Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Brukinsa

Active ingredients: Zanubrutinib

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 therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The 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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications 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
AESI	Adverse event of special interest
aPTT	Activated partial thromboplastin time
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under the concentration time curve
$AUC_{0-\infty}$	Area under the concentration time curve from time zero to infinity
$AUC_{0-24h,ss}$	Area under the concentration time curve from time zero to 24 hour at steady state
BTK	Bruton's tyrosine kinase
CVAD	Cyclophosphamide/vincristine/doxorubicin/dexamethasone
CHOP	Cyclophosphamide/doxorubicin/vincristine/prednisone
CI	Confidence interval
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration at steady state
CMI	Consumer Medicines Information
C_{min}	Minimum concentration
$C_{min,ss}$	Minimum concentration at steady state
CR	Complete response
CT	Computerised tomography
CYP	Cytochrome P450
DLP	Data lock point
DOR	Duration of response
EGFR	Epidermal growth factor receptor

Abbreviation	Meaning
EU	European Union
FDA	Food and Drug Administration (United States of America)
GVP	Good Pharmacovigilance Practices
INR	International normalised ratio
IRC	Independent Review Committee
ITK	Interleukin-2 inducible T-cell kinase
LDi	Longest transvers diameter of lesion
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI-b	Mantle Cell Lymphoma Prognostic Index (biological) score
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
ORR	Overall response rate
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PR	Partial response
PSUR	Periodic safety update report
QTcF	QT-interval corrected using Fridericia's formula
R-CHOP	Rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone
RMP	Risk management plan
r/r	Relapsed or refractory
SAE	Serious adverse event
SMQ	Standardised Medical Dictionary for Regulatory Activities queries

Abbreviation	Meaning
TTR	Time to response
US(A)	United States (of America)
WM	Waldenström's macroglobulinaemia

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Brukinsa
Active ingredient:	Zanubrutinib
Decision:	Approved for provisional registration
Date of decision:	8 October 2021
Date of entry onto ARTG:	8 October 2021
ARTG number:	338475
, *Black Triangle Scheme:*	Yes. As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
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:	***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.*
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.

	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 submission 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 mantle cell lymphoma (MCL) who have received at least one prior therapy.*
>
> *This indication was approved via the provisional approval pathway, based on the objective response rate in two single-arm trials. Continued approval for this indication depends on verification and description of clinical benefit in confirmatory trials.*

Mantle cell lymphoma (MCL) is an aggressive, phenotypically distinct, mature B-cell neoplasm that comprises approximately 4% and 7% to 9% of all malignant lymphomas in the United States of America (USA) and Europe, respectively. Australian Institute of Health and Welfare 2021 data reported the age-adjusted incidence of non-Hodgkin lymphoma in 2017 was 19.8 per 100,000 and projected it reach 20.4 per 100,000 population.[1] MCL comprises around 5% to 10% of non-Hodgkin lymphoma. It is typically diagnosed in the US and Europe above 60 years of age with a male predominance (2.5 to 3.1). Approximately 10% to 20% of patients with MCL present with bone marrow involvement, and 'B symptoms' (fever, night sweats, and weight loss) are present in approximately 40% of patients. Extranodal involvement of the gastrointestinal tract, particularly the colon, is also common; however, central nervous system involvement is uncommon.

A hallmark of MCL is a reciprocal translocation t(11;14)(q13;32) that involves *CCND1*, *PRAD1* and *bc11*, resulting in over-expression of *CCND1* which encodes cyclin D1. Cyclin D1 is involved in normal cell growth but in excess promotes the uncontrolled growth of the mantle cells. The translocation or the expression of cyclin D1 distinguish MCL from other B cell lymphomas and is found in over 90% of all diagnosed cases. Of other genetic variants, alterations in p53 are more common in the pleomorphic and blastoid variants.[2]

[1] Australian Institute of Health and Welfare (AIHW) Cancer Data in Australia, last updated on 1 July 2022. Available at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-incidence-by-age-visualisation.
[2] Schieber, M. et al. Current Overview and Treatment of Mantle Cell Lymphoma, *F1000Res*, 2018; 7: F1000 Faculty Rev-1136.

In symptomatic MCL patients and those with high tumour burden (Stages III to IV), induction chemo-immunotherapy (for example, R-CHOP combination therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or the combination of rituximab and bendamustine) is typically initiated immediately upon diagnosis. More intensive combination chemo-immunotherapy regimens (for example, hyper-fractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone (hyper-CVAD) with or without rituximab) may be used in healthier patients, and stem cell transplant may be considered in younger, fit patients. Due to the advanced age and comorbidities for many MCL patients, dose intensified chemotherapy is often contraindicated both at initial diagnosis and relapse, and therefore, less intensive chemotherapy is often utilised, primarily as palliative care. Patients with relapsed or refractory (r/r) MCL have poor outcomes, with survival of approximately one to three years.

Targeting B-cell receptor signalling through Bruton's tyrosine kinase (BTK) inhibition represents a new approach for the management of B-cell malignancies, including MCL. 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, has received accelerated approval by the US Food and Drug Administration (FDA) for the treatment of patients with MCL who have received at least one prior therapy. Imbruvica (ibrutinib)[3] was first registered on the Australian Register of Therapeutic Goods (ARTG) on 20 April 2015.[4] A second BTK inhibitor, acalabrutinib, received accelerated approval by the US FDA in October 2017 for the treatment of patients with MCL who have received at least one prior therapy. Calquence (acalabrutinib)[5] was first registered on the ARTG on 21 November 2019.[6,7] Results of confirmatory studies for ibrutinib and acalabrutinib have not yet been reported.

According to the sponsor, despite improvements in outcome for r/r MCL patients treated with earlier generation BTK inhibitors, complete response (CR) rates associated with these therapies are still relatively low and response durations unacceptably short. In addition, toxicity considerations (for example, atrial fibrillation, bleeding diarrhoea) limit the extent of exposure, particularly to ibrutinib, thereby jeopardising the ability to achieve complete and sustained BTK suppression in responsive patients. The sponsor is therefore of the opinion that 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.

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, it 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.

[3] Imbruvica was first registered on the ARTG on 20 April 2015 (ARTG number: 228499).
[4] AusPAR for Imbruvica (ibrunitib) new chemical entity, published on 5 April 2016. Available at: https://www.tga.gov.au/auspar/auspar-ibrutinib.
[5] Calquence was first registered on the ARTG on 21 November 2019 (ARTG number: 321419).
[6] AusPAR for Calquence (acalabrutinib) new chemical entity, published on 3 March 2020. Available at: https://www.tga.gov.au/auspar/auspar-acalabrutinib.
[7] AusPAR for Calquence (acalabrutinib) extension of indications, published on 10 March 2020. Available at: https://www.tga.gov.au/auspar/auspar-acalabrutinib-0.

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-2020-02814-1-6) was also under evaluation for the following indication:

> *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.*

Brukinsa (zanubrutinib) was considered a new chemical entity for both submissions. An AusPAR for this parallel submission is also available on the TGA website).[8]

At the time the TGA considered this submission, a similar submission had been approved in the USA on 14 November 2019. Similar submissions were under consideration in Canada (submitted on 14 August 2020) and Singapore (submitted on 25 November 2020).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	27 June 2019	Approved on 14 November 2019	*Brukinsa is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.* *This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*
Canada	14 August 2020	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 PI/CMI search facility.

[8] AusPAR for Brukinsa (zanubrutinib) new chemical entity, Submission PM-2020-02814-1-6, published on 17 August 2022. Available at: https://tga.govcms.gov.au/resources/auspar/auspar-brukinsa-0.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2020-03076-1-6

Description	Date
Determination (Provisional)[9]	17 June 2020
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	1 March 2021
Second round evaluation completed	15 April 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 July 2021
Sponsor's pre-Advisory Committee response	14 July 2021
Advisory Committee meeting	5 and 6 August 2021
Registration decision (Outcome)	8 October 2021
Completion of administrative activities and registration on the ARTG	8 October 2021
Number of working days from submission dossier acceptance to registration decision*	250

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

As this submission was evaluated in parallel with another similar submission, components of the quality and nonclinical evaluation for Brukinsa (zanubrutinib) were considered generalisable to both submissions. See the AusPAR for Submission PM-2020-02814-1-6

[9] As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.
The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available.

for further information on the quality and nonclinical findings applicable to this submission.[8]

Quality

The quality evaluator recommended approval from a chemistry and quality perspective.

Further information on the quality evaluation of Brukina (zanubritinib) immediate release 80 mg hard capsules is available in the AusPAR for Submission PM-2020-02814-1-6.[8]

Nonclinical

The nonclinical evaluator did not raise objections to the registration of zanubrutinib from a nonclinical perspective.

Further information on the nonclinical evaluation of Brukina (zanubritinib) immediate release 80 mg hard capsules is available in the AusPAR for Submission PM-2020-02814-1-6.[8]

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- Two Phase I studies: Study BGB-3111-AU003, Study BGB-3111-1002
- Four Phase II studies: Study BGB-3111-206, Study BGB-3111-AU003, Study BGB-3111-205, and Study BGB-3111-210
- Eight clinical pharmacology studies were presented in support of zanubrutinib in MCL. General pharmacology was described in Submission PM-2020-02814-1-6 (see the corresponding AusPAR).[8]

Pharmacology

Pharmacokinetics

Study BGB-3111-AU-003 dosed patients at 40, 80, 160, and 320 mg once daily and 160 mg twice daily. The maximum tolerated dose was not reached, and no dose limiting toxicities were observed during the dose escalation part of the study. Zanubrutinib pharmacokinetics (PK) was approximately dose proportional between 40 mg and 320 mg once daily. The terminal elimination half-life was approximately 2 to 4 hours at doses of 160 mg twice daily or 320 mg once daily.

Co-administration of zanubrutinib with a strong cytochrome P450 (CYP)[10] 3A inhibitor itraconazole (200 mg once daily for 4 days) increased exposure of zanubrutinib by 3.8-fold

[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.
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

for area under the concentration time curve from time zero to infinity ($AUC_{0-\infty}$)) and 2.6-fold for maximum concentration (C_{max}).

Population pharmacokinetics data

The PK of zanubrutinib was described in a two-compartment model with sequential zero order the first order absorption and first-order elimination from the central compartment described the PK of zanubrutinib.

Physiologically based PK simulations suggested that co-administration of multiple doses of a moderate CYP3A inhibitor increased the maximum concentration at steady state ($C_{max,ss}$) and area under the concentration time curve (AUC) of zanubrutinib by approximately 2-fold. Co-administration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg once daily for 8 days) decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0-\infty}$ and 12.6-fold for C_{max} in healthy subjects. Physiologically based PK simulations suggested a moderate CYP3A inducer could decrease the C_{max} and AUC of zanubrutinib by approximately 2- to 3-fold.

Pharmacodynamics

Nearly full BTK occupancy was seen in peripheral blood mononuclear cells from Study BGB-3111-AU-003 patients at 40 to 320 mg once daily. BTK occupancy ≥ 80% was observed in on treatment lymph node biopsies from patients receiving 160 mg twice daily and 320 mg once daily. Median BTK occupancy at steady state trough was 100% with 160 mg twice daily versus 94% with 320 mg once daily. Hence, 160 mg twice daily was selected as the study dose regimen for Study BGB-3111-206.

In Study BGB-3111-AU-003 the maximum tolerated dose was not reached and no dose limiting toxicities were observed during the dose escalation part of the study.

Efficacy

Clinical efficacy was supported by two studies: Study BGB-3111-206 in patients with relapse or refractory (r/r) mantle cell lymphoma (MCL) and Study BGB-3111-AU-003 in B-cell malignancies that included 37 patients with r/r MCL.

Study BGB-3111-206 (pivotal study)

Study BGB-3111-206 is an ongoing, Phase II, single arm, open label study in 86 adult Chinese patients with r/r MCL who had received at least one but less than 5 prior line(s) of therapy.

Study treatments

Patients were treated with oral zanubrutinib 160 mg (2 x 80 mg capsules) twice daily continuously for up to 3 years or until progressive disease, unacceptable toxicity, death, withdrawal of consent or study termination.

Outcome measurements

The primary and secondary endpoints were assessed according to the Lugano classification.[11] Screening tumour assessments included a contrast computerised

therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[11] **Lugano classification** for staging of lymphomas
Stage I - Involvement of a single lymph node region (for example, cervical, axillary, inguinal, mediastinal) or lymphoid structure such as the spleen, thymus, or Waldeyer's ring.
Stage II - Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm.
Stage III - Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm.

tomography (CT) scan (or magnetic resonance imaging (MRI)) of the neck, chest, abdomen and pelvis, fluorodeoxyglucose-positron emission tomography (PET) scan, bone marrow biopsy and endoscopic gastrointestinal biopsy (for suspected gastrointestinal involvement). For patients with fluorodeoxyglucose avid disease at screening, PET and CT or MRI were repeated 12 weekly for the first 96 weeks, then 24 weekly thereafter until progressive disease or end of study. PET and contrast CT scans were required for complete response (CR) confirmation for all subjects. Endoscopy was mandatory for CR confirmation for any patient with a documented history of gastrointestinal involvement. Bone marrow biopsy was required for CR confirmation in patients with bone marrow tumour involvement prior to study drug.

Inclusion and exclusion criteria

Key inclusion criteria

- Pathological diagnosis of MCL to include evidence for morphological and cyclin D1 and B-cell markers and CD5 co-expression or t(11;14). Tumour tissue or unstained slides sent to central laboratory for chronic myeloid leukaemia confirmation.
- Age 18 to 75 years of age.
- Eastern Cooperative Oncology Group (ECOG)[12] Performance Status score of 0 to 2.
- Measurable disease by CT/MRI
- At least one but less than 5 prior regimens for MCL.
- Documented failure to achieve any response or documented progressive disease during or after response to most recent treatment.
- Neutrophils ≥ 1 x 10^9/L independent of growth factor support ≤ 7 days of study entry.
- Platelets ≥ 75 x 10^9/L independent of growth factor support or transfusion ≤ 7 days of study entry (platelets ≥ 50 x 10^9/L if bone marrow involvement).
- Creatinine clearance of ≥ 30 mL/min
- Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x upper limit normal (ULN), total bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome).
- International normalised ratio (INR) ≤ 1.5 and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
- Relapse ≥ 6 months after autologous stem cell transplantation if no active related infections.

Key exclusion criteria

- Current or history of central nervous system lymphoma.

Stage IV - Diffuse or disseminated involvement of 1 or more extranodal organs or tissue beyond that designated 'E' with or without associated lymph node involvement.

[12] **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

- Prior BTK inhibitor use.
- Prior corticosteroids ≥ prednisone 10 mg/day or equivalent with antineoplastic intent ≤ 7 days of start of study drug. Prior chemotherapy, targeted therapy, or radiation therapy ≤ 3 weeks, antineoplastic therapy with Chinese herbal medication or antibody based therapies within 4 weeks of the start of study drug.
- Toxicity from prior chemotherapy unless recovered to ≤ Grade 1 (except for alopecia, or meeting neutrophil or platelet inclusion criterion).
- Currently clinically significant active cardiovascular disease such as uncontrolled arrhythmia, uncontrolled hypertension, congestive heart failure, any New York Heart Association (NYHA)[13] Class 3 or 4 or history of myocardial infarction ≤ 6 months of screening. Patients with echocardiogram results that demonstrated left ventricular ejection fraction < 50%.
- QT-interval corrected using Fridericia's formula (QTcF)[14] > 450 ms or other significant electrocardiogram abnormalities including Type II second degree or third degree atrioventricular block.
- Received allogenic haematopoietic stem cell transplantation prior to enrolment.

Patient characteristics

Patients were mostly male (77.9%), with a median age of 60.5 years (range 34 to 75 years) and with most (74.4%) < 65 years. ECOG Performance Status was 0 (69.8%), 1 (25.6%), and 2 (4.7%).

Patients were a median of 30.09 months since diagnosis (range 3.1to 102.4 months). 91.9% had no target lesion longest transvers diameter of lesion (LDi) ≤ 10 cm.

Most were Stage III (16.3%) or IV (74.4%. The median Ki67;[15] positive cell percentage was 30% (range 3, 80%), and 45.3% and 38.4% were Mantle Cell Lymphoma Prognostic Index (biological) score (MIPI-b);[16] intermediate and high risk, respectively. Almost 71% had extranodal disease at study entry and 45.3% had bone marrow involvement. The disease state was relapsed disease in 47.7% and refractory in 52.3%.

Patients had a median of 2 prior therapies, with 91% receiving a cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) based regimen, and 74% including rituximab as a single agent or part of the regimen, and 4% had a previous autologous stem cell transplant.

Sample size and protocol changes

A sample size of 80 patients was based on an assumed overall response rate (ORR) of 70% compared with 40% in a historical control, to provide a statistical significance at a one sided alpha of 0.025 with power of > 0.99. Of the 86 patients enrolled into the study, all received at least one dose of study drug. At the data cut of 15 February 2019, 60.5% of patients were continuing to receive study drug and 39.5% had discontinued study drug

[13] **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.
[14] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The **QTcF** is the QT interval corrected for heart rate according to Fridericia's formula.
[15] The Ki67 (MKI67) is a cellular marker for proliferation.
[16] **Mantle cell lymphoma international prognostic index (MIPI)** combined biologic index calculator. It includes age, lactate dehydrogenase, white cell count, Eastern Cooperative Oncology Group (ECOG) Performance Status and Ki67 proliferation index (%).

(mostly progressive disease (27.9%) or death (16.3%)). The major protocol violations (9.3%), mostly medication related, are unlikely to have substantially impacted the outcomes.

Study endpoints and key results

The primary endpoint was objective response rate (complete response (CR) or partial response (PR)) by Independent Review Committee (IRC). The secondary endpoints were duration of response (DOR) (by IRC and investigator), progression-free survival (PFS) (IRC and investigator), time to response (TTR) (IRC and investigator), ORR (by investigator). Overall survival (OS) was an exploratory endpoint. Patients with no post-Baseline response assessments were considered non-responders for ORR.

Primary endpoint

- Overall response rate (ORR) by IRC was 83.7% (95% confidence interval (CI): 74.2%, 90.8%). CR was 68.6%;[17] and PR was 15.1%.
- *Post-hoc* subgroup analyses of the ORR were generally consistent with the overall population.

Secondary endpoints

- Median DOR (IRC) for ORR (PR or CR): 19.5 months.
- Estimated event free rate for DOR: 78.3% at 12 months after start of response.
- Median PFS by IRC: 22.1 months. The estimated PFS event free rates (progression or death): 75.5% and 71.6% at 12 and 15 months, respectively.
- Median TTR (IRC) for OR was 2.73 months. The median time to CR was 2.89 months.
- Overall response rate (ORR) (investigator): 83.7% (95% CI 74.2% to 90.8%).

The results for the secondary endpoints by investigator were consistent with the IRC results.

Exploratory

Median OS was not reached. OS at 9 months was 89.2%, and 12 and 15 months was 84.1% each.

Updated efficacy data from Study BGB-3111-206 as of February 2020

The sponsor has provided an update to the efficacy data with topline data from a September 2020 data cut. Tabulated results from the data cuts of 15 February 2019, 31 August 2019, 8 September 2020 are included in Table 3 below.

[17] The United States Food and Drug Administration changed 8 complete response (CR) to partial responses because the patients had gastrointestinal and/or bone marrow involvement at Baseline. Repeat biopsies of involved locations were not repeated to demonstrate CR and these cases were classified partial response. This does not change the overall response rate (ORR) (CR + partial response (PR)), but the CR in the United States Package Insert (USPI) is 59% and PR is 24%.

Table 3: Study BGB-3111-206 Updated efficacy data as of February 2020

Response category	BGB-3111-206 (Investigator) n = 86	BGB-3111-206 (Investigator) n = 86	BGB-3111-206 (Investigator) n = 86
Data cut-off date	15 February 2019	31 August 2019	8 September 2020
Median follow-up time I (range)	18.43 (0.3, 23.5) months	24.84 (0.3, 30.0) months	35.2 (0.3, 41.6) months
ORR (CR + PR), n (%) (95%CI)	72 (83.7) (74.2, 90.8)	72 (83.7) (74.2, 90.8)	72 (83.7) (74.2, 90.8)
Complete response	67 (77.9)	67 (77.9)	67 (77.9)
Partial response	5 (5.8)	5 (5.8)	5 (5.8)
Stable disease	1 (1.2)	1 (1.2)	1 (1.2)
Progressive disease	8 (9.3)	8 (9.3)	8 (9.3)
Discontinued priorto first response assessment	5 (5.8)	5 (5.8)	5 (5.8)
Duration of response (DOR)			
Median follow-up time for DOR (range)	16.4 (2.3 to 9.5) months	19.4 (2.3 to 24.9) months	30.6 (2.3 to 36.2) months
Median DOR(range)	19.5 (2.3 to 19.5) months*	24.9 (2.3 to 24.9) months*	Not reached (2.3 to 36.2+ months)
Progression/death event-free rate at			
6 months (95% CI)	88.8 (78.9, 94.2)	88.8 (78.9, 94.2)	88.8 (78.9, 94.2)
12 months (95% CI)	81.8 (70.7, 89.0)	81.8 (70.7, 89.0)	81.8 (70.7, 89.0)
18 months (95% CI)	Not available	67.6 (55.4, 77.2)	67.7 (55.5, 77.2)
24 months (95% CI)	Not available	Not available	63.2 (50.9, 73.3)
30 months (95% CI)	Not available	Not available	57.3 (44.9, 67.9)
Progression-free survival (PFS)			
Median follow-uptime for PFS (range)	19.1 months (0.0 to 22.3 months)	22.2 months (0.0 to 27.6 months)	33.3 months (0.0 to 38.9 months)

Response category	BGB-3111-206 (Investigator) n = 86	BGB-3111-206 (Investigator) n = 86	BGB-3111-206 (Investigator) n = 86
Median PFS (range)	22.1 months (0.0+ to 22.3+ months)	27.5 months (0.0+ to 27.6+ months)	33.0 months (0.0+ to 38.9+ months)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; n = sample size; ORR = overall response rate; PFS = progression-free survival; PR = partial response.

*Estimates for the median DOR for the data cut-offs of 15 February 2019 and 31 August 2019 are considered unstable because the median was reached with the last event occurring while only 2 and 3 patients were at risk.

Study BGB-3111-AU-003

Study BGB-3111-AU-003 (first-in-human study) is an ongoing Phase I/II, open label, multi-dose, multicentre, to investigate the safety and PK of zanubrutinib in adult patients with B-cell malignancies, who were ECOG Performance Status 0 to 2, and who had adequate renal, liver and haematological function.

Part 1 (dose escalation) was conducted in patients with relapsed or refractory B-cell lymphoid malignancy and tested once daily oral zanubrutinib doses from 40 mg to 320 mg and a twice daily dose of 160 mg.

Part 2 (dose expansion) of the study had disease-specific cohorts. Cohorts 2a and 2g are relevant for the proposed indication. Patients were dosed at 320 mg administered either once daily or 160 mg twice daily, but in a protocol modification was confined to 160 mg twice daily for all new patients. Treatment with zanubrutinib continued until occurrence of unacceptable toxicities, disease progression, withdrawal of consent, investigator discretion, or a treatment delay of more than 28 days for unresolved toxicity.

At the data cut-off (13 December 2018), 37 patients with r/r MCL (Parts 1 and 2 combined) were enrolled and received at least one dose of study drug. The starting dose for most patients was 160 mg twice daily (14 patients (37.8%)) or 320 mg once daily (18 patients (48.6%)), with the remaining 5 patients from Part 1 of the study started at 40 mg once daily (n = 1), 80 mg once daily (n = 2), or 160 mg once daily (n = 2).

The median age of r/r MCL patients was 70.0 years. Most were male (67.6%) and White (81.1%). The median time from initial diagnosis to onset of study treatment was 4.20 years.

The efficacy evaluable analysis set included all MCL patients first dosed at least 12 weeks before the data cut-off date (13 December 2018).

Study endpoints

The primary efficacy endpoint was ORR by IRC. The secondary endpoints were IRC assessed CR rate, DOR, TTR, PFS and OS. Endpoints assessed by investigator were also analysed. For the subset of patients with r/r MCL, response was evaluated using the Lugano classification for non-Hodgkin lymphoma.[18]

Results

Primary endpoint

- Overall response rate (ORR) by IRC was 81.1%. CR was 24.3% and PR was 56.8%.

[18] Cheson, B.D. et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: the Lugano Classification, *J Clin Oncol*, 2014; 32(27): 3059-3068.

Secondary endpoints:

- Median DOR was 15.4 months and increased to 18.5 months using only data from patients who started on a total daily dose of 320 mg (160 mg twice daily or 320 mg once daily). The estimated event free rate for patients who had achieved a response was 76.1% at 12 months after the start of the response.
- Median TTR was 2.7 months and the median time to CR was 5.4 months.
- Median PFS by IRC was 17.3 months and increased to 21.1 months using only data from patients who started on a total daily dose of 320 mg. The estimated PFS event free rates (progression or death) were 71.3% and 64.2% at 12 and 15 months, respectively.
- Median OS was estimated at 27.2 months. OS was 88.6% at 9 months and 82.6% at 12 and 15 months.

Endpoints assessed by investigator yielded results consistent with those assessed by IRC.

Comparing 160 mg twice daily and 320 mg once daily, the ORR (85.7% versus 83.3%, respectively) and CR (28.6% versus 22.2%, respectively) were similar.

Safety

Safety data were presented from Studies BGB-3111-206 and BGB-3111-AU-003, and from Studies BGB-3111-1002 (Phase I study in patients with B-cell malignancies), BGB-3111-205 (Phase II, single arm, open label study in patients with relapsed or refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma), and BGB-3111-210 (Phase II, single arm, open label study in Chinese patients with relapsed or refractory Waldenstorm's macroglobulinaemia (WM)).

In the safety data set the median duration of zanubrutinib treatment was 15.41 months for r/r MCL patients and 11.01 months overall for MCL patients (that is, r/r and treatment naïve MCL patients). In Study BGB-3111-AU-003 Part 1 the median treatment duration was 30.88 months.

Safety data from Studies BGB-3111-206 and BGB-3111-AU-003 were presented separately.

Study BGB-3111-206

- 96.5% had an adverse event (AE); most commonly neutrophil count decreased (44.2%), upper respiratory tract infection (34.9%), rash (33.7%), and white blood cell count decreased (31.4%).
- 89.5% of patients had at least one treatment related AE; most commonly reported neutrophil count decreased (43.0%), white blood cell count decreased (29.1%) and rash (27.9%).
- 16.3% (14/86) patients died, most commonly cause due to AEs (8.1% (7/86)) but with no consistent pattern.
- 24.4% of patients had at least one serious adverse event (SAE), most commonly lung infection (8.1% (7/86)).
- 9.3% of patients had AEs led to treatment discontinuation, although no event was reported in more than one patient.
- No patients had atrial fibrillation or flutter.
- Haemorrhage was reported in 25.6%; most commonly reported blood urine present, haematuria, and petechiae, purpura or contusion (4 (4.7%) patients each). Major haemorrhage was reported in 3.5% (3/86). No events were fatal.

- No second primary malignancies were reported.
- 61.6% of patients had at least one infection, most commonly upper respiratory tract infection (34.9%). 14.0% had an SAE of infections (12/86; lung infection (7 patients), pneumonia (2 patients), infection, pneumonia fungal, and urinary tract infection (one patient each)). There were no opportunistic infections.
- Grade 3 or 4 anaemia, leukopenia, neutropenia, and thrombocytopenia were 7.0%, 9.3%, 19.8% and 4.7%, respectively

Study BGB-3111-AU-003 (relapsed or refractory mantle cell lymphoma patient cohort)

- 97.3% had an AE was 97.3%; most commonly diarrhoea (40.5%), contusion (37.8%), and upper respiratory tract infection and constipation (each 29.7%).
- 73.0% had at least one treatment related AE; most commonly contusion (21.6%), fatigue (13.5%), and diarrhoea (10.8%).
- 43.2% died; most commonly due to disease progression (27.0%).
- 43.2% had at least one SAE, most commonly pneumonia (8.1%).
- 21.6% had AEs that led to treatment discontinuation. The only AE reported by more than one patient was pneumonia (5.4%; 2/37).
- 5.4% (2/37) had atrial fibrillation or flutter.
- Haemorrhage was reported in 54.1%; most commonly contusion (37.8%). Major haemorrhage was reported in 8.1% (3/37). No events were fatal.
- 18.9% reported second primary malignancies; most commonly basal cell carcinoma (10.8%, 4/37).
- 73.0% had infections, most commonly upper respiratory tract infection (29.7%). Serious infections occurred in 10.8% (4/37) and opportunistic infections occurred in 8.1% (3/37).
- Grade 3 or 4 anaemia, leukopenia, neutropenia, and thrombocytopenia occurred in 16.2%, 2.7%, 18.9% and 16.2%, respectively

Updated safety data from Study BGB-3111-206 as of February 2020

Similar patterns of AEs emerged from the updated topline safety data as were seen in the initial data. Small numbers of patients (generally 1 to 3) accrued to categories of haematological AE categories in the period between 31 August 2019 to 8 September 2020.

Comparative safety of 320 once daily and 160 mg twice daily dosing

Data from 542 patients from 5 studies (Studies BGB-3111-AU-003, BGB-3111-AU-302, BGB-3111-AU-206, BGB-3111-AU-1002, and BGB-3111-AU-205) were included in an analysis of exposure response relationships between PK exposure (AUC_{0-24}, C_{max}, or minimum concentration (C_{min})) and adverse events of special interest (AESIs) in the exposure range (AUC_{0-24}) to approximately 5000 ng h/mL was conducted. This exposure was up to 2.4-fold above the mean AUC exposure of the zanubrutinib 160 mg twice daily regimen at steady state (2099 (42%) ng h/mL) and up to 2.6-fold above the mean AUC exposure of the 320 mg once daily regimen at steady state (1917 (59%) ng h/mL).

The higher C_{max} from the 320 mg once daily regimen was not associated with a higher rate of AEs relative to the 160 mg twice daily regimen.

The sponsor did not find any significant relationships between AESIs and zanubrutinib exposure from patients with a wide range of AUC exposure.

Comparative safety of 320 mg once daily and 160 mg twice daily dosing was obtained from Study BGB-3111-AU-003 in B-cell malignancies. While proportions of event were

similar and there were no events with a > 10% difference in proportion between the two dosing regimens in this study, the 160 mg twice daily group compared with the 320 mg twice daily group had an approximately 9% higher proportion of neutropenia for all grades and Grade ≥ 3 events. An almost 9% greater proportion of patients had all Grade bleeding events in the 320 mg once daily group compared with the 160 mg twice daily group. A clarification is requested from the sponsor (further details see section: 'Questions for the sponsor', below).

Risk management plan

A concurrent new chemical entity submission for indication of Waldenström's macroglobulinemia (Submission PM-2020-02814-1-6) is in progress.[8]

The sponsor has submitted European Union (EU)-risk management plan (RMP) version 0.1 (dated 11 May 2020; data lock point (DLP) 31 December 2019) and Australia specific annex (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 4. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 4: 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	–
	Teratogenicity	ü[1]	–	ü	–
Missing information	Safety in patients with severe hepatic impairment	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	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[1]	–	ü	–

1 Targeted follow-up questionnaires

- The 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.
- The clinical study plan to support provisional registration status is subject to final acceptance by the TGA Delegate.

Risk-benefit analysis

Delegate's considerations

The sponsor is requesting provisional registration of zanubrutinib for at least second line use for adult patients with MCL, based on the findings of a Phase II study (Study BGB-3111-206) and a cohort of patients from Study BGB-3111-AU-003.

Based on the in vitro findings of irreversible binding of zanubrutinib with BTK, despite the short plasma half-life long lasting PD effects are expected.

The nonclinical evaluation found zanubrutinib is likely to inhibit bone marrow X kinase / epithelial and endothelial tyrosine kinase, tyrosine-protein kinase Blk, erb-b2 receptor tyrosine kinase 4 / human epidermal growth factor receptor 4, tec protein tyrosine kinase, EGFR, TXK tyrosine kinase, breast tumour kinase and ITK; may slightly inhibit FGR

tyrosine kinase, lymphocyte specific protein tyrosine kinase and fyn related kinase / protein tyrosine kinase 5. These findings raise theoretical possibilities of off-target effects.

Clinical efficacy and safety

Primary efficacy data were derived from Studies BGB-3111-206 and BGB-3111-AU-003 in r/r MCL patients achieved an ORR in 83.4% Study BGB-3111-206 and 81.1% in Study BGB-3111-AU-003. Responses in Study BGB-3111-206 were durable, and a median DOR had not been reached by September 2020. However, around 22% patients discontinued treatment due to progressive disease. As noted above there were marked differences between CR and corresponding PR between the two studies. The median DOR 19.5 months with median follow-up from treatment start to study discontinuation of 18.4 months. Additional data from the September 2020 data cut provide some reassurance about the durability of response.

There are no concerns about the effect size. While acknowledging the limitations of cross study comparisons, ORR reported for acalabrutinib in MCL per investigator was 80.6%. For ibrutinib the ORR was 67.6% after a median of 3 (range 1 to 5) prior treatments and 71.9% after a median of 2 (range 1 to 9) prior treatments.

Common AEs were neutropenia, thrombocytopenia, upper respiratory tract infection, anaemia, rash, diarrhoea and bruising. Serious adverse events occurred in 31% and included pneumonia and haemorrhage.

Some differences in the safety data were seen between Studies BGB-3111-206 and BGB-3111-AU-003, with a higher proportion of haemorrhage (25.6% versus 54.1%); Grade 3 or 4 anaemia (7% versus 16.2%) and atrial fibrillation or flutter (0% versus 5.4%) as examples.

Based on the evidence presented from the safety data set in B-cell malignancies, and specifically for MCL, zanubrutinib has an acceptable safety profile for the context of use.

Generalisability of Study BGB-3111-206 to the Australian context

Study BGB-3111-206, the primary evidence to support the provisional registration in MCL, was conducted in China, adding some uncertainty to the generalisability of the findings to the Australian context. Study BGB-3111-AU-003 recruited from a broader geographical area including Australia, Italy, New Zealand, South Korea, the United Kingdom and the US. Study BGB-3111-206 had a 75 year age cut-off whereas 37.5% of Study BGB-3111-AU-003 were aged > 75 years. CR differences were noted for Studies BGB-3111-206 (78% CR) and BGB-3111-AU-003 (25% CR), although the ORR for both studies was 84%.

There were differences between the Study BGB-3111-206 versus Study BGB-3111-AU-003 other than the ethnicity of the patients and the location of the study including:

- more refractory disease in study: 52.3% versus 25%;
- more pre-treatment: median 2 treatments versus 1;
- expected aggressive nature of disease: blastoid variant 14% versus 6.3%.

Positron emission tomography (PET) scanning was required to assess all responses in Study BGB-3111-206, considered a standard methodology for measuring MCL response by the Lugano classification. Study BGB-3111-AU-003 was designed prior to the publication of this classification and the primary method of investigation was CT scanning, with PET scanning optional for the investigator. This adds a limitation to the cross-study comparison between the two studies. Eight patients in Study BGB-3111-AU-003 had PET scans, and 4 considered non-CR by CT were upgraded to CR on the basis of the PET results. The sponsor notes the following:

- The CR rate would likely have been higher with systematic PET imaging in all patients given that PET scan based metabolic CRs are easier to achieve than CT based CRs that

require complete resolution of extra-lymphatic sites of disease and regression of affected lymph modes to ≤ 1.5 cm in the longest transverse diameter.

Although disease characteristics and pharmacology of zanubrutinib may be similar in China and Australia, and the sponsor has noted differences in baseline characteristics between Studies BGB-3111-206 and BGB-3111-AU-003, aside from location of the study, some uncertainties regarding the generalisability of the findings to the Australian context remain so the advice of the Advisory Committee on Medicines (ACM) has been requested.

The sponsor has proposed an acceptable clinical study plan. The confirmatory study utilises a randomised design in a previously untreated patient population with a primary endpoint designed to demonstrate clinical benefit. The study is currently accruing and with a projected decision date for the submission of 2021 there is likely to be sufficient time for the sponsor to provide confirmatory data within the maximum 6 year provisional registration period. It is noted that the purpose of a confirmatory study is not necessarily to repeat the use of the provisionally registered medicine in the same line of therapy and/or specific subset of a condition. Its main purpose is to confirm the understanding of the magnitude of the benefits and risks of the medicine in the condition to inform a regulatory decision about its ongoing registration for use in that condition.

Indication

The proposed indication is in keeping with the main evidence provided, including the line of therapy given there is evidence of benefit after one previous line of therapy. A minor amendment to the text describing the provisional nature of the data is proposed. The measure of efficacy is ORR, a measure accepted in the provisional registration context. The number of contributory studies is not considered relevant to the indication.

Subject to the advice of the ACM, the proposed indication is:

> *Brukinsa is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.*
>
> *The 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 confirmatory trials.*

Dose

Study BGB-3111-206 used 160 mg twice daily dosing. The sponsor is seeking an alternative 320 mg once daily dosing based on ORR 85.7% and 83.3% with 160 mg twice daily and 320 mg once daily, respectively; CR rate: 28.6% and 22.2%, respectively in Study BGB-3111-AU-003. Linear PK suggests similar exposure with the two doses. General similarity between the two proposed alternative dosing regimens was seen in the comparative safety analysis from Study BGB-3111-AU-003. Clarification is sought from the sponsor around haematological outcomes identified in the comparative safety analysis of the two dosing regimens from Study BGB-3111-AU-003, however there was a < 10% difference between the groups for these parameters (see Question for the sponsor section of this AusPAR).

The proposed 320 mg dose requires the patient to take 4 x 80 mg capsules at a time. The sponsor is currently developing an immediate release 160 mg scored tablet.

Proposed action

While a decision is yet to be made, at this stage the Delegate is inclined to approve the registration of the product for the following indication:

> *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 the objective response rate. Continued approval for this indication depends on verification and description of clinical benefit in confirmatory trials.

If registration was approved, the Delegate would propose the following additional conditions of registration:

- The Brukinsa EU-RMP (version 0.1, dated 11 May 2020, DLP 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.

  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 periodic safety update reports (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 DLP 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 the products entire period of provisional registration.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

  Specifically, the sponsor must conduct studies as described in the clinical study plan in version 1.0 (1 June 2020) of the Australia specific annex. The following study reports should be submitted to TGA:

  – Study BGB-3111-306
- The final clinical study report for Study BGB-3111-206.

Questions for the sponsor

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

1. ***In the summary of treatment emergent adverse events in B-cell malignancies from Study BGB-3111-AU-003 there are differences in neutropenia including Grade ≥ 3 events between the 160 mg twice daily and 320 mg twice daily groups, with an approximately 9% higher proportion of all Grades and Grade ≥ 3 events in the pooled terms analysis. An almost 9% greater proportion of patients had all Grade bleeding events in the 320 mg once daily group compared with the 160 mg twice daily group. Are there any differences in patient characteristics, or***

underlying disease between these two groups that might account for this observation?

The sponsor acknowledges the question regarding the differences of neutropenia and bleeding events proportion between 160 mg twice daily and 320 mg once daily treatment groups. Relevant comparisons between the two treatment groups are shown below:

- Pharmacokinetics (PK)-pharmacodynamics (PD) relationship and population exposure response relationship for safety
  - Pharmacokinetics: exposure/AUC achieved by 160 mg twice daily and 320 mg once daily is comparable with geometric mean AUC of 2099 (42%) and 1917 (59%) ng h/mL for 160 mg twice daily and 320 mg once daily, respectively.
  - Pharmacodynamics (PD): Sustained PD effects achieved at trough concentrations at both 160 mg twice daily and 320 mg once daily. Median BTK occupancy in peripheral blood mononuclear cells was 100% for both regimens. Median BTK occupancy in lymph nodes was 94% and 100% following the 320 mg once daily and 160 mg twice daily dose, respectively.
  - Population exposure response relationship between zanubrutinib exposure metrics (model predicted area under the concentration time curve from time zero to 24 hour at steady state ($AUC_{0\text{-}24h,ss}$), $C_{max,ss}$ and minimum concentration at steady state ($C_{min,ss}$)) and safety were explored using data collected from Studies BGB-3111-AU-003, BGB-3111-1002, BGB 3111-205 and BGB-3111-206. Exposure response analysis indicated that there were no evident exposure response relationships between PK exposure ($AUC_{0\text{-}24}$, C_{max}, or C_{min}) and the safety endpoints (AESIs) including Grade ≥ 3 neutropenia, major bleeding events and any bleeding events). The higher C_{max} from the 320 mg once daily regimen was not associated with a higher rate of AEs relative to the 160 mg twice daily regimen.
- Neutropenia

  Neutropenia risk factors include advanced age, female sex, prior chemotherapy and/or radiation, pre-existing neutropenia, use of myelosuppressive agents, poor immune function, comorbidities, including hepatic or renal dysfunction and diabetes, and underlying blood malignancy.[19,20]

  The following differences in neutropenia events between the 160 mg twice daily and 320 mg once daily groups were observed in Study BGB-3111-AU-003: neutropenia of all grades (21.6% versus 12.6%) and Grade ≥ 3 neutropenia (19.1% versus 10.5%). Relevant patients' characteristics are summarized in Table 5 and Table 6 below.

  Compared with the 320 mg once daily treatment group, the following key findings observed in the 160 mg twice daily group were considered as potential contributors to the events of neutropenia.
  - More female patients (30.9% versus 21.1%).
  - Higher proportion of relapsed/refractory patients (87.1% versus 67.4%).
  - More patients received prior antineoplastic agents (87.4% versus 67.4%), radiotherapy.
  - (15.8% versus 9.5%) and transplants (6.5% versus 3.2%).

[19] Chambers, P. et al. Patient Factors and Their Impact on Neutropenic Events: a Systematic Review and Meta-Analysis, *Support Care Cancer*, 2019; 27: 2413-2424.
[20] Lyman, G.H. et al. Risk Factors for Febrile Neutropenia Among Patients with Cancer Receiving Chemotherapy: a Systematic Review, *Oncol Hematol*, 2013; 12: 1-10.

- More patients received ≥ 2 lines of prior anti-cancer regimens.
- Less recovery time from end of last regimen to first dose of zanubrunitib (11.66 months versus 15.82 months).
- Larger sample size (n = 278 versus n = 95) which might cause biases.
- More patients with Richter's transformation and diffuse large B-cell lymphomas, more aggressive types of lymphomas with higher risks of neutropenia.[21,22]

There was no significant difference observed between 160 mg twice daily and 320 mg once daily groups in terms of age (56.8% versus 55.8% for > 65 years age group), pre-existing neutropenia (4.3% versus 3.2%), renal disease (chronic kidney disease: 4.0% versus 1.1%; renal impairment: 1.1% versus 4.2%; renal failure: 1.1% versus 0.0%; renal disorder: 0.0% versus 1.1%) and diabetes (type 2 diabetes mellitus: 7.9% versus 9.5%; diabetes mellitus: 6.1% versus 3.2%; hyperglycaemia: 1.8% versus 3.2%). None of the known risk factors for neutropenia were more prevalent in the 320 mg once daily group.

[21] Colosia, A. et al. Clinical Efficacy and Safety in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: a Systematic Literature Review, *Clin Lymphoma Myeloma Leuk*, 2014; 14(5): 343-355.e6.
[22] Parikh, S.A. et al. How We Treat Richter Syndrome, *Blood*, 2014; 123(11): 1647-1657.

Table 5: Study BGB-3111-AU-003 Patient demographics summary by dosing regimen

	160 mg BID (N = 278)	320 mg QD (N = 95)	Overall[&] (N = 385)
Age (years)			
Median (Min, Max)	68 (20, 90)	68 (24, 87)	68 (20, 90)
Age group, n (%)			
> 65 years	158 (56.8)	53 (55.8)	218 (56.6)
> 75 years	56 (20.1)	17 (17.9)	76 (19.7)
Sex, n (%)			
Female	86 (30.9)	20 (21.1)	109 (28.3)
Prior Treatment Status, n (%)			
Relapsed/refractory	242 (87.1)	64 (67.4)	318 (82.6)
Patients Received Prior Radiotherapy, n (%)			
Yes	44 (15.8)	9 (9.5)	53 (13.8)
Patients Received Transplant, n (%)			
Yes	18 (6.5)	3 (3.2)	24 (6.2)
ANTINEOPLASTIC AGENTS	243 (87.4)	64 (67.4)	319 (82.9)
RITUXIMAB	194 (69.8)	58 (61.1)	263 (68.3)
CYCLOPHOSPHAMIDE	166 (59.7)	46 (48.4)	221 (57.4)
VINCRISTINE	102 (36.7)	26 (27.4)	133 (34.5)
DOXORUBICIN	78 (28.1)	20 (21.1)	102 (26.5)
ETOPOSIDE	44 (15.8)	5 (5.3)	52 (13.5)
CORTICOSTEROIDS FOR SYSTEMIC USE	120 (43.2)	37 (38.9)	165(42.9)
IMMUNOSUPPRESSANTS	11 (4.0)	3 (3.2)	14 (3.6)
Number of Prior Anti-Cancer Regimens, n (%) [a]			
2	62 (22.3)	14 (14.7)	81 (21.0)
3	45 (16.2)	9 (9.5)	56 (14.5)
4	23 (8.3)	5 (5.3)	28 (7.3)
5	12 (4.3)	1 (1.1)	14 (3.6)
≥ 6	13 (4.7)	2 (2.1)	15 (3.9)
Time from End of Last Regimen to First Dose (Months)			
N	233	62	307
Median (min, max)	11.66 (0.0, 143.0)	15.82 (0.8, 101.1)	12.16 (0.0, 143.0)

Abbreviations: BID = twice daily; N = population size; n = sample size; QD = once daily.

Data cut-off: 31 August 2019.

a Prior anti-cancer regimens do not include prior radiotherapy. Number of prior anticancer regimens is considered as zero for patients without any recorded prior systemic anticancer regimens.

& Also includes 40 mg once daily (N = 3), 80 mg once daily (N = 4) and 160 mg once daily (N = 5).

Table 6: Study BGB-3111-AU-003 Summary of underlying disease type by diagnosis and dosing regimen

	160 mg BID N=278 (%)	320 mg QD N=95 (%)
CLL/SLL (N=125)	83 (66.4)	40 (32.0)
WM (N=78)	51 (65.4)	23 (29.5)
MCL (N=57)	32 (56.1)	20 (35.1)
DLBCL (N= 45)	44 (97.8)	1 (2.2)
FL (N=33)	27 (81.8)	6 (18.2)
MZL (N=20)	17 (85.0)	3 (15.0)
RT (N=13)	13 (100.0)	0 (0.0)
HCL (N= 12)	9 (75.0)	2 (16.7)

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukaemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HCL = hairy cell leukaemia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; N = population size; QD = once daily; RT = Richter's transformation; SLL = small lymphocytic lymphoma; WM = Waldenström's macroglobulinemia.

Data cut-off: 31 August 2019.

In summary, the difference in neutropenia events, both for all grades and Grade ≥ 3, between the 160 mg twice daily and 320 mg once daily groups are probably due to the difference of patient characteristics, including age, sex, prior antineoplastic agents and immunosuppressants, as well as patients' underling disease type and the stage of the disease.

- Bleeding

  Compared with 160 mg twice daily, more patients in the 320 mg once daily treatment group of Study BGB- 3111-AU-003 had haemorrhage events of all grades (MedDRA;[23] 22.0 SMQ;[24]) (65.3% versus 56.5%). However, when analysing the haemorrhage events by severity, the incidence rates of Grade 2, Grade 3 and Grade 4 haemorrhages in these two treatment groups were comparable (Table 7). It appears that the difference in all grades is driven by more Grade 1 haemorrhages in the 320 mg once daily group (57.9% versus 45.3%). The following Grade 1 events showed differences of ≥ 4% for 320 mg once daily compared to 160 mg twice daily: Grade 1 contusion (37.9% versus 29.9%), Grade 1 Epistaxis (10.5% versus 6.5%) and Grade 1 increased tendency to bruise (6.3% versus 1.8%).

[23] The **Medical Dictionary for Regulatory Activities (MedDRA)** is a single standardised international medical terminology, developed as a project of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (that is, from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.

[24] **Standardised MedDRA Queries (SMQs)** are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

Table 7: Study BGB-3111-AU-003 Haemorrhage events by severity

	160 mg BID (N = 278)	320 mg QD (N = 95)	Overall[&] (N = 385)
Total number, n (%)	157 (56.5)	62 (65.3)	225 (58.4)
Grade 1, n (%)	126 (45.3)	55 (57.9)	186 (48.3)
Grade 2, n (%)	20 (7.2)	4 (4.2)	25 (6.5)
Grade 3, n (%)	10 (3.6)	3 (3.2)	13 (3.4)
Grade 4, n (%)	1 (0.4)	0 (0.0)	1 (0.3)

BID = twice daily; N = population size; n = sample size; QD = once daily.

& Also includes 40 mg once daily (N = 3), 80 mg once daily (N = 4) and 160 mg once daily (N = 5).

In summary, the difference of haemorrhage event rates between 160 mg twice daily and 320 mg once daily was mainly due to clinically less significant Grade 1 haemorrhage events. There was no significant difference between the 160 mg twice daily and 320 mg once daily groups for major haemorrhage (defined as serious or ≥ Grade 3 bleeding at any site, or central nervous system bleeding of any grade) (4.0% versus 3.2%), serious bleeding events (3.2% versus 3.2%) and ≥ Grade 3 haemorrhage (4.0% versus 3.2%).

Advisory Committee considerations

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. ***Advice is sought on the generalisability of the efficacy to the Australian mantle cell lymphoma population.***

The ACM noted that the majority of the efficacy data lies within Study BGB-3111-206, which has differences in baseline characteristics compared to the Australian mantle cell lymphoma (MCL) population. The ACM advised that in comparison to the Australian MCL population, Study BGB-3111-206 shows underutilisation of rituximab and autologous transplant in patients; and that the patient demographics consists of a younger cohort.

The ACM was of the view that the study population in Study BGB-3111-AU-003 is more likely to represent usage of emerging standard of care, with fewer lines of prior treatment used in the Australian MCL patients. In addition, the ACM agreed that Study BGB-3111-AU-003 did demonstrate zanubrutinib's efficacy. Studies BGB-3111-206 and BGB-3111-AU-003 showed a comparable overall response rate (ORR) between the different patient populations. The ACM was reassured by the consistency of the efficacy results between Studies BGB-3111-206 and BGB-3111-AU-003.

In summary, the ACM was of the view that the efficacy studies were generalisable to the Australian MCL population.

2. ***Some differences in safety were seen between Studies BGB-3111-206 and BGB-3111-AU-003 were identified. Advice is sought on whether these are mainly attributable to differences in stage of disease and prior treatment.***

The ACM noted that Study BGB-3111-AU-003 is an Australian based study and has an older cohort compared to Study BGB-3111-206. In addition, the ACM noted that second malignancies, such as skin cancers (mainly basal cell carcinoma) were observed in Study BGB-3111-AU-003 and were of the view that this could possibly be attributed to the

age and race of this cohort. They agreed that these differences are likely due to the Australian Study BGB-3111-AU-003 population.

Amongst the safety concerns, major bleeding event rates were similar between both studies. Cytopaenias were manageable and may be attributable to age and higher treatment intensity in Study BGB-3111-AU-003.

The ACM noted there were 2 patients with atrial fibrillation in Study BGB-3111-AU-003 and none in Study BGB-3111-206. The ACM was of the view that these differences are likely due to variation in age between the two study populations and not deemed as significant safety concern.

The ACM noted that the CR rate in Study BGB-3111-AU-003 may be underestimated due to lack of PET scan, but the overall response rate results are concordant between Studies BGB-3111-206 and BGB-3111-AU-003. The ACM agrees that the studies' results are supportive of each other.

The ACM is of the view that the differences in safety profiles of Studies BGB-3111-206 and BGB-3111-AU-003 were mainly attributed to the differences in age, stages of disease and prior treatments.

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

Outcome

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

> ***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.*

As such, the full indications at this time were:

> ***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.*
>
> ***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.*

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 the products entire period of provisional registration.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

  Specifically, the sponsor must conduct studies as described in the clinical study plan in version 1.0 (1 June 2020) of the Australian specific annex. The following study report(s) should be submitted to TGA:

  – Study BGB-3111-306 by October 2023 (first interim analysis), June 2025 (second interim analysis), September 2027 (final analysis)

  Further guidance for sponsors is available on the TGA website.
- 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.
- [The sponsor to] provide the final clinical study report for 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 PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au