due to an increased bioavailability. However, efficacy in the systemic lymphoma model was less convincing, since the animals appeared to deteriorate almost simultaneously regardless of treatment. Body weight data was recalculated in the next round of assessment and statistically significant differences was found between vehicle control and treatment group on Day 51 and 54. However, the effect of decrease in body weight over the course of treatment in the NOD-SCID mouse appear not to be clinically relevant as no apparent changes were observed in clinical trials. Increase in survival as compared to the control group was 20-40%.

The potential and possible mechanisms for resistance development to zanubrutinib was not studied in WM resistant and wild-type WM cells. However, studies are ongoing in other cancer cell lines including IMD-8 and Ramos and results are expected to be published once available.

A PKPD study in ICR mice showed rapid BTK protein binding in PBMC and spleen. Rebound was faster in spleen compared to PBMC. Exposure data indicated a 3-fold difference in bioavailability between ibrutinib and BGB-3111. Moreover, it was demonstrated that 70% BTK occupancy occurred at lower than clinically relevant plasma concentrations.

Non-clinical in vitro and in vivo studies of the pharmacology of BGB-3111 indicate proof of concept in terms of mode of action. However, since ex vivo studies using relevant primary lymphoma cells are missing and the efficacy in the systemic xenograft model appear limited, non-clinical proof of concept is not entirely convincing.

BGB-3111 was more selective than ibrutinib on known human kinases, however, still react with other kinases than BTK. The low potency on ITK and EGFR kinases compared to ibrutinib is likely to lead to lower incidence of diarrhoea and a preservation of T and MK cell functions. Moreover, it was demonstrated that in contrast to ibrutinib, BGB-3111 was 10-fold weaker in the ability to inhibit rituximab induced ADCC correlating with its low potency on ITK.

A classical safety pharmacology program of stand-alone studies in rat CNS, respiratory) and dog (cardiovascular) was presented. No concerns arose from these studies.

Pharmacokinetics

Pharmacokinetics appeared dose-linear and time-independent in rat and dog with moderate bioavailability. However, bioavailability was lower in male rats compared to female rats.

A study of the pharmacokinetics of ^{14}C-BGB-3111 in rat showed that $t_{1/2}$ values were 31.6 -34.8 hours in blood and 7.75 -10.5 hours in plasma, indicating slower elimination of BGB-3111 related radioactivity in blood than in plasma (RTC00782). This may correlate to concentration dependent preference of BGB-3111 for red blood cells in the rat. A similar evaluation was performed in humans (BGB-3111-105 CSR). This study showed similar half-life of BGB-3111 related radioactivity in plasma and blood (44.4 hours in blood and 46.7 hours in plasma), hence the difference found in rat was apparently not clinically relevant.

In a distribution study in rats, BGB-3111 (non-labelled) showed preference for the GI system and the liver. This was confirmed in a QWBA study. Half-life of BGB-3111 related radioactivity was varying with long half-life in organs associated with adverse effects in patients e.g. bone marrow, spleen, stomach wall and lung. Small intestinal wall and liver showed the highest tissue:plasma ratio of 47 and 26 respectively.

BGB-3111 is extensively metabolised in rat and human. Metabolism in dog was only investigated in vitro. The main concern for metabolism is the acrylic acid found to comprise of the major part of the total radioactivity in plasma in the human AME study. The Applicant further clarified the positive safety assessment of acrylic acid as a metabolite in human plasma by mainly referring to the fact that acrylic acid was present in the dosing material of BGB-3111 in the human AME study (radio-chromatogram submitted) and not in the ADME study in rat where the purity of the dosing material was confirmed by a radio-chromatogram. Moreover, deacrylated metabolites were present in both rat, dog and human in very low amounts indicating very low amounts of acrylic acid would be produced. Hence, the importance of this clearance pathway is minimal.

BGB-3111 related radioactivity was found to be covalently bound to plasma in a rat metabolism study but the applicant clarified that the selectivity of zanubrutinib is lower in rat as compared to human, since the covalent-bound radioactivity was high in rat plasma (22-25%) and lower in human plasma (5.5 to 6%). Comparing with ibrutinib, covalent binding in human plasma is much lower for zanubrutinib (38-51% vs 5.5 to 6%) indicating higher selectivity of zanubrutinib versus ibrutinib, which is reassuring.

BGB-3111 was metabolised to a higher degree in rat as compared to human. The active metabolite BGB-7941 was present in rat in higher amounts than in humans and is considered qualified. Otherwise BGB-3111 was extensively metabolised in both species by several routes including a broad panel of both phase 1 and phase 2 metabolites, although UGTs seem to play a minor role.

BGB-3111 is mainly metabolised by CYP3A4. BGB-3111 related radioactivity was mainly excreted via faeces in both rat and human. Potential drug-drug interaction with CYPs and transporters was evaluated using classical assays and followed up clinical studies and/or PBPK modelling.

Toxicology

The non-clinical toxicity and toxicokinetic profile of zanubrutinib (BGB-3111) was characterized in Sprague-Dawley rats and Beagle dogs in single-dose studies and 14-day, 28-day, 91-day and 6/9-month repeat-dose studies. Rats and dogs were chosen for the in vivo toxicity evaluation, as they are pharmacologically relevant species based on BTK sequence homology and functional assay.

No mortality was observed in the single-dose studies in rats and dogs at doses up to 1000 mg/kg/day and no severe toxic effects were noted.

In rat repeat dose studies up to 6-month treatment, test article related mortality was noted at the dose of 1,000 mg/kg/day (81x clinical AUC) with histopathologic findings in the gastrointestinal tract. Other findings were mainly noted in the pancreas (atrophy, fibroplasia, haemorrhage, and/or inflammatory cell infiltration) at the doses ≥ 30 mg/kg/day (3x clinical AUC), in the skin around the nose/mouth/eyes (inflammatory cell infiltration, erosion/ulcer) from the dose of 300 mg/kg/day (16x clinical AUC), and in the lung (presence of macrophages in the alveolar) at the dose of 300 mg/kg/day. All these findings were fully or partially reversed after a 6-week recovery except for the pancreatic findings which were not considered clinically relevant.

Mortality appeared to be caused by severe gastrointestinal toxicity with histopathological findings of erosion, necrosis, ulceration and acute inflammation. The findings occurring at safety margins of 62-71-fold systemic exposure in humans (AUC) and it is agreed that the risk of lethal GI toxicity is considered to be minimal. However, findings of less severe GI disturbances as e.g. diarrhea occurred

even at low doses in both rats and dogs and was considered to be clinically relevant, as it is potentially related to inhibition of EGFR in the intestine. The findings were transient in rats at 300 mg/kg/day but more pronounced in dogs, with a change into watery/mucoid diarrhoea in 50% of the male dogs at doses of ≥10 mg/kg/day and in 100% of all dogs at doses of 100 mg/kg/day (see SmPC section 5.3).

Another frequent finding in the repeat-dose studies were skin lesions in the face of the rats and face/body of the dogs. In the next round of assessment, it was agreed that the skin changes are of clinical relevance, potential caused by inhibition of EGFR in the skin and occur at doses of 300 mg/kg/day in rat and 10 mg/kg/day in dogs. Changes in clinical pathological parameters (hematology, serum chemistry and urinanalysis parameters) were also noted in both rats and dogs with a tendency of a dose-dependent increases in magnitude and number of changed parameters over time. Even though, many of the parameters were significantly changed compared to control animals, most were still within historical reference data. Additionally, an across species dose-dependent increase in neutrophils was noted but the clinical relevance was considered to be low, as the finding differed from the clinical setting, where neutropenia was observed (see discussion on clinical safety).

In dog repeat dose studies up to 9-month treatment, test article related findings were mainly noted in the gastrointestinal tract (soft/watery/mucoid stool), skin (rash, red discoloration, and thickened/ scaling), and in the mesenteric, mandibular, and gut associated lymph nodes and spleen (lymphoid depletion or erythrophagocytosis) at the doses from 10 mg/kg/day (3x clinical AUC) to 100 mg/kg/day (18x clinical AUC). All these findings were fully or partially reversed after a 6-week recovery.

Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (Chinese hamster ovary) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in rats. The absence of carcinogenicity studies with zanubrutinib is justified based on a weight of evidence argumentation and in line with the relevant guideline.

A combined male and female fertility and early embryonic development study was conducted in rats at oral zanubrutinib doses of 30, 100 and 300 mg/kg/day. No effect on male or female fertility was noted but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The dose of 100 mg/kg/day is approximately 13-fold higher than the human therapeutic exposure.

Embryo-foetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts with the incidence of 0.3 %-1.5 %) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5-fold higher than the human therapeutic exposure *(see SmPC section 5.3)*.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 70 mg/kg is approximately 25-fold higher than the human therapeutic exposure and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5-fold higher than the human therapeutic exposure.

In the fertility and early embryonic developmental study in rats, 12% post-implantation loss (compared to 6% in the control group) and abnormal sperm morphology were detected at dose of 300

mg/kg. The NOAEL was revised to 100 mg/kg/day providing a safety margin of 3-fold to human therapeutic dose.

Reproductive toxicity studies revealed a teratogenic effect of zanubrutinib in rats, observed as a dose-dependent increase in incidence (0,3%-1,5%) of two- and three chambered hearts in rat fetuses at all dose levels (≥ 30 mg/kg/day), corresponding to a safety margin of 3-4 human systemic exposure (AUC) for the lowest dose. An increased post-implantation loss (9.3% compared to 3.1% in control) in maternal rabbits at the highest dose of 150 mg/kg/day resulted in revision of the NOAEL to 70 mg/kg/day with a safety margin to human clinical exposure of approximately 25-fold.

Additionally, in TK analysis of the rabbit study, the systemic exposure of dams was considerably lower on GD18 than on GD6. The difference in systemic exposure was suggested to be caused by endogenous animal variation in exposure due to pregnancy and the low animal number (n=4) per group.

No mutagenic potential was noted for the tested 46 impurities. Further phototoxicity studies was waivered based on additional assessment of existing clinical data in accordance with ICH S10 guideline, showing that only few treatment emergent adverse event (TEAE) were reported in relation to photosensitivity. Additional clinical assessment was provided based on existing data in accordance with recommendations in ICH S10. It appears that, after > 1700 patient-years of follow-up only 12 (1.5%) patients treated with zanubrutinib reported a treatment emergent adverse event (TEAE) related to photosensitivity (see also Clinical Safety discussion). All patients except one were white and from countries where white individuals are of particular risk (i.e., Australia.).

ERA

Phase I of the ERA has been completed and Phase II is still ongoing, and the updated ERA report will be submitted to the CHMP. Additionally, a new OECD 210 study should be conducted as the submitted study did not provide reliable NOEC for the end-point body weight and hence proper environmental risk assessment of zanubrutinib according to EMEA/ CHMP/SWP/4447/00 corr 2, 01 June 2006.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical development of zanubrutinib is considered satisfactory. All relevant information is included in the PI.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

Phase I of the ERA has been completed and Phase II is still ongoing. A standard Phase II Tier A assessment is ongoing and the results triggered Tier B assessment including sediment organism study in *Chironomus sp*. and bioaccumulation study in fish. These studies have been initiated. The full package will be completed by 4th Quarter 2022, and the applicant commits to submitting the final ERA report in December 2022.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

Tabular Listing of All Clinical Studies, divided in A. clinical pharmacology studies and B. clinical studies contributing efficacy and safety, all in Adult subjects.

A. Clinical pharmacological studies.

Table 6

Phase	Study No.	Title	Test Product(s); Dosage Regimen; Route of Administration	Indication	Status Number of Subjects/Patients Enrolled (cutoff dates)
1	BGB-3111-105	A Phase 1 Study to investigate the absorption, metabolism, and excretion of [^{14}C]-BGB-3111 following single oral dose administration in healthy male subjects	Zanubrutinib capsules 320 mg single dose oral	Healthy Volunteer	Completed 6 subjects
1	BGB-3111-104	A Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of BGB-3111 in Healthy Subjects	Zanubrutinib capsules Part A: 600 mg Rifampin, 320 mg Zanubrutinib single dose Part: B 200 mg Itraconazole, 20 mg Zanubrutinib single dose Oral	Healthy Volunteers	Completed 38 subjects
1	BGB-3111-107	A Phase 1, Open-label, Multicenter Study to Evaluate the Pharmacokinetics and Safety of BGB-3111 in Subjects with Various Degrees of Hepatic Function	Zanubrutinib capsules 80 mg single dose oral	Hepatic Impaired	Completed 29 subjects
1	BGB-3111-108	An Open-label, Fixed-Sequence Study in Healthy Male Subjects to Assess the Drug Interaction Potential of Multiple Doses of Zanubrutinib With a Drug "Cocktail" Representative for CYP3A4, CYP2C9, CYP2C19, P-gP and BCRP Substrates	Zanubrutinib capsules 160 mg twice daily oral	Healthy Volunteers	Completed 18 subjects
1	BGB-3111-103	A Single Center, Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of a Single Dose of BGB-3111 Given Orally at 320 mg QD in Healthy Adult Subjects	Zanubrutinib capsules 320 mg single dose Oral	Healthy Volunteers	Completed 18 subjects
1	BGB-3111-106	A Two-Part Study Consisting of a Randomized, Placebo-Controlled, Single Dose Safety and Tolerability Study (Part A) Evaluating a Supratherapeutic Dose of Zanubrutinib Followed by a Randomized, Placebo- and Positive-Controlled, Crossover Study (Part B) to Evaluate the Effect of Zanubrutinib on Cardiac Repolarization in Healthy Volunteers	Part A: 480 mg (6x80mg capsules) zanubrutinib dose or matching placebo Part B: A. Single dose of 160 mg (4x80 mg capsules) zanubrutinib and 4 placebo capsules. B. Single dose of 480 mg (6x80 mg capsules) zanubrutinib C. Placebo to match zanubrutinib, consisting of 6 placebo capsules. D. Moxifloxacin 400 mg positive control, consisting of one 400 mg moxifloxacin tablet. oral	Healthy Volunteers	Completed 40 subjects

B. Clinical studies contributing efficacy and safety in zanubrutinib

Table 7

Study & Location	Study Design	Population	Starting Dose	N	First Patient First Dose/ Enrolment Status/ Study Status
Efficacy and Safety Data					
302 Global	Phase 3, 2 cohort 3 arm study	WM (TN & R/R)	160 mg BID	229[a] (99[a] ibrutinib)	25 Jan 2017/ Enrolment complete/ Ongoing
AU-003 Global (AU, NZ, SK, USA, IT, UK)	Phase 1/2, single-arm, dose escalation and cohort expansion	CLL/SLL (R/R & TN), NHL, MCL, WM (R/R & TN)[b], HCL (R/R), RT	160 mg BID 40 mg QD 80 mg QD 160 mg QD 320 mg QD Total	278 3 4 5 95 385	25 August 2014/ Enrolment complete/ Ongoing
Safety Data Only					
210 China	Phase 2, single-arm	WM (R/R)	160 mg BID	44	31 August 2017/ Enrolment complete Ongoing
1002 China	Phase 1, single-arm	CLL/SLL, MCL, WM/LPL, FL, MZL, HCL, nGCB DLBCL (R/R)	160 mg BID 320 mg QD Total	34 10 44	05 July 2016/ Enrolment complete/ Ongoing
205 China	Phase 2, single-arm	CLL/SLL (R/R)	160 mg BID	91	09 March 2017/ Enrolment complete/ Ongoing
206 China	Phase 2, single-arm	MCL (R/R)	160 mg BID	86	02 March 2017/ Enrolment complete/ Ongoing
Total Patients in the Integrated Safety Population				877 (98 ibrutinib)	

Abbreviations Table 3.27 b: AU, Australia; BID, twice daily; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukaemia; IT, Italy; ITT, intent-to-treat; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; N, Number of patients treated with zanubrutinib; nGCB, non-germinal centre B-cell-like; NHL, non-Hodgkin lymphoma; NZ, New Zealand; QD, once daily; R/R, relapsed or refractory; RT, Richter transformation; SK, South Korea; SLL, small lymphocytic lymphoma; TN, treatment-naive; UK; United Kingdom; USA, United States of America; WM, Waldenström's macroglobulinemia.

a Includes 2 subjects (one in each treatment group) who were randomized but did not receive study drug. These 2 subjects are excluded from the integrated safety population but were included in the ITT Analysis Set.

b N with WM = 78; 73 of whom were evaluable for efficacy.

2.4.2. Pharmacokinetics

Methods

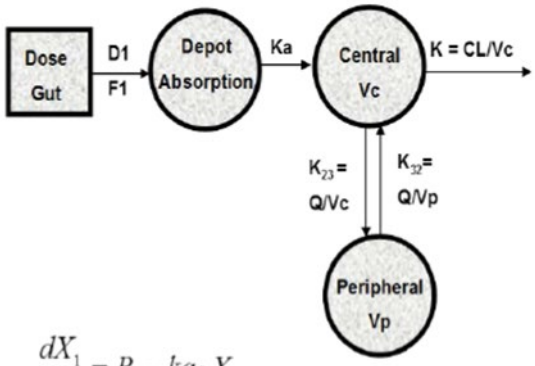
Methods

Bioanalysis: Quantification of zanubrutinib was performed using a validated LC-MS/MS method. Across clinical studies study analysis performed well and the bioanalysis conducted in support of zanubrutinib clinical development is mainly considered acceptable.

Pop PK model: The objectives of the Pop-PK analysis were to determine the effects of demographic, pathophysiologic, and disease-related covariates on the PK of zanubrutinib to better understand clinical factors that might affect exposure in individual subjects. The PK analysis dataset included data from nine 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 final Model Development Dataset included 4,925 zanubrutinib plasma concentration measurements from 632 subjects, 90 of whom were healthy volunteers and the rest were patients. Covariates were selected based on clinical judgment, mechanistic plausibility and prior knowledge. These covariates were either demographics-related or hepatic and renal function related.

The final PopPK model for zanubrutinib was based on a previous 2-compartment model with an absorption depot. The old model was updated with additional data and data with non-linear kinetics (480 mg) was excluded, thus representing a dose range of 20-320 mg zanubrutinib. Health status and baseline ALT were identified as significant covariates of CL/F.

Figure 8 ***PopPK 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

Parameter estimates for the final PopPK model for zanubrutinib are presented in Table 7. The geometric mean elimination half-life was 3.44 hours with a CV of 40.0%. The bootstrap 95% confidence intervals were in general wider than the asymptotic confidence intervals estimated by NONMEM. No trends were observed in the presented GoF plots.

Table 8 Summary of final population PK parameters

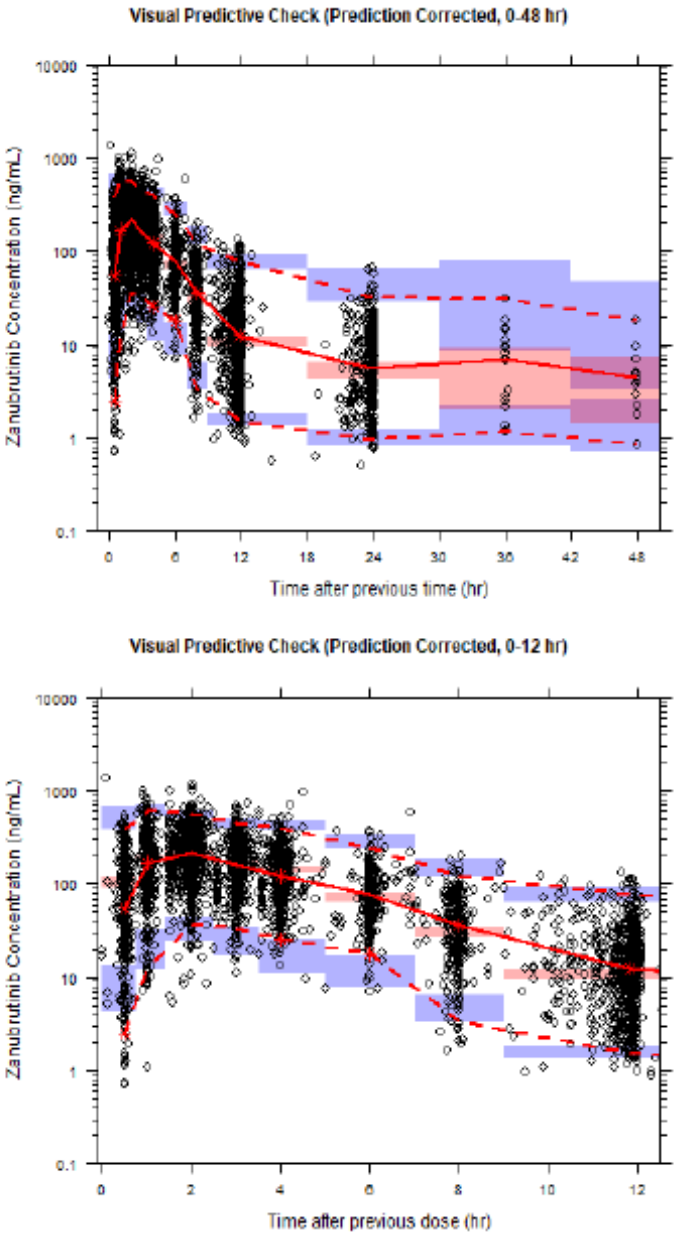
Parameter	Parameter Description		Population Estimate (%RSE)	Inter-Individual Variability (%RSE)	Inter-occasion variability (%RSE)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	Patient	170 (0.237%)	36.7 (4.99%)	28.6 (1.20%)
$exp(\theta_{10})$		HV	118 (4.96%)	-	-
θ_{11}	Influence of ALT on CL/F		-0.189 (2.16%)	-	-
$exp(\theta_2)$	Apparent central volume, V_c/F (L)		112 (0.462%)	37.1 (26.7%)	67.5 (0.56%)
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)		26.5 (0.421%)	102 (2.11%)	-
$exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)		345 (0.318%)	86.4 (8.14%)	-
$exp(\theta_5)$	Absorption rate constant, k_a (hr^{-1})		0.526 (0.05%)	-	-
$exp(\theta_6)$	Duration, D_1 (hr)		1.13 (0.124%)	62.3 (4.05%)	
$\omega^2_{CL,Vc}$	Covariance (CL/F,V_c/F)		0.129 (12.5%)	-	-
θ_9	Additive residual error (ng/mL, TFDS<5 hr)		8.69 (0.045%)	-	-
θ_7	Additive residual error (ng/mL, TFDS≥5 hr)		0.633 (0.084%)	-	-
θ_8	Proportional residual error (%)		44.9 (0.098%)	-	-

Table 9 Q103.1: Inter-individual and intra- individual (inter-occasion) variability parameters in zanubrutinib population PK model

Parameter	Parameter description	Previous value[a]	Updated value[b]
Inter-individual variability	CL/F	36.7%	38.0%
	V_c/F	37.1%	38.4%
	Q/F	102%	135%
	V_p/F	86.4%	105%
	D_1	62.3%	68.9%
Inter-occasion variability	CL/F	28.6%	29.2%
	V_c/F	67.5%	76.0%
	D_1	62.3%	68.9%
Proportional residual error		44.9%	47.3%

[a] 100%*omega; [b] 100%*sqrt(exp(omega^2)-1)

Figure 9 ***pcVPC of zanubrutinib plasma concentration- time profiles across all studies***



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 (2.5th to 97.5th %ile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5th and 97.5th predicted percentile concentrations.

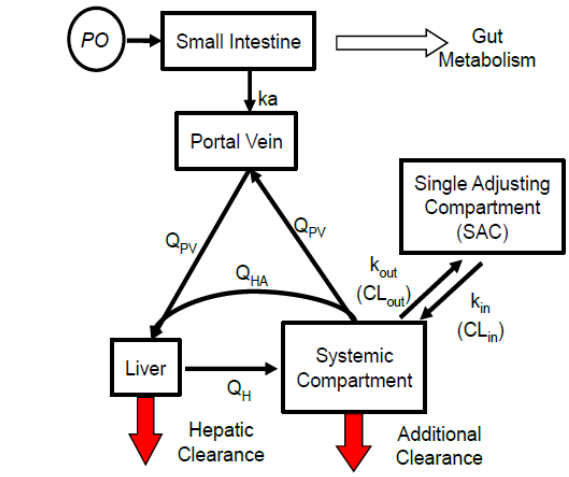
The effect of health status and baseline ALT on zanubrutinib steady-state exposure was further investigated in a sensitivity analysis. Baseline ALT had little influence on exposure metrics whereas the sensitivity analysis clearly showed a PK difference between healthy volunteers and patients, with patients having lower exposure than healthy subjects.

E-R analyses: Explorative exposure boxplots stratified by response values were plotted against the probability of response for selected measures of efficacy and safety. If any trends were detected, further evaluation by logistic regression modelling were conducted.

C-QTc relations for zanubrutinib and the positive control moxifloxacin were both described by separate linear mixed-effects models. The GOF plots for the linear model fit for both compounds were acceptable and data did not indicate any hysteresis or C-QTc relation, even the data for zanubrutinib could be fitted with a quadratic term.

PBPK model:

Figure 10 ***Minimal physiologically based pharmacokinetic model with a single adjusting compartment (SAC)***



Q_H, Q_{PV} and Q_{HA} are blood flows in the liver, portal vein and hepatic artery, respectively; CL_{in} and CL_{out} are the clearances which act on the masses of drug within the systemic compartment and the SAC respectively; PO is oral dosing route; fa is the fraction absorbed from the gut and ka is the associated first order absorption rate constant.

A PBPK model for zanubrutinib was created in Simcyp using in-vitro data, data from the human ADME study (BGB-3111-105) along with other clinical data obtained in healthy subjects (HV) and in patients in the dose range 20-320 mg QD zanubrutinib.

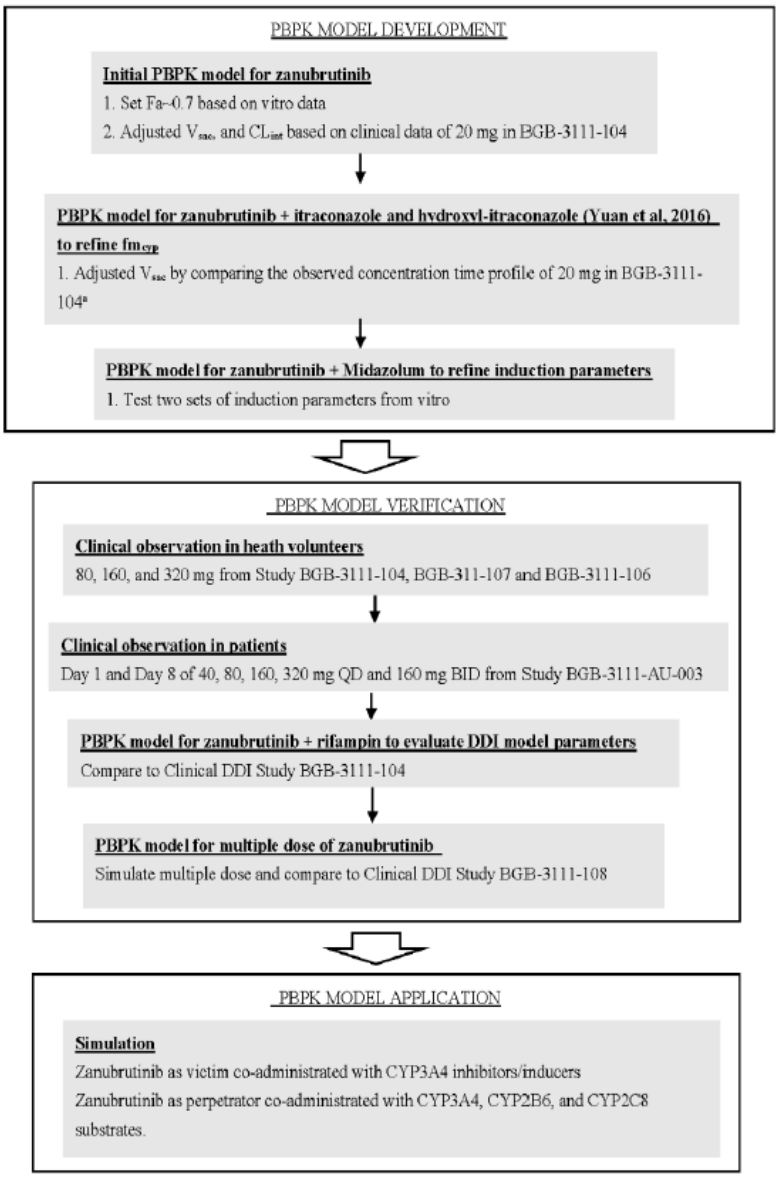
Table 10 Final input parameters for zanubrutinib PBPK model

Parameter	Value	Comment
Physicochemical Properties and Blood Binding		
MW (g/mol)	471.55	Internal data
log P	4.2	Monoprotic Base, experimental data (Study Report SR-PPD-BEI-002-001 V01)
pKa1	3.3	Experimental data (Study Report SR-PPD-BEI-002-001 V01)
B/P	0.804	Experimental data (Study Report 3D_RN016123)
f_u	0.0582	Experimental data (Study Report 3D_RN016124)
Absorption: Advanced Dissolution, Absorption and Metabolism (ADAM) Solid Formulation, Immediate Release, Diffusion Layer Model with Solubility-pH profile		
$P_{eff,man}$ (10^{-4} cm/s)	0.9	Experimental data (Study Report 3D_RN016116) Adjusted to match Fa~0.7 based on clinical data from BGB-3111-105 CSR
Qgut	5.9	Predicted by Simcyp

Table 11

Parameter	Value	Comment
Solubility (mg/mL)	0.247,0.073,0.054 and 0.052 at pH 1.2, 4.5, 6.8 and 7.4 respectively	Experimental data (Study Report SR-PPD-BEI-002-002 V01)
Distribution: Minimal PBPK model with Single Adjusting Compartment (SAC)		
CL_{in} (L/h)	188.19	Adjusted by comparing time-concentration profile of 20 mg zanubrutinib
CL_{out} (L/h)	142.15	Adjusted by comparing time-concentration profile of 20 mg zanubrutinib
V_{ss} (L/kg)	9.4	Predicted by Simcyp Method 1
V_{sac} (L/kg)	9.2	Adjusted by comparing time-concentration profile of 20 mg zanubrutinib
Elimination: Enzyme Kinetics		
CL_{int} (µL/min/mg)	120	Adjusted. Observed intrinsic clearance is 109 µL/min/mg (Study Report 3D_RN016107). Estimated fm_{CYP3A4} is 81.6%
Additional clearance HLM (µL/min/mg protein)	60	Study Report BGB-3111-104 CSR; Adjusted by the observed DDI data with itraconazole (Estimated additional HLM is 16.8%)
$f_{u\,mic}$	0.407	Predicted by Assay pH=7.4, microsomal protein 0.5 mg/mL
CL_R (L/h)	0.5	Based on human AME study (BGB-3111-105 CSR); Estimated renal contribution is 1.6% of the total CL
Interaction:		
Induction/Suppression	Ind_{max}=6.27 Ind_{C50}=0.47	Experimental data (Study Report 3D_RN016127) zanubrutinib at 0.3, 3 and 30 µM increased CYP3A4 activity by 2.02, 6.27 and 2.51-fold, respectively. Fixed Ind_{max} = 6.27, using E_{max} model to obtain ind_{C50}=0.47
Competitive inhibition	Ki_{CYP1A2}=60.5 µM; Ki_{CYP2B6}=60.5 µM; Ki_{CYP2C8}=2.015 µM; Ki_{CYP2C9}=2.845 µM; $Ki_{CYP2C19}$=3.790 µM; Ki_{CYP2D6}=36.45 µM; Ki_{CYP3A4}=7.15 µM;	Experimental data (Study Report 3D_RN016124) For a competitive enzyme inhibition, Ki calculated by $Ki=IC_{50}/2$ Fraction unbound in microsomes, fumic=0.774 (predicted by microsomal protein: 0.1 mg/mL)

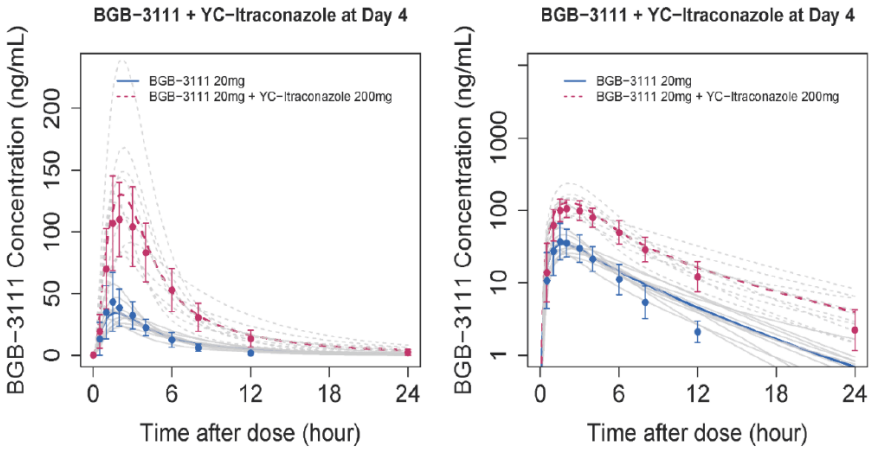
Figure 11 ***The overall model development, verification process and simulation flow chart***



The clinical data of zanubrutinib as victim of itraconazole (BGB-3111-104) was used to test and adjust CLint and fmCYP3A4. Only metabolism by CYP3A4 was assumed and therefore only modulators of CYP3A4 were investigated.

Figure 12 **Simulation of plasma concentration- time profiles of zanubrutinib in healthy subjects after a single oral dose (20mg) co administered with itraconazole**

(Left = Linear Scale; Right = Semi-Log Scale)



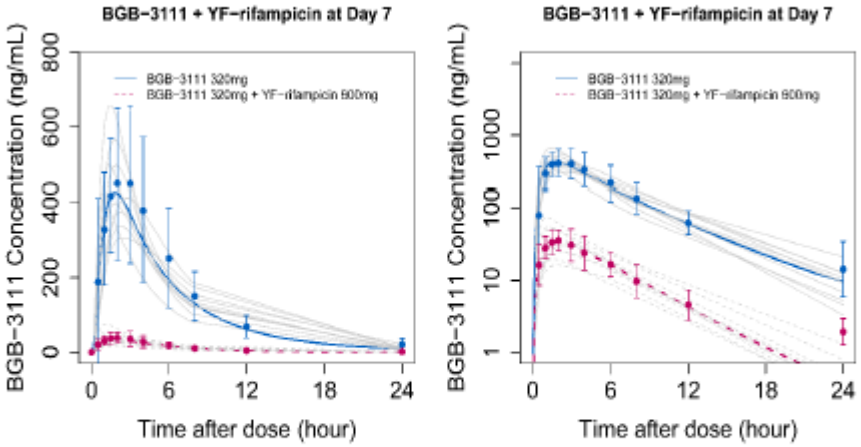
Observed (dot; Clinical DDI BGB-3111 study-104) and simulated plasma concentration-time profiles of a single dose of zanubrutinib 20 mg in the absence of itraconazole (solid lines) and on the 4th day of 4 days of dosing of itraconazole (200 mg QD) (dashed lines). The solid and dashed grey lines represent the outcomes of simulated individual trials of absence and presence itraconazole, respectively.

The zanubrutinib model was verified by comparison of model predictions to clinical data: Single dose studies in HV (BGB-3111-104, 106 and 107); multiple dose studies in HV (BGB-3111-108) and in patients (BGB-3111-AU-003) in addition to published clinical data for itraconazole and its interaction with midazolam.

The clinical data of zanubrutinib as victim of rifampin (BGB-3111-104) was used to verify the PBPK model for zanubrutinib + rifampicin.

Figure 13 **Predicted vs observed plasma concentration- time profiles of zanubrutinib (320mg) in healthy subjects with or withoutrepeated dosing of rifampicin**

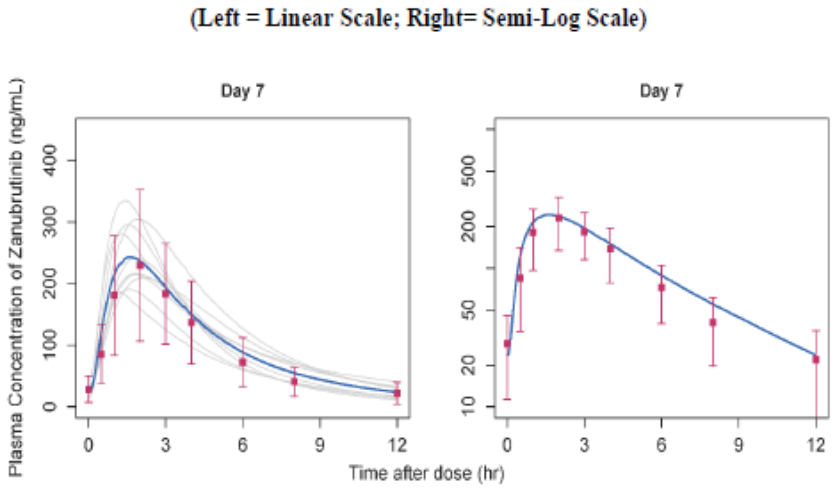
(Left = Linear Scale; Right= Semi-Log Scale)



Observed (dot; Observation from clinical study BGB-3111-104) and simulated plasma concentration-time profiles of zanubrutinib (320 mg) in the absence of rifampicin (solid blue line) and on the 7th day following multiple dosing of rifampicin (7 days, 600 mg QD) (dashed lines). Using Ind_{max} and Ind_{C50} values of 37.1 and 0.28 µM (Yamashita et al., 2013). The solid and dashed grey lines represent the outcomes of simulated individual trials in the absence and presence of rifampicin using the YF-rifampicin model parameters, respectively.

Ten virtual trials of 100 healthy subjects following multiple oral doses of zanubrutinib 160 mg BID on Days 1 - 7 were simulated and were in good agreement with the observed data (BGB-3111-108).

Figure 14 ***Predicted vs observed plasma concentration- time profiles of zanubrutinib in healthy subjects after multiple oral BID dose (160 mg) on day 7***



Observed (solid square; Observation from clinical study BGB-3111-108) and simulated plasma concentration-time profiles of multiple dose of zanubrutinib 160 mg (solid blue line). The solid grey lines represent the outcomes of simulated individual trials.

Zanubrutinib as a victim of DDI of strong CYP3A4 inhibitor (itraconazole) and strong inducer (rifampin) was investigated in clinical Study BGB-3111-104. The zanubrutinib model was used to predict DDI potential for zanubrutinib as a victim co-administered with strong CYP3A4 inhibitors, itraconazole, ritonavir and clarithromycin, respectively; moderate CYP3A4 inhibitors, erythromycin, fluconazole and diltiazem, respectively; mild CYP3A4 inhibitors, fluvoxamine, cyclosporine and cimetidine, respectively. Ongoing Study BGB-3111-113 will confirm the proposed dose recommendations for zanubrutinib in the presence of moderate (fluconazole and diltiazem) and strong (clarithromycin and voriconazole) CYP3A inhibitors.

The zanubrutinib model was used to predict the DDI potential for zanubrutinib as a victim co-administered with strong CYP3A4 inducers, rifampicin and carbamazepine, respectively, and moderate CYP3A4 inducer, efavirenz. Data from DDI study BGB-3111-112 with co-administration of rifabutin (a moderate CYP3A inducer) have also been submitted and the SmPC amended accordingly.

The impact of administration of a PPI on zanubrutinib absorption was modelled by increasing gastric pH from 1.5 to 4.5 in the standard Simcyp healthy volunteer population (fasted model). The gastric effect of omeprazole on zanubrutinib PK was also investigated in vivo as part of Study BGB-3111-108.

Zanubrutinib as a perpetrator was investigated in vivo in a cocktail DDI study (BGB-3111-108) with substrates for CYP3A4 (midazolam), CYP2C9 (S-warfarin), CYP2C19 (omeprazole), P-gp (digoxin) and BCRP (rosuvastatin, also substrate for OATP1B1, OATP1B3). The zanubrutinib model was used to predict the DDI potential for zanubrutinib as a perpetrator when co-administered with CYP3A substrate, ethinylestradiol; CYP2B6 substrate bupropion and CYP2C8 substrates, repaglinide and rosiglitazone.

Absorption

The *in vitro* studies with Caco-2 cells and with Wild-type MDCK cells and MDCK-MDR1 cells suggested that zanubrutinib may be a P-glycoprotein (P-gp) substrate. Based on its permeability constant (average Papp = 18.3 × 10^{-6} cm/s - 21.1 × 10^{-6} cm/s at 0.5 - 10 µM, respectively) in Caco-2 cells, zanubrutinib has high permeability across biological membranes when compared with high permeability marker propranolol and low permeability marker atenolol. Zanubrutinib is very slightly soluble 0.193 mg/ml in pH 1.2 hydrochloride acid buffer. The solubility shows decreasing trend when pH increases. The provided information supports the classification of zanubrutinib as BCS class II compound with low solubility and high permeability.

In the clinical pharmacology studies, zanubrutinib was rapidly absorbed with median time to maximum concentration (T_{max}) of 1.5-2.0 hours after single dose administration in healthy volunteers at fasted conditions.

The exposure of zanubrutinib seem to increase dose proportionally between the consecutive doses from 20 mg to up to 320 mg when calculating the dose adjusted AUC after single dose administration. However, there is variability in the exposure between the studies. The elimination half-life varied between the studies and shows increasing trend with dose being approximately 5 to 6 hours in healthy volunteers after 160 mg dose.

Table 12 Summary of pharmacokinetic parameters of zanubrutinib after single dose administration in healthy volunteers at fasted conditions (geometric mean (%CV), median (min., max.) for T_{max}).

Parameter (Unit)	**20 mg BGB-3111-104**	**80 mg BGB-3111-107**	**160 mg BGB-3111-106**	**320 mg BGB-3111-103**	**320 mg BGB-3111-104**	**[14C]-Zanubrutinib 320 mg BGB-3111-105**	**480 mg BGB-3111-106**
	(N = 18)	**(N = 11)**	**(N = 28)**	**(N = 14)**	**(N = 20)**	**(N = 6)**	**(N = 30)**
C_{max} (ng/mL)	47.5 (41.0)	162.8 (41.1)	216 (24.2)	444 (54.99)	532 (40.0)	478 (18.4)	406 (30.7)
$AUC_{0\text{-last}}$ (ng*h/mL)	176.1 (29.92)	663.0 (37.2)	1160 (25.1)	1851 (62.14)	3361 (35.36)	2440 (23.2)	2770 (28.9)
$AUC_{0\text{-}\infty}$ (ng*h/mL)	183.6 (29.36)	683.1 (36.2)	1230 (23.5)	2503 (41.76)	3431 (36.05)	2530 (23.6)	3060 (25.9)
T_{max} (h)	1.50 (1.00-4.00)	1.50 (1.00, 6.00)	1.5 (1.0, 6.0)	2.00 (1.00 - 4.00)	2.00 (0.500-6.00)	1.06 (1.00, 2.00)	2.0 (0.5, 6.0)
$t_{½}$ (h)	2.17 (18.2)	3.032 (64.5)	5.3 (2.3, 15)	5.63 (2.72 - 7.33)	6.79 (53.8)	5.54 (47.9)	8.1 (2.8, 46)
CL/F (L/h)	108.9 (29.36)	117.1 (36.2)	126 (29.0)	-	93.26 (36.05)	126 (23.6)	140 (38.8)
Vz/F (L)	341.2 (33.96)	512.3 (60.0)	966 (36.7)	-	914.0 (73.29)	1010 (57.1)	1630 (55.8)

BGB-3111-103, food-effect study: samples up to 24 h, median (range) for $t_{1/2}$.
BGB-3111-104, DDI-study: samples up to 48 h, geometric mean (%CV) for $t_{1/2}$.
BGB-3111-105, AME-study: zanubrutinib detected in plasma samples up to 24-48 h, geometric mean (%CV) for t1/2.
BGB-3111-106, TQT-study: samples up to 24 h, geometric mean (min, max) for $t_{1/2}$.
BGB-3111-107, hepatic impairment: Sample collection up to 48 h, geometric mean (%CV) for $t_{1/2}$.
Abbreviations: $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0\,\infty}$, AUC from time 0 extrapolated to infinity; CL/F, apparent oral clearance; C_{max}, maximum observed concentration; CV, coefficient of

variation; NA, not applicable; $t_{½}$, apparent terminal elimination half life; T_{max}, time to maximum observed concentration; Vz/F, apparent oral volume of distribution during the terminal elimination phase.

In the clinical study BGB-3111-AU-003, pharmacokinetics of zanubrutinib was characterised after single-dose and multiple dose administration in patients with B-cell lymphoid malignancies (Figure 2.3.1.1 and Table 2.3.1.2). According to the non-compartmental analysis of the pharmacokinetics in patients (Report BGB-3111-CP-006), zanubrutinib was rapidly absorbed after oral administration with a median T_{max} of around 2 to 3 hours. The apparent terminal elimination half-life ($t_{½}$) was 3-4 hours after 160 mg and 320 g doses in patients.

After a single 160 mg dose administration of zanubrutinib (in the BID group) in patients, the geometric mean (%CV) C_{max} and $AUC_{0\ \infty}$ were 304 (63.8%) ng/mL (N=76) and 1253 (59.0%) ng*h/mL (N=59), respectively. After a single 320 mg dose (n = 19), the geometric mean (%CV) C_{max} and $AUC_{0-\infty}$ were 566 (65.6%) ng/mL and 2538 (47.8%) ng*h/mL, respectively.

There seems to be a dose-dependent increase in zanubrutinib exposure (maximum concentration [C_{max}] and AUC) from 40 mg to 320 mg after single-dose and from 160 mg BID to 320 mg once daily (qd) after multiple-dose administration in patients with B-cell malignancies (Figure 2.3.1.1 and Table 2.3.1.3). The arithmetic mean ± standard deviation (SD) AUC_{0-8h} were 1079 ± 434.5 ng/ml and 1904 ± 846.8 ng/ml after one week of 160 mg BID and 320 mg dose once daily (QD), respectively, in multiple dose regimen. After multiple dose administration of 160 mg of zanubrutinib BID for one week, the arithmetic mean
± SD (%CV) C_{max}, and AUC_{0-24h} were 338±168 (49.6%) ng/mL and 2261 ± 850.4 (37.6%) ng*h/mL, respectively. After multiple 320 mg dose QD for one week, the arithmetic mean (%CV) C_{max} and AUC_{0-24h} were 603 ± 290 (48.1%) ng/mL and 2172 ± 1024 (47.2%) ng*h/mL, respectively. Accumulation ratios for C_{max} and $AUC_{0-\infty}$ indicated limited accumulation after one week of repeated administration.

In the non-compartmental analysis, the pharmacokinetics of zanubrutinib showed high variability in patients. The inter-patient variability (CV%) after single-dose administration was 47.9% to 70.3% for C_{max} and 44.6% to 63.8% for $AUC_{0-\infty}$. Coefficient of variation was 37.4% to 56.4% for C_{max} and 33.0% to 44.5% for AUC_{0-8h} after multiple dose administration.

Figure 15 ***Study BGB-3111-AU-003: Arithmetic Mean (±SD) Plasma Concentration of Zanubrutinib vs Time Profiles Following Single-Dose Administration of Zanubrutinib on Day 1 of Week 1 (left panel) and multiple dose administration on Day 1 of Week 2 (right panel) to Patients With B-Cell Lymphoid Malignancies (Top = Linear Scale; Bottom = Semi-Log Scale).***

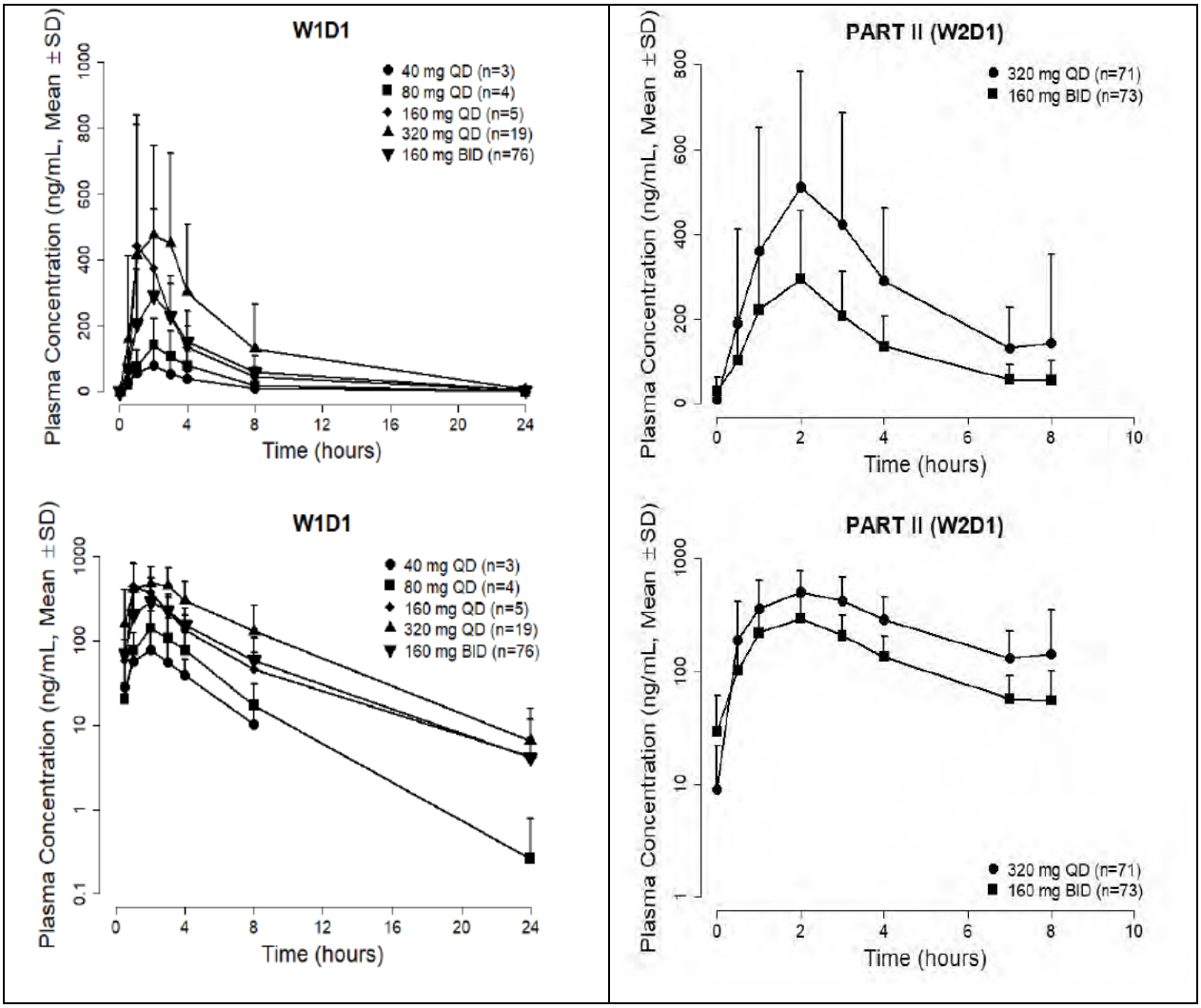


Table 13 Summary of pharmacokinetic parameters of zanubrutinib following single oral dose of zanubrutinib on day 1 of week 1 to patients with B-cell Malignancies (arithmetic mean ± SD, coefficient of variation (CV%), T_{max} median [min-max])

	40 mg QD	**80 mg QD**	**160 mg BID**	**160 mg QD**	**320 mg QD**
Number of subjects	3	4	76[1]	5	19[2]
$AUC_{0\text{-last}}$ (ng/ml*h) (CV%)	295.5 ± 144.9 (49.1)	547.9 ± 362.5 (66.2)	1300 ± 634.0 (48.8)	1630 ± 787.8 (48.3)	2614 ± 1349 (51.6)
$AUC_{0\text{-8h}}$ (ng/ml*h) (CV%)	295.6 ± 144.8 (49.0)	511.6 ± 305.6 (59.7)	1131 ± 507.5 (44.9)	1358 ± 701.2 (51.6)	2158 ± 1099 (50.9)
$AUC_{0\text{-12h}}$ (ng/ml*h) (CV%)	330.6 ± 176.3 (53.3)	563.0 ± 339.9 (60.4)	1288 ± 564.9 (43.9)	1494 ± 749.6 (50.2)	2448 ± 1243 (50.8)
$AUC_{0\text{-24h}}$ (ng/ml*h) (CV%)	373.2 ± 214.7 (57.5%)	606.9 ± 370.4 (61.0)	1394 ± 598.5 (42.9)	1631 ± 787.7 (48.3)	2748 ± 1296 (47.2)
$AUC_{0\text{-}\infty}$ (ng/ml*h) (CV%)	327.5 ± 173.1 (52.9)	571.0 ± 364.2 (63.8)	1416 ± 632.2 (44.6)	1656 ± 789.9 (47.7)	2794 ± 1272 (45.4)
C_{max} (ng/ml) (CV%)	92.2 ± 44.2 (47.9)	145 ± 77.4 (53.4)	351 ± 175 (49.8)	480 ± 337 (70.3)	661 ± 376 (56.9)
T_{max} (h)	1.00 (0.50, 1.98)	2.00 (1.17, 2.00)	2.00 (0.83, 8.00)	1.92 (0.93, 2.08)	2.00 (0.72, 3.08)
Apparent terminal $t_{1/2}$ (h)	1.99 ± 0.507 (25.5)	2.04 ± 0.647 (31.7)	3.16 ± 1.75 (55.5)	3.96 ± 0.995 (25.1)	3.90 ± 2.80 (71.7)

[1] Number of subjects is 66 for $AUC_{0\text{-}24H}$ and 59 for $AUC_{0\text{-}\infty}$
[2] Number of subjects is 18 for $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}\infty}$

Table 14:Study BGB-3111-AU-003: Summary of pharmacokinetic parameters of zanubrutinib following multiple oral doses of zanubrutinib on day 1 of week 2 to patients with B-cell malignancies (arithmetic mean ± SD, coefficient of variation [CV%], Tmax median [min-max]).

	40 mg QD	**80 mg QD**	**160 mg BID**	**160 mg QD**	**320 mg QD**
Number of subjects	3	2-4[1]	52-77[2]	4-5[3]	10-72[4]
AUC_{0-8h} (ng/ml*h) (CV%)	319.7 ± 124.5 (39.0)	413.7 ± 150.1 (36.3)	1079 ± 434.5 (40.3)	1395 ± 460.5 (33.0)	1904 ± 846.8 (44.5)
AUC_{0-12h} (ng/ml*h) (CV%)	359.7 ± 159.8 (44.4)	351.2 ± 116.8 (33.3)	1131 ± 425.2 (37.6)	1506 ± 424.1 (28.2)	2054 ± 928.8 (45.2)
AUC_{0-24h} (ng/ml*h) (CV%)	382.0 ± 187.2 (49.0)	353.4 ± 118.4 (33.5%)	2261 ± 850.4 (37.6)	1573 ± 371.9 (23.6)	2172 ± 1024 (47.2)
C_{max} (ng/ml) (CV%)	79.0 ± 29.6 (37.4)	184 ± 91.6 (49.7)	338 ± 168 (49.6)	439 ± 248 (56.4)	603 ± 290 (48.1)
T_{max} (h)	2.00 (2.00, 2.00)	2.50 (1.08, 3.00)	2.00 (0.53, 6.00)	2.00 (1.00, 3.17)	2.00 (0.33, 6.00)
Accumulation ratio (W2D1/W1D1) AUC_{0-12h}	1.12 ± 0.0998	1.38 ± 0.560	1.05 ± 0.543	1.12 ± 0.409	1.05 ± 0.644
Accumulation ratio (W2D1/W1D1) C_{max}	0.886 ± 0.127	1.45 ± 0.631	1.12 ± 0.754	1.06 ± 0.496	1.21 ± 0.585

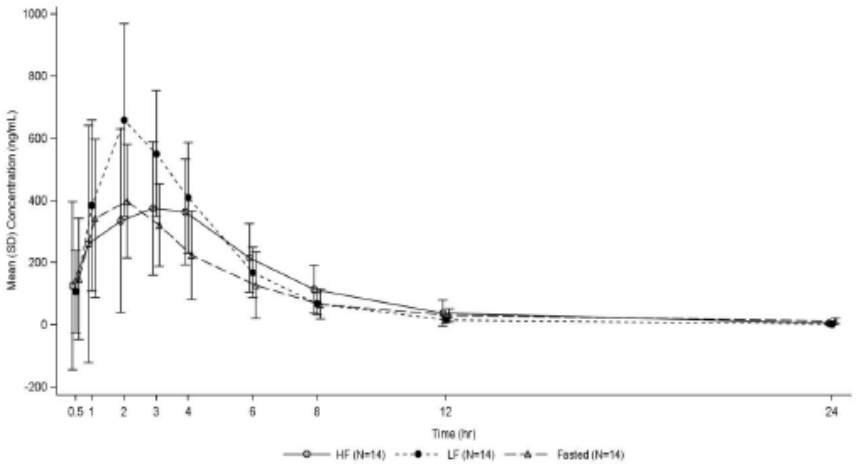
1: Number of subjects is N=2 for AUC_{0-12}, AUC_{0-24} and accumulation ratio for AUC, N=3 for AUC_{0-8} and N=4 for C_{max}, T_{max} and accumulation ratio for C_{max}.
2: Number of subjects is N=55 for AUC_{0-12} and AUC_{0-24}, N=52 for accumulation ratio for AUC, N=60 for AUC_{0-8} and N=77 for C_{max} and $T_{max,}$ and N=70 for accumulation ratio for C_{max}.
3: Number of subjects is N=4 for AUC_{0-8}, AUC_{0-12}, AUC_{0-24} and accumulation ratio for AUC, N=5 for C_{max}, T_{max} and accumulation ratio for C_{max}.
4: Number of subjects is N=28 for AUC0-8, N=27 for AUC_{0-12}, AUC_{0-24}, N=72 for C_{max} and T_{max}, N=10 for accumulation ratio for AUC, N=16 for accumulation ratio for C_{max}.

Bioavailability: No bioavailability studies were conducted with zanubrutinib. In the mass balance study (BGB-311-105), approximately 38% of radioactivity was excreted as unchanged zanubrutinib in faeces indicating that fraction absorbed of zanubrutinib may be approximately 60%. According to the PBPK modelling report, a rough estimate of 15% oral bioavailability was made based on combination of data from different sources.

Bioequivalence: The manufacturing site used for the pivotal study 302 is the intended commercial manufacturing site. The manufacturing sites for the other studies differed from the intended commercial manufacturing site. No bioequivalence studies were conducted between zanubrutinib manufactured at that site and zanubrutinib manufactured at one of the other sites. The batches manufactured at different sites were comparable, please see section 3.1 Quality aspects.

Influence of food: The geometric mean ratios of high fat/fasting were 1.03 (0.845, 1.258) and 1.14 (0.938, 1.379), whereas the ratios were higher for low fat /fasting for Cmax and AUC0-24: 1.51 (1.239, 1.846) and 1.37 (1.140, 1.658) (Figure 6). The increase in exposure of 37% (AUC0-24) and 12% (AUC0-infinite) is not considered clinically relevant, and in the pivotal study BGB-3111-302, no food restrictions were provided.

Figure 16: ***Arithmetic Mean (±SD) Zanubrutinib Plasma Concentration vs Time in Study BGB-3111-103- Linear Scale***



Source: Study BGB-3111-103 CSR Figure 11-1
Abbreviations: BGB-3111, zanubrutinib; HF, high-fat/calorie breakfast; LF, low-fat/calorie breakfast; hr, hour(s); SD, standard deviation; vs, versus.

Distribution

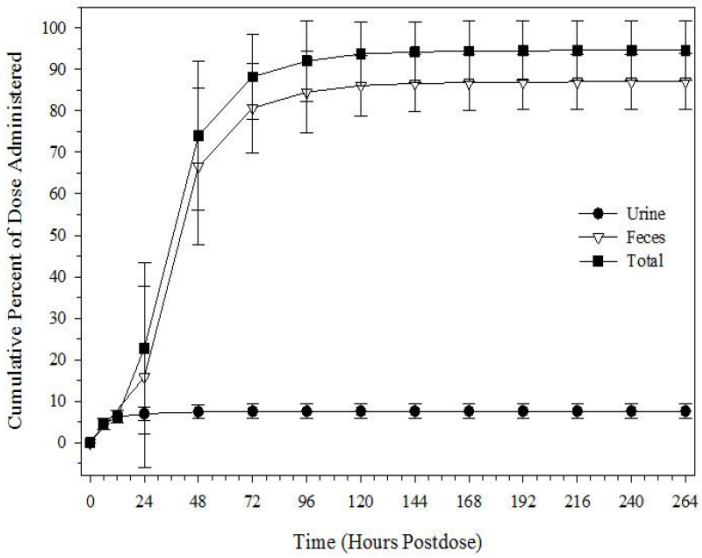
The apparent volume of distribution was estimated to 522L at a dose of 160 mg bid indicating that zanubrutinib is mainly present outside the plasma compartment. Zanubrutinib was highly bound to plasma proteins with a fraction of 94.2%. The plasma protein binding was slightly lower in patients with hepatic impairment.

Elimination

The majority of the radioactivity was captured in faeces (87.1%), and only a small amount of the radioactivity was captured in urine (7.57%) up to 11 days after exposure.

T½ was estimated to 2 to 4 hours following a single oral dose and clearance was estimated to 128 L/h.

Figure 17 ***Mean (± SD) Cumulative Percent of Radiactive Dose Recovered in Urine and Feces at Specified Intervals after a Single 320-mg (200-µCI) Oral Dose [^{14}C]- BGB-3111 to Healthy Male Subjects***



Source: Radioanalysis Report 8359693, Appendix 16.2.5.3

Metabolism: Zanubrutinib was extensively metabolised by several metabolic pathways. The main metabolic pathway was CYP3A that accounted for 70% of the metabolism and effect of genetic polymorphism on metabolism is expected to be minimal.

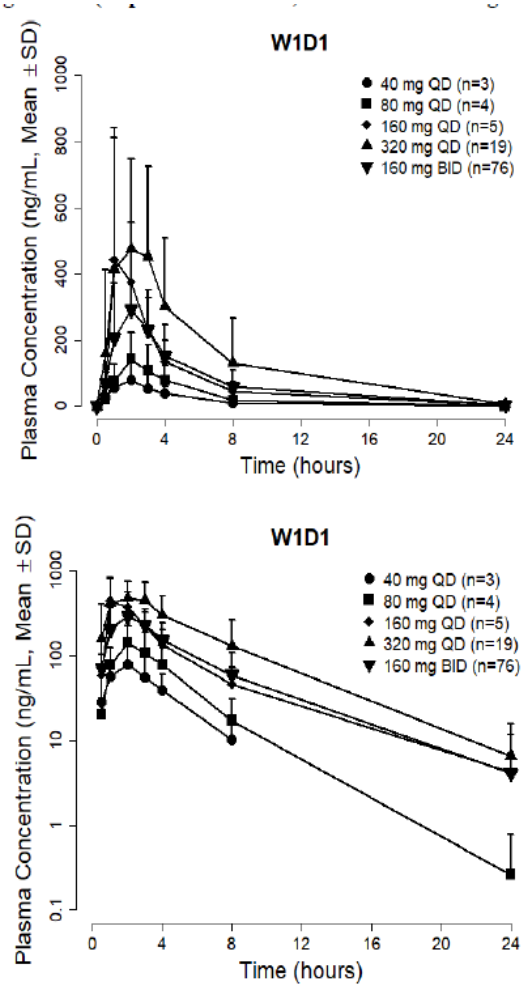
Interconversion: The active form of zanubrutinib is the S configuration. The Applicant states that the compound cannot interconvert to the R configuration. Hence, no pharmacological activity of an R-enantiomer is expected.

Dose proportionality and time dependencies

Study 003 evaluated PK at increasing single doses from 40 mg to 320 mg. The study showed a dose proportional increase in AUC0-∞ and Cmax. Similar to the dose proportionality assessment based on single dose PK data, the exposure (AUC and Cmax) after multiple-dose administration also increased approximately dose-proportionally from 40 to 320 mg of zanubrutinib.

The accumulation ratio was close to 1 for all doses (40 mg to 320 mg) with regards to AUC0-8, AUC0-12 and Cmax. Furthermore, trough concentrations at week 5 day 1 and week 9 day 1 were low for doses of 160 mg x 2 and 320 mg x 1 indicating no accumulation of zanubrutinib.

Figure 18 ***Study BGB-3111-AU-003: Arithmentic Mean (± SD) Plasma Concentration of Zanubrutinib vs Time Profiles Following Single- Dose Administration of Zanubrutinib on Day 1 of Week 1 to Patients with B-Cell Lymphoid Malignancies(Top= Linear Scale; Bottom= Semi-Long Scale***



Source: BGB-3111-CP-006 PK Report Figure 1
Abbreviations: BID, twice a day; QD, once a day; SD, standard deviation; W1D1, Week 1 Day 1.

Intra- and inter-individual variability

High inter-subject and intra-subject variability across dose groups was seen. The variability was lower after multiple dose compared with single dose.

Population PK model-based estimates of intra- and inter-individual variability are available in Table Q103.1.

Table 15: Inter-individual and intra-individual (inter-occasion) variability parameters in zanubrutinib population PK model

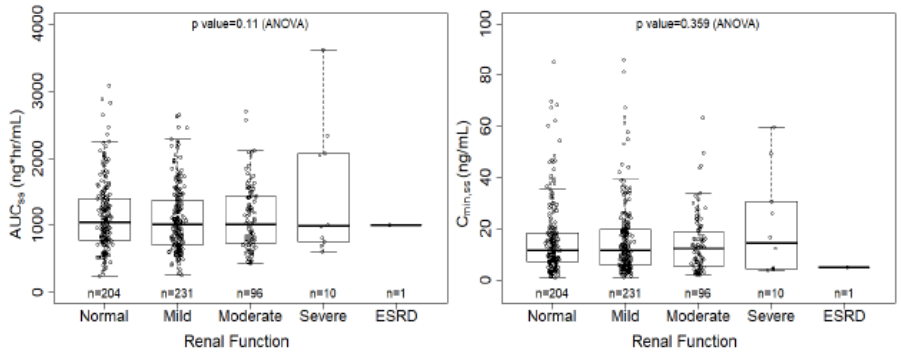
Parameter	Parameter description	Previous value[a]	Updated value[b]
Inter-individual variability	CL/F	36.7%	38.0%
	V_c/F	37.1%	38.4%
	Q/F	102%	135%
	V_p/F	86.4%	105%
	D_1	62.3%	68.9%
Inter-occasion variability	CL/F	28.6%	29.2%
	V_c/F	67.5%	76.0%
	D_1	62.3%	68.9%
Proportional residual error		44.9%	47.3%

[a] 100%*omega; [b] 100%*sqrt(exp(omega^2)-1)

Special populations

Impaired renal function: Renal impairment was not associated with increased exposure to zanubrutinib in a popPK analysis.

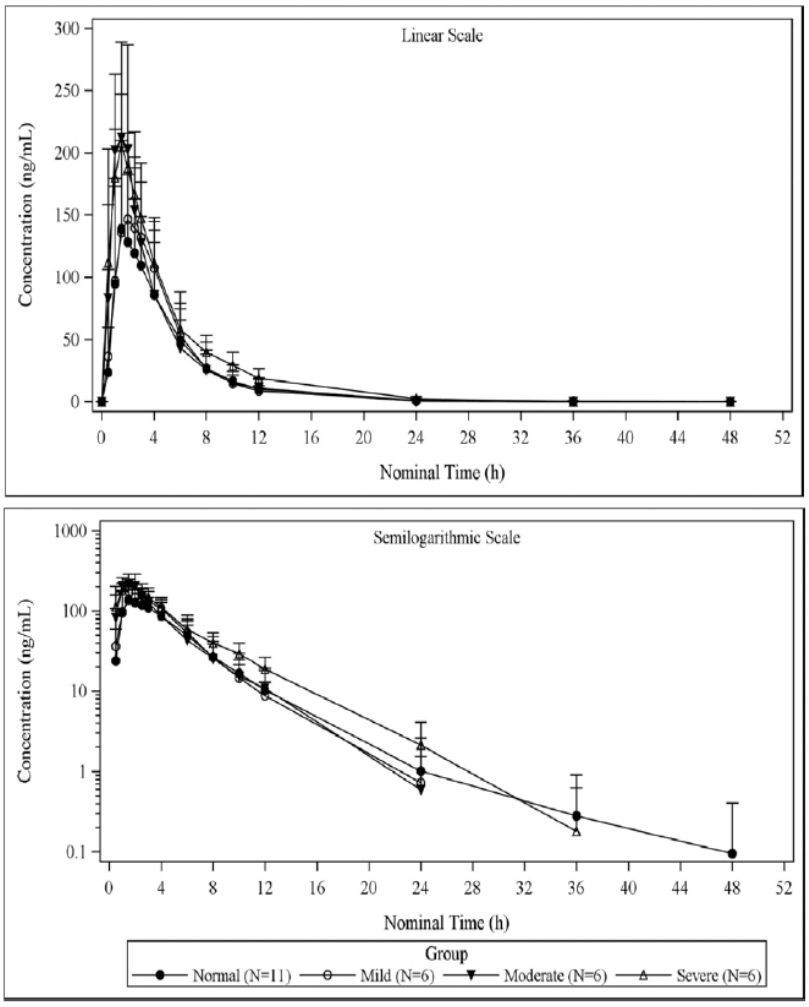
***Figure 19* Simulated steady-state exposures of zanubrutinib stratified by renal function**



Source: Population PK Report BGB-3111-CP-008 Figure 19
Abbreviations: ANOVA, analysis of variance; AUC_{ss}, steady-state area under the plasma concentration-time curve; $C_{min,ss}$, steady-state trough concentration; ESRD, end-stage renal disease.
The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range).

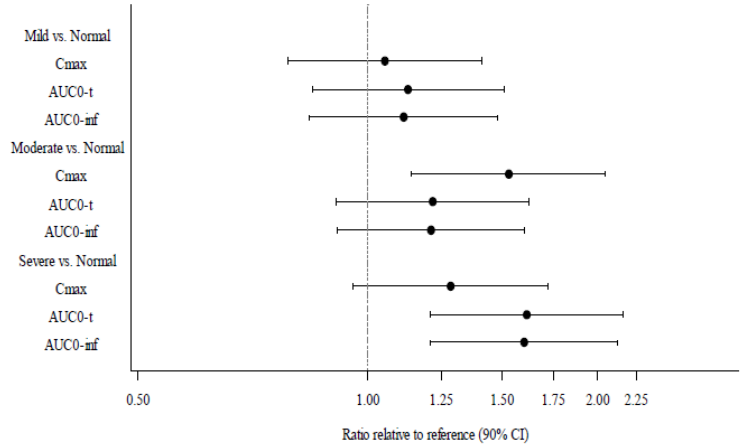
Impaired hepatic function: Severe hepatic impairment based on Child-Pugh score was associated with a 60% higher exposure to zanubrutinib compared with normal hepatic function. Moderate and mild impaired hepatic function was not associated with increased exposure. Increased exposure in subjects with severe hepatic impairment was caused by lower protein binding and lower clearance.

***Figure 20** Arithmetic mean (± SD) Plasma Zanubrutinib Concentrations vs Time Profiles in Subjects with Varying Degrees of Hepatic Impairment*



Source: BGB-3111-107 CSR Figure 11-1
Abbreviations: h, hour(s); N, number of subjects; SD, standard deviation.

Figure 21 ***Forest Plot to Assess the Effect of Hepatic Impairment on Plasma Zanubrutinib Pharmacokinetic Parameters***



Source: BGB-3111-107 CSR Figure 11-2
Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration, AUC_{0-inf}, AUC from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; vs, versus.

Gender, race, bodyweight and age: No differences in exposure was seen between men and women, races, bodyweight quartiles and between age groups. Data were limited in blacks. Subjects below 65 years had similar exposure as subjects older than 65 years.

Pharmacokinetic interaction studies

In vitro: The in vitro studies showed that GB-3111 was primarily metabolized by rCYP3A4, which was confirmed in the human DDI study. Other rP450s tested had low or minimum contribution to BGB-3111 metabolism.

In vitro studies indicated that BGB-3111 was not an inducer of CYP1A2 but has induction potential for CYP3A, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 at concentrations equal or higher than 3 µM in human hepatocytes. Induction of the enzymes was also investigated in a PBPK model. The combined in vivo and in vitro data provides adequate assurance that zanubrutinib will most likely not have clinically relevant inductive effect on CYP2B6 and CYP2C8 enzymes.

In vitro studies indicated that the inhibitory effect of zanubrutinib was of minor importance.

In vitro studies showed that BGB-3111 was not a substrate of OATP1B1, OATP1B3, OCT2, OAT1, and OAT3. But the studies indicated that BGB-3111 was likely to be a substrate of human P-gp efflux transporter. The Applicant did not further examine the effect of p-gp inhibitor on zanubrutinib but discusses that due to the high permeability, the absorption of zanubritinib is not likely to be affected by p-gp inhibition. Contribution of BCRP to total bioavailability of zanubrutinib is not expected to be significant.

Zanubrutinib did not show inhibition of transporters at concentrations up to 10 µM and 5 µM. Due to high concentrations of zanubrutinib, in vivo DDI studies on p-gp and BCRP were conducted.

In Silico: A verified PBPK model was used to predict the DDI potential for zanubrutinib as a victim when co administered with various CYP3A inhibitors and inducers. Plasma concentration profiles of

zanubrutinib (160 mg) after a single dose and at steady-state with or without multiple doses of strong CYP3A inhibitors/inducers were predicted. To maximize the impact of the CYP-modulators on steady-state zanubrutinib exposure, both CYP inducers and inhibitors were administered for 14 days and 7 days prior to starting zanubrutinib administration. The DDI were obtained for zanubrutinib co-administered with:

a. Strong CYP3A4 inhibitors, itraconazole (200 mg QD), ritonavir (BID 100 mg) and clarithromycin (250 mg BID), respectively

b. Moderate CYP3A4 inhibitors, erythromycin (500 mg Q6h), fluconazole (200 mg QD and 400 mg QD) and diltiazem (60 mg TID), respectively

c. Mild CYP3A4 inhibitors, fluvoxamine (50 mg QD), cyclosporine (200 mg QD) and cimetidine (400 mg BID), respectively

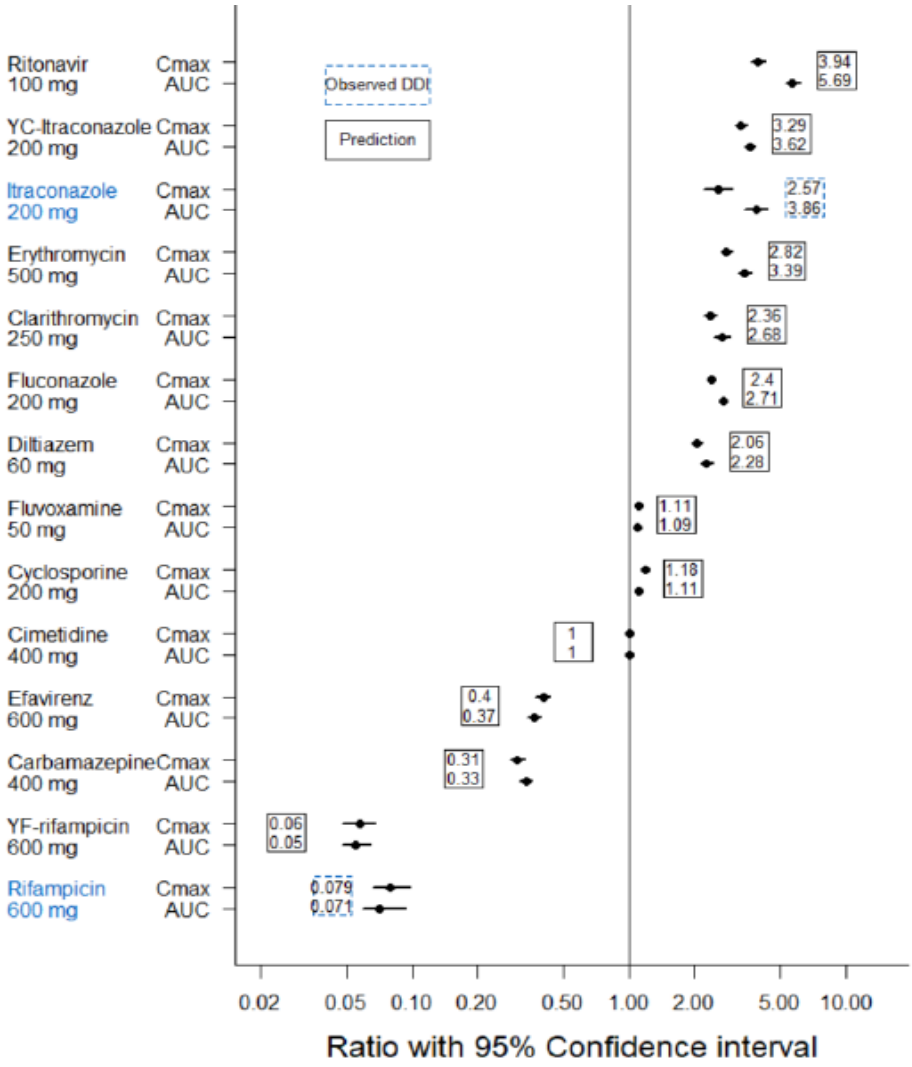
d. Strong CYP3A4 inducers, rifampicin (600 mg QD) and carbamazepine (400 mg BID), respectively

e. Moderate CYP3A4 inducer, efavirenz (600 mg QD)

The verified model was also used to predict DDI potential for zanubrutinib as a perpetrator when co-administered with CYP3A, CYP2B6 and CYP2C8 substrates. Plasma concentration profiles of these substrate drugs with or without multiple dose administration of zanubrutinib 160 mg were simulated:

- Prediction of impact of zanubrutinib 160 mg BID on the pharmacokinetics of CYP3A substrate, ethinylestradiol.
- Prediction of impact of zanubrutinib 160 mg BID on the pharmacokinetics of CYP2B6 substrate bupropion.
- Prediction of impact of zanubrutinib 160 mg BID on the pharmacokinetics of CYP2C8 substrates, repaglinide and rosiglitazone.
- Prediction of DDI with acid reducing agents due to pH-dependent solubility.

Figure 22** **Predicted zanubrutinib PK parameters (160 mg) and the ratio (with/without) co-administration of CYP3A4 inhibitors and inducers



Each subject received an inhibitor or inducer for 10 days. A single dose of zanubrutinib 160 mg was administered on Day10. The symbols and the error bars represent the geometric mean and 95% Confidence Interval.

The PBPK model showed a 3-4-fold increase in zanubrutinib AUC and Cmax when co-administered with a strong or moderate CYP3A4 inhibitor, except for ritonavir that was associated with an 8-fold increase in AUC of zanubrutinib. Mild CYP3A4 inhibitors did not affect zanubrutinib exposure substantially.

CYP3A4 inducers were associated with a decrease in zanubrutinib exposure. As such, rifampicin (a strong inducer) was associated with a 93% decrease in exposure whereas carbamazepine and efavirenz were associated with a 60% reduction in exposure.

PBPK simulations of esomeprazole indicate that acid-reducing agents such as proton-pump inhibitors do not significantly impact the PK of zanubrutinib. Predicted solubility of zanubrutinib in the stomach decreases from 0.25 to 0.13 with a gastric pH value change of 1.5 to 4.5. The predicted Cmax and AUC changes are within 3%.

Zanubrutinib is primarily metabolised by CYP3A4. The clinical DDI study (study 104) showed a 4-fold increase in exposure when co-administered with itraconazole, a strong CYP3A4 inhibitor in agreement with the PBPK modelling. In the SmPC, the Applicant has proposed a dose reduction to 25% of

recommended dose when co-administered with a strong CYP3A inhibitor and a dose reduction to 50% of recommended dose when co-administered with a moderate CYP3A inhibitor.

The clinical DDI study showed a substantial decrease in zanubrutinib exposure when administered with a strong CYP3A4 inducer (rifampin). In the SmPC, the Applicant has stated that concomitant use of a strong CYP3A inducer should be avoided.

Plasma concentrations of zanubrutinib were similar when administered with and without omeprazole, which is in agreement with the PBPK modelling. Hence, no dose adjustment is needed when administered with proton pump inhibitor.

Zanubrutinib did not affect AUC or Cmax of warfarin and rosuvastatin, hence concomitant treatment with drugs metabolised by CYP2C9 or drugs using transporter protein BCRP is acceptable.

With regards to midazolam (CYP3A substrate) and omeprazole (CYP2C19 substrate), AUC of the drugs were reduced by 47% and 36 %. The AUC of digoxin (P-gp substrate) increased by 11%. Advice on concomitant treatment with narrow therapeutic index drugs metabolised by CYP3A and CYP2C19 are provided in the SmPC.

2.4.3. Pharmacodynamics

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).

Table 16: Clinical Pharmacology studies of zanubrutinib (BGB-3111)

Region	Study Number	Title	Phase	Primary Objective and Clinical Pharmacology Analyses	Oral Dose Regimen	Evaluable Patients
Global	BGB-3111-302	A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)	3	PK	160 mg twice a day	Total = 129 (PK)
Global	BGB-3111-AU-003	A Phase 1/2, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Patients with B-Cell Lymphoid Malignancies	1/2	PK and PD	40 mg, 80 mg, 160 mg, and 320 mg once a day 160 mg twice a day	Total = 301 (PK)[a] 50 (PD)
China	BGB-3111-1002	A Phase 1 Clinical Study to Investigate the Safety, Tolerability and Pharmacokinetics/ Pharmacodynamics of the BTK Inhibitor BGB-3111 in Chinese Patients with B-cell Lymphoma	1	PK and PD	320 mg once a day 160 mg twice a day	Total = 44 44 (PK) 13 (PD)

Mechanism of action

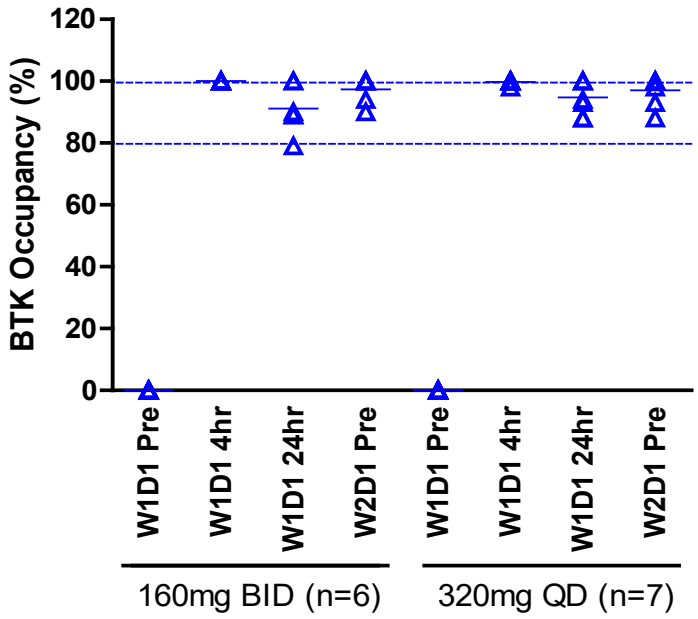
Zanubrutinib (also known as BGB-3111) is a novel, second-generation oral BTK inhibitor that forms an irreversible covalent bond at Cys481 within the adenosine triphosphate binding pocket of the BTK protein. Zanubrutinib is more selective than ibrutinib (first-generation BTK inhibitor) for BTK inhibition with less off-target kinase inhibition, including less inhibition of EGFR, JAK3, HER2, TEC, inducible tyrosine kinase (ITK), and others, as evidenced in both kinase inhibition and cell-based assays.

Primary and Secondary pharmacology

Primary pharmacology

The variability in receptor occupancy in study BGB-3111-1002 is depicted in **Figure 1.**

Figure 23: ***BTK Occupancy in PBMC Samples Following Single- and Multiple-Dose Administration of Zanubrutinib Once a Day or Twice a Day to Patients With B-Cell Malignancies in Study BGB-3111-1002***



The variability in receptor occupancy in PBMCs and lymph nodes are depicted below.

Table 17 BTK Occupancy in PBMCs (Part 1)

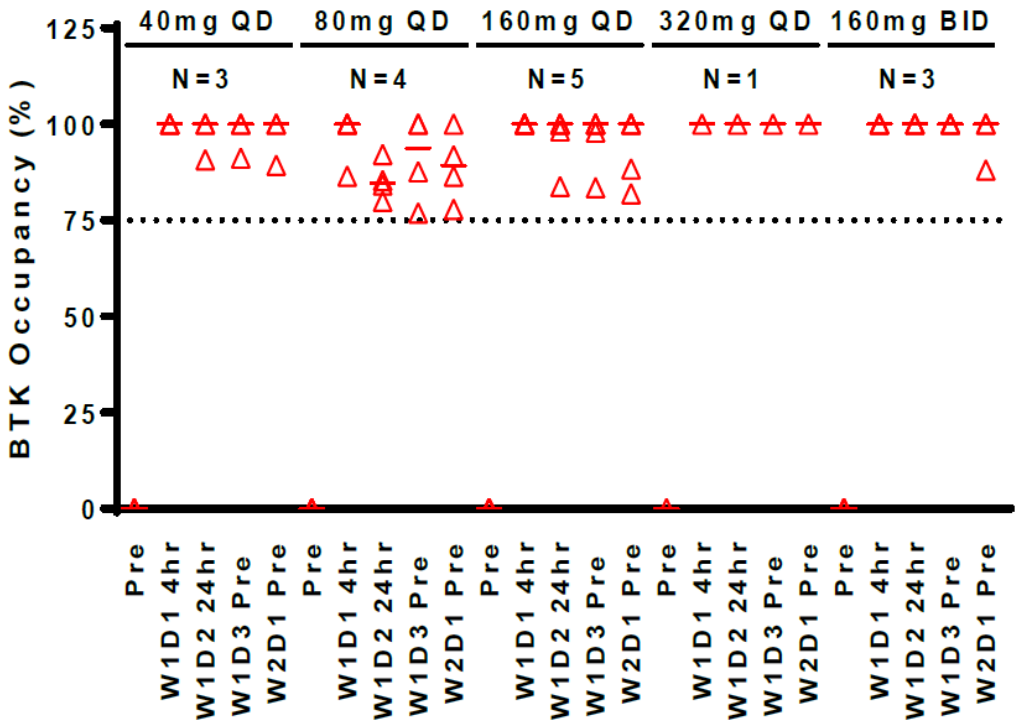
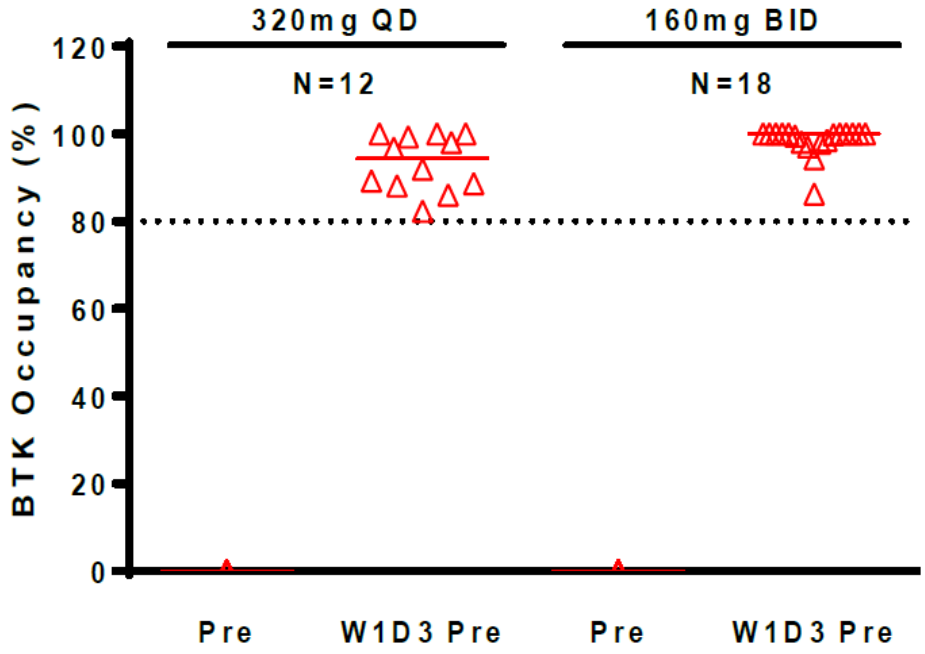


Table 18 BTK Occupancy in lymph nodes (Part 2)



BTK occupancy in lymph nodes was > 80% in all samples evaluated, and the median BTK occupancy reached 94% in the 320 mg QD group (N=12) and 100% in the 160 mg BID group (n = 18, p =

0.0189, Mann Whitney exact test). The proportion of patients with >90% occupancy was 94% (160mg BID) vs 58% (320mg QD). The figure clearly summarizes the PD data by different tumour types. Data is very limited, and the number of subjects / tumour type is very low. However, it is agreed that there was no apparent association of lymph node BTK occupancy and tumour types.

MYD88 and CXCR4 mutation status define subgroups of Waldenström's macroglobulinaemia. The mutational status of the MYD88 and CXCR4 genes has been shown to predict responsiveness of ibrutinib in WM (Treon *et al*., 2015[1]). For zanubrutinib, due to low number of samples available, no conclusion can be drawn on the effect of MYD88/CXCR4 mutational status on PD responses. In all of the available samples, BTK receptor occupancy is high in peripheral blood (85.33-100%) in line with the overall results.

Currently, there are no PD data available to elucidate the potential for development of resistance to zanubrutinib treatment or cross-resistance after prior BTK inhibitor treatment.

As regards the dosing of zanubrutinib, the Applicant proposes two different dosing regimens: 160 mg BID and 320 mg once daily. According to the presented data, the two different dosing strategies result in median BTK occupancy of 100% and 94% in lymph nodes at steady-state, respectively. A relevant difference in the clinical effect of the two dose regimens is not likely.

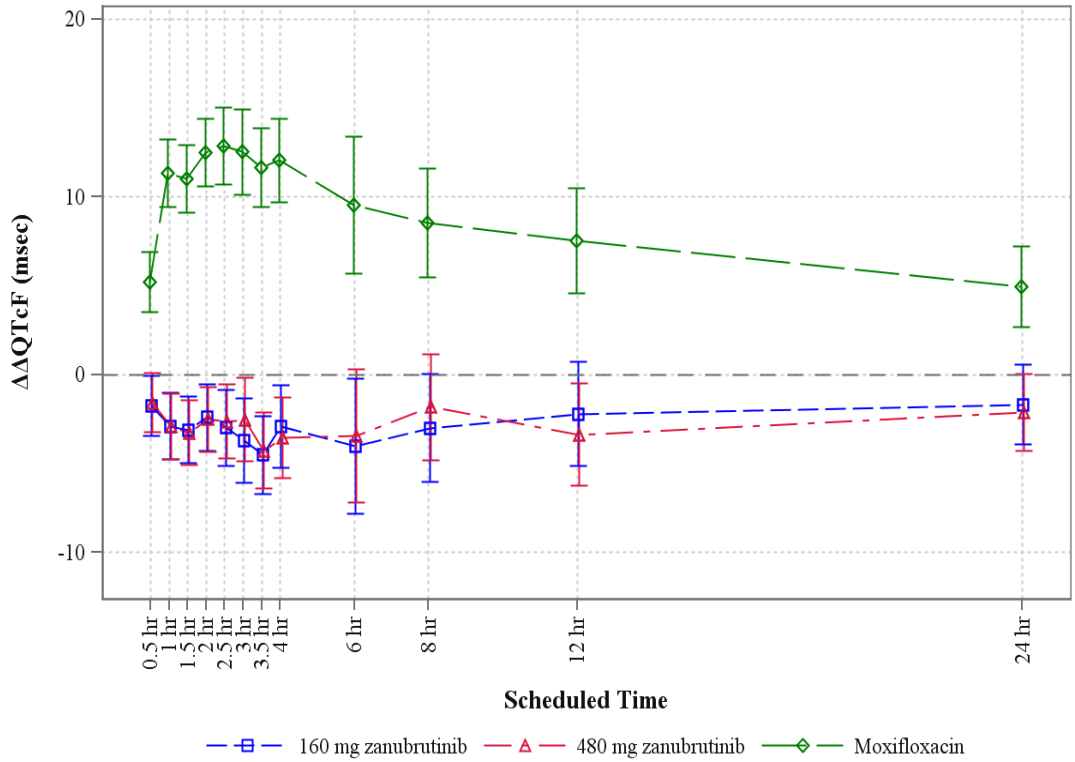
Secondary pharmacology

In study BGB-3111-106, the effect of zanubrutinib on ECG parameters was examined. The primary ECG endpoint was placebo-corrected change-from-baseline QT interval corrected for heart rate with Fridericia's formula (ΔQTcF) and the secondary ECG endpoints included QTcF, heart rate, time from the beginning of the P-wave to the beginning of the next QRS complex (PR interval), and deflections in the tracing of the ECG comprising the Q, R, and S waves that represent depolarization of the ventricles (QRS intervals). Data were available from 28, 30, 28, and 27 subjects for zanubrutinib 160 mg, zanubrutinib 480 mg, placebo, and moxifloxacin 400 mg, respectively.

The E-R analysis was based on placebo-corrected ΔQTcF (ΔΔQTcF). A small shortening of the QTc interval was observed on both doses of zanubrutinib and on placebo, with the expected level of QTc prolongation observed on active moxifloxacin treatment. The ΔΔQTcF was very small on both doses of zanubrutinib, with mean values ranging between −1.6 and −4.5 msec across all postdose timepoints without clear relation to dose or time of dosing (see below). The upper bound of the 90% CI of ΔΔQTcF of zanubrutinib did not exceed 1.2 msec at any postdose timepoint. Mean ΔΔQTcF on moxifloxacin was > 10 msec between 1 and 4 hours postdose, with a peak effect of 12.9 msec (90% CI: 10.71 to 15.02) observed at 2.5 hours postdose. There were no subjects with outlier values for QTcF values (ie, QTcF > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, or > 500 msec when not present at baseline) in any treatment group. There were no subjects with outlier values for ΔQTcF (ie, QTcF change from baseline of > 30 and ≤ 60 msec or > 60 msec) for zanubrutinib or placebo groups.

Table 19: Placebo-Corrected Change-From-Baseline QTcF (ΔΔQTcF) Across Timepoints – Part B QT/QTc Population

[1] MYD88 mutations and response to ibrutinib in Waldenström's macroglobulinaemia. Treon SP, Xu L, and Hunter Z. N Engl J Med. 2015b; 373:584-85.



Source: BGB-3111-106 CSR Figure 2-1
Abbreviations: hr, hour(s); QTc, QT interval corrected for heart rate; QTcF, QT interval corrected for heart rate with Fridericia's formula.

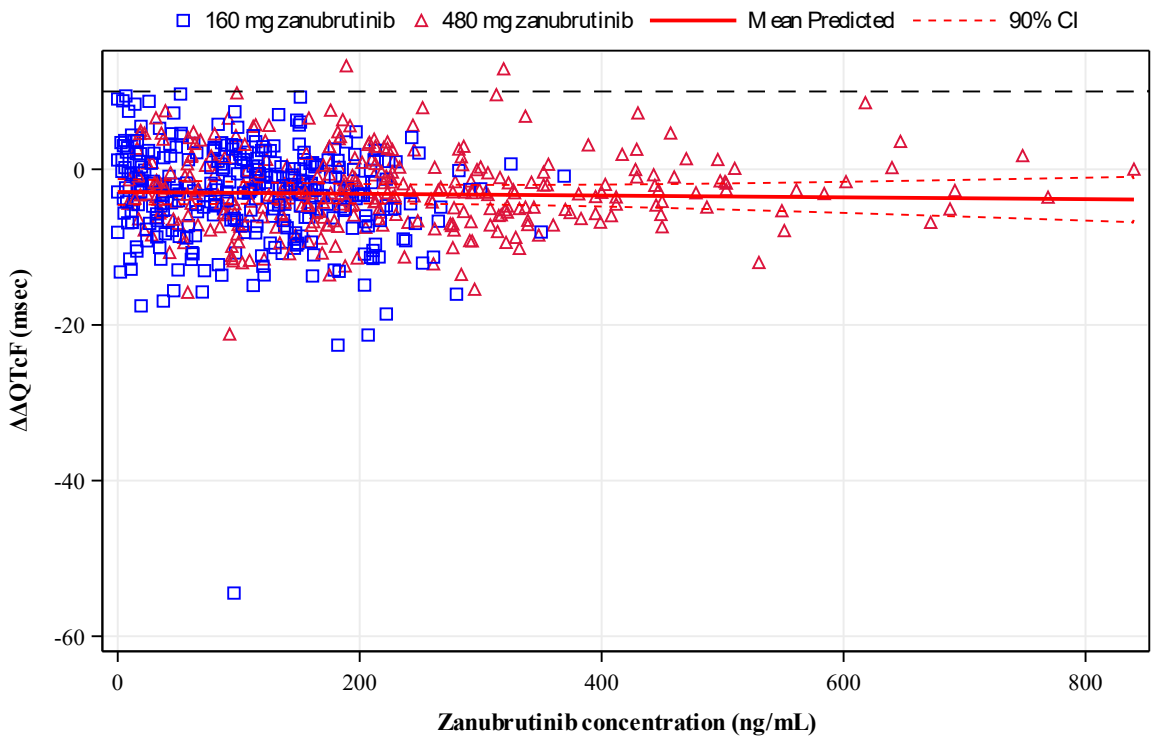
Zanubrutinib did not have an effect on heart rate or cardiac conduction (ie, PR and QRS intervals). Mean placebo-corrected change-from-baseline heart rate (ΔΔHR) values for zanubrutinib were all smaller than ± 5 bpm with values ranging between −0.4 and −3.6 bpm on zanubrutinib 160 mg and between 0.7 bpm and -2.9 bpm on zanubrutinib 480 mg. Mean placebo-corrected change-from-baseline PR interval (ΔΔPR) was smaller than 5 msec across all timepoints after dosing with zanubrutinib. Mean placebo-corrected change-from-baseline QRS intervals (ΔΔQRS) were within ± 1.0 msec at all postdose timepoints on both zanubrutinib doses.

Concentration-QTc Analysis Results

The relationship between the individual observed zanubrutinib concentrations and ΔΔQTcF was investigated using a linear mixed-effects modeling approach. In the concentration-QTc analysis using a linear model with an intercept, the slope of the relationship was not statistically significant (-0.001 msec per ng/mL [90% CI: −0.0058 to 0.0035]). Assay sensitivity was demonstrated by the moxifloxacin QT response. The predicted ΔΔQTcF at the geometric mean peak zanubrutinib concentrations after single oral doses of zanubrutinib 160 mg and 480 mg are −3.16 msec and −3.38 msec, respectively.

In summary, single oral doses of zanubrutinib 160 mg and 480 mg did not have a clinically relevant effect on ECG parameters, and an effect on the QTc interval exceeding 10 msec can be excluded within the observed plasma concentrations range.

Figure 24: Scatter Plot of Observed Zanubrutinib Plasma Concentrations and ΔΔQTcF (PK/QTc Population)



Source: BGB-3111-106 CSR Figure 11-10
Abbreviations: ΔΔQTcF, placebo-corrected change-from-baseline QT interval corrected for heart rate with Fridericia's formula; CI, confidence interval; PK, pharmacokinetic(s); QTc, QT interval corrected for heart rate; QTcF, QT interval corrected for heart rate with Fridericia's formula.
The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI. The blue squares and red triangles denote the pairs of observed zanubrutinib plasma concentrations and ΔΔQTcF by subjects for the 160 mg and 480 mg doses of zanubrutinib, respectively.

Table 20: Predicted ΔΔQTcF Interval at Geometric Mean Peak Zanubrutinib Concentration (PK/QTc Population)

Treatment	N	Geometric Mean (ng/mL) (90% CI)	ΔΔQTcF Estimate (msec) (90% CI)
160 mg zanubrutinib	27	215.4 (198.96, 233.29)	-3.16 (-4.51, -1.81)
480 mg zanubrutinib	28	401.1 (363.37, 442.82)	-3.38 (-4.86, -1.89)

Source: BGB-3111-106 CSR Table 11-5
Abbreviations: ΔΔQTcF, placebo-corrected change-from-baseline QT interval corrected for heart rate with Fridericia's formula; CI, confidence interval; PK, pharmacokinetic(s); QTc, QT interval corrected for heart rate.

Relationship between plasma concentration and effect

To support dose recommendations, exposure-response relationships for efficacy and safety were evaluated in patients with B-cell malignancies receiving zanubrutinib monotherapy in clinical studies. Exposure data ($AUC_{0\text{-}24,ss}$, C_{max}, or C_{min}) derived from the population PK analysis (Report BGB-3111-CP-008) 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 data from 2 studies (BGB-3111-AU-003 and BGB-3111-302) or safety data from 5 studies (BGB-3111-AU-003 and BGB-3111-302, -206, -1002, and -205).

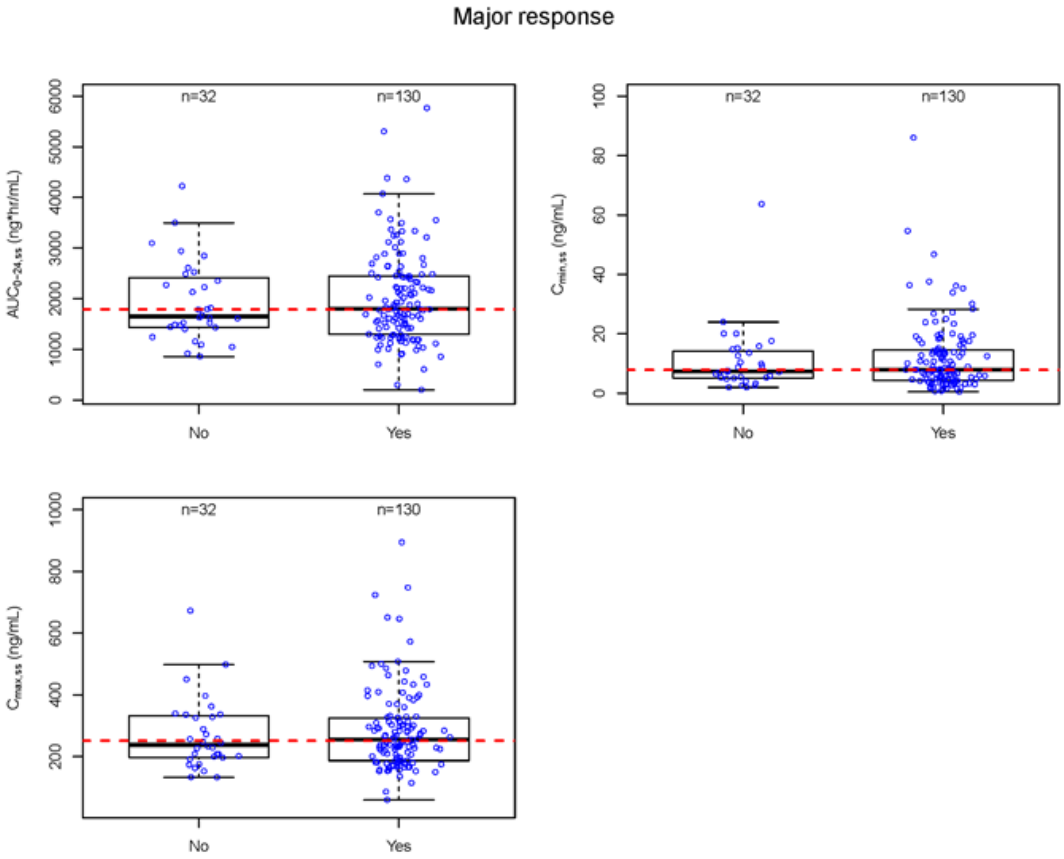
Exposure-Efficacy Relationship

Data from Study BGB-3111-AU-003 in patients with WM (n = 62) and BGB-3111-302 (n = 100) were included in the E-R analysis of efficacy outcomes. In Study BGB-3111-AU-003, zanubrutinib was administered orally as twice-a-day and once-a-day regimens (40 mg, 80 mg, 160 mg, and 320 mg once a day and 160 mg twice a day) as a starting dose. In Study BGB-3111-302, all patients received oral doses of zanubrutinib 160 mg twice a day.

The efficacy in patients with WM was investigated with the responder group, including patients with best overall response of complete response (CR), very good partial response (VGPR), or partial response (PR), and minimal response (MR); the nonresponder group included patients with best overall response of stable disease and progressive disease. A total of 162 patients with availability of both response data and PK data were included in the pooled analysis. These 162 patients included 100 patients from BGB-3111-302 and 62 patients from BGB-3111-AU-003).

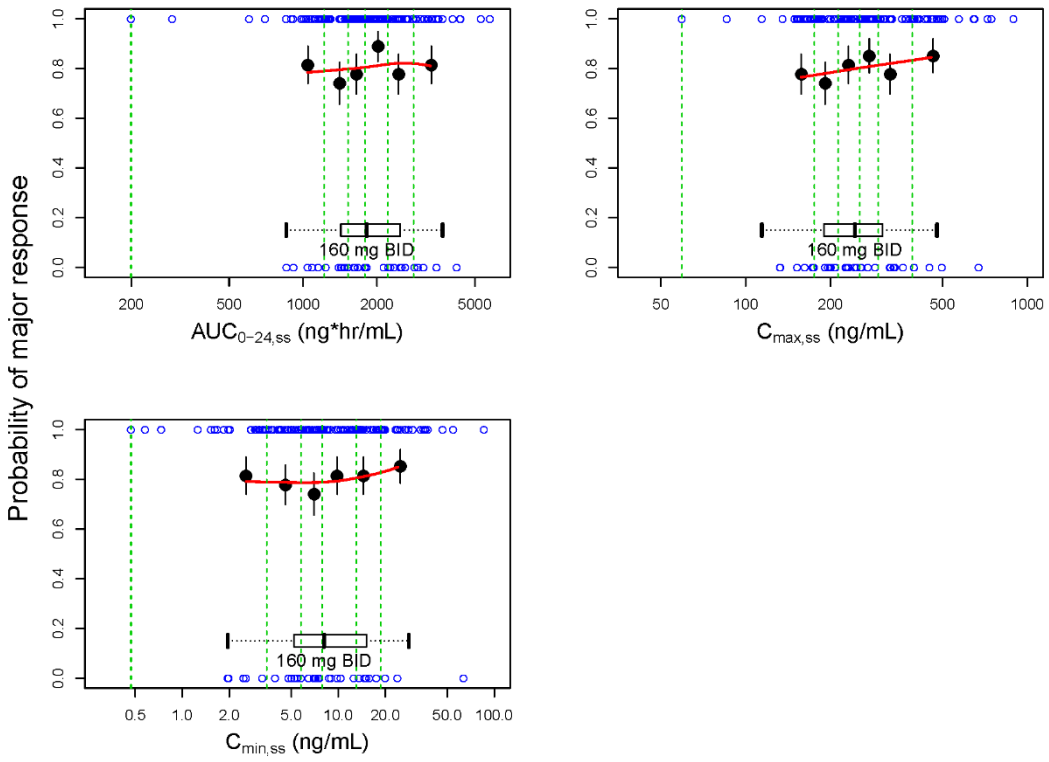
Although a range of exposures was observed in both responders and nonresponders across the dose range of 40 mg to 320 mg, the median $AUC_{0\text{-}24,ss}$ and C_{max} values appeared to be similar in responders (patients with major response rate [MRR]) compared with those of nonresponders . The median zanubrutinib C_{min} values were also similar between responders and nonresponders. The probability of MRR by quantiles of zanubrutinib exposure is shown below. The probability of ORR by quantiles of zanubrutinib exposure is shown below. Overall, there was no apparent E-R relationship for zanubrutinib, based on response assessment of CR+VGPR, MRR, and ORR.

Figure 25: Box Plot of Zanubrutinib $AUC_{0-24,ss}$ C_{max}, or C_{min} by Major Response (by Investigator Assessment) in Studies BGB-3111-AU-003 and BGB-3111-302



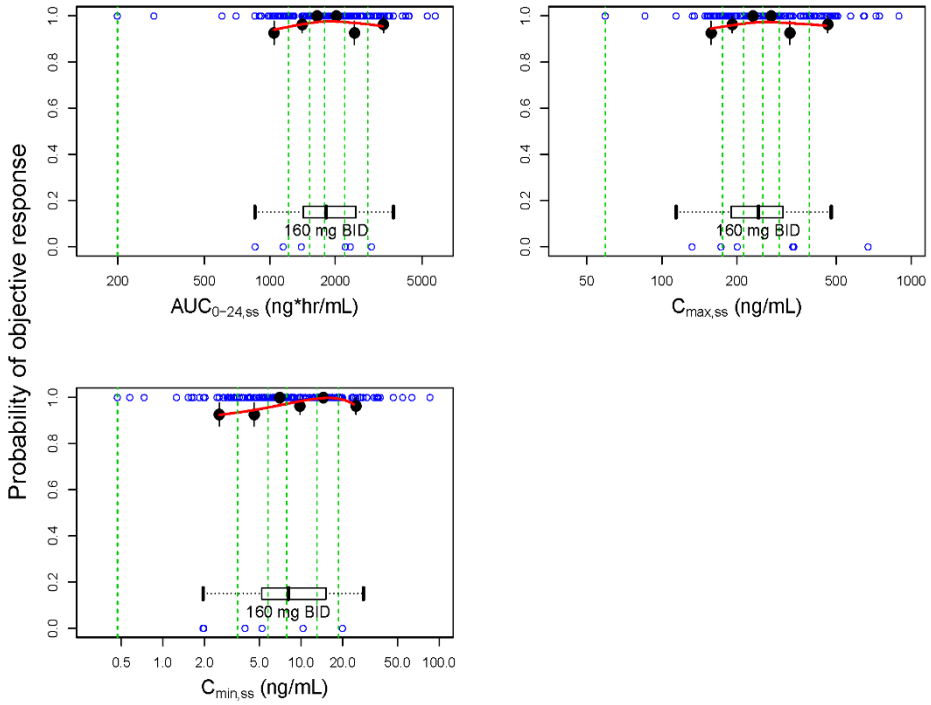
Source: Exposure-Response Report BGB-3111-CP-007 Figure 3
Abbreviations: $AUC_{0-24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}, maximum observed plasma concentration; C_{min}, trough concentration.

Figure 26: Probability of Major Response (by Investigator Assessment) in Studies BGB-3111-AU-003 and BGB-3111-302



Source: Exposure-Response Report BGB-3111-CP-007 Figure 4
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; BID, twice a day; $C_{max,ss}$ steady-state maximum observed plasma concentration; C_{min}, trough concentration; IQR, interquartile range; PK, pharmacokinetic(s).
The blue open circles reflect the observed events in zanubrutinib-treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/6) the percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between 2 variables. The boxplot represents simulated steady-state exposure of 160 mg BID using the Bayesian posthoc PK parameters of population PK model following 10 days of repeated doses of zanubrutinib for each patient. The median is represented by the vertical black line in the middle of the box. The left and right 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.

Figure 27: Probability of Objective Response (by Investigator Assessment) in Studies BGB-3111-AU-003 and BGB-3111-302

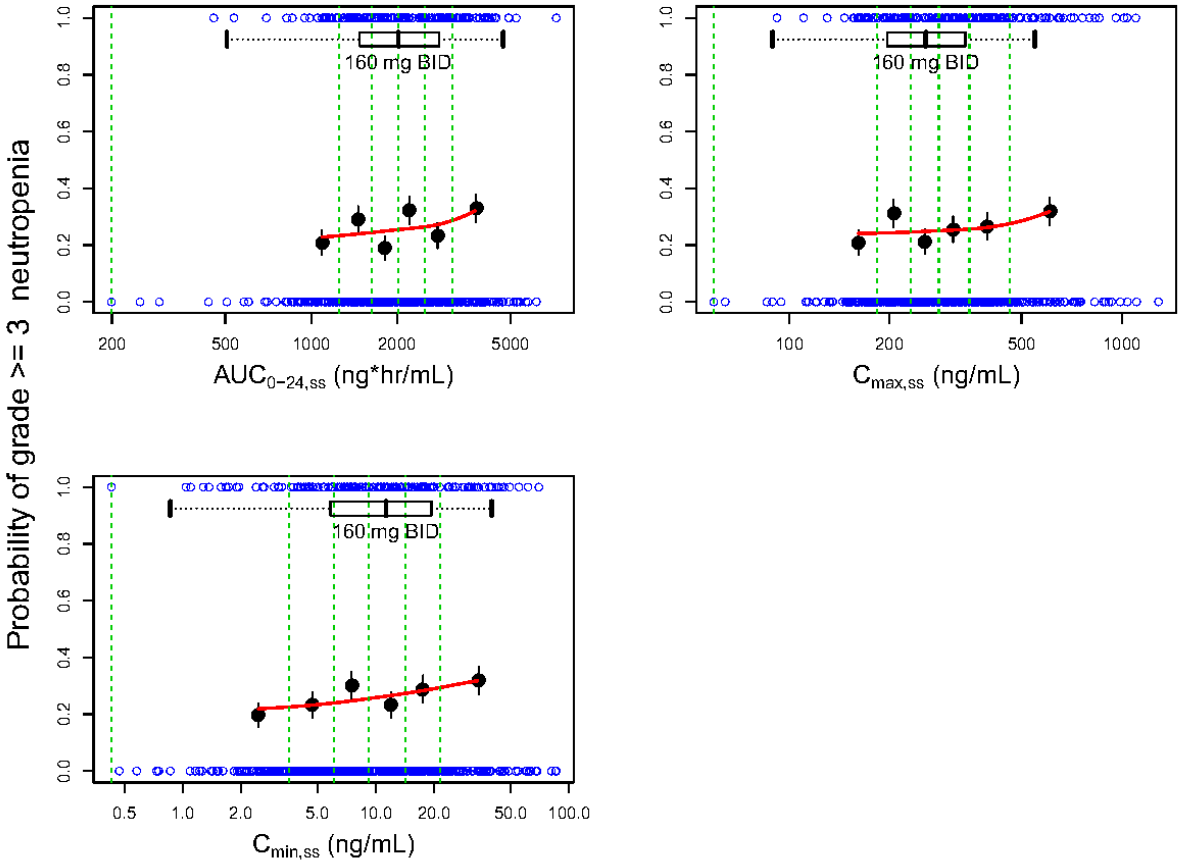


Source: Exposure-Response Report BGB-3111-CP-007 Figure 6
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; BID, twice a day; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration; IQR, interquartile range; PK, pharmacokinetic(s).
The blue open circles reflect the observed events in zanubrutinib-treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/6) the percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between 2 variables. The boxplot represents simulated steady-state exposure of 160 mg BID using the Bayesian posthoc PK parameters of population PK model following 10 days of repeated doses of zanubrutinib for each patient. The median is represented by the vertical black line in the middle of the box. The left and right 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.

Exposure-Safety Relationship

A total of 542 patients were included in the exposure-safety analyses. The exposure-safety relationship was assessed between zanubrutinib exposure metrics (model predicted $C_{min,ss}$, $C_{max,ss}$, and $AUC_{0-24,ss}$) and adverse events of interest. Plots showing a probability of Grade ≥ 3 neutropenia versus steady-state exposures (C_{max}, AUC_{0-24}, and C_{min}) are shown below

Figure 28: ***Probability of Grade ≥ 3 Neutropenia vs Steady-State Exposures***



Source: Exposure-Response Report BGB-3111-CP-007 Figure 14
Abbreviations: $AUC_{0-24,ss}$, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; BID, twice a day; $C_{max,ss}$ steady-state maximum observed plasma concentration; $C_{min,ss}$, steady-state trough concentration; IQR, interquartile range; PK, pharmacokinetic(s); vs, versus.
The blue open circles reflect the observed events in zanubrutinib-treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/6)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between 2 variables. The boxplot represents simulated steady-state exposure of 160 mg BID using the Bayesian posthoc PK parameters of population PK model following 10 days of repeated doses of zanubrutinib for each patient. The median is represented by the vertical black line in the middle of the box. The left and right 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.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The PK of zanubrutinib was evaluated by modelling and simulation studies, in vitro studies and clinical pharmacology studies.

Validated LC-MS/MS methods were used for quantification of zanubrutinib and other relevant compounds. The bioanalysis conducted in support of zanubrutinib clinical development is acceptable. Standard software and methodologies were applied for the pharmacokinetic data analysis of zanubrutinib.

Population PK analyses were performed in NONMEM. The final Pop PK model for zanubrutinib was based on a previous 2-compartment model with an absorption depot. The old model was updated with additional data and data with non-linear kinetics (480 mg) was excluded, thus representing a dose range of 20-320 mg zanubrutinib. Health status and baseline ALT were identified as significant covariates of CL/F. A sensitivity analysis indicated that patients achieve lower zanubrutinib exposure than healthy subjects. The data for population PK analysis came from nine clinical studies, and included 90 healthy volunteers and 542 patients after data exclusions.

C-QTc relations for zanubrutinib and the control moxifloxacin were both described by separate linear mixed-effects models.

A PBPK model for zanubrutinib was created in Simcyp using in-vitro data, data from the human ADME study and clinical data obtained in healthy subjects and in patients in the dose range 20-320 mg QD zanubrutinib. The zanubrutinib model was used to predict the DDI potential for zanubrutinib as a victim co-administered with various inhibitors and inducers of CYP3A4 and to predict gastric effect on zanubrutinib absorption following increase of gastric pH from 1.5 to 4.5. The zanubrutinib model was also used to predict the DDI potential for zanubrutinib as a perpetrator when co-administered with CYP3A, CYP2B6 and CYP2C8 substrates. The predicted DDI effects were used to for dose recommendations in the SmPC Section 4.2 for concomitant moderate CYP3A4 inhibitors and moderate CYP3A4 inducers. The PBPK predictions of zanubrutinib dose adjustment in the presence of CYP3A inhibitors are supported. The predicted extent of CYP3A autoinduction was less than 15%. Ongoing Study BGB-3111-113 will confirm the proposed dose recommendations for zanubrutinib in the presence of moderate (fluconazole and diltiazem) and strong (clarithromycin and voriconazole) CYP3A inhibitors. PBPK simulations of zanubrutinib PK in the presence of moderate/mild CYP3A inducers was supported by data from clinical DDI study BGB-3111-112 with rifabutin.

The PBPK model was used to predict the effect of zanubrutinib on CYP2B6 substrate bupropion, CYP2C8 substrates rosiglitatzone and repaglinide, and CYP3A4 substrate ethinylestradiol without clinical data. The simulations of CYP induction by zanubrutinib are not accepted for SmPC recommendations.

The ADME study showed a rapid absorption with a Tmax of 2-4 hours and that a large proportion of the zanubrutinib was metabolised, mainly by CYP3A4, and excreted in faeces. The volume of distribution was 522 L and zanubrutinib was highly bound to plasma proteins. The clearance was 128 L/h.

No dose dependency or time dependency were evident, however, lack of accumulation of metabolites needs to be clarified. Acrylic acid was one of the major metabolites. Formation of acrylic acid and further description of its metabolism should be provided.

Food did not have a major impact on the absorption and in the SmPC it is stated that zanubrutinib can be administered with and without food.

High inter- and intra-individual variability was seen, but the variability was lower after multiple dose compared with single dose.

Renal impairment did not affect exposure to zanubrutinib, which is in line with the limited renal excretion. However only few individuals with severe renal impairment were included in the study, which is reflected in the SmPC.

Zanubrutinib was mainly metabolised by liver enzymes and severe hepatic impairment was associated with increased exposure to zanubrutinib; in the SmPC it is stated that patients with severe hepatic impairment should be treated with zanubrutinib 80 mg x 2, which is half the recommended dose in patients with normal hepatic function. The parameters of Child-Pugh score that was associated with increased exposure to zanubrutinib are presented in the SmPC section 4.2.

Gender, age, body weight and race did not have an impact on PK.

With regards to drug-drug interaction, relevant in vitro, in silico and in vivo interaction studies have been conducted. The PBPK model showed a 3-4 fold increase in zanubrutinib AUC and Cmax when coadministered with a strong or moderate CYP3A inhibitor, except for ritonavir that was associated with an 8-fold increase in AUC of zanubrutinib. A 4-fold increase in drug exposure when administered with a strong CYP3A inhibitor was supported by the in vivo DDI study. A 25% reduction in dose when co-administered with a strong CYP3A inhibitor and a 50% reduction with a moderate CYP3A inhibitor are proposed, which is considered acceptable. Strong and moderate inducers of CYP3A4 showed a substantial decrease in zanubrutinib exposure and concomitant treatment should be avoided, which is adequately reflected in the SmPC. DDI studies showed that zanubrutinib affected the exposure to drugs metabolised by CYP3A and CYP2C19 and substrates of p-gp. This is adequately reflected in the SmPC.

Pharmacodynamics

BTK occupancy is a pharmacodynamic marker of zanubrutinib treatment. In general, the median BTK receptor occupancy observed at doses from 40 mg to 360 mg per day is close to 100%.

It is noted that the Applicant proposes two different dosing regimens: 160 mg BID and 320 mg once daily. According to the presented data, the two different posologies result in median BTK occupancy of 100% and 94% in lymph nodes at steady-state, respectively. A relevant difference in the clinical effect of the two dose regimens is not likely.

The effect of zanubrutinib at a therapeutic dose of 160 mg and a supratherapeutic dose of 480 mg on various ECG parameters was evaluated. C-QTc relations for zanubrutinib and the control moxifloxacin were both described by separate linear mixed-effects models. The study found no effect of the medication on any of the parameters examined, including heart rate, cardiac conduction (PR and QRS intervals), and placebo-corrected, baseline-corrected and heart rate–corrected QTc (ΔΔQTcF).

The Applicant argues that the short half-life and lack of accumulation seen upon multiple dosing make the results applicable for steady-state conditions. This is agreed upon.

For the evaluation of an exposure-efficacy relationship, $AUC_{0\text{-}24,ss}$, C_{max}, and C_{min} were the exposure parameters, and complete response + very good partial response (CR+VGPR), major response rate (MRR), and objective response rate (ORR) were the efficacy parameters. Collectively, no apparent exposure-efficacy relationship was demonstrated between responders and nonresponders across a range of daily doses from 40 mg to 320 mg. By quantiles of zanubrutinib exposure, an increasing trend is observed for Cmax and MRR but this effect disappears when Cmax is compared with ORR.

A total of 542 patients were included in the exposure-safety analyses. $AUC_{0\text{-}24,ss}$, C_{max}, and C_{min} were the exposure parameters. In summary, E-R analyses showed no statistically significant relationship

between steady-state PK exposure (C_{max}, $AUC_{0-24,ss}$, C_{min}), MRR, and ORR. There was no evidence of E-R relationships for adverse events of interests across dose levels from 40 mg to 320 mg.

Overall, no association of an exposure-efficacy or exposure-safety relationship has been documented. *The results of steady-state simulations were generally consistent with those after a single dose.*

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacology program of zanubrutinib is considered adequate for the evaluation of the PK and PD.

To assess the drug-drug interaction between zanubrutinib and moderate (fluconazole, diltiazem) and strong (voriconazole, clarithromycin) CYP3A inhibitors in patients with B-cell malignancies. A Drug-Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-Cell Malignancies Lymphoma will be submitted in the context of additional pharmacovigilance measures (see RMP).

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Dose-response was evaluated in a first-in-human phase 1/2, open-label, multiple-dose, dose escalation study (BGB-3111-AU-003). A total of 278 patients with B-Cell lymphoid malignancies were included, 78 patients with WM. The study was a modified "3+3" dose escalation design (Part 1), in Part 2, 2 dosing regimens were studied, 320 mg once daily or 160 mg twice daily. Part 2 was expanded to allow for further evaluation of efficacy and safety in multiple types of B-cell malignancies including WM, after dose-finding. The study population in Part 2 included patients in disease settings with limited treatment options. B-cell malignancies included a planned total of 295 patients diagnosed with chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), hairy cell leukaemia (HCL), marginal zone lymphoma (MZL) or mucosa-associated lymphoid tissue (MALT)-lymphoma.

Table 21 Planned dose escalation

Step	Dose Regimen [a]
–1 [b]	20 mg QD
1	40 mg QD
2	80 mg QD
3	160 mg QD
4a [c]	320 mg QD
4b [c]	160 mg BID

Abbreviations: BID, twice daily; QD, once daily

[a] The actual dose levels and regimens administered at each dose escalation step were based on the evaluation of available data from previous dose levels, as determined by the Safety Monitoring Committee.

[b] In the event that the maximum tolerated dose was exceeded at 40 mg/day, the next dose to be explored would have been 20 mg/day.

[c] Two dosing regimens (QD and BID) were explored in parallel.

Table 22 doses administered in WM - Study BGB-3111-AU-003

Cohort (planned sample size)	**Dose regimen**	**Disease status WM**
2d (n=20)	160 mg BID	Relapsed or refractory
2 f (n=50)	320 mg QD or 160 mg QD	Treatment-naive or relapsed/refractory WM requiring treatment per IWWM recommendations*
2m (n=15)	160 mg BID	Patients who failed to achieve a major response (PR or better) after ≥ 6 months of ibrutinib or acalabrutinib therapy, or had disease progression while receiving ibrutinib or acalabrutinib therapy

Patients with relapsed or refractory WM were assigned to either Cohort 2d or Cohort 2f by alternate allocation until Cohort 2d was filled. Patients with treatment-naive WM were assigned to Cohort 2f. BID twice daily, QD once daily.
*By previously reported criteria (Kyle et al, Semin Oncol 2003).

Dose-response relationship was demonstrated in circulating mononuclear cells and lymphoid tissue (biopsies) expressed as Bruton Tyrosine Kinase occupancy (inhibition) in a variety of B-cell malignancies, in various doses and over time, including in WM (Figure A).

***Figure 29* Bruton Kinase Occupancy.**

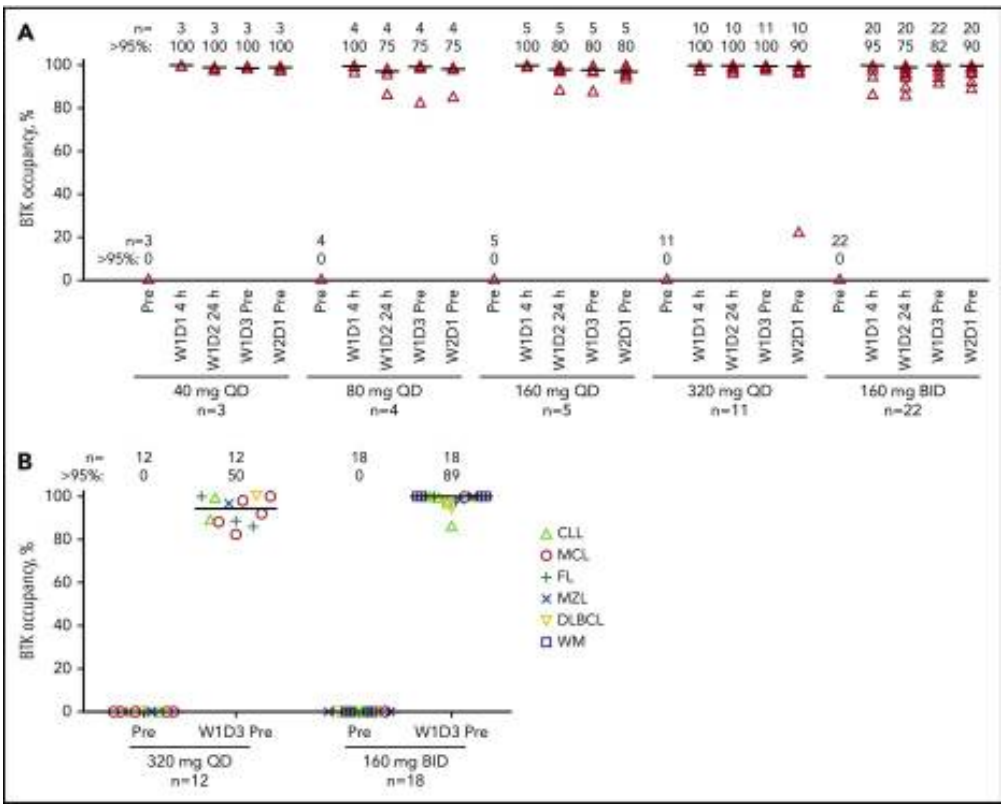


Figure A, legend**.** BTK occupancy. In (**A**) PBMCs and (**B**) nodal tissue. Data for individual patients at each time point are shown. Patient numbers and the percentage of patients with >95% BTK occupancy are noted. Triangles indicate percentages of BTK occupancy in PBMCs of patients pre-dose, at 4 and 24 hours after zanubrutinib treatment on day 1 of week 1 (W1D1), pre-dose on day 3 of week 1 (W1D3), and day 1 of week 2 (W2D1). BTK occupancy in lymph node biopsy specimens was assessed at baseline and pre-dose on W1D3 and calculated as 1 − ([free BTK on day 3 pre-dose] × [total BTK at screening])/([free BTK at screening] × [total BTK on day 3 pre-dose]). Median values are shown as lines through the individual triangles. DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma. Patients diagnosed with WWM are included (squares). Published in (Tam et al, Blood 2019).

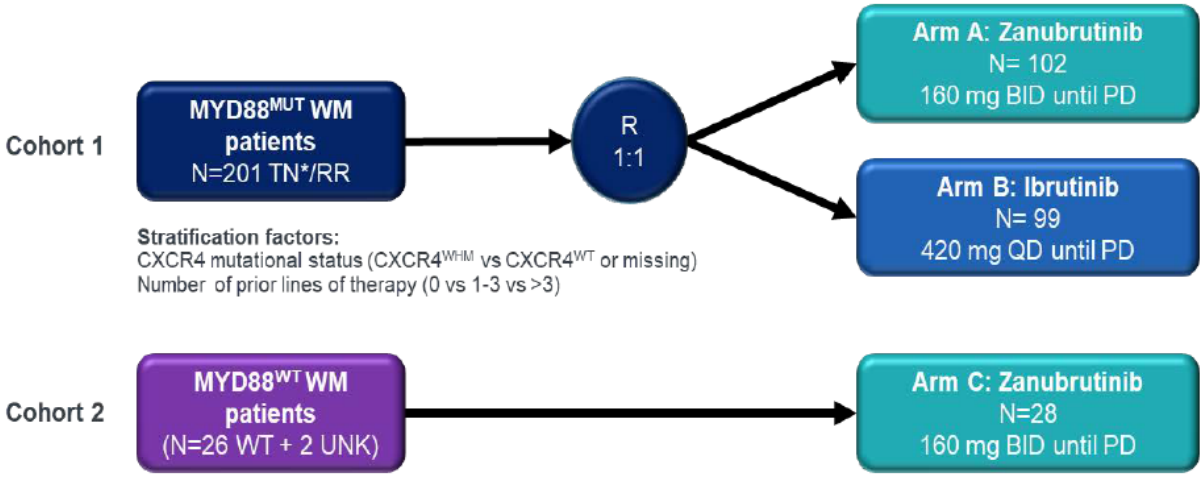
The BTKi effect was demonstrable in a dose-related manner at cellular levels in peripheral blood mononuclear cells and in nodal tissue, including in samples from patients diagnosed with WM (Figure A). The recommend daily standard dose of 160 mg zanubrutinib BID in WM is supported.

The dose selection is mainly based on BGB-3111-AU-003, a Phase 1/2, open-label, multiple-dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of the BTK inhibitor BGB-3111 in patients with B-cell lymphoid malignancies.

2.5.2. Main study(ies)

Study ASPEN BGB -3111 – 302 A phase 3, randomized, open-label, multicentre study comparing the efficacy and safety of the Bruton's tyrosine kinase (BTK) inhibitors BGB-3111 (zanubrutinib) and ibrutinib in subjects with Waldenström's macroglobulinemia (WM).

***Figure 30** Schema for Study BGB-3111-302*



Methods

The Study had a screening phase for up to 35 days to establish the diagnosis in newly diagnosed, review data in first and later line of treatment, confirm the indication, and collect baseline data including MYD88 and CXCR4 mutational status, patient-information and –accept, in accordance with GCP. Data are not provided on patients who were screened, but failed to enter the study. The time from patient randomization to study drug treatment initiation was ≤ 5 days, and performed centrally by interactive response technology. Treatment cycles were 28 days, used to structure assessment. Treatment were daily until disease progression or intolerance.

Study Participants

Table 23 Inclusion / exclusion criteria

Study	Key inclusion criteria (all)	Key exclusion criteria (any)
-302 (ASPEN) **n=229**	Adult patient with a definitive diagnosis of WM, either TN or RR Treatment indicated according to international recommendations TN patients should be "unsuitable" for treatment with a standard chemo-immunotherapy regimen based on co-morbidities and risk factors, according to and documented by treating specialist, not by patient preference Relapsed patients may have received autologous or allogeneic stem cell transplantation ECOG 0-2 with a measurable disease Acceptable bone marrow and organ functions by specified criteria	Prior exposure to BTKi Standard requirements on surgery, prior malig-nancy, viral infections Cardiac disease. QTcF, arrhythmia, NYHA gr 3-4 Significant co-morbidity or uncontrolled infections Bing-Neel syndrome (CNS involvement)

Treatments

Zanubrutinib 160mg BID start dose, available 80mg capsules, modified according to dose-guidelines. Ibrutinib 420 mg QD, tablets or capsules, available 140, 280 and 420mg, according to authorised recommendations. Supportive care as indicated, in particular plasmapheresis when indicated by manifestations and concentration of serum IgM. Anti-microbial drugs and transfusion were allowed. Interactions with strong and moderate CYP3A4 inhibitors (some anti-microbial) may be given during BTKi in accordance to recommendation for interruption.

Objectives

Table 24: Study objectives

Study objectives	
Primary	■ To compare the efficacy of zanubrutinib vs ibrutinib in patients with MYD88MUT WM
Secondary	■ To further compare the efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib versus ibrutinib in patients with $MYD88^{MUT}$ WM ■ To evaluate safety and tolerability of zanubrutinib versus ibrutinib in patients with $MYD88^{MUT}$ WM, as measured by the incidence and severity of adverse events according to the NCI CTCAE Version 4.03
Exploratory	■ To evaluate the anticancer activity and safety of zanubrutinib in patients with $MYD88^{WILD\text{-}TYPE}$ WM (Cohort 2) ■ To characterize the PK of zanubrutinib in patients with WM ■ To assess the impact of plasmapheresis on zanubrutinib PK ■ To evaluate QoL by EORTC QoL questionnaire-Core 30 and the EuroQol 5-Dimension questionnaire in $MYD88^{MUT}$ WM patients treated with zanubrutinib vs ibrutinib ■ To evaluate medical resource utilization in $MYD88^{MUT}$ WM patients treated with zanubrutinib vs ibrutinib ■ To explore mechanisms of disease resistance in samples from patients with WM who fail to respond, and from those who manifest disease relapse

Abbreviations: CTCAE Common Terminology Criteria for Adverse Events; EORTC European Organisation for Research and Treatment of Cancer; ***NCI National Cancer Institute; QoL Quality of Life.***

Outcomes/endpoints

Table 25 Endpoints

Study endpoints	
Primary	❑ The proportion of patients in each arm of Cohort 1 achieving either CR or VGPR, as determined by the IRC using an adaptation of the response criteria updated at the IWWM-6 (Owen Br J Haemtol 2013; NCCN 2015)
Secondary	❑ Major response rate as assessed by the IRC, defined as the proportion of patients achieving CR, VGPR, or PR ❑ Duration of response as assessed by the IRC, defined as the time from first determination of response (CR, VGPR, or PR) (per modified IWWM criteria) until first documentation of progression (per modified IWWM criteria) or death, whichever comes first ❑ Rate of CR or VGPR as assessed by the investigator ❑ PFS as assessed by the IRC, defined as the time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first ❑ Resolution of treatment-precipitating symptoms, defined as the absence of the symptoms that triggered initiation of study treatment (per the IWWM treatment guidelines) at any point during study treatment ❑ The incidence, timing, and severity (as assessed by the NCI-CTCAE, Version 4.03) of adverse events (safety)
Exploratory	❑ Anticancer activity of zanubrutinib (ie, CR/VGPR rate, major response rate, overall response rate, PFS, duration of response, and overall survival, as assessed by the IRC and by the investigator) in patients with $MYD88^{WILD\text{-}TYPE}$ WM (Cohort 2) ❑ Safety of zanubrutinib according to NCI-CTCAE, Version 4.03) in patients with $MYD88^{WILD\text{-}TYPE}$ WM (Cohort 2) ❑ MRR according to CXCR4 mutation status ($CXCR4^{WHIM}$ *vs* $CXCR4^{WILD\text{-}TYPE}$) in patients with $MYD88^{MUT}$ WM (Cohort 1) ❑ Overall survival, defined as the time from the date of randomization until the date of death from any cause in patients with $MYD88^{MUT}$ WM (Cohort 1) ❑ Trough plasma concentration of zanubrutinib minimum plasma concentration (Cmin) in all patients who receive zanubrutinib (Arms A and C) ❑ Evaluation of zanubrutinib PK parameters during the plasmapheresis procedure ❑ Change in quality of life as assessed by EORTC QLQ-C30 and EQ-5D in patients with $MYD88^{MUT}$ WM (Cohort 1)

Abbreviations: CR Complete Response; IRC International Review Committee; *IWWM International Workshops on Waldenström's Macroglobulinaemia; MRR Major Response Rate; PR partial Response; VGPR Very Good Partial Response; WHIM Warts, Hypogammaglobulinaemia, Infections, Myelokathexis.*

Supportive studies BGB-3111-AU-003 and -210 are single arm trials (Table 3.2.12).

The Applicant has described the sequencing method used for detection of the MYD88 / CXCR4 mutation status. As also the inclusion of all patients, regardless of the mutation status has been justified, the methods will not be used for patient selection in clinical practice.

Randomisation

Based on MYD88 gene sequencing, patients were enrolled into either Cohort 1 ($MYD88^{MUT}$) or Cohort 2 ($MYD88^{WILD\text{-}TYPE}$). Patients with either missing or inconclusive MYD88 gene sequencing results were assigned to Cohort 2 by default. Using the Interactive Response Technology system, Cohort 1 patients were randomized 1:1 to receive either zanubrutinib (Arm A) or ibrutinib (Arm B).

Stratification factors included:

- CXCR4 mutational status ($CXCR4^{WHIM}$ versus $CXCR4^{WILD\text{-}TYPE}$ versus missing) and
- the number of prior therapies for WM (0 versus 1-3 versus > 3).

Cohort 2 patients were assigned to receive zanubrutinib (Arm C) by the Interactive Response Technology system. Cohort 1 stratified randomization and Cohort 2 assignment were performed centrally by the Interactive Response Technology system on or immediately before Cycle 1 Day 1. The time from patient randomization to study drug treatment initiation was ≤ 5 days.

Blinding (masking)

Study BGB-3111-302 was not blinded, due to differences in tablet / capsule dosing and size.

Statistical methods

Analysis Sets

Cohort 1

The Intent-to-Treat (ITT) Analysis Set included all randomized patients assigned to a treatment arm in Cohort 1.

The Relapsed/Refractory Analysis Set (a subset of the ITT Analysis Set) included all randomized patients with at least 1 prior line of therapy. This will be the primary analysis set used for efficacy analyses for Cohort 1.

The Per-Protocol Analysis Set included patients in the ITT Analysis Set who met the following criteria:

• Received any dose of randomized treatment regimen

• Had a valid post-baseline measurement for either IgM (central or local) or M-protein by serum protein electrophoresis assessment (central or local)

• Did not have any important protocol deviation

The Per-Protocol Relapsed/Refractory Analysis Set included patients in the Relapsed/Refractory Analysis Set who met the above criteria. Criteria for exclusion from the Per-Protocol Analysis Set were determined and documented before the database lock for the primary analysis.

Cohort 2

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

Primary endpoint VGPR/CR rate

The superiority of the primary endpoint of VGPR/CR rate will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by the CXCR4 status (WHIM vs WT/missing), the prior line of therapy (1-3 vs. >3 for analyses in the Relapsed/Refractory Analysis Set; 0 vs 1-3 vs >3 for analyses in the ITT Analysis Set) and age group (<=65 vs >65) at a 1-sided significance level of 0.025. If the 1-sided p-value is less than 0.025, it will be concluded that the VGPR/CR rate in zanubrutinib is greater than the VGPR/CR rate in ibrutinib and that the primary objective is met.

The 95% confidence interval (CI) for the Mantel-Haenszel common risk difference (Mantel-Haenszel, 1959) will be constructed using a normal approximation and Sato's standard error (Sato 1989) stratified by the CXCR4 status (WHIM vs WT/missing), the prior line of therapy (1- 3 vs. >3 for analyses in the Relapsed/Refractory Analysis Set; 0 vs 1-3 vs >3 for analyses in the ITT Analysis Set) and age group (<=65 vs >65).

For the primary endpoint of VGPR/CR rate, an unstratified analysis will also be performed.

The primary endpoint VGPR/CR rate and key secondary endpoint MRR were, as mentioned above, analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by the CXCR4 status (WHIM vs WT/missing), the prior line of therapy (1-3 vs. >3 for analyses in the Relapsed/Refractory Analysis Set; 0 vs 1-3 vs >3 for analyses in the ITT Analysis Set) and age group (≤65 vs >65). For the primary endpoint, an unstratified analysis was planned as sensitivity analysis. For CR or VGPR rate, MRR, and ORR, subjects with missing response assessment will be considered non-responders. While VGRP/CR will be tested for superiority, the MRR will be tested for non-inferiority. The non-inferiority margin (NIM) was changed from 8 % (stated in the protocol v5 dated 26 Aug 2019) to 12 % (stated in the SAP v1 dated 18 Oct 2019). The Applicant explained in the SAP that the NIM of 12% is proposed assuming 83% of the ibrutinib benefit over a placebo is retained. With 83% of the ibrutinib effect preserved, the 12% NI margin in MRR is statistically justified. For the response definitions, please see Table X, previously.

PFS and DOR were secondary endpoints not adjusted for multiplicity. The Kaplan-Meier method was used to describe the data. PFS and DOR were right-censored for subjects who meet one of the following conditions: 1) no baseline disease assessments; 2) starting a new anti-cancer therapy before PD or death; 3) PD or death immediately after more than 6 months since the last disease assessment (more than 12 months if a subject is on the response assessment schedule of every 24 weeks); and 4) alive without documentation of PD.

The use of CMH test to compare the proportion of responders is endorsed. It is noted that age is used in the analysis despite not being included as stratification factor. This change was introduced in the SAP and an explanation from this change was not found. While it is understood that age is an important risk factor, this should have been adjusted for already in the design stage.

Key secondary endpoint: Major Response Rate

The major response rate (MRR) by IRC, defined as the proportion of subjects achieving CR, VGPR, and PR, will be tested for noninferiority of zanubrutinib compared to ibrutinib. The null and alternative hypotheses of MRR are set as follows:

H0: MRRA-MRRB ≤ -12%

Ha: MRRA- MRRB > -12%,

where MRRA is the major response rate in zanubrutinib and MRRB is the major response rate in ibrutinib. The 95% confidence interval (CI) for the Mantel-Haenszel common risk difference (Mantel-Haenszel, 1959) will be constructed with normal approximation and standard error based on Sato (1989) with strata CXCR4 status (WHIM vs WT/missing), prior line of therapy (1-3 vs. >3 for Relapsed/Refractory analysis set analysis and 0 vs 1-3 vs >3 in ITT analysis) and age group (<=65 vs >65). If the lower bound of the CI is greater than the non-inferiority margin of -12%, the null hypothesis will be rejected, and it can be concluded that the MRR in zanubrutinib is noninferior to the MRR in ibrutinib. In addition, as a sensitivity analysis, the Mantel-Haenszel common risk difference will also be estimated using the null variance estimator (Klingenberg, 2013).

If the lower bound of the CI is greater than 0, superiority is significant at the nominal level of 0.025 (1-sided). The superiority test of MRR is not included in the multiplicity adjustment for the study-wide type-I error (Figure 2).

As a sensitivity analysis, non-inferiority for MRR will be also tested in the per-protocol analysis set corresponding to the analysis set for which non-inferiority is significant.

MRR and the Clopper-Pearson 95% confidence interval (CI) will be reported for each arm.

Justification of the non-inferiority margin for MRR as described in the SAP

The same non-inferiority margin will be used for both ITT and Relapsed/Refractory analysis sets.

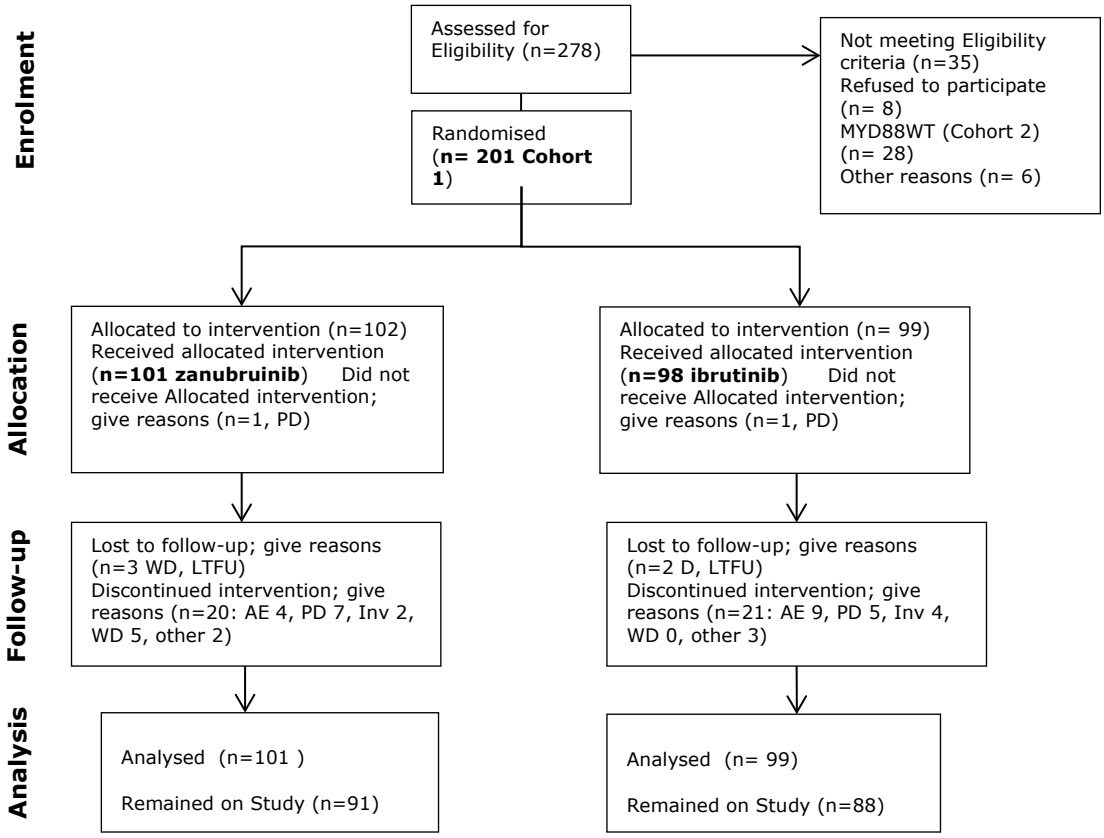
The NIM for the key secondary endpoint was increased from 8 % to 12 % in the SAP. The change of the non-inferiority margin (NIM) for MRR from -8% to -12% in the final SAP was based on emerging ibrutinib efficacy data indicating that the original MRR may have been underestimated. The ibrutinib effect over placebo was re-estimated from 60% to 75% based on the meta-analysis of the results from 3 Phase 2 studies including two new study results published after the determination of initial NIM (Treon et al, 2015a; Dimopoulos et al, 2017; Treon et al, 2018.) The revised NIM of 12% was determined by requiring 83% of the ibrutinib effect over placebo to declare NI. The same NIM was applied to the non-inferiority tests for both RR and ITT populations. No data/information from study BGB-3111-302 was used in this update.

An increase in MRR (CR+VGP+PR by IRC) of 12% in comparison with another BTKi, which has proven efficacy, is clinically meaningful if achieved and may be durable due to a continuous treatment in WM. The MRR reflects that all parameters in the response definition of IgM-protein, extramedullary disease, bone marrow function) are improved, or not worsened. It is likely that an increase in MRR also requires a longer treatment (from 12 to 15 months), an association which may be observed with kinase inhibitors that still more slow responses can be achieved. The response-definitions also state progressive disease in an objective way as: ≥25% increase in serum IgM from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease.

Results

Participant flow

***Figure 31*: Participant flow**



Legend: AE adverse event; Inv Invest discretion; LTFU lost to follow-up; PD progressive disease; WD withdrawal.

Recruitment

Patients were enrolled from 25 January 2017 in 80 sites in Europe, Australia and USA; enrolment lasted 2 years and the data cut-off was set for 31 August 2019.

Conduct of the study

In total 23 amendments were made after inclusion of all patients. There were 65 major changes in the 5 protocol amendments, summarised as follows.

Table 26 Amendments in Study BGB-3111-302 ASPEN

Date	Pts enrol-led	No of major changes	Changes (excerpts)
01 Nov 2016	67	12	Changed the primary objective to CR/VGPR Identified Patients with MYD88^{MUT} WM as the primary population for randomization and study analyses (Cohort 1) Revised sample size consideration
08 May 2017	155	14	Updated the timing of response assessments to every 4 weeks (each cycle) Clarified that up to 20% of patients may have been treatment-naïve Updated the eligibility criteria to clarify that patients may have had RR or treatment-naive WM considered by their treating physician to be inappropriate for standard chemo-immunotherapy regimens Clarified blinding of the Independent Review Committee and DMC
02 Febr 2018	7	16	Updated the total number of patients to approximately 210 Changed the timing of the primary analysis from 9 months to 12 months Revised the zanubrutinib and ibrutinib guidelines for dose modification, reduction, and discontinuation Clarified when corticosteroid usage was prohibited
01 Sept 2018	0	15	Removed the QT/QTc prolonging drug guidance Clarified that the serum IgM value at Cycle 1 Day 1 served as the baseline for all assessments except for patients who had undergone plasmapheresis Clarified that as part of the tumor assessment, the physical examination was also to be included the evaluation of the presence and degree of enlarged lymph nodes and splenomegaly
26 Aug 2019	0	8	Clarified that capsules or other dose forms and strengths were allowed for ibrutinib Added section on dose modifications for zanubrutinib when co-administered with strong/moderate CYP3A inhibitors/inducers Clarified instructions for post-baseline CT scans

Legend: Abbreviations: Pts Patients; WM Waldenström's macroglobulinaemia.

Baseline data

Table 27 Demographics and Baseline Characteristics (Cohort 2, -302) (Safety Analysis Set)

Category	Treatment-naive (N = 5)	Relapsed/Refractory (N = 23)	Overall (N = 28)
Age (Years)			
Mean (SD)	80.4 (6.31)	67.9 (13.77)	70.1 (13.57)
Median	81.0	71.0	72.0
Min, max	71, 87	39, 87	39, 87
Age Group, n (%)			
≤ 65 years	0 (0.0)	9 (39.1)	9 (32.1)
> 65 years	5 (100.0)	14 (60.9)	19 (67.9)
≤ 75 years	1 (20.0)	15 (65.2)	16 (57.1)
> 75 years	4 (80.0)	8 (34.8)	12 (42.9)
Sex, n (%)			
Male	3 (60.0)	11 (47.8)	14 (50.0)
Female	2 (40.0)	12 (52.2)	14 (50.0)
Race, n (%)			
White	4 (80.0)	23 (100.0)	27 (96.4)
Not Reported/Unknown	1 (20.0)	0 (0.0)	1 (3.6)
Ethnicity, n (%)			
Not Hispanic or Latino	4 (80.0)	20 (87.0)	24 (85.7)
Hispanic or Latino	0 (0.0)	3 (13.0)	3 (10.7)
Not Reported/Unknown	1 (20.0)	0 (0.0)	1 (3.6)
ECOG Performance Status, n (%)			
0	3 (60.0)	6 (26.1)	9 (32.1)
1	1 (20.0)	14 (60.9)	15 (53.6)
2	1 (20.0)	3 (13.0)	4 (14.3)
HBcAb, n (%)			
Positive	0 (0.0)	2 (8.7)	2 (7.1)
Negative	5 (100.0)	21 (91.3)	26 (92.9)
HCV Antibody, n (%)			
Positive	0 (0.0)	0 (0.0)	0 (0.0)
Negative	5 (100.0)	23 (100.0)	28 (100.0)
12-lead ECG at Screening			
QTcF (msec), n (%)			
> 450	0 (0.0)	1 (4.3)	1 (3.6)
> 480	0 (0.0)	0 (0.0)	0 (0.0)
> 500	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; HCV, hepatitis C virus; ITT, Intent-to-Treat; Max, maximum; Min, minimum; QTcF, QT corrected with Fridericia's formula; SD, standard deviation Cohort 2 includes patients with wild type and unknown MYD88. Baseline value is the last non-missing result before the first dose of study treatment. Data cutoff 31 August 2019

Table 28: Disease History (Cohort 2, Main Study -302 (Safety Analysis Set)

	Treatment-naive (N = 5)	**Relapsed/Refractory (N = 23)**	**Overall (N = 28)**
Time from Initial Diagnosis to First Dose [a] (Years)			
Mean (SD)	4.60 (5.560)	5.51 (4.862)	5.34 (4.895)
Median	1.51	3.99	3.65
Min, max	0.1, 12.4	0.5, 20.3	0.1, 20.3
Number of Prior Lines of Therapy, n (%)			
0	5 (100.0)	0 (0.0)	5 (17.9)
1-3	0 (0.0)	20 (87.0)	20 (71.4)
> 3	0 (0.0)	3 (13.0)	3 (10.7)
Time from Last Progression to First Dose (Months)			
n	0	13	13
Mean (SD)	NA	2.33 (1.355)	2.33 (1.355)
Median	NA	2.00	2.00
Min, max	NA	0.8, 5.6	0.8, 5.6
Baseline IgM (g/L, Central Lab)			
n	4	23	27
Mean (SD)	39.83 (25.516)	31.02 (16.697)	32.32 (17.922)
Median	36.05	28.50	28.50
Min, max	13.8, 73.4	5.6, 69.9	5.6, 73.4
Baseline IgM (Central Lab), n (%)			
≥ 40 g/L	2 (40.0)	6 (26.1)	8 (28.6)
< 40 g/L	2 (40.0)	17 (73.9)	19 (67.9)
Missing	1 (20.0)	0 (0.0)	1 (3.6)
Baseline IgG (g/L, Central Lab)			
n	4	23	27
Mean (SD)	6.09 (3.216)	4.84 (3.018)	5.03 (3.017)
Median	6.38	4.03	5.13

	Treatment-naive (N = 5)	Relapsed/Refractory (N = 23)	Overall (N = 28)
Min, max	1.9, 9.7	0.7, 12.6	0.7, 12.6
Baseline β2-Microglobulin (mg/L, Central Lab)			
n	5	23	28
Mean (SD)	4.34 (2.384)	5.05 (3.194)	4.93 (3.038)
Median	3.70	3.80	3.75
Min, max	2.2, 8.1	1.7, 13.7	1.7, 13.7
Baseline β2-Microglobulin (Central Lab), n (%)			
> 3 mg/L	3 (60.0)	17 (73.9)	20 (71.4)
≤ 3 mg/L	2 (40.0)	6 (26.1)	8 (28.6)
Genotype by LDT/Sanger Method (Central Lab), n (%)			
$MYD88^{WT}/CXCR4^{WT}$	5 (100.0)	18 (78.3)	23 (82.1)
$MYD88^{WT}/CXCR4^{WHIM}$	0 (0.0)	1 (4.3)	1 (3.6)
$MYD88^{WT}/CXCR4^{UNK}$	0 (0.0)	2 (8.7)	2 (7.1)
$MYD88^{UNK}/CXCR4^{UNK}$	0 (0.0)	2 (8.7)	2 (7.1)
Extramedullary Disease per IRC [b], n (%)			
Yes	4 (80.0)	17 (73.9)	21 (75.0)
Lymphadenopathy	4 (80.0)	16 (69.6)	20 (71.4)
Splenomegaly	1 (20.0)	5 (21.7)	6 (21.4)
Other	0 (0.0)	0 (0.0)	0 (0.0)
No	1 (20.0)	6 (26.1)	7 (25.0)
Bone Marrow Involvement (%)			
n	4	22	26
Mean (SD)	24.00 (31.791)	29.59 (31.613)	28.73 (31.065)
Median	13.00	25.00	22.50
Min, max	0.0, 70.0	0.0, 90.0	0.0, 90.0
WM IPSS per SPEP (derived) [c], n (%)			
Low	0 (0.0)	5 (21.7)	5 (17.9)
Intermediate	3 (60.0)	8 (34.8)	11 (39.3)
High	2 (40.0)	10 (43.5)	12 (42.9)
Baseline Hemoglobin (g/L)			
n	5	23	28
Mean (SD)	110.80 (16.634)	109.26 (20.172)	109.54 (19.311)
Median	105.00	108.00	108.00

Abbreviations: ANC, absolute neutrophil count; CT, computed tomography; Ig, immunoglobulin; IPSS, International Prognostic Scoring System; IRC, Independent Review Committee; LDT, laboratory developed test; Max, maximum; Min, minimum; NA, not applicable; SD, standard deviation; SPEP, serum protein electrophoresis assessment; WM, Waldenström's macroglobulinemia **Cohort 2** includes patients with wild type and unknown MYD88. Percentages are

based on N. **a** Time to randomization date if a patient was not dosed. **b** Identified by CT scan. **c** Morel et al. Int prognostic scoring system for WM, Blood 2013. IPSS is derived using M-protein by SPEP. **d** Cytopenia is defined as haemoglobin ≤110 g/L or platelet count≤100 x 109/L or ANC ≤ 1.5 x 109/L. Data cutoff 31 August 2019

Table 29 Signs and Symptoms: Indication for Initiation of Therapy (Cohort 2, Main Study - 302) (Safety Analysis Set)

	Treatment-naive (N = 5) n (%)	Relapsed/Refractory (N = 23) n (%)	Overall (N = 28) n (%)
Clinical Indications			
B-symptoms [a]	1 (20.0)	9 (39.1)	10 (35.7)
Fatigue	2 (40.0)	15 (65.2)	17 (60.7)
Hyperviscosity	2 (40.0)	4 (17.4)	6 (21.4)
Symptomatic or bulky lymphadenopathy [b]	0 (0.0)	1 (4.3)	1 (3.6)
Symptomatic hepatomegaly and/or splenomegaly	0 (0.0)	2 (8.7)	2 (7.1)
Symptomatic organomegaly and/or organ or tissue infiltration	0 (0.0)	1 (4.3)	1 (3.6)
Peripheral neuropathy due to WM	1 (20.0)	2 (8.7)	3 (10.7)
Laboratory Indications			
Symptomatic cryoglobulinemia	1 (20.0)	1 (4.3)	2 (7.1)
Cold agglutinin anemia	0 (0.0)	2 (8.7)	2 (7.1)
Immune hemolytic anemia and/or thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy related to WM	0 (0.0)	1 (4.3)	1 (3.6)
Amyloidosis related to WM	0 (0.0)	2 (8.7)	2 (7.1)
Hemoglobin ≤ 10 g/dL	1 (20.0)	8 (34.8)	9 (32.1)
Platelet count < 100 x 10^9/L	0 (0.0)	4 (17.4)	4 (14.3)

Abbreviations: WM, Waldenström's macroglobulinemia **Cohort 2** includes patients with wild type and unknown MYD88. **a** B-symptoms include recurrent fever, night sweats, and weight loss. **b** Bulky is defined as ≥ 5 cm in maximum diameter. Data cutoff 31 August 2019

Numbers analysed

Table 30 Study BGB-3111-302 Study Analysis Set

	Treatment Naive			Relapsed/Refractory			Overall		
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 24) n (%)	Total (N = 42) n (%)	Ibrutinib (N = 81) n (%)	Zanubrutinib (N = 106) n (%)	Total (N = 187) n (%)	Ibrutinib (N = 99) n (%)	Zanubrutinib (N = 130) n (%)	Total (N = 229) n (%)
Cohort 1									
n	18	19	37	81	83	164	99	102	201
Intent to Treat Analysis Set [a]	18 (100.0)	19 (100.0)	37 (100.0)	81 (100.0)	83 (100.0)	164 (100.0)	99 (100.0)	102 (100.0)	201 (100.0)
Relapsed/Refractory Analysis Set [b]				81 (100.0)	83 (100.0)	164 (100.0)			
Per-Protocol Analysis Set [c]	18 (100.0)	19 (100.0)	37 (100.0)	79 (97.5)	82 (98.8)	161 (98.2)	97 (98.0)	101 (99.0)	198 (98.5)
Per-Protocol Relapsed/Refractory Analysis Set [d]				79 (97.5)	82 (98.8)	161 (98.2)			
Safety Analysis Set [f]	18 (100.0)	19 (100.0)	37 (100.0)	80 (98.8)	82 (98.8)	162 (98.8)	98 (99.0)	101 (99.0)	199 (99.0)

	Treatment Naive			Relapsed/Refractory			Overall		
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 24) n (%)	Total (N = 42) n (%)	Ibrutinib (N = 81) n (%)	Zanubrutinib (N = 106) n (%)	Total (N = 187) n (%)	Ibrutinib (N = 99) n (%)	Zanubrutinib (N = 130) n (%)	Total (N = 229) n (%)
Cohort 2									
n		5			23			28	
Efficacy Analysis Set [e]		5 (100.0)			21 (91.3)			26 (92.9)	
Safety Analysis Set [f]		5 (100.0)			23 (100.0)			28 (100.0)	
Cohort 1 and Cohort 2									
PK Analysis Set [g]		24 (100.0)			105 (99.1)			129 (99.2)	

Data cut-off: 31AUG2019; Data extraction: 26NOV2019; Data Source: ADSL
n is the number of patients in cohort 1 and cohort 2, respectively. The percentages of the PK analysis set are based on N, and the other percentages are based on n of each cohort.
[a] The Intent to Treat (ITT) Analysis Set includes all randomized patients in cohort 1. [b] The Relapsed/Refractory Analysis Set (a subset of the ITT Analysis Set) includes all randomized patients in cohort 1 with at least 1 prior line of therapy as determined by the IRT system.
[c] The Per-Protocol Analysis Set includes patients in the ITT Analysis Set who received any dose of study treatment, had a valid post-baseline measurement of IgM (central or local) or M-protein by SPEP (central or local), and had no important protocol deviations that may affect efficacy analyses (evaluated by BeiGene).
[d] The Per-Protocol Relapsed/Refractory Analysis Set includes patients in the Relapsed/Refractory Analysis Set who received any dose of study treatment, had a valid post-baseline measurement of IgM (central or local) or M-protein by SPEP (central or local), and had no important protocol deviations that may affect efficacy analyses (evaluated by BeiGene).
[e] The Efficacy Analysis Set for Cohort 2 includes all patients who received any dose of zanubrutinib and are centrally confirmed to have wild type MYD88.
[f] The Safety Analysis Set includes all patients who received any dose of study drug.[g] The PK Analysis Set includes all subjects who have at least one postdose zanubrutinib concentration.

Outcomes and estimation

Primary efficacy endpoint

VGPR/CR

Table 31 Analysis of Disease Response per Overall Combined Assessment by Independent review Committee Cohort 1 (MYD88^{MUT}) (Intent to Treat Analysis Set)

	Treatment Naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18)	Zanubrutinib (N = 19)	Ibrutinib (N = 81)	Zanubrutinib (N = 83)	Ibrutinib (N = 99)	Zanubrutinib (N = 102)
Best Overall Response, n (%)						
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very good partial response (VGPR)	3 (16.7)	5 (26.3)	16 (19.8)	24 (28.9)	19 (19.2)	29 (28.4)
Partial response (PR)	9 (50.0)	9 (47.4)	49 (60.5)	41 (49.4)	58 (58.6)	50 (49.0)
Minor response (MR)	4 (22.2)	4 (21.1)	11 (13.6)	13 (15.7)	15 (15.2)	17 (16.7)
Stable disease (SD)	1 (5.6)	0 (0.0)	2 (2.5)	3 (3.6)	3 (3.0)	3 (2.9)
Progressive disease (PD)	0 (0.0)	1 (5.3)	2 (2.5)	1 (1.2)	2 (2.0)	2 (2.0)
Not applicable (N/A) [a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable (NE) [b]	1 (5.6)	0 (0.0)	1 (1.2)	0 (0.0)	2 (2.0)	0 (0.0)
Discontinued prior to first assessment [c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.0)

	Treatment Naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18)	Zanubrutinib (N = 19)	Ibrutinib (N = 81)	Zanubrutinib (N = 83)	Ibrutinib (N = 99)	Zanubrutinib (N = 102)
VGPR or CR Rate, n (%)	3 (16.7)	5 (26.3)	16 (19.8)	24 (28.9)	19 (19.2)	29 (28.4)
95% CI [d]	(3.6, 41.4)	(9.1, 51.2)	(11.7, 30.1)	(19.5, 39.9)	(12.0, 28.3)	(19.9, 38.2)
Risk Difference, % [e]		-		10.7		10.2
95% CI		(-, -)		(-2.5, 23.9)		(-1.5, 22.0)
p-value [f]		-		0.1160		0.0921

	Treatment Naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18)	Zanubrutinib (N = 19)	Ibrutinib (N = 81)	Zanubrutinib (N = 83)	Ibrutinib (N = 99)	Zanubrutinib (N = 102)
Major Response Rate (PR or Better), n (%)	12 (66.7)	14 (73.7)	65 (80.2)	65 (78.3)	77 (77.8)	79 (77.5)
95% CI [d]	(41.0, 86.7)	(48.8, 90.9)	(69.9, 88.3)	(67.9, 86.6)	(68.3, 85.5)	(68.1, 85.1)
Risk Difference, % [e]		-		-3.5		-0.5
95% CI		(-, -)		(-16.0, 9.0)		(-12.2, 11.1)
Overall Response Rate (MR or Better), n (%)	16 (88.9)	18 (94.7)	76 (93.8)	78 (94.0)	92 (92.9)	96 (94.1)
95% CI [d]	(65.3, 98.6)	(74.0, 99.9)	(86.2, 98.0)	(86.5, 98.0)	(86.0, 97.1)	(87.6, 97.8)

Data cut-off: 31AUG2019; Data extraction: 26NOV2019; Data Source: ADRSIRC, ADSL
Abbreviation(s): CI, confidence interval. Percentages are based on N.
Cohort 1 includes patients with activating mutations in MYD88.
[a] Includes patients whose only overall tumor response available is progressive disease unconfirmed (PDu). [b] Includes NE, UNK, and disease flare.
[c] Includes patients who discontinued study prior to the first response assessment. [d] 95% CI is calculated using the Clopper-Pearson method.
[e] Mantel-Haenszel common risk difference with the 95% confidence interval calculated using a normal approximation and Sato's standard error stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65). Ibrutinib is the reference group.
[f] Based on CMH test stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65).

Table 32 Analysis of Disease Response per Overall Combined Assessment by Independent Review Committee Cohort 2 (MYD88$^{WILD-TYPE}$) (Efficacy Analysis Set)

	Treatment Naive (N = 5)	Relapsed/Refractory (N = 21)	Overall (N = 26)
Best Overall Response, n (%)			
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Very good partial response (VGPR)	1 (20.0)	6 (28.6)	7 (26.9)
Partial response (PR)	1 (20.0)	5 (23.8)	6 (23.1)
Minor response (MR)	2 (40.0)	6 (28.6)	8 (30.8)
Stable disease (SD)	1 (20.0)	3 (14.3)	4 (15.4)
Progressive disease (PD)	0 (0.0)	1 (4.8)	1 (3.8)
Not applicable (N/A) [a]	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable (NE) [b]	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued prior to first assessment [c]	0 (0.0)	0 (0.0)	0 (0.0)

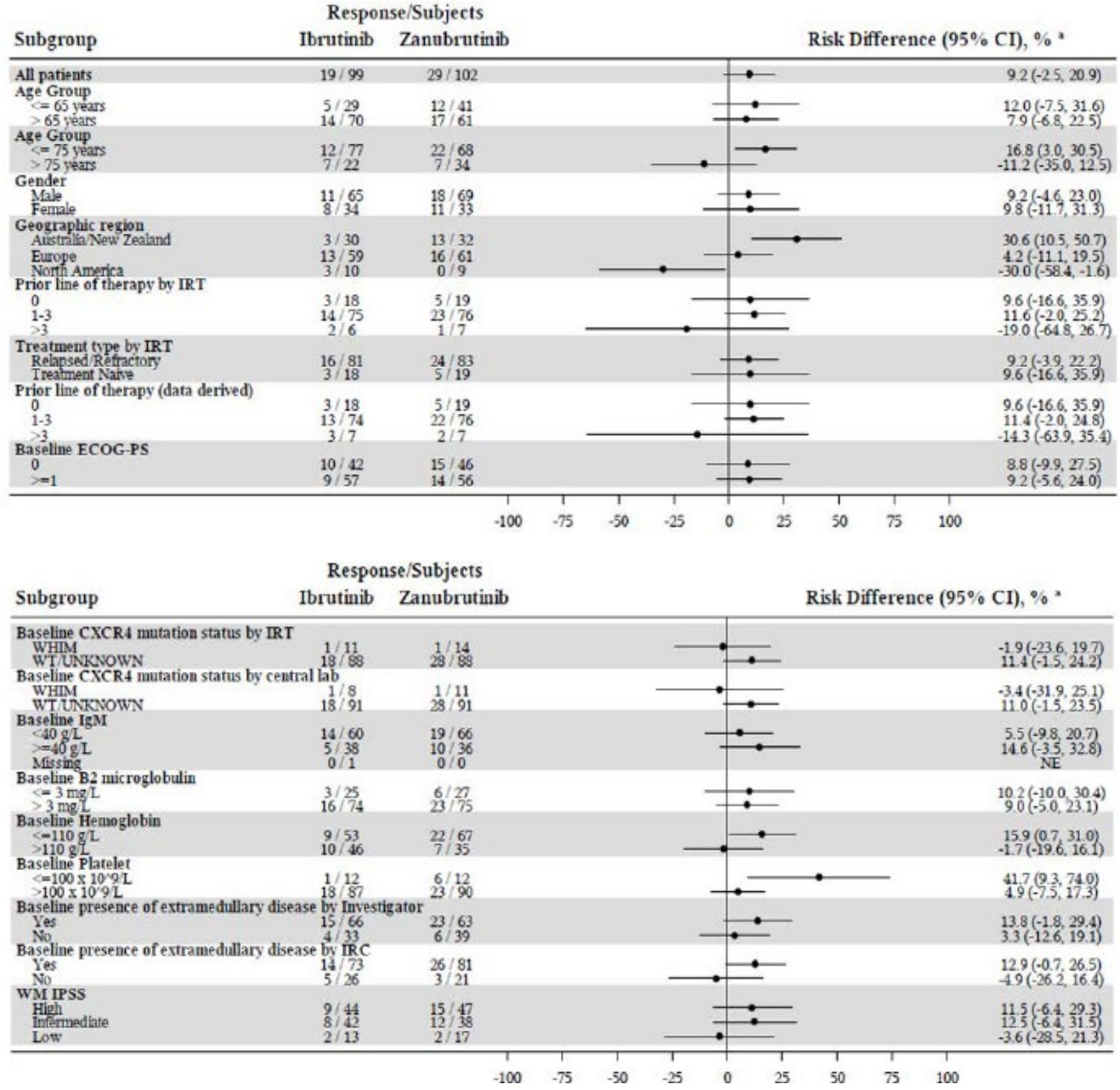
	Treatment Naive (N = 5)	Relapsed/Refractory (N = 21)	Overall (N = 26)
VGPR or CR Rate, n (%)	1 (20.0)	6 (28.6)	7 (26.9)
95% CI [d]	(0.5, 71.6)	(11.3, 52.2)	(11.6, 47.8)
Major Response Rate (PR or Better), n (%)	2 (40.0)	11 (52.4)	13 (50.0)
95% CI [d]	(5.3, 85.3)	(29.8, 74.3)	(29.9, 70.1)
Overall Response Rate (MR or Better), n (%)	4 (80.0)	17 (81.0)	21 (80.8)
95% CI [d]	(28.4, 99.5)	(58.1, 94.6)	(60.6, 93.4)

Data cut-off: 31AUG2019; Data extraction: 26NOV2019; Data Source: ADRSIRC, ADSL
Abbreviation(s): CI, confidence interval. Percentages are based on N.
Cohort 1 includes patients with activating mutations in MYD88.
[a] Includes patients whose only overall tumor response available is progressive disease unconfirmed (PDu). [b] Includes NE, UNK, and disease flare.
[c] Includes patients who discontinued study prior to the first response assessment. [d] 95% CI is calculated using the Clopper-Pearson method.

Subgroup assessments of VGPR/CR rate

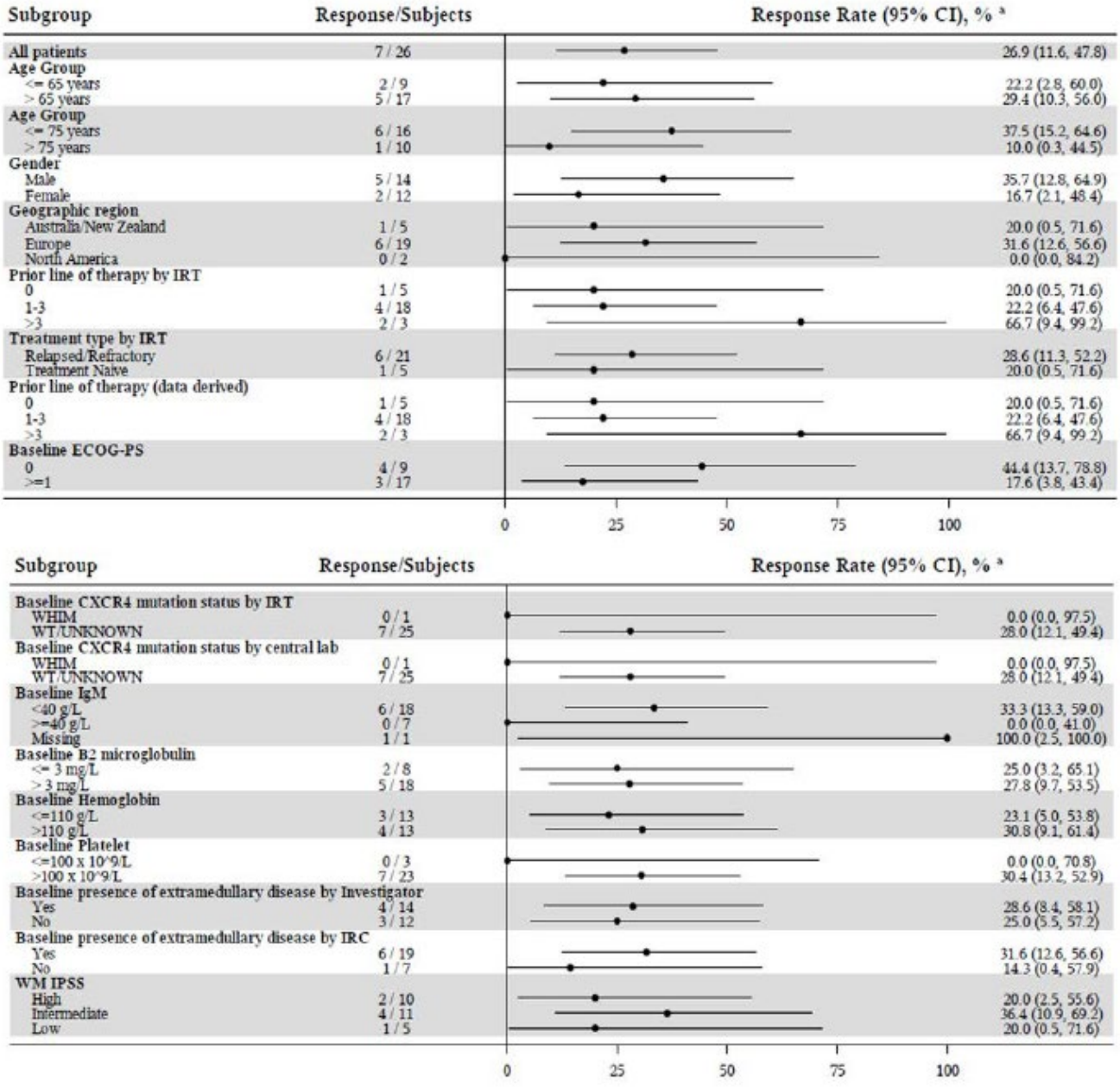
The proportions of patients in Cohort 1 who achieved a VGPR or CR per overall combined assessment were generally consistent for subgroups of interest with a few exceptions in mostly small subgroups. Zanubrutinib treatment was favoured in patients ≤ 75 years and in prognostically more difficult to treat patients such as those with higher IgM (≥ 40 g/L), cytopenias (e.g., haemoglobin concentration ≤ 110 g/L, and patients with baseline platelet count ≤ 100 x 10^9/L), extramedullary disease, and medium/high international prognostic scoring system (IPSS) scores. In terms of geographic location, patients from Australia or New Zealand fared better and patients from North America fared worse with zanubrutinib, albeit with low numbers of patient enrolled in North America (figure below).

***Figure 32** Forest Plot of VGPR or CR Rate Per Overall Combined Assessment by Independent Review Committee (Cohort 1, MYD88^{MUT}) (ITT Analysis Set)*



Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; IRC, Independent Review Committee; IRT, Interactive Response Technology; ITT, Intent-to-Treat; NE, not evaluable; VGPR, very good partial response; WM, Waldenström's macroglobulinemia Cohort 1 includes patients with activating mutations in MYD88. a Unstratified rate difference and 95% CI. Data cutoff 31 August 2019

***Figure 33** Forest Plot of VGPR or CR Rate Per Overall Combined Assessment by Independent Review Committee (Cohort 2, MYD88$^{WILD-TYPE}$) (Efficacy Analysis Set)*



Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; IRC, Independent Review Committee; IRT, Interactive Response Technology; NE, not evaluable; VGPR, very good partial response; WM, Waldenström's macroglobulinemia Cohort 2 includes patients with wild type and unknown MYD88. a Calculated using the Clopper-Pearson method. Data cutoff 31 August 2019

<u>Secondary efficacy endpoints</u>

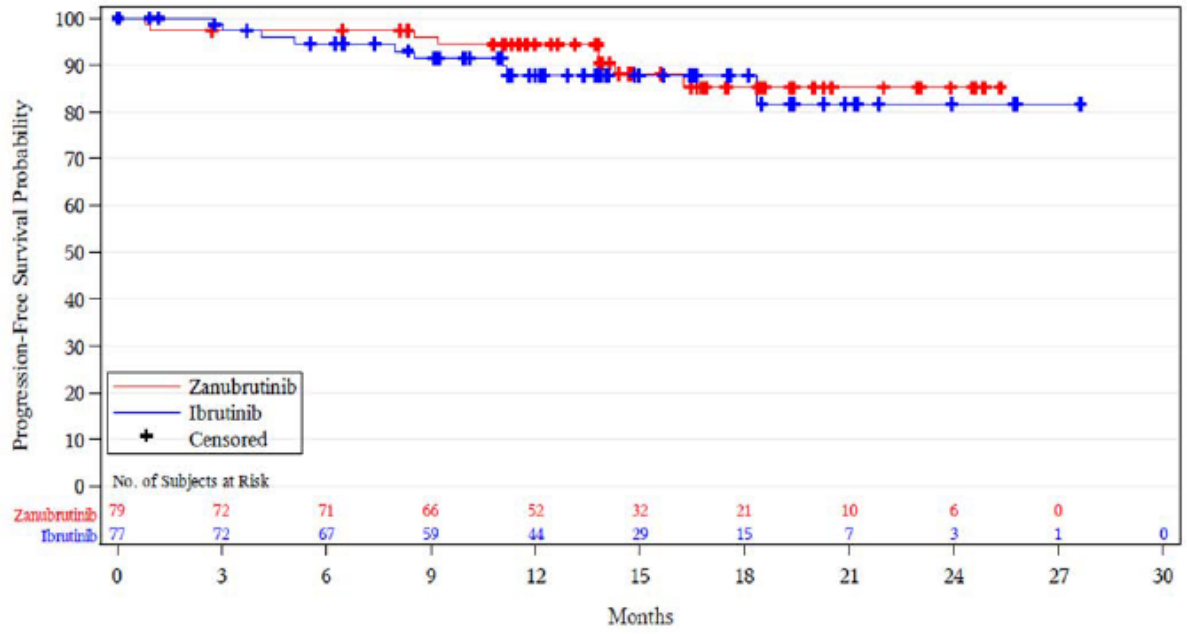
MRR

See table above.

Duration of response (DOR)

In Cohort 1, the median durations of VGPR or CR and major response per overall combined assessment had not been reached, in either treatment arm. Three patients (15%) had progressive disease in ibrutinib treatment, compared to 1 (3.4%), and one patient died during ibrutinib (5.3%) treatment, no one during zanubrutinib (Table 30, CSR 302). The differences may indicate a trend. However, the median follow-up time in months was very different. The Applicant was invited to clarify the follow-up time in months (median value, 95% CI) of 0.0 (0.0, 2.7) in TN ibrutinib group, compared 15.5 (0.0, 21.8) in TN zanubrutinib, which is comparable to 12-13 months in the RR patient population (Table 30, CSR 302). The Applicant clarified, that the short follow up for patients with VGPR in the ibrutinib arm compared to the zanubrutinib arm was due to the response occurring just prior to cutoff. One-year updated data shows longer duration of response for both arms although clearly longer for the zanubrutinib arm compared to the ibrutinib arm (27.4 months vs 13.8 months, respectively for TN patients and 23.0 months vs 16.6 months, respectively for RR patients). Although the number of responders is small, the difference in time to VGPR/CR suggests that TN zanubrutinib patients reached VGPR earlier, i.e., median (min, max) of 5.55 (4.6, 22.2) months, compared to TN ibrutinib patients, i.e. median (min, max) of 22.11 (16.9, 24.9). Consequently, the follow-up times for VGPR/CR in zanubrutinib patients are longer.

Figure 34 ***Kaplan-Meier Plot of Duration of Major Response per Overall Combined Assesment (Cohort 1) (ITT Analysis Set)***



Source: Figure 14.2.1.4.2
Abbreviations: ITT, Intent-to-Treat
Cohort 1 includes patients with activating mutations in MYD88.
Data cutoff 31 August 2019

PFS

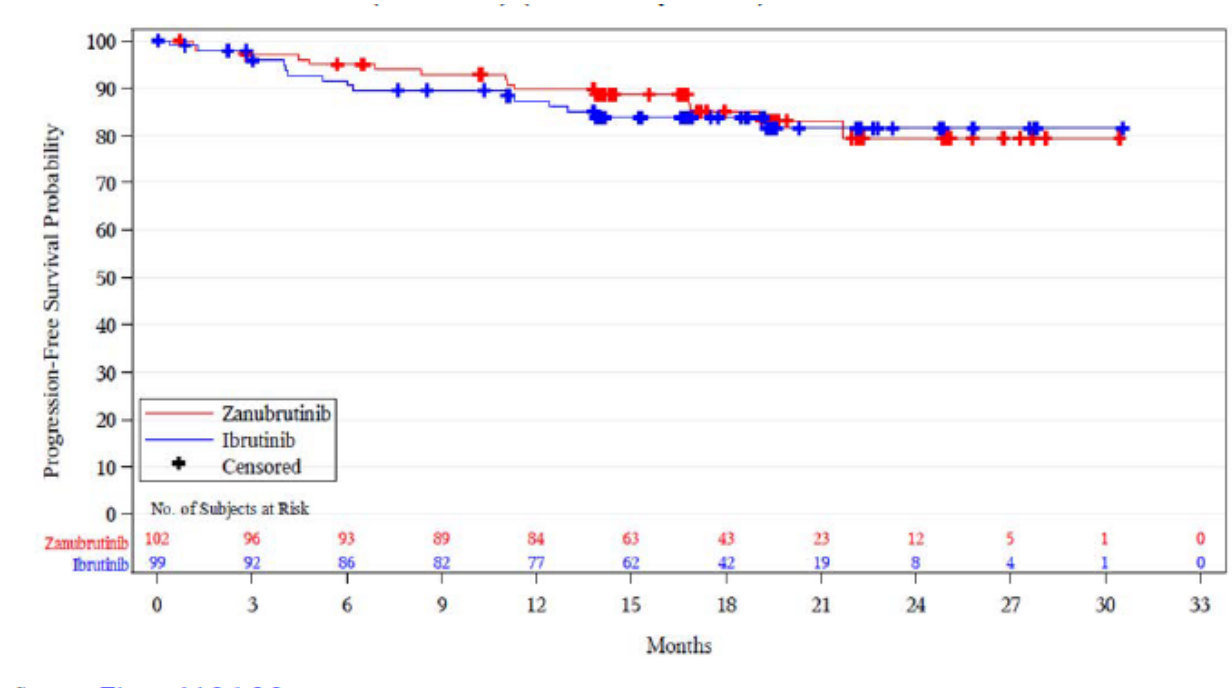
In Cohort 1, the median PFS had not been reached in overall, treatment-naive, or relapsed/refractory patients in either treatment arm.

The event-free rates at 12 months for patients overall in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 87.2% versus 89.7%, respectively, and 83.8% versus 85.0% at 18 months.

The event-free rates at 12 months for relapsed/refractory patients in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 85.9% versus 92.4%, respectively, and 81.7% versus 85.9% at 18 months.

Based on an updated data cut-off the progression free-survival event-free rate by investigator assessment was 77.6% vs 84.9% at 30 months (ibrutinib vs zanubrutinib), with an estimated overall hazard ratio of 0.734 (95% CI: 0.380, 1.415).

***Figure 35*: Kaplan – Meier Plot of Progression- Free Survival per Overall Combined Assesment (Cohort 1) (ITT Analysis Set)**



Time to response (TTR)

In the patients overall in Cohort 1, the median times to VGPR or CR per overall combined assessment were faster in the zanubrutinib arm, with 7.39 months and 4.80 months in the ibrutinib and zanubrutinib treatment arms, respectively. Conversely, time to major response and overall response were similar between arms: 2.83 months for both treatment arms for major response and 0.99 months and 1.02 months to overall response, for ibrutinib and zanubrutinib respectively.

In Cohort 2, the median times to VGPR or CR, major response, and overall response per overall combined assessment in patients overall were 5.65, 2.89, and 0.99 months, respectively. The median times to VGPR or CR, major response, and overall response were generally similar in zanubrutinib-treated patients in Cohort 1 compared with Cohort 2.

Table 33: Time to Response per Overall Combined Assessment* by Investigator *Cohort 1, MYD88^{MUT} WM (*Intent to Treat Analysis Set*)

	Treatment Naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18)	Zanubrutinib (N = 19)	Ibrutinib (N = 81)	Zanubrutinib (N = 83)	Ibrutinib (N = 99)	Zanubrutinib (N = 102)
Time to Response (VGPR or better) (months)						
Number of responders	3	5	14	24	17	29
Mean (SD)	21.31 (4.051)	9.32 (7.477)	7.94 (5.355)	6.59 (4.534)	10.30 (7.278)	7.06 (5.097)
Median	22.11	5.55	6.95	4.67	8.41	4.70
Q1, Q3	16.92, 24.90	4.80, 9.40	3.71, 11.24	2.87, 9.79	4.04, 16.59	3.02, 9.40
Min, Max	16.9, 24.9	4.6, 22.2	2.0, 19.4	1.9, 16.7	2.0, 24.9	1.9, 22.2
Time to Major Response (PR or better) (months)						
Number of responders	12	14	64	64	76	78
Mean (SD)	3.46 (3.605)	4.18 (5.605)	4.21 (3.112)	3.80 (3.670)	4.09 (3.181)	3.87 (4.043)
Median	2.38	2.37	2.92	2.83	2.89	2.83
Q1, Q3	1.41, 3.43	1.02, 4.27	1.92, 6.49	2.07, 3.02	1.91, 6.05	1.94, 3.02
Min, Max	0.9, 13.8	0.9, 22.2	0.9, 13.8	0.9, 22.1	0.9, 13.8	0.9, 22.2

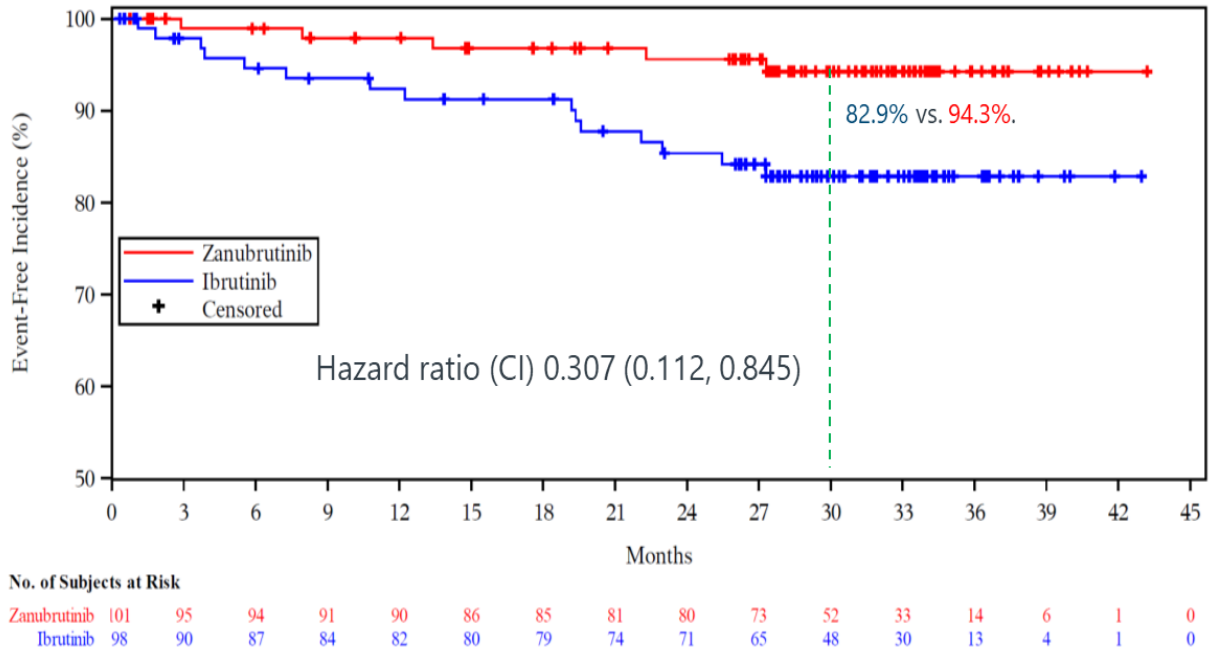
Table 34: Time to Response per Overall Combined Assessment* by Investigator *Cohort 2 MYD88$^{WILD-TYPE}$ WM (*Efficacy Analysis Set*)

	Treatment Naive (N = 5)	Relapsed/Refractory (N = 21)	Overall (N = 26)
Time to Response (VGPR or better) (months)			
Number of responders	0	7	7
Mean (SD)		7.53 (4.679)	7.53 (4.679)
Median		5.55	5.55
Q1, Q3		2.89, 13.83	2.89, 13.83
Min, Max		2.8, 13.8	2.8, 13.8
Time to Major Response (PR or better) (months)			
Number of responders	2	12	14
Mean (SD)	4.22 (1.882)	3.30 (1.639)	3.43 (1.630)
Median	4.22	2.86	2.89
Q1, Q3	2.89, 5.55	2.30, 3.42	2.73, 3.75
Min, Max	2.9, 5.6	1.9, 7.4	1.9, 7.4

Time to treatment Failure (TTTF)

On Study BGB-3111-302, zanubrutinib was found to have a longer time to treatment failure due to AE, defined as discontinuing of therapy for any AE, than ibrutinib with over 10% difference at 30 months. The 12 months AE failure-free rates for patients in the zanubrutinib and ibrutinib treatment arms were 97.9% versus 92.4% respectively, at 24 months 95.6% versus 85.4% and at 30 months 94.3% versus 82.9%.

*Figure 36**: Time to Treatment Failure due to AE***



Ancillary analyses

N/A

Summary of main study(ies)

The following tables summarise the efficacy results from the main study BGB-3111-302 (ASPEN), supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 35: Summary of efficacy for trial BGB-3111-302 (ASPEN)

Title: A Phase 3, Randomized, Open-Label, Multicentre Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)	
Study identifier	BGB-3111-302 EudraCT No.: 2016-002980-33
Design	This is an ongoing, Phase 3, randomized, open-label, multicentre study to compare the efficacy and safety of zanubrutinib and ibrutinib in patients with WM who required therapy according to the consensus panel criteria from the IWWM-7 (Dimopoulos et al 2014).

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Subjects received daily treatment during the study until progressive disease, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor Screening: Up to 35 days Safety Follow-up: All subjects who discontinued study drug and agreed to a follow-up visit had a safety follow-up visit approximately 30 days after the last dose of study drug. Efficacy Follow-up: Subjects who were discontinued from study drug for any reason other than progressive disease were followed every 12 weeks (±14 days) until disease progression, withdrawal of consent, death, lost to follow-up, end of study or study termination by sponsor, whichever occurred first. Survival Follow-up: Subjects will be followed for survival and further anticancer therapy information post progression via phone contact (with the subject's guardian, if applicable) every 12 weeks (±14 days) until study end.
Hypothesis	• Primary endpoint (VGPR or CR rate by independent review committee [IRC]): Superiority of zanubrutinib to ibrutinib; • Key Secondary endpoint (MRR by IRC): Non-inferiority under the margin of -12% (the secondary endpoints would be tested only if the primary endpoint is significant).		
Treatments groups	Arm A (Zanubrutinib Cohort 1)		Treatment: zanubrutinib 160 mg BID Duration: treat until disease progression, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or termination of the study by the sponsor Number randomized: 102
	Arm B (Ibrutinib Cohort 1)		Treatment: ibrutinib 420 mg QD Duration: same as arm A Number randomized: 99
	Arm C (Zanubrutinib Cohort 2)		Treatment: zanubrutinib 160 mg BID Duration: same as arm A Number enrolled: 28 (Arm C is not a randomized arm)
Endpoints and definitions	Primary endpoint	VGPR or CR rate by IRC	Rate of CR or VGPR, as assessed by IRC
	Key secondary endpoint	MRR by IRC	Major response rate (CR, VGPR, or PR), as assessed by IRC

	Secondary endpoint	VGPR or CR rate by INV	Rate of CR or VGPR, as assessed by investigator			
	Secondary endpoint	MRR by INV	Major response rate (CR, VGPR, or PR), as assessed by investigator			
	Secondary endpoint	DOR by IRC	Duration of response, as assessed by IRC, defined as the time from first determination of response (CR, VGPR, or PR) until first documentation of progression or death, whichever comes first			
	Secondary endpoint	DOR by INV	Duration of response, as assessed by investigator			
	Secondary endpoint	PFS by IRC	Progression-free survival, as assessed by IRC, defined as the time from randomization to the first documentation of progression or death, whichever comes first			
	Secondary endpoint	PFS by INV	Progression-free survival, as assessed by investigator			
	Secondary endpoint	TTR by IRC	Time to response, as assessed by IRC, defined as the time from randomization to the first determination of response			
Database lock	31 August 2019 (data cutoff date) 26 November 2019 (database lock date)					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Relapsed/Refractory (R/R) Analysis Set (cohort 1): included all randomised patients in cohort 1 with at least 1 prior line of therapy as determined by the IRT system. Intent-to-Treat (ITT) Analysis Set (cohort 1): included all randomised patients in cohort 1. Efficacy Analysis Set (cohort 2): included all patients who received any dose of zanubrutinib and were centrally confirmed to have $MYD88^{WT}$ Time point: data cutoff (median study follow-up: 19.4 months for cohort 1; 17.9 months for cohort 2)					
Descriptive statistics and estimate variability	Treatment group	Ibrutinib Cohort 1 (R/R)	Zanubrutinib Cohort 1 (R/R)	Ibrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 2
	Number of subjects	81	83	99	102	26
	VGPR or CR rate by IRC n (%)	16 (19.8)	24 (28.9)	19 (19.2)	29 (28.4)	7 (26.9)
	95% CI	(11.7, 30.1)	(19.5, 39.9)	(12.0, 28.3)	(19.9, 38.2)	(11.6, 47.8)
Effect estimate per comparison		Comparison groups	Ibrutinib Cohort 1	-	Ibrutinib Cohort 1 (ITT)	-
		Risk difference (zanubrutinib-Ibrutinib)	10.7	-	10.2	-
		95% CI	(-2.5, 23.9)	-	(-1.5, 22.0)	-

		P-value *CMH test	0.1160	-	0.0921	-
Notes	The testing for the primary endpoint of VGPR or CR rate superiority required testing in the R/R Analysis Set prior to testing in the ITT Analysis Set. While numerically higher rates of VGPR or CR in zanubrutinib arm were seen across analysis sets, the primary endpoint was not significant in the Relapsed/Refractory Analysis Set (2-sided p=0.1160). Therefore, testing for all subsequent endpoints and resulting p-values are descriptive.					
Descriptive statistics and estimate variability	Treatment group	Ibrutinib Cohort 1 (R/R)	Zanubrutinib Cohort 1 (R/R)	Ibrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 2
	Number of subjects	81	83	99	102	26
	VGPR or CR rate by INV n (%)	14 (17.3)	24 (28.9)	17 (17.2)	29 (28.4)	7 (26.9)
	95% CI	(9.8, 27.3)	(19.5, 39.9)	(10.3, 26.1)	(19.9, 38.2)	(11.6, 47.8)
Effect estimate per comparison		Comparison groups	Ibrutinib Cohort 1	-	Ibrutinib Cohort 1 (ITT)	-
		Risk difference	12.9	-	12.1	-
		95% CI	(-0.0, 25.9)	-	(0.5, 23.7)	-
		P-value *CMH test	0.0529	-	0.0437	-
Notes	None					
Analysis description	**Secondary Analysis**					
Analysis population and time point description	Relapsed/Refractory (R/R) Analysis Set (cohort 1): included all randomised patients in cohort 1 with at least 1 prior line of therapy as determined by the IRT system. Intent-to-Treat (ITT) Analysis Set (cohort 1): included all randomised patients in cohort 1. Efficacy Analysis Set (cohort 2): included all patients who received any dose of zanubrutinib and were centrally confirmed to have $MYD88^{WT}$ Time point: data cutoff					
Descriptive statistics and estimate variability	Treatment group	Ibrutinib Cohort 1 (R/R)	Zanubrutinib Cohort 1 (R/R)	Ibrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 2
	Number of subjects	81	83	99	102	26
	MRR by IRC n (%)	65 (80.2)	65 (78.3)	77 (77.8)	79 (77.5)	13 (50.0)
	95% CI	(69.9, 88.3)	(67.9, 86.6)	(68.3, 85.5)	(68.1, 85.1)	(29.9, 70.1)
Effect estimate per comparison		Comparison groups	Ibrutinib Cohort 1	-	Ibrutinib Cohort 1 (ITT)	-
		Risk difference	-3.5	-	-0.5	-

		95% CI	(-16.0, 9.0)	-	(-12.2,11.1)	-
Notes	none					
Descriptive statistics and estimate variability	MRR by INV n (%)	64 (79.0)	64 (77.1)	76 (76.8)	78 (76.5)	14 (53.8)
	95% CI	(68.5, 87.3)	(66.6, 85.6)	(67.2, 84.7)	(67.0, 84.3)	(33.4, 73.4)
Effect estimate per comparison		Comparison groups	Ibrutinib Cohort 1	-	Ibrutinib Cohort 1 (ITT)	-
		Risk difference	-3.7	-	-0.7	-
		95% CI	(-16.4, 9.0)	-	(-12.5, 11.1)	-
Notes	None					
Descriptive statistics and estimate variability	Treatment group	Ibrutinib Cohort 1 (R/R)	Zanubrutinib Cohort 1 (R/R)	Ibrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 2
	Number of subjects	81	83	99	102	26
	Duration of CR or VGPR by IRC Event free rate at, % (95% CI)					
	12 Months	63.9 (28.7, 85.2)	100.0 (NE, NE)	64.2 (28.8, 85.4)	100.0 (NE, NE)	75.0 (12.8, 96.1)
	18 Months	63.9 (28.7, 85.2)	90.0 (47.3, 98.5)	64.2 (28.8, 85.4)	92.9 (59.1, 99.0)	75.0 (12.8, 96.1)
	Duration of CR or VGPR by INV Event free rate at, % (95% CI)					
	12 Months	74.1 (28.9, 93.0)	100.0 (NE, NE)	74.1 (28.9, 93.0)	100.0 (NE, NE)	100.0 (NE, NE)
	18 Months	74.1 (28.9, 93.0)	91.7 (53.9, 98.8)	74.1 (28.9, 93.0)	93.8 (63.2, 99.1)	100.0 (NE, NE)
Notes	None					
Descriptive statistics and estimate variability	Treatment group	Ibrutinib Cohort 1 (R/R)	Zanubrutinib Cohort 1 (R/R)	Ibrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 2
	Number of subjects	81	83	99	102	26
	Duration of major response by IRC Event free rate at, % (95% CI)					
	12 Months	85.6 (73.1, 92.6)	95.1 (85.5, 98.4)	87.9 (77.0, 93.8)	94.4 (85.8, 97.9)	62.3 (27.7, 84.0)
	18 Months	85.6 (73.1, 92.6)	87.0 (72.5, 94.1)	87.9 (77.0, 93.8)	85.2 (71.7, 92.6)	62.3 (27.7, 84.0)
	Duration of major response by INV Event free rate at, % (95% CI)					
	12 Months	92.7 (81.7, 97.2)	100.0 (NE, NE)	93.9 (84.5, 97.7)	97.3 (89.7, 99.3)	61.2 (29.4, 82.1)

	18 Months	92.7 (81.7, 97.2)	94.3 (79.0, 98.5)	93.9 (84.5, 97.7)	90.4 (77.8, 96.0)	61.2 (29.4, 82.1)
Notes	None					
Descriptive statistics and estimate variability	Treatment group	Ibrutinib Cohort 1 (R/R)	Zanubrutinib Cohort 1 (R/R)	Ibrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 2
	Number of subjects	81	83	99	102	26
	PFS by IRC Event free rate at, % (95% CI)					
	12 Months	85.9 (75.9, 91.9)	92.4 (83.8, 96.5)	87.2 (78.6, 92.5)	89.7 (81.7, 94.3)	72.4 (50.6, 85.8)
	18 Months	81.7 (71.1, 88.8)	85.9 (73.7, 92.7)	83.8 (74.5, 89.9)	85.0 (75.2, 91.2)	68.1 (46.2, 82.6)
	PFS by INV Event free rate at, % (95% CI)					
	12 Months	88.5 (79.1, 93.9)	96.3 (88.8, 98.8)	90.4 (82.4, 94.9)	93.9 (87.0, 97.2)	69.0 (47.5, 83.2)
	18 Months	84.5 (74.4, 90.9)	91.3 (79.4, 96.5)	87.1 (78.4, 92.5)	88.9 (79.3, 94.2)	64.7 (43.0, 79.9)
Notes	In Cohort 1, the median progression-free survival had not been reached in the ITT or R/R Analysis Set in either treatment arm.					
Descriptive statistics and estimate variability	Treatment group	Ibrutinib Cohort 1 (R/R)	Zanubrutinib Cohort 1 (R/R)	Ibrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 1 (ITT)	Zanubrutinib Cohort 2
	Number of subjects	81	83	99	102	26
	Time to VGPR or CR by IRC					
	Number of responders	16	24	19	29	7
	Median	5.13	4.68	7.39	4.80	5.65
	Q1, Q3	3.12, 10.69	2.92, 10.71	3.12, 16.59	3.02, 10.32	2.89, 13.83
	Min, Max	2.0, 19.4	1.9, 16.7	2.0, 24.9	1.9, 22.2	2.8, 16.1
	Time to major response by IRC					
	Number of responders	65	65	77	79	13
	Median	2.86	2.83	2.83	2.83	2.89
	Q1, Q3	1.94, 4.76	1.91, 3.02	1.91, 4.76	1.91, 3.09	2.79, 3.71
	Min, Max	0.9, 17.5	0.9, 22.1	0.9, 19.4	0.9, 22.2	1.9, 16.1
Notes	None					

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

N/A

Clinical studies in special populations

Table 36: Zanubrutinib Exposure across Studies by Age Group

n/n (%)	**Age 65-74 (number of patients in specified age bracket/total number)**	**Age 75-84 (number of patients in specified age bracket/total number)**	**Age ≥85 (number of patients in specified age bracket /total number)**
Controlled trial (n=101)[a]	31/101 (30.7)	31/101 (30.7)	5/101 (5.0)
Non-controlled trials (n=678)[b]	221/678 (32.6)	97/678 (14.3)	19/678 (2.8)

[a] The controlled trial consists of the zanubrutinib arm (Cohort 1) of Study BGB-3111-302 (N=101).
[b] Non-controlled trials (total N=678) include Studies BGB-3111-302 Cohort 2 (N=28), BGB-3111-205 (N=91), BGB-3111-206 (N=86), BGB-3111-210 (N=44), BGB-3111-AU-003 (N=385) and BGB-3111-1002 (N=44).
Data cutoff date 31Aug2019

Supportive study(ies)

The Sponsor provides data on two studies that may be considered as a supportive study

- **Study BGB-3111-210**, NCT03332173, a phase 2 single-arm-trial in 44 Chinese RR WM patients. The study is ongoing, recruitment has ended. Efficacy results are pending, and according to the Sponsor these results will be available at Day120. Safety results are included in this submission.
- **Study BGB-3111-AU-003** NCT02343120 is an ongoing phase 1/2, open-label, multiple-dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of the BTK inhibitor BGB-3111 (zanubrutinib) in patients with B-cell lymphoid malignancies. The study is an interventional study, initiated November 26, 2014 in 23 haematological centres in six countries, in Europe (UK, Italy, USA, Australia and New Zealand, and Asia (Korea). Recruitment has been closed. Table 3.7 provides a summary of results.

***Table 37:* Summary of efficacy for trial BGB-3111-AU-003**

Title: A Phase 1/2, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Patients With B-Cell Lymphoid Malignancies	
Study identifier	BGB-3111-AU-003 EudraCT No.: 2016-003364-39

<table>
<tr><td>Design</td><td colspan="2">Phase 1/2, open-label, multiple-dose, dose-escalation, and cohort expansion study to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of zanubrutinib in patients with B-cell malignancies conducted in 2 parts.
Part 1 (Dose Escalation)
Modified 3+3 dose escalation design evaluating 5 dose/schedule levels (40 mg QD to 320 mg QD or 160 mg BID).
Part 2 (Expansion)
13 disease or patient-specific expansion cohorts including two WM specific cohorts with planned enrollment of 380 patients in total at the two dose/schedule levels (160mg BID and 320mg QD).</td></tr>
<tr><td></td><td>Duration of main phase:

Duration of Run-in phase:

Duration of Extension phase:</td><td>Daily treatment until disease progression, intolerance or death, withdrawal of consent, loss to follow-up, or study termination by sponsor

Screening: Up to 28 days

Safety Follow-up: Approximately 28 days after the last administration of the study drug.

Long-Term Follow-Up: Patients who discontinued study drug due to reasons other than disease progression remained on study and were followed every 3 months until the patient exhibited first progression, started new anticancer therapy, death, or study closure, whichever occurred first.

Survival Follow-up: Patients who discontinued study drug and had progressed (or had chosen to withdraw from long-term follow-up) entered</td></tr>
<tr><td>Hypothesis</td><td colspan="2">No hypothesis test was planned or performed.</td></tr>
<tr><td>Treatments groups</td><td>Part 1</td><td>
<table>
<tr><td>Zanubrutinib</td><td>Duration</td><td>Number treated (all/WM)</td></tr>
<tr><td>40mg QD</td><td rowspan="5">Treat until progressive disease or unacceptable toxicity</td><td>3/1</td></tr>
<tr><td>80mg QD</td><td>4/2</td></tr>
<tr><td>160mg QD</td><td>5/1</td></tr>
<tr><td>320mg QD</td><td>1/0</td></tr>
<tr><td>160mg BID</td><td>4/0</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td colspan="2">Part 2</td><td colspan="3"><table>
<tr><td>Zanubrutinib</td><td>Duration</td><td>Number treated (all/WM)</td></tr>
<tr><td>160mg BID</td><td rowspan="2">Treat until progressive disease or unacceptable toxicity</td><td>274/51</td></tr>
<tr><td>320mg QD</td><td>94/23</td></tr>
</table></td></tr>
<tr><td rowspan="7">Endpoints and definitions</td><td>Primary endpoint</td><td>VGPR/CR rate</td><td colspan="3">Rate of CR or VGPR</td></tr>
<tr><td>Secondary endpoint</td><td>OS</td><td colspan="3">Overall Survival</td></tr>
<tr><td>Exploratory endpoint</td><td>MRR</td><td colspan="3">Major Response Rate (CR, VGPR or PR)</td></tr>
<tr><td>Exploratory endpoint</td><td>ORR</td><td colspan="3">Overall Response Rate (CR, VGPR, PR or minor response)</td></tr>
<tr><td>Exploratory endpoint</td><td>DOR</td><td colspan="3">Duration of VGPR/CR, duration of major response, and duration of overall response</td></tr>
<tr><td>Exploratory endpoint</td><td>Time to response</td><td colspan="3">Time to VGPR/CR, time to major response, and time to overall response</td></tr>
<tr><td>Exploratory endpoint</td><td>PFS</td><td colspan="3">Progression-free survival</td></tr>
<tr><td>Database lock</td><td colspan="4">31 August 2019 (data cutoff date)
06 November 2019 (database lock date)</td></tr>
<tr><td colspan="5"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Efficacy evaluable set for WM, defined as all WM patients who received any dose of Zanubrutinib with baseline IgM level >= 5g/L and without prior exposure to BTK inhibitor. Timepoint: Data cutoff
Study follow-up: 30.32 months (range=4.4, 57.2)</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td colspan="2">Treatment group</td><td colspan="2">Zanubrutinib</td></tr>
<tr><td colspan="2">Number of subjects</td><td colspan="2">73</td></tr>
<tr><td colspan="2">Primary endpoint: VGPR or CR rate by Investigator
n (%)</td><td colspan="2">33 (45.2)</td></tr>
<tr><td colspan="2">95% CI</td><td colspan="2">(33.5, 57.3)</td></tr>
</table>

	MRR by Investigator n (%)	60 (82.2)
	95% CI	(71.5, 90.2)
	ORR by Investigator n (%)	70 (95.9)
	95% CI	(88.5, 99.1)
	Duration of VGPR/CR Event free rate at 12, 18 and 24 months (%) 95% CI	Event free rate at month / 95% CI 12 / 83.7 / (65.2, 92.9) 18 / 79.7 / (60.1, 90.4) 24 / 79.7 / (60.1, 90.4)
	Duration of MRR Event free rate at 12, 18 and 24 months (%) 95% CI	Event free rate at / 95% CI 12 / 91.6 / (80.9, 96.4) 18 / 88.0 / (76.4, 94.1) 24 / 83.2 / (70.0, 91.0)
	Duration of ORR Event free rate at 12, 18, 24 and 36 months (%) 95% CI	Event free rate at / 95% CI 12 / 89.6 / (79.5, 94.9) 18 / 86.4 / (75.4, 92.7) 24 / 81.8 / (69.2, 89.7) 36 / 78.8 / (64.8, 87.7)
	Time to VGPR/CR Median (months)	7.46
	Q1, Q3	3.75, 13.73
	Min, Max	2.6, 24.9
	Time to Major Response Median (months)	2.79
	Q1, Q3	2.63, 3.60
	Min, Max	0.3, 15.7
	Time to Overall Response Median (months)	2.79
	Q1, Q3	2.63, 2.86

	Min, Max	0.3, 36.9		
	PFS			
	Event free rate at 18, 24 and 36 months (%)	Event free rate at		95% CI
	95% CI	18	86.2	(75.8, 92.3)
		24	80.5	(68.5, 88.3)
		36	80.5	(68.5, 88.3)
	OS			
	Event free rate at 12, 24 and 36 months (%)	Event free rate at		95% CI
	95% CI	12	97.3	(89.5, 99.3)
		24	94.1	(84.9, 97.7)
	95% CI	36	84.8	(71.3, 92.3)

2.5.3. Discussion on clinical efficacy

In support of the application the Sponsor submitted data on one phase 3, randomized, open-label, worldwide, multicenter study BGB-3111-302 ASPEN, designed to compare the efficacy and safety of 2nd generation BTKi zanubrutinib and ibrutinib in patients with Waldenström's macroglobulinaemia (WM) who required therapy in first (treatment naïve, TN n=42) or later lines (relapsed / refractory, RR n=187). To further support the applied indication the Applicant presents results of a phase 1/2 study BGB-3111-AU-003, an open-label, multiple-dose, multicenter, dose-escalation (Part 1), and dose-expansion (Part 2) study designed to investigate the safety and PK of zanubrutinib in patients with B-cell malignancies in the single arm study of part 2 (n=73 patients with TN and RR WM).

Design and conduct of clinical studies

The target population was enrolled according to rational and reasoned detailed criteria, accepting treatment naïve (TN) and relapsed / refractory (RR) adult patients, without an upper age limit. The term TN patients "unsuitable" for treatment with a standard chemo-immunotherapy reflects a practice in real-world, when the specialist decides the optimal, individual choice of treatment according to co-morbidity and adhering to the treatment algorithms, including enrolment in a clinical trial (Kastritis et al, ESMO Ann Oncol 2018). The term may be considered to be unspecific, however it is accepted in

exactly the same wording for the comparator ibrutinib. The patient population is representative for WM by epidemiologic factors and reflecting the characteristic clinical and para-clinical manifestations, including phenotypic differences related to the genotypes of MYD88 and CXCR4 (Hunter at al, J Clin Oncol 2017). The Applicant has provided a list of patients screened and not included; no single reason(s) prevailed.

The starting dose was selected to be 160 mg zanubrutinib monotherapy BID. The therapy continues until intolerance or insufficient effect and disease progression. Dose adjustments are planned in case of adverse events, which often causes cytopenia, like other TKIs in haematology. The patients required therapy in first (TN n=42) or later lines (RR n=187). The TN and RR patients were further divided in $MYD88^{L265P}$mutated (typical, n=37 and 164) or $MYD88^{wild\text{-}type}$ WM (n=5 and 23), respectively. RR patients had a median of 1 prior treatment, some patients were heavily pretreated and time from diagnosis was 4.6 years (median). Indication for treatment was in accordance to IWWM standards (Dimopoulos et al, Blood 2014) and ESMO recommendations (Kastritis et al, Ann Oncol 2018).

As the comparator in the phase 3 study, ibrutinib was chosen, since it was approved for the treatment of WM in adults with WM from diagnosis. This "perfect match" in indication of the BTKi ibrutinib in WM further justifies the RCT design of the pivotal ASPEN study, reflected in a successful randomization. Because both BTKi are for oral treatment, but different in dose, formulation and administration, it is accepted to conduct an open-label study. It is important that the primary endpoint according to the international, objective standards (Owen et al, Br J Haematol 2013) of a very good partial response (VGPR) and/or complete response (CR), was assessed by an IRC. Secondary endpoints include the major response rate (MRR), which is a partial response, and better – an endpoint accepted with ibrutinib in WM.

In the original protocol (version 1.0 29 July 2016) the primary endpoint was MRR. However, after consulting the SAWP the primary endpoint was changed to CR/VGPR and MRR was now a secondary endpoint. In the scientific advice (EMA/CHMP/SAWP/636729/2016) there is no indication for testing for NI. According to the CHMP scientific advice theoretically, ORR would be the preferred primary endpoint. However, WM is a rare disease, and powering such a study for non-inferiority or for superiority given a projected ORR of almost 90% for ibrutinib would be a challenge. In this context, a primary comparison of MRR could be an acceptable way of demonstrating that BGB-3111 is at least similarly effective, if supported by an ORR rate that is not distinctly lower than for ibrutinib, and perhaps by secondary endpoints indicating a higher frequency of deeper responses.

In protocol version 2 (version 2.0, 01_November 2016) the Applicant introduces the non-inferiority margin and the NI testing. CR/VGPR and MRR will be tested sequentially to control the type I error in the primary and key secondary endpoint. Non-inferiority test of MRR will be performed with the possibility of demonstrating superiority if the lower bound for 95% CI of MRR rate is above zero.

In the Amendment 3, the total number of patients was increased to approximately 210 patients and the timing of the primary analysis was changed from 9 months to 12 months; both changes based on FDA feedback.

The originally proposed primary efficacy endpoint (MMR, including patients with PR, VGPR and CR) was changed to secondary efficacy endpoint and the originally planned superiority testing changed to non-inferiority during the study. Considering all clinical endpoints, the results are consistent (see discussion further below), and therefore further justification for the chosen endpoint, success criteria or testing strategy, was not pursued. Given the above methodological considerations, and despite the choices made by the Applicant with regards to the primary endpoint and the statistical analysis plan, it is worth revisiting the ibrutinib dossier (study 1118B) that established efficacy in WM based on a SAT with 63 patients, of which only 7 patients were MYD88 wt. The primary endpoint was ORR, and showed a rate of 87.3%, and a VGPR of 14.3%.

Lymphoplasmacytic lymphoma is driven by a combination of aberrant cell control systems. In particular, the MYD88 gene is mutated (L265P) in 95% of patients, and the impact is also influenced by e.g. mutational status of CXCR4, which is relevant to take into consideration, treating with BTKi. The sample size calculation in the main study is endorsed, randomizing 1:1 to zanubrutinib (n=102) or ibrutinib (n=99). Stratification factors included mutational status ($CXCR4^{WHIM}$ versus $CXCR4^{wild\text{-}type}$ versus missing) and the number of prior therapies for WM (0 versus 1-3 versus > 3) in Cohort 1, all un-mutated *MYD88* status. Cohort 2 patients in the main study were identified by $MYD88^{wild\text{-}type}$ and all treated with zanubrutinib only (n=5 TN and 23 RR WM). The study design is supported, because effect of BTKi treatment is reported to be related to mutational status as a targeted therapy, and prior therapies – but not age as a stratification factor. Age critically influenced treatment selection in WM, however in a trial context age *per* se is reflected by the clinical assessment before enrolment.

In all, 5 amendments (65 major changes) were made during the conduct of the main study. The changes in the protocol were not considered to have had an impact on study outcome and endpoints.

Patients in the phase 1/2 AU-003 study were enrolled according to the same criteria, TN (n=24) and RR (n=49), shows a compatible demographic profile. Some patients were treated with a 320 mg QD dose, instead of 160mg BID. The impact on efficacy of the two doses is most likely minimal, and results may be interpreted to assess responses, with caution.

Efficacy data and additional analyses

Results on efficacy in the phase 1/2 AU/-003 and phase 3 -302 study show a clinically relevant effect of zanubrutinib in both TN and RR WM, achieving a VGPR in 25-30%, the primary endpoint, and across all clinically relevant subgroups by Forest plots. No patient in the main study achieved a CR, which is a usual outcome in all WM (ESMO), reflecting that BTKi as monotherapy, in both TN and RR, has an impact on important signaling pathways influenced by the mutations, but not all key drivers. A trend towards a higher VGPR was noticed in both TN and RR patients, in general ibrutinib 20% and zanubrutinib 28% (primary endpoint), but not in the secondary endpoint MRR of 75-80%, overall.

Per the protocol and the SAP, the Applicant would test the secondary endpoint MRR according to a pre-planned NIM, if the study met its primary endpoint. However, since the study failed to show superiority with regards to the primary endpoint, MRR could not formally be tested for NI. Nonetheless, the risk difference for MRR was -0.5% (95%CI; -12.2, 11.1) and thus well within the NIM of 12%. Had the Applicant included more patients in the study, the 95%CI would have been narrower, and thus within the +/- 12%. This clearly reflects the fact that WM is a rare disease.

The progression free survival and the duration of response is of key importance in daily treatment in an elderly population. It is valuable that BTKi therapy showed a satisfactory 80% at 24 months in both time-dependent endpoints, although equal in both treatment Arms (Cohort 1). Results in the AU-003 study indicate that the response is slowly declining in the next 24 months to 70%, which is acceptable and still clinically relevant. In study 302 prior treatment was registered in all patients. Quite a high number of patients, although comparable between arms, did not have a known PD date ahead of the study. –

Mutational status has an impact on response to BTKi (Treon et al, Hemasphere 2020). Nineteen WHIM mutated patients were observed in Cohort 1, and the results indicate BTKi to be less effective than in CXCR4 un-mutated subjects, as expected. However, no significant difference in efficacy were indicated according to MYD88 mutational status (or BTKi), expecting $^{MYD88WILD\text{-}}$TYPE to be less sensitive. Given the similar VGPR rate for zanubrutinib in MYD88MUT and MYD88WT, and the higher rate compared to

ibrutinib in Cohort 1, it is agreed that this suggests that zanubrutinib may be a good therapeutic option for patients with Waldenström macroglobulinemia independent of MYD88 mutational status.

A major response was achieved in 75-80% of patients, irrespective of randomization to zanubrutinib or ibrutinib, and in both Cohort 1 ($MYD88^{MUT}$ or Cohort $2^{WILD\text{-}TYPE}$, TN or RR, which by itself is satisfactory, albeit it is considered to be different from SOC with chemo-immunotherapy. The major response on resolutions of symptoms (hyperviscosity, severe anaemia, IgM tissue deposition dependent manifestations, like neuropathy, cryoglobulinaemia, night-sweats etc) is considered to be clinically very meaningful.

A significant difference is noticed in the follow-up time in months (median value, 95% CI) of 0.0 (0.0, 2.7) in TN ibrutinib group, compared with 15.5 (0.0, 21.8) in TN zanubrutinib, which is comparable to 12-13 months in the RR patient population; the short follow up for patients with VGPR in the ibrutinib arm compared to the zanubrutinib arm was due to the response occurring just prior to cutoff. One-year updated data shows longer duration of response for both arms although clearly longer for the zanubrutinib arm compared to the ibrutinib arm (27.4 months vs 13.8 months, respectively for TN patients and 23.0 months vs 16.6 months, respectively for RR patients). Although the number of responders is small, the difference in time to VGPR/CR suggests that TN zanubrutinib patients reached VGPR earlier, i.e., median (min, max) of 5.55 (4.6, 22.2) months, compared to TN ibrutinib patients, i.e. median (min, max) of 22.11 (16.9, 24.9). Consequently, the follow-up times for VGPR/CR in zanubrutinib patients are longer.

The median time to response (VGPR) was 7 months (Cohort 2). The effect is considered to be comparable between the two BTKi and indicate that treatment is not ameliorating symptoms from the first day in most patients. The steady response also means that BTKi monotherapy does not alleviate the need for e.g. plasmapheresis in aggressive WM disease, and has to be combined in subjects with severe rheological and autoimmune phenomena, which is relatively frequent in patients in need of treatment.

The CHMP concluded that this single pivotal study provided sufficient evidence to establish efficacy and safety of ibrutinib in both MYD88-mutated and MYD88-wt patient in both the R/R setting and in first-line in patients unsuitable for chemo-immunotherapy. In comparison, the Applicant has provided a head-to-head comparison in a phase 3 study, supported by further data from a phase 1/2 study. In total 201 patients were randomized 1:1. The result by IRC shows CR/VGPR in the ibrutinib arm around 19%, which is in line with the observations made in study 1118B. A CR/VGPR of 28% is observed in the zanubrutinib arm. With regards to MRR the IRC concluded 77.8% vs. 77.5% in ibrutinib and zanubrutinib respectively.

The results in Study AU-003 overall support the data in the pivotal study 302, across line of therapy, sub-group analysis and response criteria, although with the caveat that patients had received either 320 mg zanubrutinib QD or zanubrutinib 160 mg BID.

The median OS was not reached, as expected in Studies with a follow-up up to 4-5 years in WM. A sub-group was planned in the supportive study AU-003 to examine the effect of zanubrutinib on patients previously treated with a BTKi for WM (Cohort m, 20 patients). However, only 1 patient among 54 RR WM patients had received ibrutinib. Given that the addition of cohort m was done late in the course of Study BGB-3111-AU-003 and the cohort failed to enroll a significant number of patients, it is not possible to evaluate the efficacy of zanubrutinib in patients previously treated with a BTKi using this study.

2.5.4. Conclusions on the clinical efficacy

Efficacy of the 2nd generation BTKi zanubrutinib is clearly shown in WM, across treatment and disease status, all relevant information has been included in section 5.1 of the SmPC.

2.6. Clinical safety

The main safety information is derived from the phase 3 study 302 conducted in a Western population only.

Furthermore, safety is evaluated in study BGB-3111-AU-003: "A first-in-human, Phase 1/2, dose-selection, PK/PD, safety, and efficacy study in adult patients with relapsed/refractory or treatment-naïve B-cell malignancies conducted in Australia, New Zealand, Italy, South Korea, United Kingdom (UK), and USA (N = 385). This study includes 78 patients with relapsed/refractory (n=54) or treatment-naïve (n=24) WM.

Patient exposure

In the pivotal Study BGB-3111-302 Cohort 1, the median duration of exposure was 18.55 months and 18.73 months for patients in the ibrutinib and zanubrutinib treatment arms, respectively; 84% and 89% of patients had a minimum exposure of 12 months. The total exposure (in patient months) was 1706.58 and 1836.62, respectively, in the ibrutinib- and zanubrutinib-treated arms. Median relative dose intensities for patients in the ibrutinib and zanubrutinib arms were 98.18% (range: 51.6% to 100.0%) and 97.64% (range: 29.0% to 100.0%), respectively. Twenty-one (21.4%) and 15 (14.9%) patients in the ibrutinib and zanubrutinib arms respectively, required 1 or more dose reductions.

In addition to the pivotal 302 study, data from the supportive study BGB-3111-AU-003: "A first-in-human, Phase 1/2, dose-selection, PK/PD, safety, and efficacy study in adult patients with relapsed/refractory or treatment-naïve B-cell malignancies conducted in Australia, New Zealand, Italy, South Korea, United Kingdom (UK), and USA (N = 385) are included. This study includes 78 patients with relapsed/refractory (n=54) or treatment-naïve (n=24) WM. This supportive study is ongoing and contributes PK, PD, efficacy, and safety data to this submission, with a median follow-up of 31.5 months." This study is included in the All WM group (n=253), which also includes 44 R/R WM Chinese patients and the entire study 302 (Cohort 1; 101 patients and Cohort 2; 28 patients) so that study 302 constitutes 50% of the All WM population.

In the following the adverse events from study 302, Cohort 1, will also be compared to the WM patients from study AU-003.

The Applicant was further asked to provide an updated safety analysis based on pivotal study data and data derived from all patients with WM. The updated exposure data for the All Zanubrutinib population (n=779), which contains a variety of B-cell malignancies, demonstrate a mean and median durations of exposure of 26.81 months and 30.32 months, respectively equating to 20884.73 patient-months (1,740 patient-years) of follow-up.

Subjects who have MY88 wild type ($MYD88^{WT}$) constituted the zanubrutinib treated cohort 2 (in study BGB-3111-302).

Adverse events

Table 38 Overview of adverse events in Study 302: Cohort 1 : Safety analysis set

Category	Treatment-naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Patients with at least 1 AE	18 (100.0)	19 (100.0)	79 (98.8)	79 (96.3)	97 (99.0)	98 (97.0)
Grade 3 or higher [a]	12 (66.7)	14 (73.7)	50 (62.5)	45 (54.9)	62 (63.3)	59 (58.4)
Serious	9 (50.0)	10 (52.6)	31 (38.8)	30 (36.6)	40 (40.8)	40 (39.6)
Leading to death	0 (0.0)	0 (0.0)	4 (5.0)	1 (1.2)	4 (4.1)	1 (1.0)
Leading to treatment discontinuation	3 (16.7)	0 (0.0)	6 (7.5)	4 (4.9)	9 (9.2)	4 (4.0)
Leading to dose reduction	4 (22.2) [c]	2 (10.5)	19 (23.8) [c]	12 (14.6)	23 (23.5) [c]	14 (13.9)
Leading to dose hold	11 (61.1)	11 (57.9)	44 (55.0)	36 (43.9)	55 (56.1)	47 (46.5)
Patients with at least 1 treatment-related AE [b]	15 (83.3)	15 (78.9)	69 (86.3)	65 (79.3)	84 (85.7)	80 (79.2)
Patients with at least 1 AE of special interest	15 (83.3)	16 (84.2)	66 (82.5)	70 (85.4)	81 (82.7)	86 (85.1)

Source: Table 14.3.1.2.1.1, Table 14.3.1.2.8.1
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events
Cohort 1 includes patients with activating mutations in MYD88.
MedDRA Version 22.0.
[a] AE grades are evaluated based on NCI-CTCAE (Version 4.03).
[b] Treatment-related AEs are defined as related or with missing relationship.
[c] Includes 2 patients who had a temporary dose reduction of ibrutinib due to AE by investigator decision (1 treatment-naive) or by patient's own decision (1 relapsed/refractory).
Data cutoff 31 August 2019

Treatment-emergent adverse events

In the SOC "Infections and Infestations" the incidence is 67.3% in the ibrutinib arm vs 66.3% for zanubrutinib; a marked difference was the PT for pneumonia (12.2% and 2%, respectively). In the 12 months safety update the incidence is higher but still comparable between arms.

There were generally more infections in study AU-003 by SOC within the PT Pneumonia; similar to the zanubrutinib arm in study 302 whereas the incidence of Lower respiratory infection was comparable to the ibrutinib arm. Comparing the added incidences of the two terms Lower respiratory tract infection and Pneumonia the incidence is still higher in the ibrutinib arm compared to the zanubrutinib arm in study 302; 21.4% vs 9.9%, respectively.

In Study BGB-3111-302, Cohort 1, the incidence of diarrhoea among zanubrutinib recipients was half that of ibrutinib recipients on an exposure-adjusted basis (1.3 and 2.6 persons/100 person-years, respectively).

The frequency of atrial fibrillation was lower in the zanubrutinib group than in the ibrutinib group (BGB 3111-302, 2 % and 15.3 %, respectively).

In the below table difference between the two arms in study 302, Cohort 1, greater than 10% is marked in bold.

Table 39: Adverse Events by System Organ Class and Preferred Term Reported in >10% of Patients in Either Overall Arm (Cohort 1) (Safety Analysis Set)

System Organ Class/ Preferred Term [a]	Treatment-naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Patients with at least 1 AE	18 (100.0)	19 (100.0)	79 (98.8)	79 (96.3)	97 (99.0)	98 (97.0)
Blood and lymphatic system disorders						
Neutropenia	1 (5.6)	5 (26.3)	11 (13.8)	**20 (24.4)**	12 (12.2)	**25 (24.8)**
Anaemia	0 (0.0)	6 (31.6)	10 (12.5)	6 (7.3)	10 (10.2)	12 (11.9)
Thrombocytopenia	0 (0.0)	2 (10.5)	10 (12.5)	8 (9.8)	10 (10.2)	10 (9.9)
Infections and infestations						
Upper respiratory tract infection	4 (22.2)	3 (15.8)	24 (30.0)	21 (25.6)	28 (28.6)	24 (23.8)
Nasopharyngitis	0 (0.0)	2 (10.5)	7 (8.8)	9 (11.0)	7 (7.1)	11 (10.9)
Urinary tract infection	2 (11.1)	1 (5.3)	8 (10.0)	9 (11.0)	10 (10.2)	10 (9.9)
Pneumonia	2 (11.1)	0 (0.0)	**10 (12.5)**	2 (2.4)	**12 (12.2)**	2 (2.0)
Gastrointestinal disorders						
Diarrhoea	5 (27.8)	5 (26.3)	**26 (32.5)**	16 (19.5)	**31 (31.6)**	21 (20.8)
Constipation	1 (5.6)	4 (21.1)	6 (7.5)	12 (14.6)	7 (7.1)	16 (15.8)
Nausea	4 (22.2)	6 (31.6)	9 (11.3)	9 (11.0)	13 (13.3)	15 (14.9)
Vomiting	4 (22.2)	1 (5.3)	9 (11.3)	8 (9.8)	13 (13.3)	9 (8.9)
General disorders and administration site conditions						
Fatigue	2 (11.1)	4 (21.1)	13 (16.3)	15 (18.3)	15 (15.3)	19 (18.8)
Pyrexia	0 (0.0)	3 (15.8)	12 (15.0)	10 (12.2)	12 (12.2)	13 (12.9)
Oedema peripheral	3 (16.7)	1 (5.3)	**16 (20.0)**	8 (9.8)	**19 (19.4)**	9 (8.9)

System Organ Class/ Preferred Term [a]	Treatment-naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Nervous system disorders						
Headache	2 (11.1)	3 (15.8)	9 (11.3)	12 (14.6)	11 (11.2)	15 (14.9)
Dizziness	2 (11.1)	4 (21.1)	7 (8.8)	9 (11.0)	9 (9.2)	13 (12.9)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11.1)	3 (15.8)	4 (5.0)	11 (13.4)	6 (6.1)	14 (13.9)
Arthralgia	3 (16.7)	2 (10.5)	13 (16.3)	11 (13.4)	16 (16.3)	13 (12.9)
Pain in extremity	2 (11.1)	1 (5.3)	5 (6.3)	10 (12.2)	7 (7.1)	11 (10.9)
Muscle spasms	6 (33.3)	3 (15.8)	**17 (21.3)**	7 (8.5)	**23 (23.5)**	10 (9.9)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	1 (5.6)	2 (10.5)	5 (6.3)	12 (14.6)	6 (6.1)	14 (13.9)
Cough	2 (11.1)	3 (15.8)	15 (18.8)	10 (12.2)	17 (17.3)	13 (12.9)
Epistaxis	4 (22.2)	4 (21.1)	15 (18.8)	9 (11.0)	19 (19.4)	13 (12.9)
Skin and subcutaneous tissue disorders						
Rash	4 (22.2)	3 (15.8)	12 (15.0)	10 (12.2)	16 (16.3)	13 (12.9)
Injury, poisoning and procedural complications						
Contusion	4 (22.2)	3 (15.8)	**19 (23.8)**	10 (12.2)	**23 (23.5)**	13 (12.9)
Vascular disorders						
Hypertension	3 (16.7)	3 (15.8)	13 (16.3)	8 (9.8)	16 (16.3)	11 (10.9)
Renal and urinary disorders						
Haematuria	3 (16.7)	3 (15.8)	7 (8.8)	4 (4.9)	10 (10.2)	7 (6.9)
Cardiac disorders						
Atrial fibrillation	3 (16.7)	0 (0.0)	**11 (13.8)**	2 (2.4)	**14 (14.3)**	2 (2.0)

Table 40

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

ystem Organ Class Preferred Term	302 Cohort 1 Ibrutinib (N = 98) n (%)	302 Cohort 1 Zanubrutinib (N = 101) n (%)	All WM Zanubrutinib (N = 253) n (%)	All China Zanubrutinib (N = 265) n (%)	All Non-China Zanubrutinib (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
atients with at least one TEAE	98 (100.0)	100 (99.0)	250 (98.8)	261 (98.5)	506 (98.4)	767 (98.5)
fections and infestations	74 (75.5)	75 (74.3)	205 (81.0)	198 (74.7)	395 (76.8)	593 (76.1)
Upper respiratory tract infection	31 (31.6)	31 (30.7)	93 (36.8)	113 (42.6)	194 (37.7)	307 (39.4)
Pneumonia	15 (15.3)	4 (4.0)	27 (10.7)	69 (26.0)	58 (11.3)	127 (16.3)
Urinary tract infection	15 (15.3)	11 (10.9)	38 (15.0)	39 (14.7)	82 (16.0)	121 (15.5)
Nasopharyngitis	7 (7.1)	11 (10.9)	25 (9.9)	18 (6.8)	40 (7.8)	58 (7.4)

Grade 3 and higher adverse events

Pneumonia ≥ Grade 3 was seen more frequently in the ibrutinib arm compared to the zanubrutinib arm [7 (7.1%) versus 1 (1.0%)]. For the entire SOC ≥ Grade 3 Infections and Infestations the difference between the two arms was much smaller (19.4% vs 17.8%). Comparing the added incidences of the three terms Lower respiratory infection, Lung infection, and Pneumonia the difference between the ibrutinib arm and the zanubrutinib arm in study 302 becomes smaller: 7.1% vs 4.0%, respectively.

Grade 3 and higher hypertension, were seen more frequently in the ibrutinib arm compared to the zanubrutinib arm (11.2% versus 5.9%, respectively). Looking at the All Zanubrutinib (N=779), All Non-China (N=514), and study AU-003 (N=78) the incidences were comparable to or lower than in study 302 for zanubrutinib.

Only 1 patient experienced diarrhoea as ≥ Grade 3.

Table 41: Grade 3 or Higher Adverse Events by System Organ Class and Preferred Term Reported in >2% of Patients in Either Overall Arm (Cohort 1) (Safety Analysis Set)

System Organ Class/ Preferred Term [a]	Treatment-naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Patients with at least 1 Grade 3 or higher AE	12 (66.7)	14 (73.7)	50 (62.5)	45 (54.9)	62 (63.3)	59 (58.4)
Blood and lymphatic system disorders						
Neutropenia	0 (0.0)	2 (10.5)	8 (10.0)	**14 (17.1)**	8 (8.2)	**16 (15.8)**
Thrombocytopenia	0 (0.0)	1 (5.3)	3 (3.8)	5 (6.1)	3 (3.1)	6 (5.9)
Anaemia	0 (0.0)	1 (5.3)	5 (6.3)	4 (4.9)	5 (5.1)	5 (5.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.9)	0 (0.0)	4 (4.0)
Vascular disorders						
Hypertension	2 (11.1)	1 (5.3)	**9 (11.3)**	5 (6.1)	**11 (11.2)**	6 (5.9)
Musculoskeletal and connective tissue disorders						
Back pain	0 (0.0)	1 (5.3)	0 (0.0)	3 (3.7)	0 (0.0)	4 (4.0)
Arthralgia	0 (0.0)	1 (5.3)	0 (0.0)	2 (2.4)	0 (0.0)	3 (3.0)
Investigations						
Neutrophil count decreased	0 (0.0)	0 (0.0)	1 (1.3)	4 (4.9)	1 (1.0)	4 (4.0)
Nervous system disorders						
Syncope	1 (5.6)	3 (15.8)	1 (1.3)	1 (1.2)	2 (2.0)	4 (4.0)
Gastrointestinal disorders						
Diarrhoea	0 (0.0)	1 (5.3)	1 (1.3)	2 (2.4)	1 (1.0)	3 (3.0)
Infections and infestations						
Sepsis	1 (5.6)	0 (0.0)	2 (2.5)	2 (2.4)	3 (3.1)	2 (2.0)

System Organ Class/ Preferred Term [a]	Treatment-naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Pneumonia	1 (5.6)	0 (0.0)	**6 (7.5)**	1 (1.2)	**7 (7.1)**	1 (1.0)
Cardiac disorders						
Atrial fibrillation	1 (5.6)	0 (0.0)	2 (2.5)	0 (0.0)	3 (3.1)	0 (0.0)

Source: Table 14.3.1.2.2.3
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE; National Cancer Institute-Common Terminology Criteria for Adverse Events
Cohort 1 includes patients with activating mutations in MYD88.
Patients with multiple events for a given preferred term and system organ class are counted only once for each preferred term and system organ class, respectively.
Adverse event grades are evaluated based on NCI-CTCAE (Version 4.03).
MedDRA Version 22.0
[a] Sorted by most common incidence in Overall Zanubrutinib column.
Data cutoff 31 August 2019

Adverse Events of Special Interest

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

Table 42 Criteria for Adverse Events of Special interest

Adverse Event of Special Interest Category	Search Criteria
Haemorrhage (including minor bleeding such as contusion and petechiae)	Haemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major haemorrhage - Defined as serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade	Major haemorrhage: • Subdural haematoma PT, Subdural haemorrhage PT • All Haemorrhage PTs if adverse event SOC is "Nervous system disorders" or • Serious or ≥ Grade 3 haemorrhage PT if adverse event SOC is not "Nervous system disorders"
Atrial fibrillation and flutter	Atrial fibrillation PT, Atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Second primary malignancies Skin cancers	Malignant Tumours (SMQ) Narrow Subcategory - Skin malignant tumours (SMQ) narrow
Tumour lysis syndrome	Tumour lysis syndrome (SMQ) Narrow
Infections Opportunistic Infections	Infections: Infections and Infestations SOC Subcategory - Opportunistic infections: Opportunistic infections (CMQ)
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
Anaemia	Anaemia PT, Haemoglobin decreased PT

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

Haemorrhage

In Study BGB-3111-302 Cohort 1, the incidence of haemorrhage of any grade was 59.5% among ibrutinib-treated patients compared to 48.5% in the zanubrutinib-treated patients and exposure-adjusted incidence rates (EAIR) (6.95 versus 4.43 persons/100 person-months). Of these 10 (of 58 patients) (10.2%) and 6 (of 49 patients) (5.9%) ibrutinib- and zanubrutinib-treated patients, respectively, had antecedent thrombocytopenia and 14 (14.3%) and 12 (11.9%), respectively, reported the use of antithrombotic medication.

Most haemorrhage events in both arms were Grade 1 or 2 in severity. Grade 3 or higher haemorrhage was reported for 8 ibrutinib-treated patients and 6 zanubrutinib-treated patients and SAEs were reported in 6 and 5 patients, respectively. No events of haemorrhage in either arm led to death.

In the All Zanubrutinib and All WM patient groups, haemorrhage of any severity grade was similar among patients in terms of overall crude incidence (52.8% and 52.2%, respectively), EAIRs (5.30 and 4.70 persons/100 person-months, respectively). Major bleeding events were uncommon in both patient groups (0.20 and 0.27 persons/100 person-months for the All Zanubrutinib and All WM patient

groups, respectively), and events that met the criteria for seriousness occurred in 3.1% and 4.3% of patients, respectively. The EAIR for ≥ Grade 3 haemorrhage was 0.18 patients/100 person-months.

Atrial Fibrillation/Flutter

In the pivotal study 302, the incidence of atrial fibrillation (Afli) / flutter was higher in the ibrutinib arm (15.3%) compared to the zanubrutinib arm (2.0%), (EAIR 0.96 persons/100 person-months ibrutinib versus 0.11 persons/100 person-months zanubrutinib). In the ibrutinib arm, 3/8 with a history of Afli compared to 0/10 in the zanubrutinib arm relapsed during treatment.

The incidence of Afli was higher in the supportive phase 1/2 study AU-003 (5.1% in the WM cohort) compared to study 302 (2.0%); the total number of patients is small, though (4/78 WM patients, and 14/385=3.6% in the entire study).

Hypertension

In Study BGB-3111-302 Cohort 1, the incidence of hypertension was higher among ibrutinib-treated patients (17.3%) compared with zanubrutinib-treated patients (10.9%) despite the fact that there were more patients with prior hypertension in the ibrutinib arm (43.9%) compared to the zanubrutinib arm (37.6%).

In the supportive phase 1/2 study AU-003 (Western population) the incidence of hypertension in the WM population was higher with 12/78 (15.4%) all-grade hypertension; this despite the fact that only 2 patients had a history of hypertension. ≥Grade 3 hypertension was seen in 3/78 (3.8%) patients.

Second primary malignancies

In the pivotal study 302, Cohort 1, the incidences of second primary malignancies (and the subpopulation of various skin cancers excluding melanoma) were 11.2% (9.2%) and 11.9% (7.9%) for ibrutinib and zanubrutinib, respectively. In the supportive phase 1/2 study AU-003 the incidence of second primary malignancies in the WM population was 19/78 (24.4%). mostly various skin cancers; 14/78 (18%). 13 of these 14 patients came from AUS/NZ and 1 patient came from Arizona, USA (68% of the overall study population came from Australia and New Zealand). In the pivotal study 302 (Cohort 1) only 31% were recruited from Australia/New Zealand, which explains the lower incidence of both melanoma and non-melanoma skin cancer.

Table 43: AESIs of Second Primary Malignancies (including skin cancers) reported in > 1 patient in any treatment group (safety analysis set)

	Ibrutinib	Zanubrutinib				
Preferred term	**BGB-3111-302 Cohort 1 (N = 98) n (%)**	**BGB-3111-302 Cohort 1 (N = 101) n (%)**	**All WM (N = 253) n (%)**	**All China (N = 265) n (%)**	**All Non-China (N = 514) n (%)**	**All Zanubrutinib (N = 779) n (%)**
Patients with at least one AESI of second primary malignancies	11 (11.2)	12 (11.9)	38 (15.0)	7 (2.6)	87 (16.9)	94 (12.1)
Basal cell carcinoma[a]	2 (2.0)	4 (4.0)	16 (6.3)	0 (0.0)	35 (6.8)	35 (4.5)
Squamous cell carcinoma of skin[a]	4 (4.1)	2 (2.0)	9 (3.6)	0 (0.0)	22 (4.3)	22 (2.8)
Malignant melanoma[a]	0 (0.0)	1 (1.0)	1 (0.4)	0 (0.0)	8 (1.6)	8 (1.0)
Squamous cell carcinoma of head and neck [b]	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	7 (1.4)	7 (0.9)
Bowen's disease[a]	1 (1.0)	1 (1.0)	4 (1.6)	0 (0.0)	6 (1.2)	6 (0.8)
Prostate cancer	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	5 (1.0)	5 (0.6)
Skin cancer[a]	2 (2.0)	1 (1.0)	2 (0.8)	0 (0.0)	5 (1.0)	5 (0.6)
Adenocarcinoma gastric	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.8)	1 (0.2)	3 (0.4)
B-cell lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.2)	2 (0.3)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.3)
External ear neoplasm malignant	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Invasive ductal breast carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
Lentigo maligna[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
Lung neoplasm malignant	0 (0.0)	1 (1.0)	2 (0.8)	1 (0.4)	1 (0.2)	2 (0.3)
Squamous cell carcinoma[b]	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Squamous cell carcinoma of the parotid gland[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)

Source: Table 2.7.4.2.6.1.1
Abbreviations: AESI, adverse event of special interest; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; TEAE, treatment-emergent adverse event; WM, Waldenström's macroglobulinaemia.

Percentages are based on N, unless otherwise specified.
Adverse event grades are evaluated based on National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.03).
[a] Terms within the AESI of second primary malignancies that are a part of the subcategory of skin cancers.
[b] Nine patients from Study BGB-3111-AU-003 were reported to have adverse events of squamous cell carcinomas of the head and neck or unspecified squamous cell carcinomas. Closer evaluation of these cases has revealed that these were non-melanoma skin cancers, all reported at study sites in Australia and New Zealand.

Tumour lysis syndrome:

No cases of TLS were seen in the pivotal study 003 in either arm or in the supportive study AU-003.

Infections

Across all patient groups, infections were the most commonly reported adverse events of special interest.

In the pivotal study 302, Cohort 1, infections were reported at similar incidences in both treatment arms: 67.3% vs 66.3%, respectively for ibrutinib and zanubrutinib. The most commonly reported infections were upper respiratory tract infection (28.6% versus 23.8%, respectively) and urinary tract infection (10.2% versus 9.9%, respectively). There were more reports of pneumonia in the ibrutinib-treated patients (12.2%) compared with zanubrutinib-treated patients (2.0%). On the other hand, there were more Respiratory infections in the zanubrutinib arm (6) compared to the ibrutinib arm (2). In the supportive phase 1/2 study AU-003 the incidence of infections in the WM population was higher than in study 302 (70/78; 89.7%). On the other hand, the incidence of Pneumonia (PT) was only 5.1% although the incidence of Lower respiratory tract infection was 10.3% in the WM population (8/78). Upon request, the Applicant has pooled the various pneumonia-related AEs (using 12 months updated data) and there is still a difference in favour of zanubrutinib (26.5% vs 16.8 %; see Table below).

Table 44: Pneumonia and Lower respiratory infections in ASPEN Cohort 1

	Ibrutinib (N = 98) n (%)	**Zanubrutinib (N = 101) n (%)**
Patients with at least one Pneumonia related Adverse Event[a]	26 (26.5)	17 (16.8)
Lower respiratory tract infection	10 (10.2)	10 (9.9)
Lung infection	0	0
Pneumonia	15 (15.3)	4 (4.0)
Pneumonia viral	1 (1.0)	0 (0.0)
Respiratory tract infection	3 (3.1)	6 (5.9)

[a] Include PTs containing the key word pneumonia (excluding 1 case of Aspiration pneumonia) and the PTs Lower respiratory tract infection, Lung infection or Respiratory tract infection.
Patients with multiple events for a given preferred term and system organ class are counted only once for each preferred term and system organ class, respectively.
Source: ISS Table 2.7.4.2.2.1; data on file
Data Cut 31 August 2020

The incidence of serious infections was similar between treatment arms (19 [19.4%] patients in the ibrutinib treatment arm and 15 [14.9%] patients in the zanubrutinib treatment arm) despite the higher frequency of neutropenia reported with zanubrutinib treatment (≥ Grade 3 AEs: 8.2% vs 19.8%, respectively; see Cytopenias below).

Study 302, Cohort 1: Influenza was more common among zanubrutinib-treated patients (5.0% versus 1.0%, respectively). The incidence of ≥ Grade 3 infections was comparable between arms (19.4% and 17.8% in the ibrutinib- and zanubrutinib-treated patients, respectively) whereas SAEs were reported in 19.4% and 14.9%, respectively.

Table 45: Infections Reported in ⩾ 5% of Patients in Any Patient Group (Safety Analysis Set)

	Ibrutinib	Zanubrutinib				
Preferred term	**BGB-3111-302 Cohort 1 (N = 98) n (%)**	**BGB-3111-302 Cohort 1 (N = 101) n (%)**	**All WM (N = 253) n (%)**	**All China (N = 265) n (%)**	**All Non-China (N = 514) n (%)**	**All Zanubrutinib (N = 779) n (%)**
Patients with at least one infection	66 (67.3)	67 (66.3)	194 (76.7)	198 (74.7)	374 (72.8)	572 (73.4)
Upper respiratory tract infection	28 (28.6)	24 (23.8)	82 (32.4)	106 (40.0)	176 (34.2)	282 (36.2)
Urinary tract infection	10 (10.2)	10 (9.9)	37 (14.6)	36 (13.6)	75 (14.6)	111 (14.2)
Pneumonia	12 (12.2)	2 (2.0)	15 (5.9)	18 (6.8)	42 (8.2)	60 (7.7)
Nasopharyngitis	7 (7.1)	11 (10.9)	25 (9.9)	18 (6.8)	37 (7.2)	55 (7.1)
Lung infection	1 (1.0)	1 (1.0)	10 (4.0)	47 (17.7)	7 (1.4)	54 (6.9)
Sinusitis	7 (7.1)	5 (5.0)	13 (5.1)	5 (1.9)	42 (8.2)	47 (6.0)
Lower respiratory tract infection	9 (9.2)	8 (7.9)	18 (7.1)	1 (0.4)	38 (7.4)	39 (5.0)
Cellulitis	6 (6.1)	4 (4.0)	16 (6.3)	0 (0.0)	38 (7.4)	38 (4.9)
Skin infection	4 (4.1)	2 (2.0)	7 (2.8)	15 (5.7)	19 (3.7)	34 (4.4)
Oral herpes	5 (5.1)	1 (1.0)	5 (2.0)	4 (1.5)	23 (4.5)	27 (3.5)
Localised infection	7 (7.1)	1 (1.0)	8 (3.2)	1 (0.4)	21 (4.1)	22 (2.8)
Conjunctivitis	6 (6.1)	1 (1.0)	6 (2.4)	4 (1.5)	17 (3.3)	21 (2.7)
Influenza	1 (1.0)	5 (5.0)	8 (3.2)	5 (1.9)	16 (3.1)	21 (2.7)
Gastroenteritis	5 (5.1)	2 (2.0)	6 (2.4)	6 (2.3)	14 (2.7)	20 (2.6)
Pharyngitis	1 (1.0)	1 (1.0)	3 (1.2)	17 (6.4)	2 (0.4)	19 (2.4)
Respiratory tract infection	2 (2.0)	6 (5.9)	12 (4.7)	1 (0.4)	17 (3.3)	18 (2.3)
Rhinitis	4 (4.1)	5 (5.0)	6 (2.4)	1 (0.4)	8 (1.6)	9 (1.2)

Source: Table 2.7.4.2.6.1.1
Abbreviations: AESI, adverse event of special interest; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; WM, Waldenström's macroglobulinaemia.

Cytopenia:

Anaemia: The occurrence of anaemia was of the same magnitude in the ibrutinib- and zanubrutinib-arm of study 302 both overall (10.2% vs 11.9%, respectively) and ≥ Grade 3 despite there being more patients with baseline anaemia (haemoglobin <110 g/L) in the zanubrutinib arm (53.1% vs 65.3%, respectively). The incidence of anaemia was higher in the WM patients in study AU-003 (14.1%).

Thrombocytopenia: The incidence of thrombocytopenia was comparable between the ibrutinib- and zanubrutinib arm in study 302; 12.2% and 9.9%, respectively. The same percentage of patients had a platelet count < 100 x 10^9/L at baseline. In study AU-003 (WM patients) the incidence was 7.7%.

Neutropenia: In study 302 more zanubrutinib-treated than ibrutinib-treated patients reported at least 1 occurrence of treatment-emergent neutropenia (including preferred terms of neutropenia, decreased neutrophil count, febrile neutropenia, and/or neutropenic sepsis); 29.7% vs 13.3%, respectively. ≥ Grade 3 AEs were reported in 20 (19.8%) zanubrutinib-treated and 8 (8.2%) ibrutinib-treated patients and SAEs for Neutropenia (grouped term) were only seen in the zanubrutinib arm; 6 (5.9%).

Table 46: TEAEs of Special interest

Table 2.7.4.2.6.1.1
TEAE of Special Interest by Category and Preferred Term
(Safety Analysis Set)

AESI Category Preferred Term	302 Cohort 1 Ibrutinib (N = 98) n (%)	302 Cohort 1 Zanubrutinib (N = 101) n (%)	All WM Zanubrutinib (N = 253) n (%)	All China Zanubrutinib (N = 265) n (%)	All Non-China Zanubrutinib (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Opportunistic infections (continued)						
Oesophageal candidiasis	2 (2.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Scedosporium infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Anal candidiasis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	13 (13.3)	30 (29.7)	76 (30.0)	158 (59.6)	109 (21.2)	267 (34.3)
Neutrophil count decreased	2 (2.0)	5 (5.0)	36 (14.2)	153 (57.7)	25 (4.9)	178 (22.8)

Table 2.7.4.2.6.1.1
TEAE of Special Interest by Category and Preferred Term
(Safety Analysis Set)

AESI Category Preferred Term	302 Cohort 1 Ibrutinib (N = 98) n (%)	302 Cohort 1 Zanubrutinib (N = 101) n (%)	All WM Zanubrutinib (N = 253) n (%)	All China Zanubrutinib (N = 265) n (%)	All Non-China Zanubrutinib (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Neutropenia (continued)						
Neutropenia	12 (12.2)	25 (24.8)	42 (16.6)	16 (6.0)	81 (15.8)	97 (12.5)
Febrile neutropenia	0 (0.0)	4 (4.0)	6 (2.4)	2 (0.8)	12 (2.3)	14 (1.8)
Neutropenic sepsis	0 (0.0)	1 (1.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)

Table 2.7.4.2.6.2.1
Grade 3 or Higher TEAE of Special Interest by Category and Preferred Term
(Safety Analysis Set)

AESI Category Preferred Term	302 Cohort 1 Ibrutinib (N = 98) n (%)	302 Cohort 1 Zanubrutinib (N = 101) n (%)	All WM Zanubrutinib (N = 253) n (%)	All China Zanubrutinib (N = 265) n (%)	All Non-China Zanubrutinib (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Opportunistic infections (continued)						
Cryptococcal fungaemia	0 (0.0)	1 (1.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Listeria sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pneumonia cryptococcal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Scedosporium infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Neutropenia	8 (8.2)	20 (19.8)	50 (19.8)	88 (33.2)	88 (17.1)	176 (22.6)

Table 2.7.4.2.6.2.1
Grade 3 or Higher TEAE of Special Interest by Category and Preferred Term
(Safety Analysis Set)

AESI Category Preferred Term	302 Cohort 1 Ibrutinib (N = 98) n (%)	302 Cohort 1 Zanubrutinib (N = 101) n (%)	All WM Zanubrutinib (N = 253) n (%)	All China Zanubrutinib (N = 265) n (%)	All Non-China Zanubrutinib (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Neutropenia (continued)						
Neutrophil count decreased	1 (1.0)	4 (4.0)	22 (8.7)	85 (32.1)	20 (3.9)	105 (13.5)
Neutropenia	8 (8.2)	16 (15.8)	28 (11.1)	6 (2.3)	64 (12.5)	70 (9.0)
Febrile neutropenia	0 (0.0)	4 (4.0)	6 (2.4)	2 (0.8)	12 (2.3)	14 (1.8)
Neutropenic sepsis	0 (0.0)	1 (1.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Second primary malignancies	1 (1.0)	2 (2.0)	15 (5.9)	7 (2.6)	28 (5.4)	35 (4.5)

In study AU-003 (WM patients only) neutropenia was seen in 14 (17.9%) patients with 12 (15.4%) having ≥ Grade 3 neutropenia and 3 (3.8%) experiencing an SAE (total WM). As these 3 SAEs were all in the R/R WM pool, the incidence was 5.6% (3/54) in the R/R pool.

Clearly neutropenia is occurring more frequently with zanubrutinib compared to ibrutinib.

Serious adverse events and deaths

SAEs

There were generally more SAEs Infections (SOC) in the ibrutinib arm compared to the zanubrutinib arm (19.4% vs 14.9%) in the pivotal study 302. The lung-related PTs were as described for ≥ Grade 3 AEs.

PTs related to the SOC Blood and lymphatic system disorders were more frequent in the zanubrutinib arm of study 302 (7.9% vs 2.0%).

The incidence of Atrial fibrillation / flutter overall in study 302 was 14.3% vs 2.0% in the ibrutinib vs zanubrutinib arms, respectively.

Table 47: Serious TEAEs in BGB 3111-302

Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Cohort 1
(Safety Analysis Set)

System Organ Class Preferred Term	Treatment Naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Patients with at least 1 Serious TEAE	9 (50.0)	10 (52.6)	31 (38.8)	30 (36.6)	40 (40.8)	40 (39.6)
Infections and infestations	6 (33.3)	5 (26.3)	13 (16.3)	10 (12.2)	19 (19.4)	15 (14.9)
Influenza	1 (5.6)	1 (5.3)	0 (0.0)	2 (2.4)	1 (1.0)	3 (3.0)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	2 (2.0)
Sepsis	1 (5.6)	0 (0.0)	2 (2.5)	2 (2.4)	3 (3.1)	2 (2.0)
Arthritis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.0)
Cryptococcal fungaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.0)
Diverticulitis	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

Table 14.3.1.2.2.5
Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Cohort 1
(Safety Analysis Set)

System Organ Class Preferred Term	Treatment Naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Infections and infestations (continued)						
Urosepsis	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Wound infection staphylococcal	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Blood and lymphatic system disorders	2 (11.1)	1 (5.3)	0 (0.0)	7 (8.5)	2 (2.0)	8 (7.9)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.7)	0 (0.0)	3 (3.0)
Neutropenia	0 (0.0)	1 (5.3)	0 (0.0)	2 (2.4)	0 (0.0)	3 (3.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	2 (2.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	2 (2.0)

A patient in study 302, was presented on Day 35 with an SAE of Grade 3 Pulmonary tuberculosis. Reactivation of TB could be caused by the immunosuppressive effect of zanubrutinib as well as by the disease itself. Review of the data of the All zanubrutinib safety group (N=779) by the Applicant did not show any additional cases of TB reactivation.

Deaths

Table 48: Summary of All Deaths (Safety Analysis Set)

	Ibrutinib	Zanubrutinib				
	BGB-3111-302 Cohort 1 (N = 98) n (%)	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 253) n (%)	All China (N = 265) n (%)	All Non-China (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Total number of deaths	7 (7.1)	6 (5.9)	23 (9.1)	36 (13.6)	89 (17.3)	125 (16.0)
Cause of death						
Progressive disease	3 (3.1)	3 (3.0)	8 (3.2)	15 (5.7)	54 (10.5)	69 (8.9)
Adverse event	2 (2.0)	1 (1.0)	10 (4.0)	14 (5.3)	19 (3.7)	33 (4.2)
Unknown	2 (2.0)	1 (1.0)	3 (1.2)	0 (0.0)	9 (1.8)	9 (1.2)
Other	0 (0.0)	1 (1.0)	2 (0.8)	7 (2.6)	7 (1.4)	14 (1.8)
Deaths within 30 days of last dose date	5 (5.1)	1 (1.0)	6 (2.4)	16 (6.0)	32 (6.2)	48 (6.2)
Cause of death						
Adverse event	2 (2.0)	1 (1.0)	5 (2.0)	11 (4.2)	15 (2.9)	26 (3.3)
Progressive disease	1 (1.0)	0 (0.0)	1 (0.4)	5 (1.9)	14 (2.7)	19 (2.4)
Unknown	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Deaths > 30 days of last dose date	2 (2.0)	5 (5.0)	17 (6.7)	20 (7.5)	57 (11.1)	77 (9.9)
Cause of death						
Progressive disease	2 (2.0)	3 (3.0)	7 (2.8)	10 (3.8)	40 (7.8)	50 (6.4)
Adverse event	0 (0.0)	0 (0.0)	5 (2.0)	3 (1.1)	4 (0.8)	7 (0.9)
Unknown	0 (0.0)	1 (1.0)	3 (1.2)	0 (0.0)	7 (1.4)	7 (0.9)
Other	0 (0.0)	1 (1.0)	2 (0.8)	7 (2.6)	6 (1.2)	13 (1.7)

Source: Table 2.7.4.2.16
Abbreviations: eCRF, electronic case report form; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; WM, Waldenström's macroglobulinaemia.
Notes: Patients with multiple events for a given preferred term are counted only once for that preferred term. Events are sorted by decreasing frequency of preferred terms and then alphabetically in the All Zanubrutinib group.
Percentages are based on N, unless otherwise specified.

Table 49: Adverse Events Leading to Death by preferred term (Safety Analysis Set)

	Ibrutinib	Zanubrutinib				
System Organ Class Preferred Term	BGB-3111-302 Cohort 1 (N = 98) n (%)	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 253) n (%)	All China (N = 265) n (%)	All Non-China (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Patients with at least one TEAE leading to death	4 (4.1)	1 (1.0)	8 (3.2)	13 (4.9)	22 (4.3)	35 (4.5)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	4 (0.8)	5 (0.6)
Death	1 (1.0)	0 (0.0)	1 (0.4)	3 (1.1)	1 (0.2)	4 (0.5)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.8)	2 (0.4)	4 (0.5)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.3)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
Abdominal sepsis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Acute hepatitis B	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.1)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Adenocarcinoma gastric	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Arthritis bacterial	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Brain herniation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Bronchiectasis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Cardiomegaly	0 (0.0)	1 (1.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Central nervous system lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Cerebral infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)

	Ibrutinib	Zanubrutinib				
System Organ Class Preferred Term	BGB-3111-302 Cohort 1 (N = 98) n (%)	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 253) n (%)	All China (N = 265) n (%)	All Non-China (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Road traffic accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Scedosporium infection	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Sepsis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Squamous cell carcinoma of head and neck	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Toxic epidermal necrolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Bacterial sepsis	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure acute	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 2.7.4.2.2.4
Abbreviations: eCRF, electronic case report form; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; TEAE, treatment-emergent adverse event; WM, Waldenström's macroglobulinaemia.
Notes: Patients with multiple events for a given preferred term are counted only once at the preferred term. Events are sorted by decreasing frequency first by preferred term for the All Zanubrutinib group, then alphabetically.

In Study BGB-3111-302 Cohort 1, 7 patients in the ibrutinib arm and 6 patients in the zanubrutinib arm died. The most common cause of death was progressive disease (3 patients in each arm). Five patients in the ibrutinib arm and 1 patient in the zanubrutinib arm died within 30 days of last study treatment. A patient died on Day 242 (49 days after the last zanubrutinib dose discontinued due to an SAE of Respiratory failure) due to progressive disease. Given the high proliferation index and expression of c-Myc it is considered that this patient had transformed disease (from WM to an aggressive lymphoma). The Applicant showed that four CLL-patients and 3 WM patients in the All zanubrutinib safety population (N=779) transformed to a more aggressive disease, which is not considered unexpected.

In study AU-003 deaths generally occurred a long time after end of treatment and are considered not related.

Laboratory findings

Haematology:

In the pivotal phase 3 study 302, Cohort 1, more patients in the zanubrutinib treatment arm had Grade 3 or 4 haematology laboratory toxicities compared with the ibrutinib treatment arm (39 [38.6%] patients versus 26 [26.5%] patients) (Table 79). This was mainly due to a higher proportion of Grade 3 or 4 decreased neutrophils in the zanubrutinib treatment arm compared with the ibrutinib treatment arm (22 [21.8%] patients versus 8 [8.2%] patients). See also AESIs – Cytopenia, above.

Table 50: Summary of Grade 3 and 4 Postbaseline Toxicities: Hematology (Cohort 1) (Safety Analysis Set)

Laboratory Test (Direction of Toxicity)	Treatment-naive		Relapsed/Refractory		Overall	
	Ibrutinib (N = 18) n (%)	Zanubrutinib (N = 19) n (%)	Ibrutinib (N = 80) n (%)	Zanubrutinib (N = 82) n (%)	Ibrutinib (N = 98) n (%)	Zanubrutinib (N = 101) n (%)
Patients with ≥ 1 Grade 3 or 4 toxicity	2 (11.1)	5 (26.3)	24 (30.0)	34 (41.5)	26 (26.5)	39 (38.6)
Hemoglobin (low)	1 (5.6)	1 (5.3)	5 (6.3)	4 (4.9)	6 (6.1)	5 (5.0)
Leukocytes (low)	0 (0.0)	0 (0.0)	3 (3.8)	7 (8.5)	3 (3.1)	7 (6.9)
Leukocytes (high)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.0)
Lymphocytes (low)	0 (0.0)	0 (0.0)	10 (12.7) [a]	15 (18.3)	10 (10.3) [b]	15 (14.9)
Lymphocytes (high)	1 (5.6)	1 (5.3)	0 (0.0) [a]	2 (2.4)	1 (1.0) [b]	3 (3.0)
Neutrophils (low)	0 (0.0)	2 (10.5)	8 (10.1) [a]	20 (24.4)	8 (8.2) [b]	22 (21.8)
Platelets (low)	0 (0.0)	1 (5.3)	6 (7.5)	7 (8.5)	6 (6.1)	8 (7.9)

Source: Table 14.3.5.1.3
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events
Cohort 1 includes patients with activating mutations in MYD88.
Percentages are based on n, number of patients with at least 1 postbaseline result.
Laboratory results were graded using CTCAE (Version 4.03).
[a] N = 79, [b] N = 97
Data cutoff 31 August 2019

Chemistry

In study 302, Cohort 1, the proportion of patients with worsening shifts of 2 or more toxicity grades from baseline was generally comparable between the ibrutinib and zanubrutinib treatment arms for each of the serum chemistry analytes evaluated except for increased potassium (higher in the zanubrutinib treatment arm) and increased bilirubin (higher in the ibrutinib treatment arm).

The 3 cases in the All zanubrutinib group that met 2 of 3 cases for Hy's Law 2 were due to hepatitis B activation (studies performed in China only where Hepatitis B infection is more prevalent than in Europe) and the third had normal parameters the next day.

Patients with severe renal and hepatic impairment were excluded from study 302.

Table 51: Worsening Shifts of ⩾ 2 CTCAE Toxicity Grades Compared with Baseline Serum Chemistry Analytes Parameters (Safety Analysis Set)

Laboratory Test (Direction of Toxicity)	Cohort 1 Zanubrutinib Patients (N = 101) n (%)	Cohort 1 Ibrutinib Patients (N = 98) n (%)	Cohorts 1 and 2 All Zanubrutinib Patients (N = 129) n (%)
ALT (high)	1 (1.0)	4 (4.1)	2 (1.6)
Alkaline phosphatase (high)	0 (0.0)	2 (2.0)	1 (0.8) [a]
AST (high)	0 (0.0)	3 (3.1) [b]	1 (0.8)
Bilirubin (high)	2 (2.0)	8 (8.2)	4 (3.1)
Biochemistry albumin (low)	5 (5.0)	1 (1.0)	7 (5.4)
Calcium (low)	2 (2.0)	0 (0.0)	2 (1.6)
Corrected calcium (low)	2 (2.0)	1 (1.0)	2 (1.6)
Corrected calcium (high)	0 (0.0)	0 (0.0)	1 (0.8)
Creatinine (high)	1 (1.0)	1 (1.0)	1 (0.8)
Glucose (low)	5 (5.3) [c]	3 (3.3) [d]	5 (4.1) [e]
Glucose (high)	4 (4.2) [c]	6 (6.6) [d]	5 (4.1) [e]
Magnesium (low)	1 (1.0)	0 (0.0)	1 (0.8)
Magnesium (high)	1 (1.0)	0 (0.0)	1 (0.8)
Phosphate (low)	13 (12.9)	12 (12.4) [b]	16 (12.4)
Potassium (low)	1 (1.0)	0 (0.0)	1 (0.8)
Potassium (high)	6 (5.9)	0 (0.0)	7 (5.4)
Sodium (low)	4 (4.0)	0 (0.0)	6 (4.7)
Urate (high)	3 (3.1) [f]	3 (3.1) [b]	3 (2.4) [e]

Source: Table 14.3.5.2.7, Table 14.3.5.2.8, Table 14.3.5.2.9
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events
Percentages are based on the number of patients with at least 1 assessment (either baseline or postbaseline).
Laboratory results were graded using CTCAE (Version 4.03).
[a] N = 127, [b] N = 97, [c] N = 95, [d] N = 91, [e] N = 123, [f] N = 96
Data cutoff 31 August 2019

Safety in special populations:

Table 52 ASPEN Study Cohort 1: All- Grade Adverse Events Across Age Groups (Data cut off date 31 Aug 2019)

	Ibrutinib N=98				Zanubrutinib N=101			
SOC/SMQ/Group names MedDRA Terms	**Age <65 N=23 n, (%)**	**Age 65-74 N=50 n, (%)**	**Age 75-84 N=21 n, (%)**	**Age 85+ N=4 n, (%)**	**Age <65 N=34 n, (%)**	**Age 65-74 N=31 n, (%)**	**Age 75-84 N=31 n, (%)**	**Age 85+ N=5 n, (%)**
Total AEs	23 (100.0)	49 (98.0)	21 (100.0)	4 (100.0)	32 (94.1)	31 (100.0)	30 (96.8)	5 (100.0)
Serious AEs – Total[a]	7 (30.4)	19 (38.0)	**11 (52.4)**	**3 (75.0)**	12 (35.3)	10 (32.3)	**15 (48.4)**	**3 (60.0)**
- Fatal	0	0	**3 (14.3)**	**1 (25.0)**	0	0	1 (3.2)	0
- Hospitalization/prolong existing hospitalization	7(30.4)	19 (38.0)	10 (47.6)	3 (75.0)	11 (32.4)	10 (32.3)	15 (48.4)	3 (60.0)
- Life-threatening	0	1 (2.0)	1 (4.8)	1 (25.0)	1 (2.9)	1 (3.2)	3 (9.7)	1 (20.0)
- Disability/incapacity	0	1 (2.0)	0	0	1 (2.9)	0	0	1 (20.0)
- Other (medically significant)	0	0	0	0	0	4 (12.9)	0	0
AE leading to drop-out	0	4 (8.0)	4 (19.0)	1 (25.0)	0	1 (3.2)	3 (9.7)	0
Psychiatric disorders[b]	2 (8.7)	8 (16.0)	2 (9.5)	2 (50.0)	2 (5.9)	5 (16.1)	3 (9.7)	1 (20.0)
Nervous system disorders[b]	12 (52.2)	19 (38.0)	6 (28.6)	3 (75.0)	13 (38.2)	12 (38.7)	11 (35.5)	3 (60.0)
Accidents and injuries[c]	6 (26.1)	15 (30.0)	**13 (61.9)**	**3 (75.0)**	9 (26.5)	9 (29.0)	**18 (58.1)**	1 (20.0)
Cardiac disorders[b]	5 (21.7)	19 (38.0)	5 (23.8)	0 (0.0)	9 (26.5)	5 (16.1)	7 (22.6)	**3 (60.0)**
Vascular disorders[b]	6 (26.1)	11 (22.0)	7 (33.3)	1 (25.0)	2 (5.9)	10 (32.3)	5 (16.1)	1 (20.0)
Cerebrovascular disorders [c]	1 (4.3)	1 (2.0)	0	0	0	0	1 (3.2)	0

	Ibrutinib N=98				Zanubrutinib N=101			
SOC/SMQ/Group names MedDRA Terms	**Age <65 N=23 n, (%)**	**Age 65-74 N=50 n, (%)**	**Age 75-84 N=21 n, (%)**	**Age 85+ N=4 n, (%)**	**Age <65 N=34 n, (%)**	**Age 65-74 N=31 n, (%)**	**Age 75-84 N=31 n, (%)**	**Age 85+ N=5 n, (%)**
Infections and infestations[b]	15 (65.2)	30 (60.0)	17 (81.0)	4 (100.0)	27 (79.4)	19 (61.3)	19 (61.3)	2 (40.0)
Anticholinergic syndrome[c]	0	0	0	0	0	0	0	0
Quality of life decreased (PT)	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[d]	4 (17.4)	8 (16.0)	5 (23.8)	0 (0.0)	5 (14.7)	5 (16.1)	9 (29.0)	1 (20.0)
Other AE appearing more frequently in older patients [e]	20 (87.0)	35 (70.0)	17 (81.0)	4 (100.0)	24 (70.6)	25 (80.6)	27 (87.1)	2 (40.0)

a If an SAE meets more than one serious criterion, it is included in the corresponding rows. It is counted only once in the total.
b Based on System Organ Class with the same name
c Based on SMQ (narrow) with the same name; Cerebrovascular Disorder is based on 'Central nervous system vascular disorders SMQ (narrow).
d Include the PTs of Orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, and HLGT for fractures.
e Include the PTs of Urinary tract infection, lower respiratory tract infection, Pruritus, Constipation, Fatigue, Oedema peripheral, Dizziness, Contusion, Fall; and SOCs of Musculoskeletal and connective tissue disorders, Injury, poisoning and procedural complications, Vascular disorders, Neoplasms benign, malignant and unspecified (incl cysts and polyps).]
Data cutoff date 31Aug2019
Source: RTQ Table 14.3.1.2.1.1, Table 14.3.1.2.2.1, Table 14.3.1.2.3.1

Comparable frequencies of ≥ Grade 3 adverse event and serious adverse events as well as those leading to treatment discontinuation were observed between male and female patients in the All WM group.

Table 53: Overview of adverse events by sex (Safety Analysis Set)

	All WM		All Zanubrutinib	
	Males (N = 173) n (%)	Females (N = 80) n (%)	Males (N = 528) n (%)	Females (N = 251) n (%)
Patients with at least 1 TEAE	169 (97.7)	77 (96.3)	516 (97.7)	246 (98.0)
Grade 3 or higher	105 (60.7)	51 (63.8)	321 (60.8)	169 (67.3)
Serious	79 (45.7)	33 (41.3)	226 (42.8)	107 (42.6)
Leading to death	8 (4.6)	0 (0.0)	28 (5.3)	7 (2.8)
Leading to treatment discontinuation	15 (8.7)	7 (8.8)	49 (9.3)	24 (9.6)
Leading to dose reduction	17 (9.8)	7 (8.8)	36 (6.8)	17 (6.8)

Source: Table 2.7.4.2.12.4, Table 2.7.4.2.12.5
Abbreviations: N, number of patients who received at least 1 dose of zanubrutinib; TEAE, treatment-emergent adverse event; WM, Waldenström's macroglobulinaemia.
Notes: Patients with multiple events for a given preferred term and with multiple preferred terms within a system organ class are counted only once at the preferred term and system organ class levels, respectively.
Percentages are based on N, unless otherwise specified.

The results indicated that more patients in the white than Asian group experienced AEs leading to dose reduction (11.6% versus 3.5%). With extended follow-up, many of the disparities between the Asian and White populations have resolved. The number of subjects reporting TEAEs, Grade 3 or higher AEs, AEs leading to death and AEs leading to treatment discontinuation is similar between the Asian and White treatment groups both in the All WM and All Zanubrutinib populations.

Renal and hepatic insufficiency

The number of patients with severe renal impairment and end stage renal disease was low, and thus the safety of zanubrutinib in these patients has not been established.

The clinical studies did not include patients with severe hepatic impairment.

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

See section Clinical pharmacology.

Discontinuation due to adverse events

Table 54: Patient Disposition and Reasons for Treatment/ Study Discontinuation (Safety Analysis Set)

	Ibrutinib	Zanubrutinib				
	BGB-3111-302 Cohort 1 (N = 98) n (%)	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 253) n (%)	All China (N = 265) n (%)	All Non-China (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Number of patients treated	98	101	253	265	514	779
Patients discontinued from treatment	21 (21.4)	20 (19.8)	71 (28.1)	113 (42.6)	193 (37.5)	306 (39.3)
Reason for discontinuation						
Progressive disease	5 (5.1)	7 (6.9)	31 (12.3)	78 (29.4)	113 (22.0)	191 (24.5)
Adverse event	9 (9.2)	4 (4.0)	23 (9.1)	28 (10.6)	46 (8.9)	74 (9.5)
Withdrawal by subject	0 (0.0)	5 (5.0)	6 (2.4)	2 (0.8)	15 (2.9)	17 (2.2)
Investigator's discretion	4 (4.1)	2 (2.0)	6 (2.4)	3 (1.1)	12 (2.3)	15 (1.9)
Protocol deviation	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.1)
Other	3 (3.1)	2 (2.0)	4 (1.6)	1 (0.4)	7 (1.4)	8 (1.0)
Patients remaining on treatment	77 (78.6)	81 (80.2)	182 (71.9)	152 (57.4)	321 (62.5)	473 (60.7)
Patients discontinued from study	10 (10.2)	10 (9.9)	38 (15.0)	69 (26.0)	129 (25.1)	198 (25.4)
Reason for discontinuation						
Death	7 (7.1)	6 (5.9)	23 (9.1)	35 (13.2)	89 (17.3)	124 (15.9)
Withdrawal by subject	3 (3.1)	4 (4.0)	11 (4.3)	23 (8.7)	25 (4.9)	48 (6.2)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.4)	8 (3.0)	3 (0.6)	11 (1.4)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.4)
Other	0 (0.0)	0 (0.0)	3 (1.2)	3 (1.1)	9 (1.8)	12 (1.5)
Patients remaining in study	88 (89.8)	91 (90.1)	215 (85.0)	196 (74.0)	385 (74.9)	581 (74.6)
Study follow-up time (months)[a]						
n	98	101	253	265	514	779
Mean (SD)	19.10 (5.706)	19.29 (5.353)	22.60 (10.025)	20.99 (7.987)	23.24 (12.496)	22.47 (11.214)
Median	19.53	19.48	20.57	22.24	21.70	21.91

	Ibrutinib	Zanubrutinib				
	BGB-3111-302 Cohort 1 (N = 98) n (%)	BGB-3111-302 Cohort 1 (N = 101) n (%)	All WM (N = 253) n (%)	All China (N = 265) n (%)	All Non-China (N = 514) n (%)	All Zanubrutinib (N = 779) n (%)
Min, Max	0.5, 31.1	1.6, 31.2	1.6, 57.2	0.3, 37.9	0.1, 58.3	0.1, 58.3

Source: Table 2.7.4.1.2.2
Abbreviations: max, maximum; min, minimum; N, number of patients who received at least one dose of ibrutinib or zanubrutinib; SD, standard deviation; WM, Waldenström's macroglobulinaemia.
Note: Percentages are based on N, unless otherwise specified.
[a] Study follow-up time is defined as the time from the first dose date to the end of study or death date (whichever is earlier), or the database cutoff date for ongoing patients.

Post marketing experience

Zanubrutinib (BRUKINSA) has only recently received marketing authorisation in the United States for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. The post-authorisation safety of zanubrutinib has been summarized in 3 quarterly PADERs and 1 annual PBRER (DCO 13 November 2020). No new safety signals have been confirmed for zanubrutinib.

2.6.1. Discussion on clinical safety

The main safety information is derived from study 302 (BGB-3111-302) Cohort 1 conducted in a Western population. Supportive safety data was derived from 78 WM patients in the phase 1/2 study AU-003 performed in a mainly Western population.

Demographics and disease characteristics as well as the median duration of exposure and median dose intensities were comparable between the ibrutinib and zanubrutinib arms in study 302. One or more dose reductions were seen in 21.4% and 14.9% of patients in the ibrutinib and zanubrutinib arms respectively.

Subjects who have MY88 wild type ($MYD88^{WT}$) constituted the zanubrutinib treated cohort 2 (in study BGB-3111-302). There is doubt whether this subset of patients would have any safety characteristics of its own. The Applicant summarised the safety features of Brukinsa in the MYD88WT population using the data from the additional 1-year follow-up, and it can be agreed that the results do not show any clinically significant differences when compared to the MYD88MUT population.

In most cases the incidences of adverse events were comparable between the two arms. The incidences for the treatment naïve patients vary, but as these are few (app. 20% of the entire study population in both arms corresponding to 18 and 19 patients in the ibrutinib vs zanubrutinib arms) the overall population (treatment-naïve and R/R patients) are the main focus of the assessments.

Adverse events in the SOC Infections and Infestation were comparable between the two arms in study 302 (66-67%) though there were more AEs of PT Pneumonia in the ibrutinib arm compared to the zanubrutinib arm (12.2% and 2%, respectively). Comparing the added incidences of the two PTs Lower respiratory tract infection and Pneumonia the incidence is still higher in the ibrutinib arm compared to the zanubrutinib arm in study 302; 21.4% vs 9.9%, respectively. There were generally more SAEs Infections (SOC) in the ibrutinib arm compared to the zanubrutinib arm (19.4% vs 14.9%) in the pivotal study 302. One patient experienced an SAE of Grade 3 Pulmonary tuberculosis. Reactivation of TB could be caused by the immunosuppressive effect of zanubrutinib as well as by the disease itself. Review of the data of the All zanubrutinib safety group (N=779) by the Applicant did not show any additional cases of TB reactivation.

Greater than Grade 3 hypertension, which is a well-known ibrutinib AE, was seen more frequently in the ibrutinib arm compared to the zanubrutinib arm (11.2% versus 5.9%, respectively).

For the Adverse events of special interest (AESI) no clear difference between the two arms in study 302 were seen for haemorrhage, anaemia, thrombocytopenia, or second primary malignancies. These are also considered safety concerns for zanubrutinib as well as for ibrutinib.

In study 302. more zanubrutinib-treated than ibrutinib-treated patients reported at least 1 occurrence of treatment-emergent neutropenia (including preferred terms of neutropenia, decreased neutrophil count, febrile neutropenia, and/or neutropenic sepsis); 29.7% vs 13.3%, respectively. ≥ Grade 3 AEs were reported in 20 (19.8%) zanubrutinib-treated and 8 (8.2%) ibrutinib-treated patients and SAEs for Neutropenia (grouped term) were only seen in the zanubrutinib arm; 6 (5.9%).

The incidence of the well-known ibrutinib-associated adverse event of atrial fibrillation/ flutter was higher in the ibrutinib arm (15.3%) compared to the zanubrutinib arm (2.0%). The low frequency was a consistent finding also in the All WM and All Zanubrutinib groups.

It is notable that in Study BGB-3111-302, Cohort 1, the incidence of diarrhoea among zanubrutinib recipients was half that of ibrutinib recipients on an exposure-adjusted basis (1.3 and 2.6 persons/100

person-years, respectively). This is likely to be due to less zanubrutinib-mediated EGFR inhibition compared with ibrutinib.

Seven patients in the ibrutinib arm and 6 patients in the zanubrutinib arm died, three in each arm of progressive disease. Given the few deaths no pattern for AE-related deaths is seen.

In Study BGB-3111-302 Cohort 1, the incidence of haemorrhage of any grade was 59.5% among ibrutinib-treated patients compared to 48.5% in the zanubrutinib-treated patients and exposure-adjusted incidence rates (EAIR) (6.95 versus 4.43 persons/100 person-months). Of these 10 (of 58 patients) (10.2%) and 6 (of 49 patients) (5.9%) ibrutinib- and zanubrutinib-treated patients, respectively, had antecedent thrombocytopenia and 14 (14.3%) and 12 (11.9%), respectively, reported the use of antithrombotic medication. Thus, both thrombocytopenia and the use of anti-thrombotic medication potentially contribute to the higher incidence of haemorrhage (all grades) in the ibrutinib arm. Most haemorrhage events in both arms were Grade 1 or 2 in severity. Grade 3 or higher haemorrhage was reported for 8 ibrutinib-treated patients and 6 zanubrutinib-treated patients and SAEs were reported in 6 and 5 patients, respectively. In the All Zanubrutinib and All WM patient groups, haemorrhage of any severity grade was similar among patients in terms of overall crude incidence (52.8% and 52.2%, respectively), EAIRs (5.30 and 4.70 persons/100 person-months, respectively). Major bleeding events were uncommon in both patient groups (0.20 and 0.27 persons/100 person-months for the All Zanubrutinib and All WM patient groups, respectively), and events that met the criteria for seriousness occurred in 3.1% and 4.3% of patients, respectively. The EAIR for ≥ Grade 3 haemorrhage was 0.18 patients/100 person-months.

Bleeding events have been reported with the use of BTK inhibitors. The Applicant has discussed the effects of zanubrutinib on platelets; Grade 3 or higher bleeding events have been reported in 2% of patients treated with zanubrutinib monotherapy (Brukinsa USPI 2019). According to the Applicant, BTK inhibitor-associated haemostatic defects are believed to be mediated through effects on platelet function (the von Willebrand factor-GPIb and collagen-GPVI axes in platelets) rather than on the coagulation cascade. The following has been added under Special warnings and precautions for use (section 4.4 of SmPC): Warfarin or other vitamin K antagonists therefore should not be administered concomitantly with BRUKINSA. Patient should be monitored for signs and symptoms of bleeding and monitor complete blood counts. Dose modification may be necessary for Grade 3 or greater adverse reactions as recommended.

The incidence of neutropenia was higher in the zanubrutinib arm in the pivotal study 302 but the incidence of Infections (SOC) was comparable. Despite this, there were more AEs of PT Pneumonia in the ibrutinib arm compared to the zanubrutinib arm (12.2% and 2%, respectively). Adding the two PTs Lower respiratory tract infection and Pneumonia the incidence is still higher in the ibrutinib arm compared to the zanubrutinib arm in study 302; 21.4% vs 9.9%, respectively. There were also generally more SAEs Infections and Infestations (SOC) in the ibrutinib arm compared to the zanubrutinib arm (19.4% vs 14.9%) in the pivotal study 302 despite the higher incidence of neutropenia in the zanubrutinib arm.

The higher incidence of Grade 3 or higher neutropenia did not result in a higher infection rate, possibly due to the more frequent use of granulocyte colony stimulating factor among zanubrutinib recipients within 30 days of neutropenia onset (46.7% zanubrutinib versus 30.8% ibrutinib). Rates of neutropenia were consistent across integrated safety analysis subsets. The Applicant provided a summary and discussion concerning the use of granulocyte colony stimulating factors in different study arms. The data is descriptive in nature and does not allow more detailed conclusions regarding the cytopenias or their responsiveness to G-CSF in association with Zanubrutinib.

The occurrence of anaemia was of the same magnitude in the ibrutinib- and zanubrutinib-arm of study 302 both overall (10.2% vs 11.9%, respectively) and ≥ Grade 3 despite there being more patients

with baseline anaemia (haemoglobin <110 g/L) in the zanubrutinib arm (53.1% vs 65.3%, respectively). The incidence of anaemia was higher in the WM patients in study AU-003 (14.1%) despite the fact that there were more treatment-naïve patients here compared to study 302 (31% vs 19%) and baseline haemoglobin <110 g/L was comparable (60%). Clearly anaemia is a concern of seemingly the same magnitude as for ibrutinib.

In the pivotal study 302 there were more SAEs overall in the treatment naïve patients in both arms, which is considered unexpected given that these patients have not been exposed to prior cytotoxic treatment. This was also the case in the SOCs Blood and lymphatic system disorders and Infections and infestations. Differences in age, ECOG score, suitability for standard chemoradiation, and burden of concomitant disease could partly explain the higher SAE incidence in the TN patients compared to the R/R population in study 302 as well as uncertainties related to the low number of TN patients.

A patient was presented on Day 35 with an SAE of Grade 3 Pulmonary tuberculosis. Reactivation of TB could be caused by the immunosuppressive effect of zanubrutinib as well as by the disease itself. Review of the data of the All zanubrutinib safety group (N=779) by the Applicant did not show any additional cases of TB reactivation.

In the pivotal study 302, Cohort 1, the incidences of second primary malignancies (and the subpopulation of various skin cancers excluding melanoma) were comparable between the two arms; 11.2% (9.2%) and 11.9% (7.9%) for ibrutinib and zanubrutinib, respectively. In the supportive phase 1/2 study AU-003 the incidence of second primary malignancies in the WM population was much higher; 19/78 (24.4%). This was primarily driven by the high incidence of various skin cancers; 14/78 (18%). 13 of these 14 patients came from AUS/NZ and 1 patient came from Arizona, USA (68% of the overall study population came from Australia and New Zealand). In the pivotal study 302 (Cohort 1) only 31% were recruited from Australia/New Zealand, which explains the lower incidence of both melanoma and non-melanoma skin cancer (see also SmPC section 4.4). It is notable, that 5/78 (6.4%) of the WM patients in the supportive phase 1/2 study AU-003 discontinued due to neoplastic events (all different). This can be explained by a higher incidence of skin cancers in the Australian patients, though.

Comparable frequencies of ≥ Grade 3 adverse event and serious adverse events as well as those leading to treatment discontinuation were observed between male and female patients in the All WM group. The Applicant has presented adverse events by gender in study 302. Comparing this to the ISS results, it is agreed that given there are fewer female patients (particularly in the 302 study) and no consistent trend observed in AESI neutropenia integrated safety analysis, there are no discernible adverse event risks associated with gender at present time.

The number of patients with severe renal impairment and end stage renal disease was low, and thus the safety of zanubrutinib in these patients has not been established and it need to be further evaluated. The SmPC text related to renal impairment is agreed.

The clinical studies did not include patients with severe hepatic impairment, and thus the safety of zanubrutinib in patients with severe hepatic impairment is missing. The dose modification in this group may be agreed. In patients with severe hepatic impairment, the total and unbound zanubrutinib exposures were 1.6- and 2.9-fold higher compared to healthy subjects while the mean total and unbound exposures of zanubrutinib were 1.21 and 1.43-fold higher in subjects with moderate hepatic impairment. The exposure in moderate impairment group after single 80 mg dose overlaps with mild impairment group and healthy volunteers. No dose adjustment is proposed for patients with mild or moderate hepatic impairment in the SmPC.

There is drug-drug interaction potential between zanubrutinib and other concomitant medications, particularly with strong cytochrome P450 (CYP)3A inhibitors and inducers. The pharmacokinetics of

zanubrutinib was assessed in 2 dedicated clinical drug-drug interaction studies, BGB-3111-104 and BGB-3111-108. In addition, a physiologically-based pharmacokinetics model was developed to predict the effect of moderate and mild CYP3A inhibitors and CYP3A inducers on the pharmacokinetics of zanubrutinib.

In overall, the safety of zanubrutinib was generally comparable to ibrutinib where as importantly,

Atrial fibrillation is seen at a higher incidence with ibrutinib. The finding of a lower rate of atrial fibrillation – also confirmed in studies in other indications - is a valuable improvement over ibrutinib.

On Study BGB-3111-302, zanubrutinib was found to have a longer time to treatment failure due to AE, defined as discontinuing of therapy for any AE, than ibrutinib with over 10% difference at 30 months. These differences in tolerability between zanubrutinib and ibrutinib seem to increase over time, and is an important finding indicating an improved tolerability - given the need for long-term treatment with BTK inhibitors.

From the safety database, all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety of zanubrutinib was generally comparable to ibrutinib with some important exceptions, a lower risk for several events, known to be associated with ibrutinib treatment (atrial fibrillation, bleeding, diarrhoea, and hypertension), were seen in patients treated with zanubrutinib.

The submission of the results of study BGB-3111-LTE1 - an Open-label, Multi-center, Long-term Extension Study- in the context of additional pharmacovigilance (category 3 measures) is agreed in order to evaluate the long-term safety of zanubrutinib, as monotherapy or in combination, in patients with B-cell malignancies treated with zanubrutinib (see RMP).

2.7. Risk Management Plan

Safety concerns:

Table 55: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Haemorrhage
Important potential risks	Cardiac arrhythmia, mainly presented as atrial fibrillation and flutter Infections (including hepatitis B reactivation) Second primary malignancies (other than non-melanoma skin cancer) Second primary non-melanoma skin cancer 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 56: Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Additional pharmacovigilance activities				
BGB-3111-113 A Drug-Drug Interaction Study of Zanubrutinib with Moderate/Strong CYP3A Inhibitors in Patients with B-Cell Malignancies Lymphoma Ongoing	To assess the drug-drug interaction between zanubrutinib and moderate (fluconazole, diltiazem) and strong (voriconazole, clarithromycin) CYP3A inhibitors in patients with B-cell malignancies.	Drug-drug interaction	Study Completion (database lock): Final Report Submission:	2nd Quarter, 2022 3rd Quarter, 2022
BGB-3111-LTE1 An Open-label, Multi-center, 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 (>2 years) safety	Annual DSUR: Estimated study completion date:	3rd quarter annually until study completion 4th quarter 2025

Risk minimisation measures

Table 57: Risk minimisation measures

Safety concern	Risk minimisation measures
Haemorrhage	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription
Cardiac arrhythmia, mainly presented as atrial fibrillation and flutter	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties Package leaflet: Information for the patient Section 2: Warnings and precautions Additional risk minimisation measures: None Legal status: medical prescription
Infections (including hepatitis B reactivation)	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Package leaflet: Information for the patient Section 2: Warnings and precautions Package leaflet: Information for the patient Section 4: Possible side effects Additional risk minimisation measures: None Legal status: medical prescription
Second primary malignancies (other than non-melanoma skin cancer)	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None Legal status: medical prescription
Second primary non-melanoma skin cancer	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None Legal status: medical prescription

Safety concern	Risk minimisation measures
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 Additional risk minimisation measures: None Legal status: medical prescription
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
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
Safety in patients with severe renal impairment/on dialysis	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.8 Undesirable effects 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

Safety concern	Risk minimisation measures
Long-term safety (> 2 years)	Routine risk minimisation measures: Not specifically addressed Additional risk minimisation measures: None Legal status: medical prescription

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14 November 2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of zanubrutinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

2.10.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The request is for an authorisation of zanubrutinib monotherapy in the treatment of adult patients with Waldenström's macroglobulinaemia (WM), who have received at least 1 prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

WM is an acquired disorder, which has an indolent to aggressive course, with haemorheologic and autoimmune manifestations and systemic symptoms due to bone marrow infiltration, lymphoid involvement and tissue deposits. The elderly patient population present with bleeding, cardiac failure, neuropathy, anaemia and infection, night-sweats and weight-loss. The aim of treatment is to control any acute life-threatening complications (hyperviscosity), to alleviate the variety of chronic symptoms (malignant lymphoma), to prolong survival, and to preserve QoL, reflected in standardized response criteria.

3.1.2. Available therapies and unmet medical need

Curative intended treatment requires allogeneic stem cell transplantation, indicated in very few patients. Various mono- and combination therapies with alkylators, proteasome inhibitors, immune-modulating agents and antibody have been established as effective interventions, and in a third of patients supported by plasmapheresis initially to clear the M-component. The development of BTK inhibitors, which play a role in B-lymphocyte malignancies, and introduction five years ago of ibrutinib (Imbruvica) offers an alternative, oral and daily targeted monotherapy until progression or intolerance. So far, no other BTK inhibitors have been authorised in WM substantiated to prolong survival, improve disease control and alleviate adverse events in order to further mitigate an unmet medical need

3.1.3. Main clinical studies

Study 302 (ASPEN) was a phase 3, randomized (n=229), open-label, multicenter study comparing the efficacy and safety of the Bruton's Tyrosine Kinase inhibitors BGB-3111 (zanubrutinib, 160mg BID) and ibrutinib (420mg QD) in adult subjects with Waldenström's Macroglobulinemia, in first or later lines.

Eligible patients were at least 18 years of age with a clinical and definite histological diagnosis of relapsed/refractory WM or treatment-naïve when considered unsuitable for standard chemo-immunotherapy regimens by their treating physician. Patients had to meet at least one criterion for treatment according to consensus panel criteria from the Seventh International Workshop on Waldenström's Macroglobulinemia (IWWM) and have measurable disease, as defined by a serum IgM level > 0.5 g/dl. Patients with MYD88 mutation ($MYD88^{MUT}$) were assigned to Cohort 1 (N=201) and were randomized 1:1 to receive either zanubrutinib 160 mg twice daily (Arm A) or ibrutinib 420 mg once daily (Arm B) until disease progression or unacceptable toxicity. Subjects found to have MYD88 wildtype ($MYD88^{WT}$) by gene sequencing (estimated to be present in approximately 10 % of enrolled subjects), were enrolled to Cohort 2 (N = 28) and received zanubrutinib 160 mg twice daily on a third, non-randomized, study arm (Arm C). Primary endpoints were the proportion of patients achieving either CR or VGPR, as determined by the IRC according to the same definitions as in Study -210. The study designed to compare the efficacy and safety of 2^{nd} generation BTKi zanubrutinib and ibrutinib in

patients with Waldenström's macroglobulinaemia (WM) who required therapy in first (treatment naïve, TN n=42) or later lines (relapsed / refractory, RR n=187).

3.2. Favourable effects

A CR/VGPR of 28% is observed in the zanubrutinib arm compared to 19% in the ibrutinib arm.

Per the protocol and the SAP, the Applicant would test the secondary endpoint MRR according to a pre-planned NIM, but ONLY if the study met its primary endpoint. Nonetheless, it is clinically encouraging to see a risk difference for MRR of -0.5% (-12.2, 11.1) and thus well within the NIM of 12%.

Zanubrutinib is as effective in first line as later lines. This effect was also induced across disease characteristics.

The major response rate was also comparable in treatment naïve and in relapsed / refractory patients of 75%, which is durable in 70-80% of patients for 2 – 4 years.

No significant difference in efficacy between patients treated in first lines or less than 3 lines for WM, which offers flexibility when to introduce this agent in the treatment algorithm for the individual patient.

The response is accompanied by a high degree of resolution of treatment-precipitating symptoms like hyperviscosity, severe anaemia, neuropathy, night-sweats and weight-loss, autoimmune manifestations and lymphoid organomegaly as bulky glands, liver and spleen.

Responses were observed with zanubrutinib across subgroups, including $MYD88^{WT}$ patients (Cohort 2) who had a VGPR or CR rate of 26.9 % and an MRR of 50 % thus $MYD88^{WILD\text{-}TYPE}$ genotype showed a similar response as $MYD88^{L265P}$ mutated WM patients, which was not expected.

3.3. Uncertainties and limitations about favourable effects

Results may indicate a better response in $MYD88^{L265P}$ mutated WM patients with high or intermediate IPSSWM score, than in low risk patients.

CR was a very rare event, in both zanubrutinib as ibrutinib treatment. More CR may have been expected by a targeted treatment, however, up to 10% CR may be achieved in other (combination-) treatments, and the issue may reflect that BTK-dependent pathways are not key-drivers in WM.

3.4. Unfavourable effects

Adverse events in the SOC Infections and Infestation were comparable between the two arms in study 302 (66-67%) though there were more AEs of PT Pneumonia in the zanubrutinib arm compared to the ibrutinib arm (12.2% and 2%, respectively). Comparing the added incidences of the two PTs Lower respiratory infection and Pneumonia the incidence is still higher in the ibrutinib arm compared to the zanubrutinib arm in study 302; 21.4% vs 9.9%, respectively.

≥ Grade 3 hypertension, which is a well-known ibrutinib AE, were seen more frequently in the ibrutinib arm compared to the zanubrutinib arm (11.2% versus 5.9%, respectively).

≥ Grade 3 AEs were reported in 20 (19.8%) zanubrutinib-treated and 8 (8.2%) ibrutinib-treated patients and SAEs for Neutropenia (grouped term) were only seen in the zanubrutinib arm; 6 (5.9%).

As for the Adverse events of special interest (AESI) no clear difference between the two arms in study 302 were seen for haemorrhage, anaemia, thrombocytopenia, or second primary malignancies. These are also considered safety concerns for zanubrutinib as well as for ibrutinib.

The incidence of the well-known ibrutinib-associated adverse event of atrial fibrillation/ flutter was higher in the ibrutinib arm (15.3%) compared to the zanubrutinib arm (2.0%).

Seven patients in the ibrutinib arm and 6 patients in the zanubrutinib arm died, three in each arm of progressive disease. Given the few deaths no pattern for AE-related deaths is seen.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety of zanubrutinib seems at least comparable to ibrutinib and no major uncertainties or limitations have been identified.

Any long-term adverse events, in particular haematologic long-term toxicity or any organ-manifestations, have not yet been determined. Routine pharmacovigilance activities are expected to resolve this (see RMP).

3.6. Effects Table

Table 58: Effects table for zanubrutinib

Effect	Short description	Unit	Control	Treatment	Uncertainties / Strength of evidence	References per 31.08.19
Favourable Effects						
Endpoints (Owen er al, BJH 2013)			**ibrutinib N = 99**	**zanubrutinib N=102**	Randomized, multicentre trial of 201 patients in all, randomized 1:1	**Pivotal trial BGB-3111-302 (**ASPEN**)**
			ibrutinib N = 18	**zanubrutinib N = 19**		**Cohort 1 1.line (TN)**
Primary endpoint	CR + VGPR	No. (%) 95% CI	3/18 (16.7) 3.6, 41.4	5/19 (26.3) 9.1, 51.2	NS (No Pt achieved CR)	
Secondary endpoint	MR (>PR)	No. (%) 95% CI	12/18 (66.7) 41.0, 86.7	14/19 (73.7) 48.8, 90.9	NS	
Secondary endpoint	Duration of CR or VGPR	Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NS	
Exploratory endpoint	Time to CR+VGPR	Median mo Q1, Q3 min, max	22.11 16.92, 24.90 16.9, 24.9	5.54. 4.80, 9.40 4.6, 22.2	NS	
Exploratory endpoint	Time to MR	Median mo Q1, Q3 min, max	2.38 1.41, 3.43 0.9, 19.4	2.89 1.87, 5.62 1.0, 22.2	NS	
			ibrutinib N = 81	**zanubrutinib N = 83**		**Cohort 1 2.line+ (RR)**
Primary endpoint	CR + VGPR	No. (%) 95% CI	16/81 (19.8) 11.7, 30.1	24/83 (28.9) 19.5, 39.9	NS (No Pt achieved CR)	
Secondary endpoint	MR (>PR)	No. (%) 95% CI	65/81 (80.2) 69.9, 88.3	65 (78.3) 67.9, 86.6	NS	
Secondary endpoint	Duration of CR or VGPR	Median (95% CI)	NE (8.0, NE)	NE (13.8, NE)	NS Acceptable follow-up in a chronic disease	
Exploratory endpoint	Time to CR+VGPR	Median mo Q1, Q3 min, max	5.13 3.12, 10.69	4.68 2.92, 10.71 1.9, 16.7	NS	

Effect	Short description	Unit	Control	Treatment	Uncertainties / Strength of evidence	References per 31.08.19
Exploratory endpoint	Time to MR	Median mo Q1, Q3 min, max	2.86 1.94, 4.76 0.9, 17.5	2.83 1.91, 3.02 0.9, 22.1	NS	
Unfavourable Effects			**Ibrutinib N = 98**	**Zanubrutinib N=101**		**Pivotal trial BGB-3111-302**
TEAE	Afli	%	14.3	2.0	Few ≥ Grade 3	Table 45*
(All grades)	Diarrhoea	%	31.6	20.8	≥ Grade 3 were comparable	"
	Pneumonia/ LRTI	%	12.2/ 9.2	2.0/ 7.9	21.4% vs 9.9% for the PTs combined	
≥ Grade 3	(All events)	%	63.3	58.4		Table 47*
	Afli	%	3.1	0		"
	Diarrhoea	%	1.0	3.0		"
	Hypertension	%	11.2	5.9		"
	Neutropenia	%	8.2	15.8		"
SAE	(All events)	%	40.8	39.6		Table 16+
	Infections (SOC)	%	19.4	14.9		"
Discontinuation due to AE		%	9.2	4.0		Table 43*

Abbreviations: Afli atrial fibrillation; CI confidence interval; Cohort 1 $MYD88^{L265P}$; Cohort 2 $MYD88^{wild\text{-}type}$; CR complete response; inv investigator; IRC Independent Review Committee; max maximum; min minimum; LRTI lower respiratory tract infection; MR major response; NE non-evaluable (not reached); No. Number; NS not significant; PR partial response; Pt patient; Q quartile; RR relapsed/refractory; TN treatment naive; VGPR very good partial response; WT wild type. * CSR BGB-3111-302; + SCS.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the context of a rare disease, the Applicant has provided a head-to-head comparison in a phase 3 study, supported by further data from a phase 1/2 study. In total 201 patients were randomized 1:1. The result by IRC shows CR/VGPR in the ibrutinib arm around 19%, which is in line with the observations made in study 1118B. A CR/VGPR of 28% is observed in the zanubrutinib arm. With regards to MRR the IRC concluded 77.8% vs. 77.5% in ibrutinib and zanubrutinib respectively.

With respect to safety, a trend towards a lower risk for several events, known to be associated with ibrutinib treatment (atrial fibrillation, diarrhoea, and hypertension), were seen in patients treated with zanubrutinib. The finding of a lower rate of atrial fibrillation indicates that this is not a mere me-too; it is a valuable improvement over ibrutinib in this elderly population.

The incidence of neutropenia was higher in the zanubrutinib arm in the pivotal study 302 but the incidence of Infections (SOC) was comparable. Despite this, there were more AEs of PT Pneumonia in the ibrutinib arm compared to the zanubrutinib arm (12.2% and 2%, respectively). Adding the two PTs Lower respiratory tract infection and Pneumonia the incidence is still higher in the ibrutinib arm compared to the zanubrutinib arm in study 302; 21.4% vs 9.9%, respectively. There were also generally more SAEs Infections and Infestations (SOC) in the ibrutinib arm compared to the zanubrutinib arm (19.4% vs 14.9%) in the pivotal study 302 despite the higher incidence of neutropenia in the zanubrutinib arm.

Overall, clinically meaningful results have been shown. Efficacy and safety of zanubrutinib are considered established. Zanubrutinib offers another treatment option in the armamentarium for patients with WM, which is highly welcomed, especially in older patients with cardio-vascular comorbidity.

3.7.2. Balance of benefits and risks

Efficacy has been established, while the safety profile is considered superior in the context of derogations from market exclusivity. The majority of AEs observed are manageable in the clinical setting. The B/R balance is therefore positive.

3.7.3. Additional considerations on the benefit-risk balance

In view of the similarity with Imbruvica, and for the purposes of applying for a derogation to its market exclusivity, the applicant submitted the following arguments to establish superiority on the basis of greater safety in a substantial portion the target patient population.

For the detailed assessment to the evidence submitted in support of the claim of clinical superiority in the context of Regulation (EC) No 141/2000, reference is made to the "CHMP Assessment Report on derogations applicable to similar orphan products" in Appendix 2.

As a conclusion, the clinically most important result that the occurrence of atrial fibrillation is lower in the Zanubrutinib treated patients than in the Ibrutinib population can be agreed upon. From a clinical point of view the improved safety profile and tolerability -as also reflected in a longer time to treatment failure- is considered a relevant advantage in the target population and thus provides a basis for clinical superiority and derogation from market exclusivity.

3.8. Conclusions

The overall B/R of Brukinsa as monotherapy for the 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 - is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Brukinsa is similar to Imbruvica within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Derogation(s) from market exclusivity

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000 the following derogation laid down in Article 8.3 of the same Regulation applies:

the applicant could establish in the application that the medicinal product, although similar to ibrutinib, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication (see appendix 2).

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Brukinsa is favourable in the following indication:

Brukinsa as monotherapy is indicated for the 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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that zanubrutinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendices

1. CHMP AR on similarity dated 16 September 2021
2. CHMP AR on clinical superiority dated 16 September 2021