Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Zanubrutinib

Proprietary Product Name: Brukinsa

Sponsor: BeiGene AUS Pty Ltd

August 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AUC	Area under the concentration time curve
$AUC_{0\text{-}8h}$	Area under the concentration time curve from time zero to 8 hours
$AUC_{0\text{-}inf}$	Area under the concentration time curve from time zero to infinity
AUC_{ss}	Area under the concentration time curve at steady state
BCS	Biopharmaceutics Classification System
BGB-3111	Sponsor's drug development code
BTK	Bruton's tyrosine kinase
CD20	Cluster of differentiation 20
CHMP	Committee for Medicinal Products for Human Use (European Union)
CL/F	Apparent clearance
C_{max}	Maximum observed concentration
$C_{max,ss}$	Maximum concentration at steady state
CMI	Consumer Medicines Information
CNS	Central nervous system
CPMP	Committee for Proprietary Medicinal Products (European Union)
CR	Complete response
CXCR4	Chemokine receptor type 4
CYP	Cytochrome P450

Abbreviation	Meaning
DLP	Data lock point
ERBB4	Erb-b2 receptor tyrosine kinase 4
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency (European Union)
EMEA	European Medicines Evaluation Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
GvHD	Graft versus host disease
GVP	Good Pharmacovigilance Practices
HPLC	High performance liquid chromatography
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITK	Interleukin-2 inducible T-cell kinase
IRC	Independent Review Committee
ITT	Intent(ion)-to-treat
IWWM	International Workshop on Waldenström's Macroglobulinaemia
MRR	Major response rate
mut	Mutation
MYD88	Myeloid differentiation primary response 88
NCCN	National Comprehensive Cancer Network (United States of America)
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PR	Partial response
PSUR	Periodic safety update report
Q/F	Apparent inter-compartmental clearance
QTcF	Corrected QT-interval using Fridericia's formula
r/r	Relapsed/refractory
SAE	Serious adverse event
TEC	Tec protein tyrosine kinase
T_{max}	Time to maximum observed concentration
TRAE	Treatment-related adverse event
ULN	Upper limit normal
US(A)	United States (of America)
V_c/F	Apparent volume of the central compartment
VGPR	Very good partial response
V_p/F	Apparent volume of the peripheral compartment
WHIM	Warts, hypogammaglobulinaemia, immunodeficiency, and myelokathexis
WM	Waldenström's macroglobulinaemia
WT	Wild type
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Brukinsa
Active ingredient:	Zanubrutinib
Decision:	Approved
Date of decision:	7 October 2021
Date of entry onto ARTG:	7 October 2021
ARTG number:	338475
, *Black Triangle Scheme:*[1]	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	BeiGene AUS Pty Ltd 1C/528 Compton Road Stretton QLD 4116
Dose form:	Capsule
Strength:	80 mg
Container:	Bottle
Pack size:	120
Approved therapeutic use:	***Waldenström's macroglobulinemia (WM)*** *Brukinsa 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.*
Route of administration:	Oral
Dosage:	The recommended total daily oral dose of zanubrutinib is 320 mg. Zanubrutinib may be taken as either 320 mg (four 80 mg capsules) once daily, or as 160 mg (two 80 mg capsules) twice daily.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by BeiGene AUS Pty Ltd (the sponsor) to register Brukinsa (zanubrutinib) 80 mg, capsule for the following proposed indication:

> *Brukinsa 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 chemoimmunotherapy.*

Waldenström's macroglobulinemia (WM) is a generally indolent and relatively rare B-cell malignancy, characterised by the overproduction and bone marrow infiltration of monoclonal, immunoglobulin M (IgM) secreting, lymphoplasmacytic cells. The presence of monoclonal IgM protein adds a unique dimension to the disorder because it can result in hyperviscosity syndrome, peripheral neuropathy, haemolytic anaemia, and immune complex vasculitis. In contrast to other lymphoid malignancies, the morbidity and mortality associated with WM is typically due to excessive concentration of serum IgM, rather than mass effect from tumour infiltration, and detection of IgM forms the basis of response assessment.

Activating mutations (mut) in the myeloid differentiation primary response 88 (*MYD88*) gene (denoted as $MYD88^{mut}$) are present in 67% to 90% of cases of WM. A second set of mutations with prognostic significance, found in *CXCR-4*, the gene encoding for the C-X-C chemokine receptor type 4 are seen in approximately 30% of cases. Either or both of these mutations can be found in patients.

Waldenström's macroglobulinemia (WM) has an overall incidence of one in 260,000 persons per year in the United States of America (USA) and a prevalence estimate of about 1.4 in every 10,000 persons in the European Union (EU).[2] In Australia, the incidence of WM has been estimated to be 0.16 to 0.32 per 100,000 in males and 0.11 to 0.22 per 100,000 in females.[3] WM is a disease of the elderly, with a median age of 63 to 68 years.

[2] European Medicines Agency (EMA), Public Summary of Opinion on Orphan Designation Zanubrutinib for the Treatment of Lymphoplasmatic Lymphoma, EMADOC-628903358-942, 2 August 2019 Available at: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/19/2167-public-summary-opinion-orphan-designation-zanubrutinib-treatment-lymphoplasmatic-lymphoma_en.pdf.
[3] Australian Institute of Health and Welfare (AIHW) Cancer Data in Australia, last updated 1 July 2022. Available at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia.

There is a male predominance, with incidence twice as high in men than in women, and higher in whites than blacks and other races.

Although WM is classified as an indolent disease, it poses a major clinical challenge for the treating physician, as it often causes considerable morbidity in the mostly elderly patient population. Despite substantial progress in treating WM patients, only few patients achieve complete remission, and relapse has not been preventable despite improved therapeutic tools such as the first-in-class Bruton's tyrosine kinase (BTK) inhibitor ibrutinib.

Therapeutic approaches for WM have historically been based on alkylating agents, anti-cluster of differentiation 20 (anti-CD20) therapies, purine analogues, and proteasome inhibitors, used either as single agents or in combination, with the goal of long-term control of plasma IgM levels, to which the morbidity and mortality associated with WM are related. Frontline treatments include dexamethasone, rituximab, and cyclophosphamide; bortezomib and rituximab; bortezomib, dexamethasone and rituximab; bendamustine and rituximab; rituximab alone; fludarabine.

Targeting B-cell receptor signalling through BTK inhibition represents a new approach for the management of B-cell malignancies, including WM. An advantage of BTK inhibitors is that they offer a relatively non-myelosuppressive, non-immunosuppressive treatment option, avoiding two of the major toxicities of conventional therapies that confound the management of patients with these diseases. The first-in-class BTK inhibitor, ibrutinib, was approved for the treatment of patients with WM by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2015. Ibrutinib;[4] was approved for use in Australia in December 2016;[5] for the treatment of patients with WM who have received at least one prior therapy, or in first line treatment of patients unsuitable for combination chemo-immunotherapy.

Despite the benefit of ibrutinib treatment in patients with WM, adverse events, particularly cardiac events such as atrial fibrillation and hypertension, can be treatment limiting. Specific adverse events that have been associated with ibrutinib treatment discontinuation or disruption include atrial fibrillation, hypertension, bleeding, diarrhoea, and arthralgia. The sponsor is therefore of the opinion that while ibrutinib is active in WM, there remains a need for BTK inhibitors with improved pharmacologic properties resulting in high efficacy response rates with greater selectivity, and yielding a superior safety profile relative to ibrutinib in the treatment of WM.

Zanubrutinib is a novel, oral, second generation BTK inhibitor designed to be more selective and have more favourable pharmacokinetic (PK) and pharmacodynamic (PD) properties than the approved first-in-class BTK inhibitor, ibrutinib. In preclinical studies, zanubrutinib demonstrated superior oral bioavailability, and achieved higher plasma exposure and more complete BTK inhibition in tissues than ibrutinib. In kinase inhibition and cell-based assays, zanubrutinib was more selective than ibrutinib for inhibition of BTK, exhibiting less off-target activity against epidermal growth factor receptor (EGFR), tyrosine kinase expressed in hepatocellular carcinoma, interleukin-2 inducible T-cell kinase (ITK) and other kinases, the inhibition of which have been implicated in ibrutinib-associated toxicities such as rash and diarrhoea (EGFR inhibition), bleeding, and atrial fibrillation.

[4] Imbruvica was first registered on the ARTG on 20 April 2015 (ARTG number: 228499).
[5] AusPAR for Imbruvica (ibrunitib) new chemical entity, published on 5 April 2016. Available at: https://www.tga.gov.au/auspar/auspar-ibrutinib.

Regulatory status

This product was considered a new chemical entity for Australian regulatory purposes.

At the time this submission was evaluated, another similar submission (Submission PM-2020-03076-1-6) was also under evaluation for the following indication:

> *Mantle cell lymphoma (MCL)*
>
> *Brukinsa is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.*
>
> *This indication was approved via the provisional approval pathway, based on objective response rate. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.*

Brukinsa (zanubrutinib) was considered a new chemical entity for both submissions. An AusPAR for this parallel submission is also available on the TGA website).[6]

At the time the TGA considered this application, a similar application had been approved in Canada on 1 March 2021. Similar applications were under consideration in the EU (submitted on 29 May 2020), USA (submitted on 18 December 2020), Switzerland (submitted on 4 June 2021) and Singapore (submitted on 25 November 2020).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	29 May 2020	Under consideration	Under consideration
United States of America	18 December 2020	Under consideration	Under consideration
Canada	12 August 2020	Approved 1 March 2021	*Brukinsa (zanubrutinib) is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).*
Switzerland	4 June 2021	Under consideration	Under consideration
Singapore	25 November 2020	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[6] AusPAR for Brukinsa (zanubrutinib) new chemical entity, Submission PM-2020-03076-1-6, published on 17August 2022 Available at: https://tga.govcms.gov.au/resources/auspar/auspar-brukinsa.

II. Registration timeline

The following table captures the key steps and dates for this application, and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-02814-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2020
First round evaluation completed	24 December 2020
Sponsor provides responses on questions raised in first round evaluation	26 February 2021
Second round evaluation completed	15 April 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 July 2021
Sponsor's pre-Advisory Committee response	14 July 2021
Advisory Committee meeting	5 and 6 August 2021
Registration decision (Outcome)	7 October 2021
Completion of administrative activities and registration on the ARTG	7 October 2021
Number of working days from submission dossier acceptance to registration decision*	240

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- National Comprehensive Cancer Network (NCCN), Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma Guidelines, Version 1.2022.
- European Medicines Evaluation Agency (EMEA), Committee for Proprietary Medicinal Products (CPMP), Points to Consider on Switching Between Superiority and Non-inferiority, CPMP/EWP/482/99, 27 July 2000.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Draft Agenda for the Meeting on 21-24 June 2021, EMA/CHMP/347670/2021, 21 June 2021.

Quality

The submission seeks registration of immediate release 80 mg hard capsules in a high density polyethylene bottle with a child resistant closure. The quality evaluator recommended approval from a chemistry and quality perspective. The following is summary of the findings:

- Zanubrutinib is structurally related to other antineoplastic protein kinase inhibitors including ibrutinib, acalabrutinib and bosutinib.
- The drug substance is Biopharmaceutics Classification System (BCS) class II (low solubility, high permeability).[7]
- The drug substance is produced by chemical synthesis in a six stage process from two defined starting materials. Synthetic steps include condensation, reduction, deprotection, chiral isolation, hydrolysis and addition under enantioselective conditions before seed crystallisation and drying. Six intermediates are isolated in the process. The un-milled drug substance (sponsor's drug development code: BGB-3111) is then micronised by jet-milling.
- The manufacturing process description includes process parameters and in-process controls for all steps. The drug substance specification adequately controls appearance, identification, assay, water content, chiral purity, polymorphism, related substances, residual solvents, elemental impurities, loss on drying, residue on ignition and particle size distribution.
- The retest period is 24 months for this drug substance stored below 30°C in a low density polyethylene bag, tied with a nylon tie within a second low density polyethylene bag and anti-tamper tie within a fibre drum and lid with tamper evident seal.
- The capsule appearance is Size 0, white to off-white opaque capsule of 22 mm in length, printed with 'ZANU 80' in black ink containing white to off-white powder.
- The capsule length is 21.7 ± 0.3 mm, diameter 7.64 mm. The capsules contain no overfill.
- The capsule fill contains the drug substance, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and sodium lauryl sulfate. The fill is contained within a hard gelatin capsule and printed with a printing ink. The gelatin is of porcine and bovine origin.
- The proposed capsule formulation is the same as used in the pivotal clinical study. The proposed formulation is made by direct blending and encapsulation. The process has not changed from clinical to the proposed commercial process.
- The finished product specification includes tests and limits for appearance, identification by fourier transform infrared spectroscopy, high performance liquid chromatography (HPLC) and chiral HPLC, assay, related substances, content uniformity, dissolution, microbial quality, chiral purity and impurities.
- There are two specified impurities and no specified degradation products.
- Stability data were provided to support the proposed shelf life of the drug product of 30 months when stored below 30°C with the condition 'store in original container'.

[7] The **Biopharmaceutics Classification System (BCS)** is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Nonclinical

The nonclinical evaluation has been undertaken for Submission PM-2020-03076-1-6;[8] evaluated in parallel with this submission. The nonclinical evaluator did not raise an objection to the registration of zanubrutinib from a nonclinical perspective.

The nonclinical evaluation had no concerns regarding the overall quality of the submission, the scope of the nonclinical program and Good Laboratory Practice;[9] compliance of the studies.

In vitro, zanubrutinib inhibited the BTK receptor with nanomolar affinity. Zanubrutinib inhibited the autophosphorylation of BTK and inhibited tumour growth in mantle cell lymphoma and diffuse large B-cell lymphoma cell-lines. *In vivo*, zanubrutinib showed dose dependent inhibition in tumour growth and an increase in life span in xenograft mouse models of B-cell malignancies. No animal studies were submitted to directly support the WM indication.

In secondary screens against 326 human kinases, zanubrutinib had inhibitory activity against 13 kinases, excluding BTK. Zanubrutinib is likely to inhibit bone marrow X kinase / epithelial and endothelial tyrosine kinase, B-lymphocyte kinase, erb-b2 receptor tyrosine kinase 4 (ERBB4)/human epidermal growth factor receptor 4, tec protein tyrosine kinase (TEC), EGFR, TXK, breast tumour kinase and ITK; may slightly inhibit fetal growth restriction, lymphocyte specific protein tyrosine kinase and fyn-related kinase / protein tyrosine kinase 5; and is unlikely to inhibit Janus kinase 3 and human epidermal growth factor receptor 2 kinases at the proposed clinical dose. Inhibition of multiple kinases present on B-cell and T-cell lineages by zanubrutinib may result in altered and/or compromised immune response to certain infections. ERBB4 and TEC appear to have cardioprotective roles and TEC plays a role in platelet activation. The secondary pharmacodynamic (PD) studies did not include general screening for potential off target effects on a large panel of receptors, enzymes, transporters and ion channels. This is considered a deficiency.

No adverse effects on central nervous system (CNS), respiratory or cardiovascular function were seen in adequately conducted safety pharmacology studies. Bleeding episodes and atrial fibrillation observed in patients may be due to off-target effects.

Zanubrutinib was rapidly absorbed with a similar time to maximum observed concentration (T_{max}) (≤ 2 hours) in animal (rats and dogs) species and humans. Bioavailability was moderate in dogs and female rats, whereas it was low in male rats. The terminal elimination half-life was short in both rats and dogs following IV dosing (≤ 1.1 hours) and moderate in rats, dogs and humans following oral dosing (1 to 4 hours). Plasma protein binding of zanubrutinib was high in laboratory animal species (> 92% in mice, rats, dogs and monkeys) and humans (93.5% to 95%). Tissue distribution of zanubrutinib was wide in rats and dogs but penetration into brain was limited. The predominant circulating metabolite in human plasma was acrylic acid. Significant metabolites in rat plasma were also identified in humans. Cytochrome P450 (CYP);[10] 3A4

[8] Submission for the following approved (as of 8 October 2021) indication:
Mantle cell lymphoma (MCL)
Brukinsa is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication was approved via the provisional approval pathway, based on objective response rate. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.

[9] **Good Laboratory Practice** is a code of standards following the International Council on Harmonisation (ICH) relevant to testing of medicines in laboratories during drug development.

[10] **Cytochrome P450 (CYP)** enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

is the main enzyme involved in zanubrutinib metabolism. Drug-related material was excreted predominantly via faeces (approximately 90%) in humans and rats after oral administration. Biliary excretion of metabolites was demonstrated in rats.

Inhibitors or inducers of CYP3A are expected to significantly alter zanubrutinib exposure in clinical use. Strong P-glycoprotein inhibitors or inducers may alter the *in vivo* distribution profile of zanubrutinib. *In vitro* data also indicate the potential for zanubrutinib to increase exposures to co-administered drugs that are CYP2C8 substrates. Zanubrutinib weakly induces CYP2C19 and it has a net weak induction effect on CYP3A enzymes. It is likely to decrease exposures of substrates of these isozymes. Zanubrutinib is likely to increase exposure of P-glycoprotein substrates by inhibition of these efflux pumps in gut.

Zanubrutinib had a low order of acute oral toxicity in rats and dogs.

Repeat-dose toxicity studies by the clinical route (orally) were conducted in rats (up to 6 months duration) and dogs (up to 9 months duration). Maximum exposures area under the concentration time curve (AUC) were adequate in the pivotal studies. Target organs for toxicity were the skin (both species), lymphoid tissues (both species), gastrointestinal tract (rats), adrenal glands (rats), pancreas (rats), lungs (rats), thyroid gland (rats) and skeletal muscle (rats). Effects in the adrenal and thyroid glands are not expected to be clinically relevant. Findings of clinical relevance included gastrointestinal disturbances, skin lesions and haemorrhage. Based on the primary pharmacology of the drug, an immunosuppressive effect is expected in patients (B-cell and immunoglobulin deficiencies).

Zanubrutinib was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in Chinese hamster ovary cells) or *in vivo* (in the rat micronucleus test). No carcinogenicity studies have been conducted with zanubrutinib. This is acceptable given the proposed indication.

Pregnancy Category D;[11] is recommended. Female fertility was unaffected in rats, however embryotoxicity and abnormal sperm morphology were reported at zanubrutinib exposure levels around 19 to 32 times those anticipated clinically. Zanubrutinib was teratogenic (2 or 3 chambered hearts) in rats at 4 times the anticipated clinical exposure. Zanubrutinib was embryotoxic in rabbits at maternotoxic doses around 25 times those anticipated clinically. Ocular abnormalities were observed in rat pups from dams dosed from gestation through weaning (the no-observed adverse effect level is not established). The significance of which is unclear.

The proposed limits for impurities in the drug product have been adequately qualified or are controlled to the applicable qualification threshold.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[11] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Clinical

The clinical dossier consisted of the following studies:

- Two Phase I studies: Study BGB-3111-1002 and Study BGB-3111-AU-003
- Five Phase II studies: Study BGB-3111-AU-003, Study BGB-3111-210 (Study 210), Study BGB-3111-205, Study BGB-3111-206 and Study BGB-3111-210
- One Phase III study: Study BGB-3111-302 (also known as the ASPEN trial)

The clinical evaluator recommended approval of the submission. It was communicated to the sponsor at the time of evaluation this conclusion did not necessarily represent the view of the Delegate.

Pharmacology

Pharmacokinetics

The summarised findings from the evaluation of the pharmacokinetic (PK) of zanubrutinib are included below.

The clinical evaluator accepted the sponsor's justification for not providing data to demonstrate absolute bioavailability for zanubrutinib.

After a single oral 320 mg once daily dose in healthy adult subjects following a high fat or low fat meal or under fasted conditions the median T_{max} values were 3.02, 2.00 and 2.00 hours, respectively and the population pharmacokinetics (PopPK) estimate of the absorption rate constant was 0.526 $hour^{-1}$. Increased zanubrutinib exposure after low and high fat meals compared to the fasted were considered unlikely to be clinically significant. The evaluator supported dosing with or without food.

Zanubrutinib appeared to increase dose proportionally 40 to 320 mg to patients with B-cell malignancies, although the evaluator concluded that due to the small sample sizes and high interpatient variability, linearity is more indicative than conclusive. There was limited systemic accumulation with multiple-dose administrations of 40 to 320 mg.

The proposed dosing is 320 mg once daily or 160 mg twice daily. Following multiple dosing in the same population, the geometric mean maximum observed concentration (C_{max}) and area under the concentration time curve from time zero to 8 hours (AUC_{0-8h}) values were 533 ng/mL and 1706 ng h/mL, respectively, following 320 mg once daily dosing and 299 ng/mL and 944 ng h/mL, respectively, following 160 mg twice daily dosing.

Around 94.2% of zanubrutinib bound to human plasma proteins in a concentration independent manner, and distribution to erythrocytes was low.

Zanubrutinib is primarily metabolised by CYP3A with minor contributions from Phase II enzymes such glutathione S transferases, and the contribution of uridine 5'-diphospho-glucuronosyltransferases is minimal. Zanubrutinib and its metabolites were excreted primarily in faeces, with no major active metabolites in circulation.

Given CYP3A plays a major role in the metabolism of zanubrutinib and that there is a growing body of literature examining the effects of functional mutations in CYP3A4 on drug metabolism, the evaluator was unable to agree with the sponsor that genetic polymorphism will not have significant effects on its metabolism.

Drug-drug interactions

Zanubrutinib is a sensitive CYP3A substrate, as compared to when it is administered alone. Exposure decreased by approximately 14-fold when zanubrutinib was co-administered

with rifampin and increased approximately 3.78-fold when co-administered with itraconazole.

Multiple 160 mg twice daily doses had no clinically significant effects on warfarin, digoxin or rosuvastatin PK. Omeprazole co-administration had no effect on the PK of zanubrutinib but zanubrutinib reduced midazolam and omeprazole AUC by approximately 36 to 47% indicating it has some inhibitory effects on CYP3A and CYP2C19.

Population pharmacokinetics

Population pharmacokinetic (PopPK) modelling based on 6 Phase I, 2 Phase II and one Phase III trials indicated that across the dose range of 20 mg to 320 mg the zanubrutinib PK was best described by a two-compartment model with first order elimination from the central compartment and redistribution from the peripheral compartment.

Race, baseline age, body weight, aspartate aminotransferase, bilirubin, creatinine clearance, gender, tumour type and use of acid-reducing agents did not statistically significant effect zanubrutinib PK.

Baseline alanine aminotransferase (ALT) and health status were significant covariates on apparent clearance (CL/F), so that for patients who were within the tenth and ninetieth percentiles for ALT, CL/F values were 11.8% higher and 12.8% lower, respectively, whereas, CL/F was 30.4% lower in healthy subjects than in patients with B-cell malignancies.

From the popPK modelling a typical patient with an ALT level of 18 U/L, the estimated apparent volume of the central compartment (V_c/F) and apparent volume of the peripheral compartment (V_p/F) were 112 L and 345 L, respectively.

Estimates of the inter-individual variability on CL/F, V_c/F, V_p/F, apparent inter-compartmental clearance (Q/F) and duration were 36.7%, 37.1%, 102%, 86.4% and 62.3%, respectively. The estimated inter-occasion variability on CL/F and V_c/F were 28.6% and 67.5%, respectively and the proportional residual error was 44.9%.

Special populations

In the PopPK analysis, AUC_{ss} and maximum concentration at steady state ($C_{max,ss}$) were 43.7% and 26.8% higher, respectively, in healthy volunteers than in patients with B-cell malignancies.

Maximum observed concentration (C_{max}) was 1.05-, 1.53- and 1.28-fold higher in subjects with mild, moderate and severe hepatic impairment, respectively than healthy subjects and the corresponding values for area under the concentration time curve from time zero to infinity ($AUC_{0\text{-}inf}$) were 1.11-, 1.21- and 1.60-fold, respectively.

No studies have been undertaken in subjects with renal impairment. The popPK analysis indicated mild and moderate renal impairment do not affect exposure in patients with B-cell malignancies, but dataset limitations precluded a definitive conclusion for severe renal impairment or end stage renal disease.

Pharmacodynamics

The pharmacodynamics (PD) findings for zanubrutinib were concluded in the clinical evaluation:

- It acts by inhibiting BTK-mediated activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis and adhesion.
- In peripheral blood mononuclear cells isolated from patients with B-cell malignancies, induced maximum BTK occupancy after single and multiple-doses from 40 mg to 320 mg.

- In lymph nodes, BTK occupancy was 100% and 94% after 160 mg twice daily and 320 mg once daily, respectively.
- There was minimal effect on heart rate and QT-interval[12] from 480 mg and 160 mg doses.
- In patients with B-cell malignancies, there were no apparent E-R relationships between zanubrutinib exposure and the probability of complete response (CR) / very good partial response (VGPR), major response rate (MRR), overall response rate or QT effects or any of the adverse events (AEs) of interest.

Efficacy

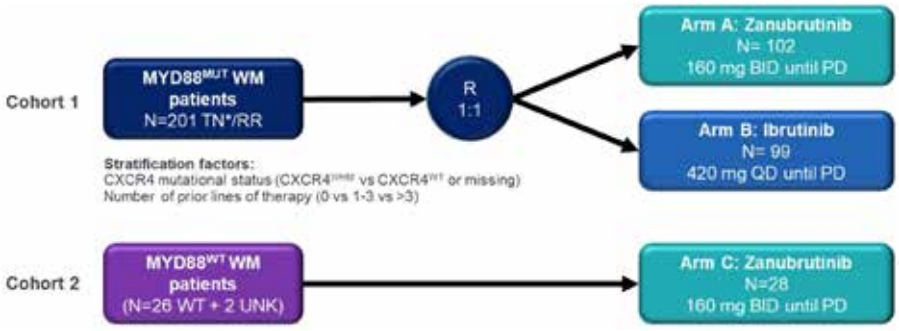
To support the clinical efficacy of zanubrutinib in WM the sponsor included two primary studies and one additional study:

- Study BGB-3111-302 (the ASPEN trial) a Phase III, randomised, open label, multicentre study to compare ibrutinib and zanubrutinib in relapsed/refractory (r/r) and treatment-naïve WM.
- Study BGB-3111-AU-003 a Phase I/II, single arm, multicentre, dose escalation (Part 1) and cohort expansion (Part 2) study to investigate the safety and PK of zanubrutinib in B-cell malignancies.
- Study BGB-3111-210 a Phase II, single arm, multicentre, efficacy and safety study of zanubrutinib in Chinese patients with r/r WM was included as an additional supportive study.

Study BGB-3111-302

Study BGB-3111-302 (the ASPEN trial) is an ongoing Phase III, randomised, open label, multicentre, multinational, superiority study comparing the efficacy and safety of zanubrutinib 160 mg twice daily and ibrutinib 420 mg once daily with WM. The study schema is shown in Figure 1 below.

Figure 1: Study BGB-3111-302 Study schematic



Abbreviations: BID = twice daily; CXCR4 = chemokine receptor type 4; MYD88 = myeloid differentiation primary response 88 gene; MUT = mutant; PD = progressive disease; QD = once daily; R = randomisation; RR = relapsed or refractory; TN = treatment-naïve; UNK = unknown; WHIM = warts, hypogammaglobulinaemia, immunodeficiency, and myelokathexis syndrome; WT = wild type.

* Treatment-naïve: treatment-naïve and unsuitable for chemoimmunotherapy (up to 20% of overall population)

[12] The **QT interval** is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

Treatment was to continue until progressive disease, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by the sponsor.

Inclusion criteria

- Clinical and definitive histologic diagnosis of WM. Patients must either have had relapsed or refractory disease or been treatment-naïve and considered by their treating physician to be unsuitable for standard chemoimmunotherapy regimens.
  - For patients who had received no prior therapy for WM: 'unsuitable' for treatment with a standard chemoimmunotherapy regimen must have been a physician determined status based on co-morbidities and risk factors. Physicians needed to provide and document organ system(s) and specific reason(s) for the patient being considered unsuitable. Patient preference did not meet the eligibility requirement for a treatment-naïve patient to be unsuitable for treatment with a standard chemoimmunotherapy regimen.
- Meeting no less than one criterion for treatment according to consensus panel criteria from the International Workshop on Waldenström's Macroglobulinaemia (IWWM)-7.[13]
- Measurable disease, as defined by serum IgM level > 0.5 g/dL.
- Age ≥ 18 years old.
- Eastern Cooperative Oncology Group (ECOG) Performance Status;[14] 0 to 2.
- Adequate bone marrow function defined as:
  - neutrophils ≥ 0.75 x 10^9/L, independent of growth factor support within 7 days of study entry;
  - platelets ≥ 50 x 10^9/L, independent of growth factor support or transfusion within 7 days of study entry.
- Creatinine clearance of ≥ 30 mL/min (estimated by Cockcroft-Gault equation or estimated glomerular filtration rate by modification of diet in renal disease) based on ideal body mass.
- Aspartate aminotransferase and ALT ≤ 3 x upper limit normal (ULN).
- Bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome).
- International normalised ratio ≤ 1.5 x ULN and activated partial thromboplastin time ≤ 1.5 x ULN.
- If relapsed after autologous stem cell transplant were eligible if they were≥3 months post-transplant and if after allogeneic transplant were ≥ 6 months post-transplant. Also, they should have had no active infections or active acute graft versus host

[13] Dimopoulos, M.A. et al. Treatment Recommendations for Patients with Waldenström Macroglobulinemia (WM) and Related Disorders: IWWM-7 Consensus, *Blood*, 2014; 124(9): 1404-1411.

[14] **Eastern Cooperative Oncology Group (ECOG) Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

disease (GvHD) of any grade and no chronic GvHD other than mild skin, oral, or ocular GvHD not requiring systemic immunosuppression.

- Life expectancy of > 4 months.

Exclusion criteria

- Prior exposure to a BTK inhibitor.
- Evidence of disease transformation at the time of study entry.
- Corticosteroids given with antineoplastic intent within 7 days, or chemotherapy, targeted therapy, or radiation therapy within 4 weeks, or antibody based therapy within 4 weeks of the start of study drug.
- Ongoing toxicity of ≥ Grade 2 from prior anticancer therapy (except for alopecia, absolute neutrophil count and platelets). For absolute neutrophil count and platelets, inclusion criteria 5;[15] was followed.
- History of other active malignancies within 2 years of study entry, with exception of adequately treated *in situ* carcinoma of cervix; localised basal cell or squamous cell carcinoma of skin; previous malignancy confined and treated locally (surgery or other modality) with curative intent.
- Currently active, clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease (congestive heart failure) as defined by the New York Heart Association (NYHA) Functional Classification,[16] or history of myocardial infarction within 6 months of screening.
- QT-interval corrected using the Fridericia's formula (QTcF) prolongation (defined as a QTcF > 480 ms).
- Active, clinically significant electrocardiogram abnormalities including second degree Type II atrioventricular block, or third degree atrioventricular block.
- Uncontrolled active systemic infection or recent infection requiring parenteral antimicrobial therapy completed ≤ 14 days before first dose of study drug.
- Known infection with human immunodeficiency virus, or serologic status reflecting active hepatitis B or hepatitis C infection.
- Taking any medications which were strong CYP3A inhibitors or strong CYP3A inducers.
- Taking warfarin or other vitamin K antagonists.
- Known CNS haemorrhage or stroke ≤ 6 months before study entry.
- Central nervous system (CNS) involvement by WM. Patients with a previous history of CNS involvement must have undergone magnetic resonance imaging and cerebrospinal fluid cytology studies to document no evidence of CNS disease prior to study entry.

[15] Inclusion criteria 5: Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 2

[16] **New York Heart Association (NYHA) classification**:
Class I: No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic left ventricular dysfunction). Metabolic equivalent (MET) > 7.
Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild congestive heart failure). MET = 5.
Class III: Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate congestive heart failure). MET = 2–3.
Class IV: Unable to carry on any physical activity without discomfort. Symptoms of congestive heart failure present at rest (severe congestive heart failure). MET = 1.6.

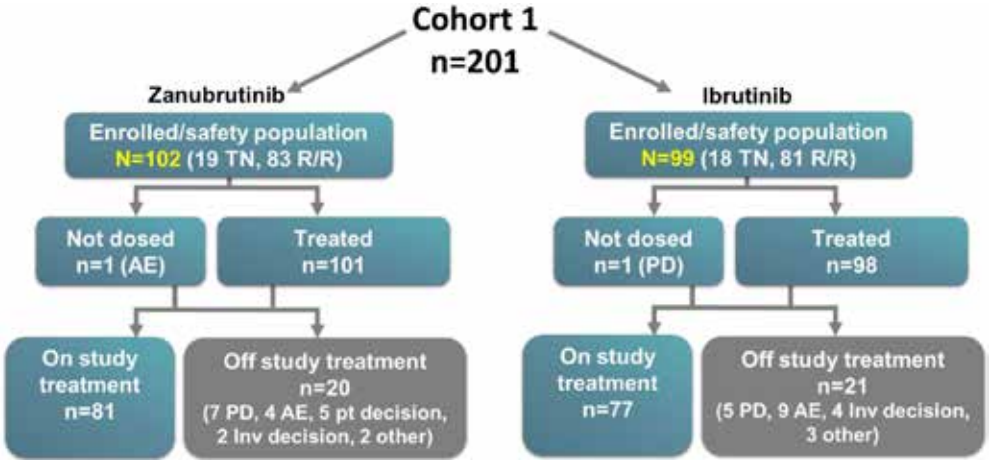
Baseline characteristics

Most patients were male (66.7%), White (91.0%), a median age of 70 years, and had an ECOG Performance Status score of 0 or 1 (93.5%). The median time from initial diagnosis to first dose of study drug was 4.94 and 4.25 years in the ibrutinib and zanubrutinib groups, respectively. Median baseline IgM level was 34.15 and 31.75 g/L, respectively. In Cohort 2, the median time from initial diagnosis to first dose of study drug was 3.65 years. Median baseline IgM level was 28.50 g/L.

In Cohort 1, *MYD88^{mut}* patients were randomised to zanubrutinib or ibrutinib 1:1. stratification factors in this cohort included *CXCR4* status (CXCR4 WHIM (warts, hypogammaglobulinaemia, immunodeficiency, and myelokathexis) versus CXCR4 WT (wild type) versus status unknown) and number of prior lines of therapy (0 versus 1 to 3 versus > 3). All *MYD88^{WT}* patients were included in the single arm Cohort 2.

Patient disposition is summarised diagrammatically in Figure 2 for Cohort 1 followed by Figure 3 for Cohort 2.

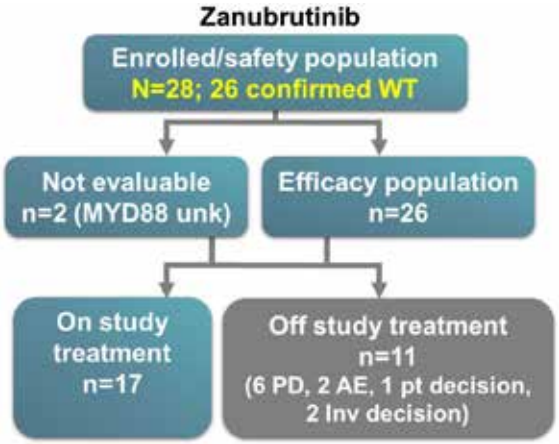
Figure 2: Study BGB-3111-302 Patient disposition flow diagram for Cohort 1



Abbreviations: AE = adverse event; Inv = investigator; N = population size; PD = progressive disease; pt = patient; R/R = relapsed/refractory; TN = treatment-naïve

Data cut-off: 31 August 2019.

Figure 3: Study BGB-3111-302 Patient disposition flow diagram for Cohort 2



Abbreviations: AE = adverse event; Inv = investigator; N = population size; PD = progressive disease; unk = unknown; WT = wild type.

Data cut-off: 31 August 2019.

Important protocol deviations occurred in 2.0% and 4.9% with of the ibrutinib and zanubrutinib arms in Cohort 1.

Statistical methods

The hierarchy of testing for the primary endpoint of very good partial response (VGPR)/complete response (CR) commenced with the relapsed/refractory (r/r) intention-to-treat (ITT)[17] population then moved to the ITT analysis set. If the result at the r/r analysis was statistically significant testing would be performed in the ITT analysis set at one-sided alpha of 0.025.

Non-inferiority for the major response rate (MRR) of partial response (PR), VGPR. or CR by Independent Review Committee (IRC) was to be tested with a 12% non-inferiority margin only if the primary endpoint was statistically significant in the analysis set in which the VGPF/CR rate was superior. If the lower bound of the 95% CI was greater than -12% it could be concluded that zanubrutinib was non-inferior to ibrutinib for MRR.

Two *post hoc* efficacy analysis were conducted:

- Non-inferiority for VGPF/CR using a -4.5% margin.
- Comparison of baseline adjusted IgM levels over time for the two treatment arms using a likelihood-based linear mixed model for related measures and a non-parametric comparison of comparison of the plasma AUC of IgM over time by the Mantel-Haenszel test.

Cohort 2 was an exploratory arm of the study.

Efficacy endpoints

The primary analysis was based on the data cut-off of 31 August 2019. The sponsor provided an updated data analysis from August 2020 in response to TGA questions.

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. The primary overall combined response was used to assess the primary endpoint of the study. The categorical response definitions of the endpoints were based on the IWWM-6 and included extramedullary disease. Analyses were also conducted for overall IgM response that used IgM reduction and immunofixation for response assessment.

Response assessments were performed every 4 weeks (every cycle) starting from Cycle 2, Day 1 for the first 48 weeks (12 cycles) then every 12 weeks (every 3 cycles) thereafter.

The secondary endpoints for Cohort 1 included MRR, duration of response, rate of CR or VGPR by investigator, progression free survival, resolution of treatment precipitating symptoms, anti-lymphoma effects and incidence and timing and severity of treatment-related adverse events (TRAEs). The exploratory endpoints of Cohort 1 include time to response, overall survival, time to next treatment, change in quality of life measures and medical resource utilisation

The primary endpoint was CR/VGPR (by IRC) based on the best overall response, analysed in the r/r analysis set in Cohort 1 (*MYD88^{mut}*) conducted approximately 12 months after the assignment of the last r/r patient, and 92% of the r/r analysis population had ≥ 15 months follow up.

[17] The randomised clinical trials analysed by the **intention-to-treat (ITT)** approach provide unbiased comparisons among the treatment groups. In the ITT population, none of the subjects are excluded, regardless of treatment compliance or attrition due to dropout or crossover, and the subjects are analysed according to the randomisation scheme. A modified intention-to-treat analysis (mITT) may sometimes be conducted excluding subjects post-randomisation.

The primary endpoint, VGPR/CR in the relapsed/refractory population in Cohort 1 by IRC was 19.8% and 28.9% in the ibrutinib and zanubrutinib treatment arms, respectively, with an estimated difference adjusted for the stratification factors and age group was 10.7% (95% CI: -2.5, 23.9), p = 0.1160).

The same comparison for the overall Cohort 1 population was 19.2% and 28.4% in the ibrutinib and zanubrutinib treatment arms, respectively, with an adjusted risk difference of 10.2% (95% CI: -1.5, 22.0), p = 0.0921).

A summary of the efficacy findings is included in Table 3, below.

The results for the primary endpoint were similar using overall IgM only (by IRC) as compared to the overall combined assessments. Median duration of response was not reached for VGPR/CR.

Table 3: Study BGB-3111-302 Efficacy results, primary analysis, relapsed/refractory and overall population, overall combined response criteria

Response Category	Cohort 1				Cohort 2
	Relapsed/Refractory		Overall		Overall
	Ibrutinib (N = 81)	Zanubrutinib (N = 83)	Ibrutinib (N = 99)	Zanubrutinib (N = 102)	Zanubrutinib (N = 26)
Best overall response, n (%)					
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very good partial response (VGPR)	16 (19.8)	24 (28.9)	19 (19.2)	29 (28.4)	7 (26.9)
Partial response (PR)	49 (60.5)	41 (49.4)	58 (58.6)	50 (49.0)	6 (23.1)
Minor response (MR)	11 (13.6)	13 (15.7)	15 (15.2)	17 (16.7)	8 (30.8)
Stable disease (SD)	2 (2.5)	3 (3.6)	3 (3.0)	3 (2.9)	4 (15.4)
Progressive disease (PD)	2 (2.5)	1 (1.2)	2 (2.0)	2 (2.0)	1 (3.8)
Not evaluable (NE) [a]	1 (1.2)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)
Discontinued prior to first assessment [b]	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.0)	0 (0.0)
VGPR or CR rate, n (%)	**16 (19.8)**	**24 (28.9)**	**19 (19.2)**	**29 (28.4)**	**7 (26.9)**
95% CI [c]	(11.7, 30.1)	(19.5, 39.9)	(12.0, 28.3)	(19.9, 38.2)	(11.6, 47.8)
Risk difference [d]	—	10.7	—	10.2	—
95% CI	—	(-2.5, 23.9)	—	(-1.5, 22.0)	—
p-value [e]	—	**0.1160**	—	**0.0921**	—
MRR (PR or better), n (%)	65 (80.2)	65 (78.3)	77 (77.8)	79 (77.5)	13 (50.0)
95% CI [c]	(69.9, 88.3)	(67.9, 86.6)	(68.3, 85.5)	(68.1, 85.1)	(29.9, 70.1)
Risk difference [d]	—	-3.5	—	-0.5	—
95% CI	—	(-16.0, 9.0)	—	(-12.2, 11.1)	—
ORR (MR or better), n (%)	76 (93.8)	78 (94.0)	92 (92.9)	96 (94.1)	21 (80.8)
95% CI [c]	(86.2, 98.0)	(86.5, 98.0)	(86.0, 97.1)	(87.6, 97.8)	(60.6, 93.4)

Abbreviations: CI = confidence interval; CR = complete response; MR = minor response; MRR = major response rate; N = population size, n = sample size; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response

Percentages are based on N.

Cohort 1 includes patients with activating mutations in myeloid differentiation primary response 88 gene (*MYD88*).

Cohort 2 includes patients with wild type and unknown *MYD88*.

a Includes not estimable, unknown, and disease flare.

b Includes patients who discontinued study prior to the first response assessment.

c 95% CI is calculated using the Clopper-Pearson method.

d Mantel-Haenszel common risk difference with the 95% CI calculated using a normal approximation and Sato's standard error stratified by the stratification factors per IRT (strata chemokine receptor type 4 (*CXCR4*) wild type and unknown are combined) and age group (≤ 65 and > 65). Ibrutinib is the reference group.

e Based on Cochran-Mantel-Haenszel test stratified by the stratification factors per IRT (strata *CXCR4* wild type and unknown are combined) and age group (≤ 65 and > 65).

Data cut-off: 31 August 2019.

The key secondary endpoint was a non-inferiority comparison of MRR (partial response or better). In the r/r population of Cohort 1 the risk difference for zanubrutinib versus ibrutinib was -3.5% (95% CI: -16.0%, 9.0%) and for the overall population -0.5% (95% CI: -12.2%, 11.1%).

Per investigator assessment, the VGPR/CR results were similar to IRC in both Cohort 1 and Cohort 2:

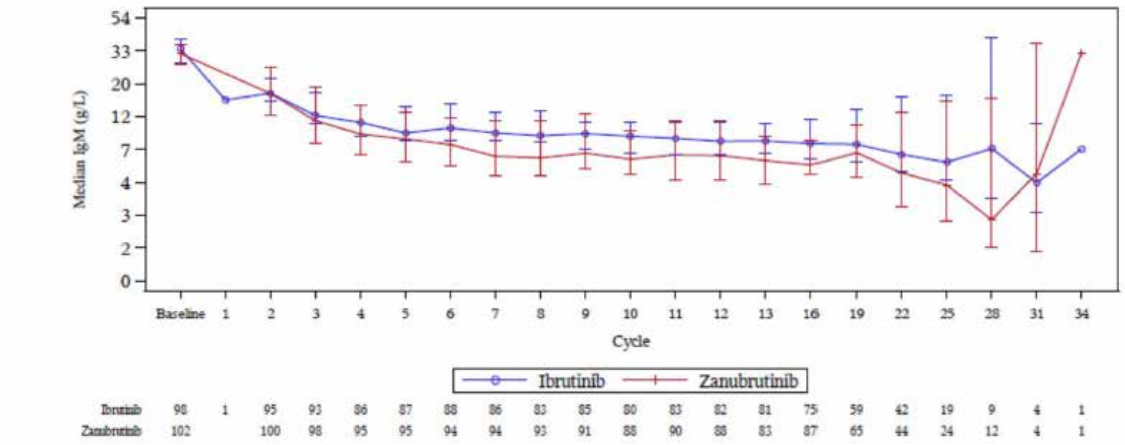
- Cohort 1 r/r population: zanubrutinib 28.9% versus ibrutinib 17.3% (risk difference 12.9%, 95% CI: 0%, 25.9%).
- Cohort 1 overall population: zanubrutinib 28.4% versus ibrutinib 17.2% (risk difference 12.1%, 95% CI: 0.5, 23.7; nominal p = 0.0437).
- Cohort 2 overall combined response r/r population 33.3%, overall population 26.9%.

Median progression-free survival had not been reached. In the overall analysis for Cohort 1, event free rate at 12 months was 87.2% (95% CI: 78.6%, 92.5%) versus 89.7% (95% CI: 81.7% versus 94.3%) and at 24 months was 81.5% (95% CI: 71.1%, 88.5%) versus 79.4% (95% CI: 62.2%, 88.0%) for ibrutinib and zanubrutinib, respectively.

Overall survival was exploratory and for Cohort 1 in the overall analysis at 12 months was 93.9% (95% CI: 86.8%, 97.2%) versus 97.0% (95% CI: 90.9% versus 99.0%) and at 24 months was 91.0% (95% CI: 82.5%, 95.5%) versus 89.5% (95% CI: 76.4%, 95.5%) for ibrutinib and zanubrutinib, respectively.

Immunoglobulin M measured over the course of the study was similar for ibrutinib and zanubrutinib (Figure 4).

Figure 4: Study BGB-3111-302 Changes in serum immunoglobulin M over time Cohort 1 overall analysis



Abbreviation: IgM = immunoglobulin M.

A *post hoc* non-inferiority comparison for the primary analysis (VPFR/CR by IRC) using a margin of -4.5% revealed the lower bound of the 95% CI for the r/r population and overall population of Cohort 1 was within this boundary.

Updated efficacy data

The updated efficacy analysis from the August 2020 data cut was presented similarly to the primary analysis. At the time of analysis, 66.7% of the ibrutinib and 74.5 % of the zanubrutinib patients remained on treatment in Cohort 1. There were no CRs in either treatment group.

Very good partial response (VGPR) or CR (by investigator per overall combined assessment):

- Cohort 1 r/r population: 21.0% ibrutinib versus 33.7% zanubrutinib. Risk difference 14.3% (95%CI: 0.6%, 27.9%).
- Cohort 1 overall population: 20.2% ibrutinib versus 33.3% zanubrutinib. Risk difference 14.2% (95%CI: 2.0%, 26.4%).
- Cohort 2: 30.8% (95%CI: 14.3%, 51.8%).

Median duration of response was not yet reached.

Major response rate (MRR) (by investigator per overall combined assessment, risk difference):

- Cohort 1 r/r population: 80.2% ibrutinib versus 78.3% zanubrutinib. Risk difference -4.2% (95%CI: -16.6%, 8.3%).
- Cohort 1 overall population: 20.2% ibrutinib versus 33.3% zanubrutinib. Risk difference 1.0% (95%CI: -10.6%, 12.5%).
- Cohort 2: 53.8% (95%CI: 33.4%, 73.4%).

Overall response rate (by investigator per overall combined assessment):

- Cohort 1 r/r population: 95.1% ibrutinib versus 94.0% zanubrutinib.
- Cohort 1 overall population: 93.9% ibrutinib versus 95.1% zanubrutinib.
- Cohort 2: 80.8% (95%CI: 60.6%, 93.4%)

Study BGB-3111-AU-003

This Phase I/II dose escalation and dose consolidation study of zanubrutinib in patients with B-cell malignancies that included 78 patients with Waldenstrom's macroalbuminaemia (WM) including 54 patients with relapsed or refractory (r/r) WM. Genotyping from 70/78 patients showed 52.6% had the $MYD88^{mut}/CXCR4^{WT}$ genotype. The Phase II cohort expansion specifically recruited patients with r/r WM into Cohort 2d, and r/r WM and treatment-naïve patients who were unsuitable for standard chemotherapy into Cohort 2f. The median time from initial diagnosis to study time was 4.31 years, the median number of prior therapies was 2, most commonly anti-CD20 antibodies, alkylating agents and glucocorticoids.

The median treatment duration was 26 months for the total WM group and 28.8 months for the r/r WM group. The starting dose of zanubrutinib was 160 mg twice daily in 68.5% and 320 mg once daily 24.1%. Median study follow-up was 30.3 months for the total WM group and 35.8 months for the r/r WM group.

Almost equal proportions of 31.5% of the r/r WM population and 28.2% of the total WM population who discontinued did so due to adverse events and disease progression.

Primary endpoint (data from patients who received ≥ 1 dose of zanubrutinib, had baseline IgM or M-protein ≥ 5 g/L and with no prior exposure to a BTK inhibitor, n = 49) with either a very good partial response (VGPR) or complete response (CR):

- patients with VGPR or CR (total WM population): 45.2% (95% CI: 33.5%, 57.3%).
- patients with VGPR or CR (r/r WM population): 51.0% (95% CI: 36.3%, 65.6%).
- patients with CR: one patient in the r/r WM group, zero patients in the treatment-naïve group.
- eight of 24 patients in the treatment-naïve group achieved VGPR.

Other endpoints included major response (partial response (PR) or better):

- total WM population: 82.2% (95% CI: 71.5%, 90.2%),
- r/r WM population: 79.6% (95% CI: 65.7%, 89.8%);
- twenty-one of 24 in the treatment-naïve group

Study BGB-3111-210

This is an ongoing, Phase II, single arm, multicentre, efficacy and safety study of 160 mg twice daily zanubrutinib in 44 adult Chinese patients with documented who had failed to achieve a minor response or who had documented progressive disease after the most recent treatment and who had at least one line of a standard chemotherapy containing regimen. This was presented as a supportive efficacy study.

Patients had a median age of 65 years, were mostly male (61.4%) and had a median of two prior anticancer regimens. The median time from progression from last therapy to first study drug was 1.22 years: 70% had a best response of stable disease or progressive disease with their last therapy, with 25% having a best response of progressive disease. Disease characteristics include anaemia (75%), extramedullary disease (72.7%), IgM ≥ 40 g/L (43.2%) and 77.3% with serum β2- microglobulin > 3 mg/L. By genotype 72.7% were $MYD88^{L265P}/CXCR4^{WT}$, 11.4% were $MYD88^{L265P}/CXCR4^{WT}$ and 15.9% were $MYD88^{WT}$.[18]

Discontinuation had occurred in 36.4% (16 patients), mostly with progressive disease, and a further five patients had died while on study treatment. One patient was found ineligible on central review of enrolment criteria.

Key findings

- Median treatment duration: 404.5 days.
- Primary endpoint of complete response (CR), very good partial response (VGPR), or partial response (PR; considered major response by IRC) according to IWWM-6 response criteria: 69.8% (95% CI: 53.87% to 82.82%; one-sided p-value < 0.0001).
- Patients with VGPR: 32.6%.
- IgM response (by IRC): 32.6% achieved ≥ 90% reduction from Baseline (23.3% normalised serum IgM).

Safety

Study BGB-311-302

Table 4 below summarises the safety findings from Study BGB-3111-302 (the ASPEN trial). Where adverse events (AEs) are reported in the clinical evaluation report for events from Cohort 1 with proportions reported for Cohort 2 these have been included in the Table 4, below.

Table 4: Study BGB-3111-302 Safety summary

	Cohort 1 zanubrutinib (n=101)	Cohort 1 ibrutinib (n=)	Cohort 2 zanubrutinib (n=28)
Exposure			
Median duration of exposure, months	18.7	18.6	16.4
Median intensity of treatment	97%	98%	97%
Deaths			
Patients who had a fatal (treatment-emergent) adverse event, n (%)	1 (1.0%)	4 (4.1%)	0

[18] $MYD88^{L265P}$ = L265P mutation of *MYD88* gene.

	Cohort 1 zanubrutinib (n=101)	Cohort 1 ibrutinib (n=)	Cohort 2 zanubrutinib (n=28)
Treatment-emergent adverse events (TEAEs)			
Subjects with at least one TEAE, %	97	90	85.7
Most common TEAEs (>10% in either arm):			
diarrhoea, %	*20.8*	*31.6*	*28.6*
upper respiratory tract infection,%	*28.6*	*23.8*	*21.4*
neutropenia, %	*24.8*	*12.2*	*14.3*
contusion, %	*12.9*	*23.5*	*21.4*
muscle spasms, %	*9.9*	*23.5*	*14.3*
peripheral oedema, %	*8.9*	*19.4*	*14.3*
epistaxis, %	*12.9*	*19.4*	*3.6*
constipation, %	*7.1*	*15.8*	*14.3*
fatigue, %	*18.8*	*15.3*	*14.3*
cough, %	*12.9*	*17.3*	*17.9*
rash,%	*12.9*	*16.3*	*10.7*
arthralgia, %	*12.9*	*16.3*	*10.7*
hypertension, %	*10.9*	*16.3*	*10.7*
nasopharyngitis	*10.9*	*7.1*	*7.1*
dyspnoea,%	*13.9*	*6.1*	*3.6*
nausea, %	*14.9*	*13.3*	*3.6*
headache, %	*14.9*	*11.2*	*10.7*
atrial fibrillation, %	*2*	*14.3*	
back pain, %	*13.9*	*6.1*	*14.3*
vomiting, %	*8.9*	*13.3*	
dizziness, %	*12.9*	*9.2*	*3.6*
pyrexia, %	*12.9*	*12.2*	*21.4*
pneumonia %	*2*	*12.2*	
pain in extremity, %	*10.9*	*7.1*	
anaemia, %	*11.9*	*10.2*	*21.4*
urinary tract infection,%	*9.9*	*10.2*	*14.3*
thrombocytopenia, %	*9.9*	*10.2*	*10.7*
haematuria %	*6.9*	*10.2*	
Serious TEAEs (SAE)			
Subjects with at least one SAE, %	39.6	40.8	39.3
Most common SAEs (>2% in either arm, and > 1 patient):			
Febrile neutropenia, %	*3*	*0*	
neutropenia, %	*3*	*0*	
influenza %	*3*	*1*	
pneumonia, %	*1*		*10.7*
Higher grade TEAEs			
Subjects with at least 1 ≥Grade 3 AE, %	58.4	63.3	64.3
Most common Grade 3-4 AEs (≥5% in either arm):			
hypertension, %	*5.9*	*11.2*	
pneumonia %	*1.0*	*7.1*	
neutropenia %	*15.8*	*8.2*	
Treatment-related AEs (%)			
Subjects with at least 1 TRAE	79.2	85.7	78.6
Most common TRAEs (>= 10% in either arm)			
neutropenia, %	*21.8*	*11.2*	*10.7*
diarrhoea, %	*10.9*	*23.5*	*17.9*
contusion, %	*9.9*	*22.4*	*14.3*
epistaxis,%	*6.9*	*14.3*	
hypertension, %	*5.9*	*13.3*	
Upper respiratory tract infection	*5.9*	*13.3*	

	Cohort 1 zanubrutinib (n=101)	Cohort 1 ibrutinib (n=)	Cohort 2 zanubrutinib (n=28)
atrial fibrillation,%	*1*	*13.3*	
rash,%	*7.9*	*11.2*	
muscle spasm, %	*6.9*	*11.2*	
fatigue, %	*10.9*	*9.2*	
Adverse events of special interest			
atrial fibrillation, %	*2.0*	*14.3*	
hypertension,%	*10.9*	*17.3*	
second primary skin malignancy, %	*7.9*	*9.2*	
Adverse events leading to discontinuation (%)	4.0	9.2	7.1
Adverse events leading to dose reductions (%)	13.9	23.5	7.1
Adverse events leading to dose interruptions (%)	46.5	56.1	50

Abbreviations: AE = adverse event; n = sample size; SAE = serious adverse event; TEAE = treatment emergent adverse event; TRAE = treatment related adverse event.

Grade ≥ 3 atrial fibrillation or atrial flutter events were reported in 4 patients in the ibrutinib arm, zero in the zanubrutinib arm, but no patient discontinued study treatment as result. In patients with a history of atrial fibrillation or flutter, zero of 12 patients from the zanubrutinib arm and 3 of 8 patients from the ibrutinib arm had further events.

There were no consistent trends observed over time in the serum levels of immunoglobulin A (IgA) or immunoglobulin G (IgG) for patients in either treatment arm compared to Baseline.

Study BGB-3111-AU-003

The median duration of treatment for the WM population was 26 months (23.2 months in the treatment-naïve WM population and 28.8 months in relapse/refractory (r/r) WM population).

All patients with WM experienced at least one treatment-emergent adverse events, most commonly upper respiratory tract infection (51.3% overall; 45.8% of the treatment-naïve WM group, 53.7% of the r/r WM group) and contusion (32.1% overall; 29.2% in the treatment-naïve WM group, 33.3% in the r/r WM group). Other AEs occurring in > 15% of patients included cough, urinary tract infection, diarrhoea, headache, rash, back pain, fatigue, and constipation.

Around 75% of treatment-naïve WM and r/r WM patients reported treatment-related adverse events (TRAEs). Most commonly were contusion (24.4% overall; 25.0% and 24.1% in the treatment-naïve and r/r WM groups, respectively), neutropenia (10.3% overall; 12.5% and 9.3% in the treatment-naïve and r/r WM groups, respectively), and diarrhoea (6.4% overall; 4.2% and 7.4% in the treatment-naïve and r/r WM groups, respectively).

Haematological grade ≥ 3 events were reported for anaemia (15.4%), leukopenia (9.0%), lymphocytopaenia (23.1%), neutropenia (20.5%) and thrombocytopenia (7.7%).

Deaths occurred in 11.5% but only one patient, with septic arthritis, had events considered related to zanubrutinib. At least one serious adverse event (SAE) occurred in 50% of patients. The most common event was cellulitis (6.4%). Treatment related discontinuations were reported for 14.1% of the WM group, but no single event was reported for more than one patient.

Atrial fibrillation/flutter occurred in 5.1%. Bleeding events occurred in 62.8% and major haemorrhage occurred in 5.1%. None were fatal. Second primary malignancies occurred in 24.4% (mostly basal cell carcinoma, 11.5%). Infection occurred in 89.7%, most commonly

upper respiratory tract infection. Opportunistic infections occurred in 5.1% and fatal infections in 3.8%.

Study BGB-3111-210

The safety in Study BGB-3111-210 was consistent with the safety findings of Study BGB-3111-302 (the ASPEN trial).

Other studies

Severe cutaneous skin reactions is of concern due to possible off-target effects on epidermal growth factor receptors (EGFR). One fatal case of toxic epidermal necrolysis was reported in the Phase I study of B-cell malignancies.

Updated safety data

Updated safety data were provided for the studies contributing to the total safety data for zanubrutinib in a report provided on 29 March 2021 in response to TGA questions. Cut-off dates for the analyses varied by the individual contributory studies. These data were not evaluated in the clinical evaluation report. Data were provided separately for study are derived from Study BGB-3111-302, for the whole WM population that included data from 44 patients from Study BGB-3111-210 and 2 patients from Study BGB-3111-1002, studies that included only Chinese patients, and for a broad zanubrutinib data set from a variety of haematological malignancies. A brief summary of the updated data is included below.

Study BGB-3111-302 (data cut-off of 31 August 2020)

Cohort 1

- Median duration of exposure for ibrutinib was 29.9 months for the ibrutinib arm and 30.3 months for zanubrutinib arm.
- 32.7% of the ibrutinib arm and 24.8% of the zanubrutinib arm discontinued study treatment (median time to discontinuation 11.5 and 13.4 months, respectively).
- 15.3% of the ibrutinib arm and 5% of the zanubrutinib arm discontinued due to AEs and 8.2% of the ibrutinib arm and 9.9% of the zanubrutinib arm discontinued due to progressive disease.
- Adverse events reported in >20% of patients were:
  - Ibrutinib arm: diarrhoea (33.7%), upper respiratory tract infection (31.6%), muscle spasms (27.6%), contusion (25.5%), hypertension (21.4%), and epistaxis, peripheral oedema, and arthralgia (20.4% each).
  - Zanubrutinib arm: upper respiratory tract infection (30.7%), neutropenia (26.7%), fatigue (24.8%), diarrhoea (21.8%).
- Deaths were reported for 8.2% of the ibrutinib arm and 8.9% of the zanubrutinib arm
- Serious adverse events were reported for 46.9% of the ibrutinib arm and 48.5% of the zanubrutinib arm:
  - Ibrutinib arm: pneumonia (11.2%); atrial fibrillation (5.1%); sepsis (4.1%); pyrexia, syncope, and pericarditis (3.1% each); and urinary tract infection, upper respiratory tract infection, pleural effusion, loss of consciousness, acute myocardial infarction, cholecystitis, and bladder transitional cell carcinoma (2.0% each).
  - Zanubrutinib arm: influenza, febrile neutropenia, neutropenia, and pyrexia (3.0% each); and pneumonia, lower respiratory tract infection, sepsis, pleural effusion, anaemia, thrombocytopenia, and basal cell carcinoma (2.0% each).

Whole of Waldenström's macroglobulinaemia population

- Median duration of exposure was 31.5 months.
- 34.8% discontinued due to progressive disease (15.8%) and AEs (10.7%).
- Adverse events of any grade reported in > 20% were upper respiratory tract infection (36.8%) and diarrhoea (23.3%).
- Deaths occurred in 12.6%.
- Serious adverse events were reported in 51%. Events reported in ≥ 2% of patients were pneumonia (7.5%), cellulitis (2.8%), febrile neutropenia and pyrexia (2.4% each), and pleural effusion (2.0%).

Risk management plan

The sponsor has submitted EU-RMP version 0.1 (dated 11 May 2020; DLP 31 December 2019) and ASA version 1.0 (dated 1 June 2020) in support of this application. No differences are planned between Australia and EU with respect to pharmacovigilance or risk minimisation activities. Evaluation of EU application and EU-RMP is in progress.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5.[19]

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Haemorrhage	ü[1]	–	ü	–
Important potential risks	Cardiac arrhythmia, mainly presented as atrial fibrillation and flutter	ü[1]	–	ü	–
	Cytopenia	ü	–	ü	–
	Infections	ü	–	ü	–
	Second primary malignancies	ü	–	ü	–
	Drug-drug interaction	ü	–	ü	–

[19] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Teratogenicity	ü[1]	–	ü	–
Missing information	Safety in patients with severe hepatic impairment	ü	–	ü	–
	Safety in patients with severe renal impairment/on dialysis	ü	–	ü	–
	Long-term safety (> 2 years)	ü	–	–	–
	Safety in paediatric patients	ü	–	ü	–
	Safety in pregnancy and lactation	ü	–	ü	–

1 Targeted follow-up questionnaires

- The RMP summary of safety concerns is considered acceptable from an RMP perspective. Risks are associated with class effects of BTK inhibitors. The sponsor is requested to amend the nonclinical part of the RMP safety specification in an RMP Update to the TGA to address particulars of repeated dose toxicity.
- Routine pharmacovigilance activities are proposed for all safety concerns. No additional pharmacovigilance activities are proposed, but the sponsor agrees to implement targeted follow-up questionnaires to address risks of haemorrhage, cardiac arrhythmias, and teratogenicity as an enhancement to routine pharmacovigilance activities. The pharmacovigilance plan is considered acceptable from an RMP perspective.
- Routine risk minimisation measures are proposed for all concerns, except long-term safety which is being further characterised in sponsor's ongoing clinical trials program. These measures are considered sufficient to manage risks associated with Brukinsa use. As requested, the sponsor has improved the risk communication to consumers in the Consumer Medicines Information (CMI) document to align with the PI and has also added additional reproductive toxicity precautions. The risk minimisation plan is considered acceptable from an RMP perspective.

Risk-benefit analysis

Delegate's considerations

Waldenström's macroglobulinaemia is a rare clonal B-cell lymphoproliferative disorder characterised by lymphoplasmacytic bone marrow infiltration and the presentence of monoclonal IgM paraprotein, whose symptoms arise from tumour infiltration, the IgM component activity and/or deposition of paraprotein in in organs. It exhibits some heterogeneity and while generally with an indolent course, may rarely transform to diffuse B-cell lymphoma. While a number of treatments are currently in use none is considered

curative. The sponsor is seeking an indication in the relapsed or refractory setting or first line in patients who are ineligible for chemoimmunotherapy.

The main efficacy findings for zanubrutinib for the proposed indications are derived from Cohort 1 of the ASPEN trial (Study BGB-3111-302). This was a head-to-head comparison with ibrutinib, the first-in-class BTK inhibitor that is registered for use in the proposed population. Zanubrutinib was not superior to ibrutinib for very good partial response (VGPR) or complete response (CR) in the relapse/refractory (r/r) Waldenstrom's macroalbuminaemia (WM) population. The absolute results for the overall Cohort 1 population are similar to the r/r population and the nominal p-value for the comparison was 0.09.

The key secondary endpoint was not a reassessment of the parameters of the primary endpoint of VGPR/CR in a non-inferiority comparison. It was for a broader endpoint of major response rate that includes patients with partial response (PR), VGPR or CR, and therefore was designed test a slightly different hypothesis. Notwithstanding the failure of the primary endpoint that renders all subsequent comparisons in the statistical analysis descriptive, based on the pre-specified non-inferiority margin of the lower bound of the 95% CI being greater than -12%, zanubrutinib was not non-inferior to ibrutinib in the r/r WM population and in the overall WM population.

The comparison of zanubrutinib and ibrutinib in patients with VGPR or CR as a non-inferiority analysis was a *post hoc* analysis. It is in this post-hoc analysis using a -4.5% margin and using data for the overall and the r/r populations the results for zanubrutinib and ibrutinib fell within the non-inferiority margin. Until an early protocol change, this had been the primary endpoint of the study.

The missed primary endpoint and key secondary endpoint raises some uncertainty regarding how these results should be interpreted from a clinical and regulatory perspective, in particular, whether they have met the threshold for supporting full registration in the setting of a rare disease.

Only 19 treatment-naïve patients were included in the zanubrutinib arm of the ASPEN trial (Study BGB-3111-302) and 24 chemotherapy ineligible patients in Study BGB-3111-AU-003. Of those on the treatment, after 5 discontinued the study only 14 remained on treatment. Patient numbers in this subgroup are limited. From Study BGB-3111-AU-003 33% achieved a VGPR and most achieved a major response. It is difficult to draw firm conclusions on the efficacy of zanubrutinib in this setting based on so few patients, although there is no specific concern.

The ASPEN trial (Study BGB-3111-302) Cohort 2 results in *MYD88^{WT}* WM variant did not raise specific concerns but these were not part of the primary analysis of the study.

Important exclusions from the study were patients with cardiac disease, relevant for the comparator ibrutinib, but that limits the assessment of cardiac safety in patients with an increased background risk. The sponsor proposes to include a brief precautionary statement in Section 4.4 of the Product Information of Brukinsa (zanubrutinib).

Another limitation of the study was the exclusion of patients with CNS disease. Although this is a rare form of a rare condition, it has been an area of interest for ibrutinib. The nonclinical evaluator found there was minimal penetration of the blood brain barrier with zanubrutinib.

The sponsor has provided updated efficacy analyses from the ongoing study data. As the study has progressed the number of susceptible patients on treatment in each treatment arm has diminished, potentially adding bias to the results and uncertainty to the interpretation of the results. In addition, the analysis was based on investigator assessment, and small but important differences were seen between the investigator assessment and the independent review in the primary analysis.

Common adverse events include neutropenia, thrombocytopenia, upper respiratory tract infection, diarrhoea other infections hyperglycaemia, hyperuricaemia, hypokalaemia, and pyrexia. Neutropenia occurred more commonly with zanubrutinib (24.8% versus 12.2% for ibrutinib in the ASPEN trial (Study BGB-3111-302)). The neutropenia appeared for most patients manageable (although febrile neutropenia occurred in 3% of patients). Conversely, there were fewer reported atrial fibrillation/flutter events with zanubrutinib. In Cohort 1, 14.3% of ibrutinib patients, including Grade 3 events or higher in 4.1%, and a further 2% had atrial flutter and 2% of zanubrutinib patients had atrial fibrillation events. Stevens-Johnson syndrome is mentioned in the ibrutinib product information and one fatal case of toxic epidermal necrolysis was reported in the zanubrutinib data set.

The sponsor has undertaken a head-to-head comparison with ibrutinib. While this approach is commendable, it has its challenges for zanubrutinib in demonstrating efficacy for regulatory purposes. It appears to produce numerically similar results to ibrutinib, but a degree of uncertainty is introduced because of the outcomes of the pre-specific comparisons with ibrutinib in the ASPEN trial (Study BGB-3111-302).

The efficacy results however for zanubrutinib alone are numerically greater but of the same order of magnitude as those accepted for ibrutinib for its initial registration for use in WM. If considered in isolation of the comparator arm of the study, taking into account the rarity of the condition and the clinical value of alternatives to ibrutinib there may be a place for zanubrutinib in the landscape of WM treatment. In correspondence dated 28 June 2021 the sponsor provided the Delegate with a copy of the NCCN guidelines V1.2022;[20] dated 26 June 2021 that include zanubrutinib as an option in the WM treatment algorithm, suggesting clinical acceptance in this setting.

From the nonclinical findings there is binding to epidermal growth factor receptors (EGFR) and tec protein tyrosine kinase (TEC), the targets thought contributory to the bleeding and atrial fibrillation associated with the class. The performance of zanubrutinib in a real world setting in comparison with ibrutinib is yet uncertain, particularly in a broader population with more underlying cardiovascular risk. The lower risk of cardiovascular events with zanubrutinib may be offset to a certain extent by an increased risk of neutropenia and would be a factor to consider at an individual patient level.

Proposed action

The Delegate has yet to make a decision on the registration of this product. The advice of the Advisory Committee on Medicines (ACM) is sought regarding the evidence supporting the efficacy of zanubrutinib for the proposed indication.

If a decision were taken to register zanubrutinib for the proposed indications, the following conditions of registration would be imposed. The sponsor should be aware that additional conditions of registration may be imposed, subject to the advice of the ACM.

The Delegate was (at the time) yet to make a decision on the registration of this product. The advice of the ACM is sought regarding the evidence supporting the efficacy of zanubrutinib for the proposed indication.

If a decision were taken to register zanubrutinib for the proposed indications, the following conditions of registration would be imposed. The sponsor should be aware additional conditions of registration may be imposed, subject to the advice of the ACM.

- The Brukinsa EU-RMP (version 0.1, dated 11 May 2020, data lock point (DLP) 31 December 2019), with Australian specific annex (ASA) (version 0.1, dated

[20] National Comprehensive Cancer Network (NCCN), Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma Guidelines, Version 1.2022.

1 June 2020), included with Submission PM-2020-02814-1-6, to be revised to the satisfaction of the TGA, will be implemented in Australia.

- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Brukinsa (zanubrutinib)] is to be included in the Black Triangle Scheme. The PI and CMI for Brukinsa must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- Provide the final study report of Study BGB-3111-206 for evaluation.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***The Brunkisa(zanubrutinib) capsule is almost 22 mm long. Given the typical age of the Waldenström's macroglobulinaemia patients and their potential comorbidities, does the sponsor have guidance for patients/health professionals advising patients if the patient is unable to swallow the tablet whole?***

The possibility of opening the capsules before administration was evaluated to assess the risk of affecting bioavailability of zanubrutinib due to variations in recovery of the capsule content and unknown stability of capsule content in specific liquids and food (for example, apple sauce, yogurt and Coca-Cola). Results indicate the content in the capsules can be completely and consistently recovered in a laboratory setting, and the capsule content is stable for up to 24 hours in the assessed liquids and food. However, results from controlled *in vitro* studies may not translate well into the real-world setting due to uncertainty in how patients (mostly elderly populations) would handle open capsules. As such, there is a risk of lower bioavailability resulting in patients not receiving the full dose due to loss of content in capsule handling, as well as loss of content during the administration of the content with liquid and/or food.

Due to lack of clinical data regarding opening capsules, the sponsor recommends that patients follow the administration procedure as described in the proposed label to swallow the capsules whole with water, and not to open, break, or chew the capsules.

2. ***Please provide an update of the current status of zanubrutinib for Waldenström's macroglobulinaemia internationally.***

A full summary of the global status of zanubrutinib is provided to the TGA. Applications for zanubrutinib in Waldenström's macroglobulinaemia have been submitted in Canada, the EU, Israel, South Korea, Taiwan and the USA. Health Canada approved the application under their Priority Review pathway for the following indication:

> *Brukinsa (zanubrutinib) is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).*

The submissions to the EU, Israel, Taiwan, South Korea and the USA are still under review.

Advisory Committee considerations[21]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Please advise on the interpretation of the evidence from the pivotal trial given the study failed to meet its primary endpoint at the prespecified interim analysis.***

The ACM noted that the primary endpoint for the APSEN trial (Study BGB-3111-302) is the superiority of zanubrutinib over ibrutinib in the proportion of patients who achieve a very good partial response (VGPR) or better. The ACM were of the opinion that this primary outcome was a very high bar to set in a disease where few complete responses (CRs) are usually seen. The ACM noted that with 201 participants, the APSEN trial is considered a large study for WM due to the rarity of the disease.

The ACM commented that the difference in VGPR/CR was 9.2% in favour of zanubrutinib and agreed that zanubrutinib is not likely to be clinically inferior to ibrutinib. The ACM noted that multiple subsequent secondary analyses also concur that zanubrutinib had similar outcomes to ibrutinib.

The ACM commented that zanubrutinib responses appear to improve over time, as evident in Study BGB-3111-AU-003, with the best response of VGPR/CR being 32.9% at 12 months compared to 43.8% at 24 months.[22] Thus, the ACM advised that this should be followed up in the ASPEN trial to determine if the response to zanubrutinib improves with time.

In summary, the ACM agreed that the interpretation of the overall evidence is supportive of the efficacy of zanubrutinib.

2. ***If zanubrutinib were to be approved, has sufficient evidence been presented to support the first line use in patients unsuitable for chemotherapy?***

The ACM commented that due to the rarity of the disease, there is no standard of care for WM. The treatment plan is decided on a case by case basis between patients and their physicians. The ACM noted that international guidelines include ibrutinib monotherapy as first line or subsequent treatment for WM, and agreed that zanubrutinib has shown efficacy in both initial and subsequent treatment for WM. Due to the limited treatment

[21] The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

[22] Trotman, J et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up, Blood, 2020 Oct 29; 136(18): 2027–2037.

options for chemotherapy unsuitable patients, the ACM advised that zanubrutinib could be considered as a first line treatment for chemotherapy-unsuitable WM patients.

The ACM were of the opinion that there is insufficient evidence to support the use of one therapy over another for the treatment of WM.

3. If zanubrutinib were to be registered for use in Waldenström's macroglobulinaemia does the ACM recommend any conditions of registration in addition to those already proposed?

The ACM advised that they were no specific issues that would require any conditions of registration in addition to those already proposed.

However, the ACM advised that patients with central nervous system disease such as Bing-Neel syndrome, and WM patients that have transformed to having aggressive lymphoma are not suitable for zanubrutinib treatment, emphasising there are no significant data on these cohorts as they were excluded from the main studies.

4. The ACM is invited to provide advice on any other matters it considers may contribute to the decision.

The ACM regarded zanubrutinib to be an effective and safe addition to the available treatments for WM.

The ACM commented that zanubrutinib had a lower incidence of atrial flutter/fibrillation, bleeding, pneumonia and peripheral oedema compared to ibrutinib, hence may be a more suitable option for the elderly patient demographic.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Brukinsa 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 chemoimmunotherapy.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Brukinsa (zanubrutinib) 80 mg, capsule, bottle, indicated for:

> ***Waldenström's macroglobulinemia (WM)***
>
> *Brukinsa 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.*

Specific conditions of registration applying to these goods

- Brukinsa (zanubrutinib) is to be included in the Black Triangle Scheme. The PI and CMI for Brukinsa must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Brukinsa EU-risk management plan (RMP) (version 0.1, dated 11 May 2020, data lock point 31 December 2019), with Australian specific annex (version 0.1, dated 1 June 2020), included with Submission PM-2020-02814-1-6, to be revised to the satisfaction of the TGA, will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Provide the final study report of Study BGB-3111-206 for evaluation.

Attachment 1. Product Information

The PI for Brukinsa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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