

NEW ZEALAND DATA SHEET

BRUKINSA (zanubrutinib)

1 PRODUCT NAME

BRUKINSA 80 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 80 mg zanubrutinib.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White to off-white opaque hard capsule of 22 mm in length (size 0), marked with “ZANU 80” in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

Chronic Lymphocytic Leukaemia (CLL)/Small Lymphocytic Lymphoma (SLL)

BRUKINSA is indicated as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), including patients with deletion 17p and/or TP53 mutation.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended total daily oral dose of BRUKINSA is 320 mg. BRUKINSA may be taken as either 320 mg (four 80 mg capsules) once daily, or as 160 mg (two 80 mg capsules) twice daily.

Dose Modification for Adverse Reactions

Recommended dose modifications of BRUKINSA for severe (Grade 3) or life-threatening (Grade 4) adverse reactions are provided in Table 1:

Table 1: Recommended Dose Modification for Adverse Reaction

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

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

Missed Dose

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.

Method of administration

BRUKINSA capsules should be administered orally as 320 mg once daily or 160 mg twice daily approximately every twelve hours. BRUKINSA can be taken with or without food. Patients should be instructed to swallow capsules whole with water, and not to open, break or chew the capsules.

Special populations

Use in Children

The safety and efficacy of BRUKINSA have not been established in pediatric patients.

Use in the Elderly

No specific dose adjustment is required for elderly patients (aged ≥ 65 years).

Patients with Renal Insufficiency

No dosage modification is recommended in patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis (see section 5.2 *Pharmacokinetic properties*).

Patients with Hepatic Insufficiency

Dose modifications are not needed in patients with mild or moderate hepatic impairment. Patients with mild or moderate hepatic impairment were treated in BRUKINSA clinical studies. The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice

daily. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse reactions of BRUKINSA (see section 5.2 *Pharmacokinetic properties*).

Interactions Requiring Dose Adjustments

Dose modification for use with CYP3A inhibitors or inducers:

Table 2: Recommended Dose Modifications [see 4.5 *Interactions with other medicines and other forms of interactions and 5.2 Pharmacokinetic properties*]:

CYP3A	Co-administered Drug	Recommended Dose
Inhibition	Strong CYP3A inhibitor (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily Interrupt dose as recommended for adverse reactions [see <i>Dose and method of administration (4.2)</i>].
	Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily Modify dose as recommended for adverse reactions [see <i>Dose and method of administration (4.2)</i>].
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampicin, St. John's wort) and moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use of strong CYP3A inducers. Avoid concomitant use of moderate inducers. If these inducers cannot be avoided, increase BRUKINSA dose up to 320 mg twice daily.

After discontinuation of a CYP3A inhibitor, resume previous dose of BRUKINSA.

4.3 CONTRAINDICATIONS

None

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemorrhage

Serious and fatal haemorrhagic events have occurred in patients with haematological malignancies treated with zanubrutinib monotherapy. Grade 3 or higher bleeding events occurred in 3.9% of patients, including intracranial and gastrointestinal haemorrhage, haematuria and haemothorax have been reported uncommonly in patients. Bleeding events of any grade occurred in 48.1% of patients with haematological malignancies, including purpura and petechiae.

Bleeding events have occurred in patients taking zanubrutinib with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of haemorrhage and patients should be monitored for signs of bleeding. Discontinue BRUKINSA if intracranial haemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with haematological malignancies treated with zanubrutinib monotherapy. Grade 3 or higher infections occurred in these patients. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) or herpes zoster virus reactivation have occurred.

Consider prophylaxis according to standard of care in patients who are at increased risk for infections. Monitor patients for signs and symptoms of infection and treat appropriately.

Effects on Laboratory Tests - Cytopenias

Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia, and anaemia based on laboratory measurements were reported in patients with haematologic malignancies treated with zanubrutinib monotherapy (see Section 4.8 *Adverse effects (Undesirable effects)*).

Monitor complete blood counts during treatment. See Section 4.2 *Dose and method of administration* for recommended dose modifications.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma of any grade have occurred in 12.4% of patients with haematological malignancies treated with zanubrutinib monotherapy. The most frequent second primary malignancy was skin cancer reported in 7.4% of patients (basal cell carcinoma [4.4%] and squamous cell carcinoma of skin [2.7%]). Skin cancers were observed predominantly in patients at high risk of developing skin cancer including those who had medical history of skin cancers. Perform routine skin checks and advise patients to use sun protection. Second primary malignancies of Grade 3 or higher have occurred in 5.4% of patients.

Atrial Fibrillation and Flutter

Atrial fibrillation and atrial flutter of any grade have occurred in 3.2% of patients with haematological malignancies treated with zanubrutinib monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections. Grade 3 or higher events occurred in 1.4% of patients. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Paediatric use

The safety and efficacy of BRUKINSA in children below 18 years of age have not been established.

Use in the elderly

No specific dose adjustment is required for elderly patients (aged \geq 65 years).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of Other Drugs on BRUKINSA

Table 3: Drug Interactions that Affect BRUKINSA

Moderate and Strong CYP3A Inhibitors	
<i>Clinical Impact</i>	<ul style="list-style-type: none"> Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC [see <i>Pharmacokinetic Properties (5.2)</i>] which may increase the risk of BRUKINSA toxicities.
<i>Prevention or management</i>	<ul style="list-style-type: none"> Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors [see <i>Dose and Method of Administration (4.2)</i>].
Moderate and Strong CYP3A Inducers	
<i>Clinical Impact</i>	<ul style="list-style-type: none"> Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC [see <i>Pharmacokinetic Properties (5.2)</i>] which may reduce BRUKINSA efficacy.
<i>Prevention or management</i>	<ul style="list-style-type: none"> Avoid co-administration of BRUKINSA with strong CYP3A inducers [see <i>Dose and Method of Administration (4.2)</i>]. Avoid co-administration of BRUKINSA with moderate CYP3A inducers. If these inducers cannot be avoided, increase BRUKINSA dosage up to 320 mg twice daily [see <i>Dose and Method of Administration (4.2)</i>].

Drug Interaction Studies

Agents that may increase zanubrutinib plasma concentrations

CYP3A Inhibitors: The coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) in healthy volunteers increased the C_{max} of zanubrutinib by 2.6-fold and AUC by 3.8-fold. The coadministration of multiple doses of strong CYP3A inhibitors voriconazole and clarithromycin (inpatients with B-cell malignancies) resulted in increased zanubrutinib exposures by 3.30-fold and 1.92-fold for dose-normalized AUC_{0-24h} and 3.29-fold and 2.01-fold for dose-normalized C_{max} . The coadministration of multiple doses of moderate CYP3A inhibitors fluconazole and diltiazem (in patients with B-cell malignancies) resulted in increased zanubrutinib exposures by 1.88-fold and 1.62-fold for dose-normalized AUC_{0-24h} and 1.81-fold and 1.62-fold for dose-normalized C_{max} . Physiologically based PK (PBPK) simulations indicate that coadministration of multiple doses of a moderate CYP3A inhibitor (e.g. fluconazole, diltiazem and erythromycin) may increase the C_{max} and AUC of zanubrutinib by approximately 2-fold.

Concomitant use of zanubrutinib and medicinal products that strongly or moderately inhibit CYP3A can increase zanubrutinib exposure.

Agents that may decrease zanubrutinib plasma concentrations

CYP3A Inducers: Co-administration of multiple doses of rifampicin (strong CYP3A inducer) decreased the zanubrutinib C_{max} by 92 % and AUC by 93%. Co-administration of multiple doses of rifabutin (moderate CYP3A inducer) decreased the zanubrutinib C_{max} by 48% and AUC by 44%.

PBPK model simulations suggest that coadministration of a moderate CYP3A inducer (such as efavirenz) may decrease the C_{max} and AUC of zanubrutinib by approximately 2 to 3-fold.

Concomitant use of zanubrutinib and strong or moderate inducers of CYP3A can decrease zanubrutinib plasma concentrations.

Gastric Acid Reducing Agents: No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists).

Agents that may have their plasma concentrations altered by zanubrutinib

CYP3A Substrates: Co-administration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) C_{max} by 30% and AUC by 47%.

CYP2C19 Substrates: Co-administration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} by 20% and AUC by 36%.

Other CYP Substrates: No clinically significant differences were observed with warfarin (CYP2C9 substrate) pharmacokinetics or predicted with rosiglitazone (CYP2C8 substrate) pharmacokinetics when co-administered with zanubrutinib.

Transporter Systems: Co-administration of multiple doses of zanubrutinib increased digoxin (P-gp substrate) C_{max} by 34% and AUC by 11%. No clinically significant differences in the pharmacokinetics of rosuvastatin (BCRP substrate) were observed when co-administered with zanubrutinib.

In Vitro Studies

CYP Enzymes: Zanubrutinib is a weak inducer of CYP2B6.

Transporter Systems: Zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No effect on male or female fertility was noted in rats but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 19 and 32 times the human recommended dose in male and female rats, respectively, based on AUC.

Use in pregnancy – Category D

Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

Women should avoid becoming pregnant while taking BRUKINSA and for at least one week after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking BRUKINSA and for at least one week after stopping treatment. Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy. Men should be advised to avoid fathering a child while receiving BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

Malformations in the heart (2- or 3-chambered hearts) were observed in rats given zanubrutinib at all oral doses of 30, 75 or 150 mg/kg/day during organogenesis, in the absence of maternal toxicity. The lowest dose of 30 mg/kg/day is approximately 4 times the human recommended dose, based on AUC.

Embryotoxicity (post-implantation loss) was observed in rabbits given zanubrutinib during the period of organogenesis at doses of 150 mg/kg/day and was associated with maternal toxicity. The dose of 150 mg/kg/day is approximately 25 times the human recommended dose, based on AUC.

Use in lactation

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from zanubrutinib in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

In a pre- and postnatal developmental toxicity study, zanubrutinib was administered to rats at doses of 30, 75, and 150 mg/kg from implantation through weaning. At doses from 75 mg/kg/day, offspring had decreased body weights pre-weaning. All dose groups had offspring with increased incidences of adverse ocular findings (e.g. cataract, protruding eye). The significance of which is unclear. The dose of 30 mg/kg/day is approximately 4 times the human recommended dose, based on AUC.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to evaluate the influence of BRUKINSA treatment on the ability to drive or operate heavy machinery.

Fatigue, dizziness, and asthenia have been reported in some patients taking BRUKINSA and should be considered when assessing a patient's ability to drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety profile is based on pooled data from 1550 patients with B-cell malignancies treated with zanubrutinib in 9 clinical trials, including one Phase 1 clinical study (BGB-3111-1002), one Phase 1/2 clinical study (BGB-3111-AU-003), four Phase 2 studies (BGB-3111-205, BGB-3111-206, BGB-3111-210, BGB-3111-214), and three Phase 3 clinical study (BGB-3111-302, BGB-3111-304, BGB-3111-305).

The most commonly occurring adverse reactions in the 9 studies combined ($\geq 20\%$) were neutropenia[†], thrombocytopenia[†], upper respiratory tract infection[§], bruising[§], haemorrhage/haematoma[§], rash[§], anaemia[†], and musculoskeletal pain[§]. The most common Grade 3 or higher adverse reactions ($\geq 5\%$) were neutropenia[†], pneumonia[§], thrombocytopenia[†], and hypertension.

Discontinuation and dose reduction

Of the 1550 patients treated with zanubrutinib monotherapy, 45 (2.9%) patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment

discontinuation was pneumonia[§] (1.4%). Adverse reactions leading to dose reduction and dose interruption occurred in 5.2% and 23.9% of patients, respectively.

Presented in Table 4 below are adverse reactions that have been reported in association with the use of zanubrutinib monotherapy in the 9 clinical studies. Adverse reactions are listed below by MedDRA body system organ class and by frequency. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 4: Adverse Reactions in Patients Treated with Zanubrutinib

MedDRA SOC	Group Terms/PTs	Zanubrutinib N=1550	
		All Grades*(%)	Grade≥3 (%)
Infections and infestations	Upper respiratory tract infection [§]	Very Common (32.8)	1.9
	Pneumonia ^{§ #}	Very Common (17.8)	9.4
	Pneumonia	Very Common (11.9)	7.0
	Lower respiratory tract infection	Common (4.5)	0.5
	Urinary tract infection [§]	Very Common (11.6)	1.7
	Bronchitis	Common (3.5)	0.6
	Hepatitis B reactivation	Uncommon (0.9)	0.5
Blood and lymphatic system disorders	Neutropenia [†]	Very Common (48.8)	20.5
	Thrombocytopenia [†]	Very Common (35.8)	6.9
	Anaemia [†]	Very Common (22.9)	3.6
Nervous system disorder	Dizziness [§]	Very Common (10.7)	0.3
Vascular disorders	Bruising [§]	Very Common (30.4)	0.5
	Contusion	Very Common (18.1)	0.0
	Petechiae	Common (6.5)	0.1
	Purpura	Common (5.3)	0.2
	Ecchymosis	Common (2.4)	0.1
	Hypertension [§]	Very Common (13.0)	6.5
	Haemorrhage/Haematoma ^{§ #}	Very Common (27.0)	2.8
	Haematuria	Common (9.5)	0.6
	Epistaxis	Common (7.4)	0.1
	Gastrointestinal haemorrhage	Uncommon (0.3)	0.1

Gastrointestinal disorders	Diarrhea	Very Common (18.8)	1.5
	Constipation	Very Common (12.3)	0.3
Skin and subcutaneous tissue disorders	Rash [§]	Very Common (23.2)	0.5
	Pruritis	Common (6.9)	0.1
Musculoskeletal and connective tissue disorders	Musculoskeletal pain [§]	Very Common (22.9)	1.6
	Arthralgia	Very Common (12.8)	0.7
	Back pain	Very Common (9.5)	0.5
General disorders and administration site conditions	Fatigue [§]	Very common (16.2)	1.2
	Fatigue	Very common (11.9)	0.8
	Asthenia	Common (3.5)	0.3
	Oedema peripheral	Common (7.4)	0.2
Respiratory, thoracic and mediastinal disorders	Cough	Very Common (18.6)	0.1

*Adverse events were graded by NCI-CTCAE (v5.0 in LTE1 study and v4.03 in all other studies), except for haematologic toxicities in BGB-3111-304 and -305 studies where IWCLL 2008 Grading Scale were used; Grade 3 = Severe; Grade 4 = Life-threatening

† Based on laboratory measurements.

§ Includes multiple adverse reaction terms.

Includes events with fatal outcome

Hemorrhage: Serious and fatal hemorrhagic events have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Infections: Cases of fatal and non-fatal infections have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Cytopenias: Cases of neutropenia, anemia and thrombocytopenia have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Second primary malignancies: Cases of second primary malignancies have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Atrial fibrillation and flutter: Cases of atrial fibrillation and flutter have been reported in patients treated with zanubrutinib (See section 4.4 *Special Warnings and Special Precautions for Use*)

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was evaluated in relapsed/refractory (RR) or treatment-naïve WM patients with *MYD88* mutation (*MYD88^{MUT}*) in a Phase 3, randomised, open-label clinical trial, BGB-3111-302, that included 101 patients treated with BRUKINSA at a dose of 160 mg twice daily and 98 patients treated with ibrutinib (Cohort 1). Additionally, 28 patients with RR or treatment-naïve WM

found to have *MYD88* wildtype (*MYD88^{WT}*) (N=26) or missing/inconclusive *MYD88* status (N=2) were treated with BRUKINSA in a non-randomised exploratory arm (Cohort 2).

In Cohort 1, the median duration of treatment was 30.3 months in the BRUKINSA arm and 29.9 months in the ibrutinib arm. In Cohort 2, the median duration of treatment was 27.8 months.

Serious treatment-emergent adverse events occurred in 48.5% of patients in the BRUKINSA arm. The most frequent serious adverse events were febrile neutropenia, influenza, pyrexia, and neutropenia (3% each); and anaemia, pneumonia, basal cell carcinoma, lower respiratory tract infection, pleural effusion, sepsis, and thrombocytopenia (2% each).

Of the 101 patients randomised and treated with BRUKINSA, 5% patients discontinued due to adverse events. The events leading to discontinuation were cardiomegaly, neutropenia, plasma cell myeloma, drug-induced liver injury and subdural hemorrhage (1% each). Adverse events leading to dose reduction occurred in 14.9% of patients. The most common adverse events leading to dose reduction were neutropenia (3%) and diarrhea (2%).

Death due to adverse events within 30 days of last dose occurred in 1 (1%) patient. The adverse event leading to death was cardiomegaly.

Table 5 summarises treatment emergent adverse events in patients randomised in Cohort 1 in BGB-3111-302.

Table 5: Treatment-Emergent Adverse Events in $\geq 10\%$ (All Grades*) of Patients with WM in Zanubrutinib or Ibrutinib Arm of Cohort 1 in BGB-3111-302 Trial (ASPEN)

System Organ Class Adverse Event	BRUKINSA (N = 101)		Ibrutinib (N = 98)	
	All Grades* (%)	Grade 3 or Higher (%)	All Grades* (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia	26.7	18.8	14.3	9.2
Anaemia	12.9	5.9	15.3	6.1
Thrombocytopenia	12.9	6.9	12.2	5.1
Cardiac disorders				
Atrial fibrillation	5.0	0	17.3	6.1
Palpitation	5.0	0	10.2	0
Gastrointestinal disorders				
Diarrhoea	21.8	3	33.7	2.0
Nausea	17.8	0	15.3	1.0
Constipation	16.8	0	7.1	0
Vomiting	12.9	0	15.3	1.0
General disorders and administration site conditions				
Fatigue	24.8	1.0	19.4	1.0
Pyrexia	15.8	4.0	13.3	2.0
Peripheral oedema	13.9	0	20.4	0
Infections and infestations				

System Organ Class Adverse Event	BRUKINSA (N = 101)		Ibrutinib (N = 98)	
	All Grades* (%)	Grade 3 or Higher (%)	All Grades* (%)	Grade 3 or Higher (%)
Upper respiratory tract infection	30.9	0	31.6	1.0
Pneumonia [§]	12.9	4	24.5	10.2
Nasopharyngitis	10.9	0	7.1	0
Urinary tract infection	10.9	0	15.3	2.0
Localised infection	1.0	0	11.2	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [§]	36.3	7.9	32.7	1.0
Pain in extremity	13.9	1.0	8.2	0
Muscle spasms	9.9	0	27.6	1.0
Nervous system disorders				
Headache	17.8	1.0	14.3	1.0
Dizziness	13.9	1.0	12.2	0
Renal and urinary disorders				
Haematuria	9.9	1.0	12.2	2.0
Respiratory, thoracic and mediastinal disorders				
Cough	16.8	0	19.4	0
Epistaxis	15.8	1.0	20.4	0
Dyspnoea	14.9	0	7.1	0
Injury, poisoning and procedural complications				
Contusion	14.9	0	25.5	0
Skin and subcutaneous tissue disorders				
Bruising [§]	19.8	0	33.7	0
Rash [§]	19.8	0	23.5	0
Pruritus	12.9	1.0	6.1	0
Vascular disorders				
Haemorrhage [§]	24.8	5.0	27.6	5.1
Hypertension	13.9	8.9	21.4	15.3

* Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Grade 3 = Severe; Grade 4 = Life-threatening

[§] Includes multiple preferred terms:

Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.

Hemorrhage includes all related terms containing hemorrhage, hematoma.

Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

Pneumonia includes pneumonia, pneumonia viral, pneumonia aspiration, lower respiratory tract infection.

Rash includes all related terms containing rash

The safety profile of BRUKINSA in patients with WM in the non-randomised Cohort 2 (*MYD88*^{WT} or missing/inconclusive *MYD88* status, N = 28) was generally consistent with the safety profile for BRUKINSA in Cohort 1.

Hematologic and Chemistry laboratory abnormalities are shown below.

Table 6: Laboratory Abnormalities* (>10%) in Patients with WM in Cohort 1 of BGB-3111-302 Trial (ASPEN)

Laboratory Parameter	BRUKINSA (N = 101)		Ibrutinib (N = 98)	
	All Grades* (%)	Grade 3 or 4 (%)	All Grades* (%)	Grade 3 or 4 (%)
Haematologic laboratory abnormalities				
Haemoglobin decreased	20.8	6.9	22.4	9.2
Neutrophils decreased	52.0	25.0	36.1	9.3
Platelets decreased	35.6	8.9	39.8	5.1
Chemistry laboratory abnormalities				
Alanine aminotransferase increased	15.8	2.0	14.4	2.1
Aspartate aminotransferase increased	12.0	1.0	18.9	2.1
Bilirubin increased	13.0	2.0	33.0	1.0
Creatinine increased	30.7	1.0	23.5	1.0
Urate increased	17.0	3.2	35.6	5.6

* Based on laboratory measurements. Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Grade 3 = Severe; Grade 4 = Life-threatening

Mantle Cell Lymphoma (MCL)

The safety of zanubrutinib was evaluated in 118 patients with MCL who received at least one prior therapy at a dose of 320 mg daily in two single-arm clinical trials, BGB-3111-206 and BGB-3111-AU-003. The median duration of treatment was 22.8 months.

Serious treatment-emergent adverse events occurred in 33.9% of patients. The most frequent ($\geq 2\%$ of patients) serious adverse events were lung infection (6.8%), pneumonia (4.2%), and anaemia (2.5%).

Of the 118 MCL patients treated with zanubrutinib, 13.6% patients discontinued treatment due to adverse events. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%; grouped terms). Adverse events leading to dose reduction occurred in 3.4% of patients; these included hepatitis B, neutropenia, allergic dermatitis, and peripheral sensory neuropathy (in 1 patient each).

Death due to adverse events within 30 days of last dose occurred in 9 (7.6%) patients. The adverse events leading to death were road traffic accident, cerebral hemorrhage, cerebral infarction, congestive cardiac failure, pneumonia (in 2 patients; grouped terms) and unknown reason (in 3 patients).

Table 7 summarises treatment emergent adverse events in BGB-3111-206 and BGB-3111-AU-003.

Table 7: Treatment-Emergent Adverse Events in $\geq 10\%$ (All Grades*) of Patients With Previously Treated MCL in BGB-3111-206 and BGB-3111-AU-003 Trials

System Organ Class Adverse Event	BRUKINSA (N = 118)	
	All Grades* (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders		
Neutrophil count decreased and neutropenia	38	15
Platelet count decreased and thrombocytopenia	31	7
White blood cell count decreased and leukopenia	26	6
Anaemia and haemoglobin decreased	15	8
Gastrointestinal disorders		
Diarrhoea	23	1
Constipation	14	1
Infections and infestations		
Upper respiratory tract infection [§]	37	0
Pneumonia [§]	17	12
Urinary tract infection	13	1
Investigations		
Alanine aminotransferase increased	12	1
Metabolism and nutrition disorders		
Hypokalaemia	14	2
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [§]	14	3
Respiratory, thoracic and mediastinal disorders		
Cough	14	0
Skin and subcutaneous tissue disorders		
Rash [§]	37	0
Bruising [§]	14	0
Vascular disorders		
Haemorrhage [§]	12	3
Hypertension	11	3

* Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Grade 3 = Severe; Grade 4 = Life-threatening

[§] Includes multiple preferred terms:

Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.

Hemorrhage includes all related terms containing hemorrhage, hematoma.

Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis. Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.

Rash includes all related terms containing rash.

Upper respiratory tract infection includes PTs of upper respiratory tract infection and viral upper respiratory tract infection.

Hematologic and Chemistry laboratory abnormalities are shown below.

Table 8: Selected Laboratory Abnormalities*(>10%) in Patients With MCL in BGB-3111-206 and BGB-3111-AU-003 Trials

Laboratory Parameter	BRUKINSA (N = 101)	
	All Grades* (%)	Grade 3 or 4 (%)
Hematologic laboratory abnormalities		
Neutrophils decreased	45	20
Platelets decreased	44	9
Haemoglobin decreased	30	6
Lymphocytes increased	41	16
Chemistry laboratory abnormalities		
Alanine aminotransferase increased	30	1
Bilirubin increased	26	1
Urate increased	31	3

* Based on laboratory measurements (at least 1 severity grade higher than at baseline). Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCA E) version 4.03. Grade 3 = Severe; Grade 4 = Life-threatening

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL)

The safety of BRUKINSA was evaluated in 938 patients with CLL/SLL across 5 clinical studies: two phase 3 [BGB-3111-304 (SEQUOIA) (n=391) and BGB-3111-305 (ALPINE) (n=324)] and three early phase studies (Phase 2, Phase 1/2 and Phase 1) [Study BGB-3111-205 (n=91), Study BGB-3111-AU-003 (n=123) and Study BGB-3111-1002 (n=9)].

In the BRUKINSA group, approximately 66% of patients were ≥ 65 years of age at study entry, which allowed for an adequate assessment of the safety of BRUKINSA in older patients. Sixty-six percent of patients in the BRUKINSA group were male; 74% of patients were White and 21% were Asian.

Of the 938 patients with CLL/ SLL treated with BRUKINSA, adverse events led to treatment discontinuation in 8.0%, dose reduction in 7.5% and dose interruptions in 41.4% of patients. Adverse events leading to death were reported in 36 (3.8%) patients.

SEQUOIA (BGB-3111-304)

The safety of BRUKINSA monotherapy was evaluated in previously untreated CLL/SLL patients in a randomised, multicentre, open-label, actively controlled phase 3 trial. Patients without del(17p) mutation (Cohort 1) were randomised to receive either BRUKINSA (n=240) until disease progression or unacceptable toxicity or bendamustine plus rituximab (BR) (n = 227) up to 6 cycles. The safety of BRUKINSA monotherapy was also evaluated in 111 previously untreated CLL/SLL patients with del(17p) mutation in a non- randomised single arm (Cohort 2). Patients received BRUKINSA monotherapy until disease progression or unacceptable toxicity.

Cohort 1

The overall median durations of exposure were 6 months and 26 months among patients treated with bendamustine plus rituximab, and BRUKINSA, respectively.

Table 9 summarises treatment-emergent adverse events in SEQUOIA (Cohort 1).

Table 9: Treatment-Emergent Adverse Events Occurring in $\geq 10\%$ (All Grades*) of Patients With Treatment Naïve CLL/SLL in BGB-3111-304 (SEQUOIA) (Cohort 1)

System Organ Class Preferred Term	BRUKINSA (N=240)		Bendamustine/Rituximab (N=227)	
	All Grade %	\geq Grade 3 %	All Grade %	\geq Grade 3 %
Blood and lymphatic system disorders				
Neutropenia ^a	15.8	11.7	55.9	49.3
Thrombocytopenia ^a	4.6	2.1	16.7	7.9
Anaemia ^a	4.6	0.4	17.6	1.3
Gastrointestinal disorders				
Diarrhoea	13.8	0.8	11.5	1.8
Constipation	10.0	0.4	17.6	0.0
Nausea	10.0	0.0	32.6	1.3
Vomiting	7.1	0.0	13.7	0.9
General disorders and administration site conditions				
Fatigue ^a	14.2	1.3	20.7	1.8
Pyrexia	7.1	0.0	26.4	3.5
Infections and infestations				
Upper respiratory tract infection ^a	21.7	0.8	11.5	0.4
Injury, Poisoning and procedural complications				
Infusion related reaction	0.4	0.0	18.9	2.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^a	24.6	0.8	11.9	0.4
Nervous system disorders				
Headache	10.8	0.0	6.6	0.0
Dizziness ^a	10.8	0.8	4.8	0.0
Respiratory, thoracic and mediastinal disorders				

System Organ Class Preferred Term	BRUKINSA (N=240)		Bendamustine/Rituximab (N=227)	
	All Grade %	≥ Grade 3 %	All Grade %	≥ Grade 3 %
Cough ^a	15.0	0.0	9.7	0.0
Skin and subcutaneous tissue disorders				
Rash ^a	17.9	1.3	28.6	4.4
Bruising ^a	27.9	0.4	2.6	0.0
Vascular disorders				
Haemorrhage/Haematoma ^{a†}	24.2	2.9	4.0	0.4
Hypertension	12.1	6.3	4.0	2.2

^a Include multiple preferred terms; Grade 3 = Severe; Grade 4 = Life-threatening

Haematologic and Chemistry laboratory abnormalities are shown below.

Table 10: Selected Laboratory Abnormalities*(>10%) in Treatment naïve Patients With CLL/SLL in BGB-3111-304 (SEQUOIA) (Cohort 1)

Laboratory Abnormality	BRUKINSA (N = 240)		Bendamustine/Rituximab (N = 227)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic Abnormalities				
Platelets decreased	30.5	2.5	73.1	23.8
Neutrophils decreased	40.2	14.2	82.4	52.4
Haemoglobin decreased	16.3	0.4	54.2	0.4
Chemistry Abnormalities				
Alanine Aminotransferase increased	21.3	2.1	23.8	2..6
Aspartate aminotransferase increased	12.1	2.1	28.3	1.8

* Based on laboratory measurements (at least 1 severity grade higher than at baseline); Grade 3 = Severe; Grade 4 = Life-threatening

Cohort 2

In this group of previously untreated CLL/SLL patients (n=111) with del(17p) mutation, the overall median treatment duration was 30 months. Serious treatment-emergent adverse events occurred in 45 (40.5%) patients. The most frequent serious treatment-emergent adverse event was pneumonia (6 [5.4%] patients).

The rates of individual treatment-emergent adverse events were similar between Cohorts 1 and 2 patients without and with del(17p) given BRUKINSA, respectively.

ALPINE (BGB-3111-305)

The safety of BRUKINSA monotherapy was evaluated in patients with previously treated CLL/SLL in a randomised, multicentre, open-label, Phase 3 actively controlled trial. In ALPINE, 324 patients received BRUKINSA monotherapy, and 324 patients received ibrutinib monotherapy until disease progression or unacceptable toxicity.

In ALPINE, the median durations of exposure were 14 months for BRUKINSA and 13 months for ibrutinib.

Seventy patients in the BRUKINSA arm (22%) reported ≥ 1 serious treatment-emergent adverse event. The most frequent serious adverse event was pneumonia (3.1%).

Table 11 summarises the rates of atrial fibrillation and flutter with BRUKINSA vs ibrutinib based on a pre-specified analysis.

Table 11: Rate of Atrial Fibrillation/Flutter in BGB-3111-305 (ALPINE)Error! No document variable supplied.

	BRUKINSA (N = 204)	Ibrutinib (N = 207)
Rate of Atrial Fibrillation/Flutter ^a , n(%)	5 (2.5)	21 (10.1)
(95% CI)	(0.8, 5.6)	(6.4, 15.1)
Rate difference ^b , % (95% CI)	-7.7 (-12.3, -3.1)	
	2-sided p-value = 0.0014	

^a Patients reported a treatment-emergent adverse event with a preferred term of atrial fibrillation or atrial flutter.

^b Rate difference is the BRUKINSA rate minus the ibrutinib rate.

Table 12 summarises treatment-emergent adverse events in BGB-3111-305 (ALPINE).

Table 12: Treatment-Emergent Adverse Events Occurring in $\geq 10\%$ (All Grades*) of Patients With Previously Treated CLL/SLL in BGB-3111-305 (ALPINE)

System Organ Class Preferred Term	BRUKINSA (N = 324)		Ibrutinib (N = 324)	
	All Grades (%)	\geq Grade 3 %	All Grades (%)	\geq Grade 3 %
Blood and lymphatic system disorders				
Neutropenia ^a	21.3	13.9	17.3	12.7
Anaemia ^a	11.7	2.2	13.9	2.5
Thrombocytopenia	9.3	2.8	10.8	2.8
Gastrointestinal disorders				
Diarrhoea	11.7	1.2	18.8	0.3
General disorders and administration site conditions				

Fatigue ^a	11.1	0.3	10.8	0.3
Infections and infestations				
Upper respiratory tract infection ^a	17.0	0.3	14.2	1.2
Pneumonia ^a	9.9	4.6	10.8	5.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^a	13.3	0.0	17.9	0.3
Skin and subcutaneous tissue disorders				
Rash ^a	13.6	0.6	14.8	0.3
Bruising ^a	19.4	0.0	12.7	0.0
Vascular disorders				
Haemorrhage/Haematoma ^a	18.2	0.9	17.6	2.2
Hypertension	12.3	8.0	9.6	5.2

^a Include multiple preferred terms; Grade 3 = Severe; Grade 4 = Life-threatening

Haematologic and Chemistry laboratory abnormalities are shown in Table 13.

Table 13: Selected Laboratory Abnormalities (≥ 10%) in Patients With Previously Treated CLL/SLL in BGB-3111-305 (ALPINE)

Laboratory Abnormality	BRUKINSA (N = 324)		Ibrutinib (N = 324)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic Abnormalities				
Platelets decreased	25.9	1.9	31.0	2.8
Neutrophils decreased	40.3	10.9	28.1	12.5
Hemoglobin decreased	16.9	0.3	18.8	0.6
Chemistry Abnormalities				
Alanine aminotransferase increased	10.9	0.0	9.4	0.9

* Based on laboratory measurements (at least 1 severity grade higher than at baseline); Grade 3 = Severe; Grade 4 = Life-threatening

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <https://nzphvc.otago.ac.nz/reporting/>.

4.9 OVERDOSE

There is no specific antidote for BRUKINSA. For patients who experience overdose, closely monitor and provide appropriate supportive treatment.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, Bruton's tyrosine kinase inhibitors. ATC code: L01EL03.

Mechanism of action

Zanubrutinib is a small-molecule inhibitor of BTK. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.

Pharmacodynamic effects

BTK occupancy in peripheral blood mononuclear cells and lymph node biopsies

The median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100% over 24 hours at a total daily dose of 320 mg in patients with B-cell malignancies. The median steady-state BTK occupancy in lymph nodes was 94% and 100% following the approved recommended dosage of 320 mg once daily, or 160 mg twice daily respectively.

Effect on QT/QTc interval and cardiac electrophysiology

At the approved recommended doses (320 mg once daily or 160 mg twice daily), there were no clinically relevant effects on the QTc interval. At a single dose 1.5 times the maximum recommended dose (480 mg), zanubrutinib did not prolong the QT interval to any clinically relevant extent (i.e., ≥ 10 msec).

Clinical trials

Waldenström's Macroglobulinemia (WM)

BGB-3111-302 (ASPEN): A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton tyrosine kinase Inhibitors BGB-3111 and Ibrutinib in Patients with Waldenström Macroglobulinemia

BGB-3111-302 is a randomised, open-label, multicentre study comparing zanubrutinib and ibrutinib in subjects with Waldenström macroglobulinemia (WM). Eligible patients were at least 18 years of age with a clinical and definite histological diagnosis of relapsed/refractory WM or treatment-naïve when considered by their treating physician to be unsuitable for standard chemo-immunotherapy regimens. Patients had to meet at least one criterion for treatment according to consensus panel criteria from the Seventh International Workshop on Waldenström's Macroglobulinemia (IWWM)

and have measurable disease, as defined by a serum IgM level > 0.5 g/dl. Patients with *MYD88* mutation (*MYD88^{MUT}*) were assigned to Cohort 1 (N = 201) and were randomised 1:1 to receive either zanubrutinib 160 mg twice daily (Arm A) or ibrutinib 420 mg once daily (Arm B) until disease progression or unacceptable toxicity. Subjects found to have *MYD88* wildtype (*MYD88^{WT}*) by gene sequencing (estimated to be present in approximately 10% of enrolled subjects), were enrolled to Cohort 2 (N = 26) and received zanubrutinib 160 mg twice daily on a third, non-randomised, study arm (Arm C). In addition, those subjects whose *MYD88* mutational status was missing or inconclusive (N = 2) were assigned to Cohort 2, Arm C.

In Cohort 1 overall, the median age was 70 years (range, 38 to 90 years), 27.9% were > 75 years (22.2% on the ibrutinib arm, 33.3% on the zanubrutinib arm), 67 % were male, and 91% were Caucasian. At study entry, patients had an International Prognostic Scoring System (IPSS) high categorisation, derived using M-protein by serum protein electrophoresis (SPEP), as follows: 44.4% of patients in the ibrutinib arm and 46.1% of patients in the zanubrutinib arm. Ninety-four percent of patients had a baseline ECOG performance status of 0 or 1, and 6.5% had a baseline ECOG performance status of 2. One-hundred-sixty-four patients had relapsed or refractory disease; the median number of prior therapies was 1 (range, 1 to 8). The median time from initial diagnosis was 4.63 years. Overall, 74 (37 %) patients had IgM levels \geq 40 g/L.

In Cohort 2, the median age was 72 years (range, 39 to 87), 42.9% were > 75years, 50% were male, and 96.4 % were Caucasian. At study entry, 42.9% of the patients had an IPSS high categorisation (derived using M-protein by SPEP). Baseline ECOG performance status score was 0 or 1 in 86 % of patients and 14 % had a baseline ECOG performance status of 2. Twenty-three of the 28 patients in Cohort 2 had relapsed or refractory disease, with a median number of prior therapies of 1 (range, 1 to 5). The median times from initial diagnosis was slightly shorter than in Cohort 1 (median 3.65 years versus 4.6 years). Eight (29 %) patients in Cohort 2 had IgM levels \geq 40 g/L.

In Cohort 1, the primary outcome measure was rate of Complete Response (CR) or Very Good Partial Response (VGPR), as assessed by IRC with adaptation of the response criteria updated at the Sixth IWWM. The secondary endpoints for Cohort 1 include MRR, duration of response, rate of CR or VGPR determined by investigator, PFS, resolution of treatment-precipitating symptoms, and anti-lymphoma effects in bone marrow and extramedullary disease. The median follow-up was 19.4 months (range 0.5 to 31.1 months) for ibrutinib -treated patients and 19.5 months (range 0.4 to 31.2 months) for zanubrutinib-treated patients. The study did not meet statistical significance for the pre-specified efficacy outcome of superior CR+VGPR as assessed by IRC, tested first in patients with R/R disease in ASPEN. Results are shown in Table 14.

Table 14: Analysis of Disease Response Per Overall Combined Assessment by Independent Review Committee (Study BGB-3111-302; Cohort 1) (Overall WM Population)

	Ibrutinib N = 99	Zanubrutinib N = 102
Response Category		
VGPR or CR rate, n (%)	19 (19.2)	29 (28.4)
95% CI ^a	(12.0, 28.3)	(19.9, 38.2)
Risk difference (%) ^b	10.2	
95% CI ^a	(-1.5, 22.0)	
p-value ^c	0.0921	
MRR (PR or better), n (%)	77 (77.8)	79 (77.5)
95% CI ^a	(68.3, 85.5)	(68.1, 85.1)

	Ibrutinib N = 99	Zanubrutinib N = 102
Response Category		
Risk difference (%) ^b	-0.5	
95% CI	(-12.2, 11.1)	
ORR (MR or better), n (%)	92 (92.9)	96 (94.1)
95% CI ^a	(86.0, 97.1)	(87.6, 97.8)

Percentages are based on N.

^a 2-sided Clopper-Pearson 95% confidence interval.

^b Mantel-Haenszel common risk difference with the 95% confidence interval calculated using a normal approximation and Sato's standard error stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65). Ibrutinib is the reference group.

^c Based on CMH test stratified by the stratification factors per IRT (strata CXCR4 WT and UNK are combined) and age group (≤ 65 and > 65)

In the overall population in Cohort 1, the event-free rates at 12 months for patients in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 87.2% versus 89.7%, respectively, and 83.8% versus 85.0% at 18 months. The event-free rates at 12 months for relapsed/refractory patients in the ibrutinib and zanubrutinib treatment arms per overall combined assessment were 85.9% versus 92.4%, respectively, and 81.7% versus 85.9% at 18 months.

Results for Cohort 2 are presented in Table 15.

Table 15: Analysis of Disease Response Per Overall Combined Assessment by Independent Review Committee (Study BGB-3111-302; Cohort 2) (Efficacy Analysis Set)

Response Category	Zanubrutinib N = 26
VGPR or CR rate, n (%)	7 (26.9)
95% CI ^a	(11.6, 47.8)
MRR (PR or better), n (%)	13 (50.0)
95% CI ^a	(29.9, 70.1)
ORR (MR or better), n (%)	21 (80.8)
95% CI ^a	(60.6, 93.4)

Percentages are based on N.

^a Includes patients whose only overall tumor response available is progressive disease unconfirmed (PDU).

In the overall population in Cohort 2, the event-free rates at 12 and 18 months were 72.4% and 68.1%, respectively, per overall combined assessment.

BGB-3111-AU-003: A Phase I/II, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB 3111 in Patients With B-Cell Lymphoid Malignancies

BGB-3111-AU-003 is a Phase 1/2 open-label, dose-escalation, multicentre, single arm trial of B-cell malignancies including 78 WM patients. Zanubrutinib was given orally at starting doses ranging from 40 mg daily to 160 mg twice daily until disease progression or unacceptable toxicity. Most patients (93%) received a total daily dose of 320 mg daily (either 320 mg once daily or 160 mg twice daily).

The median age of patients was 67 years (range 40 to 87), 80% were male, and 86 % were Caucasian. Ninety-six percent of patients had a baseline ECOG performance status of 0 or 1, and 4 % had a baseline ECOG performance status of 2. Fifty-four patients had relapsed or refractory disease; the

median number of prior therapies was 2 (range, 1 to 8). The median time from initial diagnosis was 4.31 years. Overall, 24 (31%) patients had IgM levels \geq 40 g/L.

Seventy-three patients were evaluable for efficacy. Assessment of response was evaluated using the combined response criteria updated at the Sixth IWWM. Results by investigator are shown in Table 16.

Table 16: Assessment of Response (WM Efficacy Evaluable Set) Per Overall Combined Assessment by Investigator (BGB-3111-AU-003)

Response Category	Relapsed/Refractory WM (N = 49)	Total WM (N = 73)
Best Overall Response, n (%)		
CR	1 (2.0)	1 (1.4)
VGPR	24 (49.0)	32 (43.8)
PR	14 (28.6)	27 (37.0)
VGPR or CR Rate, n (%)	25 (51.0)	33 (45.2)
95% CI ^a	(36.3, 65.6)	(33.5, 57.3)
Major Response Rate (PR or Better), n (%)	39 (79.6)	60 (82.2)
95% CI ^a	(65.7, 89.8)	(71.5, 90.2)
Overall Response Rate (MR or Better), n (%)	46 (93.9)	70 (95.9)
95% CI ^a	(83.1, 98.7)	(88.5, 99.1)
Median Study Follow-up (Range)	35.81 (4.44, 57.17)	30.32 (4.44, 57.17)

Abbreviations: BTK, Bruton tyrosine kinase; CI, confidence interval; CR, complete response; NE, not estimable; PR, partial response, R/R, relapsed/refractory; VGPR, very good partial response; WM, Waldenström's macroglobulinemia. Percentages are based on N, the number of patients in the WM Efficacy Evaluable Set (i.e., received \geq 1 dose of zanubrutinib, had baseline IgM or M-protein \geq 5 g/L, and no prior exposure to a BTK inhibitor).

^a Calculated using the Clopper-Pearson method.

Data cut-off 31 August 2019

The median durations of VGPR or CR, major response, and overall response have not been reached for the total WM population or relapsed/refractory patients who achieved a response to study treatment.

The estimated event-free rates at 12, 18, and 24 months for the total WM patient population who achieved a major response were 91.6%, 88.0%, and 83.2%, respectively.

Mantle Cell Lymphoma (MCL)

BGB-3111-206: A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL)

BGB-3111-206 is a Phase 2 open-label, multicentre, single arm trial of 86 previously treated MCL patients. Zanubrutinib was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity.

The median age of patients was 60.5 years (range 34 to 75) and the majority were male (77.9%). The median time since diagnosis was 30 months and the median number of prior therapies was 2 (range 1 to 4) and 74.4% of patients had a rituximab regimen. The majority of patients had extranodal involvement (70.9%) and refractory disease (52.3%). Blastoid variant of MCL was present in 14% of patients. The combined biologic MIPI score (which includes age, ECOG score, baseline lactate dehydrogenase, WBC count and Ki-67% staining in tumor cells) was intermediate in 45.3% and high risk in 38.4%.

Tumor response was according to the 2014 Lugano Classification and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee (IRC).

Table 17: BGB-3111-206 Efficacy Results in MCL Patients by Independent Review Committee

	Study BGB-3111-206 (N=86)
Median Follow Up Time	18.4 months
ORR (95% CI)	83.7% (74.2, 90.8)
CR	68.6%
PR	15.1%
Median DoR in months (95% CI)	19.5 (16.6, NE)

Note: Percentages were based on N.

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: non-evaluable.

BGB-3111-AU-003: A Phase I/II, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB 3111 in Patients With B-Cell Lymphoid Malignancies

BGB-3111-AU-003 is a Phase 1/2 open-label, dose-escalation, multicentre, single arm trial of B-cell malignancies including 37 previously treated MCL patients. Zanubrutinib was given orally at starting doses ranging from 40 mg daily to 160 mg twice daily until disease progression or unacceptable toxicity. Most patients (32/37) received a total daily dose of 320 mg daily (either 320 mg once daily or 160 mg twice daily).

The median age of patients of the 32 R/R MCL patients receiving 320 mg daily was 70 years (range 42 to 86), and 37.5% of patients were ≥ 75 years old. The majority of patients were male (68.8%). The median time since diagnosis was 4.5 years and the median number of prior therapies was 1 (range 1 to 4) and 93.8% had a prior rituximab regimen. The majority of patients had extranodal involvement (78.1%), and 25% had refractory disease. The MIPI score (which includes age, ECOG score, baseline lactate dehydrogenase and WBC count) was intermediate in 40.6% and high risk in 31.3%.

Tumour response was according to the 2014 Lugano Classification and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee. PET scans were not required per protocol, and most responses were assessed using CT imaging.

Table 18: BGB-3111-AU-003 Efficacy Results in MCL Patients by Independent Review Committee

	Study BGB-3111-AU-003 (N=32)
Median Follow Up Time	14.75 months
ORR (95% CI)	84.4% (67.2, 94.7)
CR	25.0%*
PR	59.4%
Median DoR in months (95% CI)	18.53 (12.58, NE)

Note: Percentages were based on N.

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, PFS: progression free survival, CI: confidence interval, NE: non-evaluable.

* Only CT scans were mandated.

This medicine has been given provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited regarding the Mantle Cell Lymphoma (MCL) indication, specifically additional data to support clinical benefit from confirmatory trials.

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL)

The efficacy of BRUKINSA in patients with CLL/SLL was evaluated in two randomised-controlled trials.

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

BGB-3111-304 is an ongoing randomised multicentre, open-label, active controlled Phase 3 trial with 4 treatment cohorts in patients with previously untreated CLL/SLL. Cohorts 1 and 2 were included in an interim study report. In Cohort 1 patients without del(17p) were randomised to receive BRUKINSA 160 mg bd until disease progression or unacceptable toxicity (Arm A, n=241) or bendamustine (B) 90 mg/m²/day via IV infusion on the first 2 days of each cycle for 6 x 28 day cycles and rituximab (R) 375 mg/m² via IV infusion for Cycle 1 and 500 mg/m² for Cycles 2 to 6 (Arm B, n=238). Randomisation in Cohort 1 was stratified by age (<65 yrs vs. ≥65 yrs), Binet stage (C vs. A or B), IGHC mutational status (mutated vs. unmutated) and geographic region (N. America vs. Europe vs. Asia Pacific). In Cohort 2 patients with del(17p) all received open-label BRUKINSA (Arm C, n=110) with the same dose regimen as in Arm A.

Demographic and baseline characteristics were generally balanced between Arm A and Arm B of Cohort 1; Arm A had a slightly higher proportion of white patients (91.7%) compared with Arm B (86.6%). In both arms, the median age was 70.0 years, with a slightly higher proportion of patients of ≥ 75 years (26.1%) in Arm A compared with Arm B (22.3%) and a slightly lower proportion of patients 65-75 years old (55.2%) in Arm A compared with Arm B (58.4%).

Demographic and baseline characteristics were generally similar between Arm A in Cohort 1 and Cohort 2 (Arm C). The median age in Cohort 2 was 70.0 years. The proportion of patients 65-75 years

old was 55.2% in Arm A and 61.3% in Cohort 2. Arm A included 13.7% and Cohort 2 included 42.3% patients from the Asia Pacific region.

For Cohorts 1 and 2, the primary endpoint was progression-free survival, assessed by an independent central review committee (ICRC) using the 2008 IWCLL guidelines for CLL and the Lugano criteria for SLL. Secondary endpoints included the overall response rate based on ICRC assessment.

In Cohort 1, the median duration of follow-up was 25.0 months (range: 0.0 to 41.4). The estimated progression event-free rate at 24 months was 85.5% (95% CI 80.1, 89.6) for BRUKINSA and 69.5% (95% CI 62.4, 75.5) for bendamustine + rituximab. In Cohort 2, the median duration of follow up was 27.9 (range: 1.0 to 38.8) and the estimated progression event-free rate at 24 months 88.9% (95% CI 81.3, 93.6).

There were 228 (94.6%) patients with an overall response (complete or partial response) in the BRUKINSA arm and 203(85.3%) in the B+R arm in Cohort 1. The estimated 18-month event-free rate in these patients was 91.7% in the BRUKINSA arm and 81.3% in the B+R arm. The estimated 24-month event-free rate was 87.5% in the BRUKINSA arm and 70.3% in the B+R arm.

Additional efficacy results are presented in Table 19.

Table 19: Efficacy Results in BGB-3111-304 (SEQUOIA)

Endpoint	Cohort 1* Patients without del(17p)		Cohort 2 Patients with del(17p)
	BRUKINSA (N = 241)	Bendamustine + Rituximab (N = 238)	BRUKINSA (N = 110)
Progression-Free Survival			
Number of Events, n (%)	36 (14.9)	71 (29.8)	15 (13.6)
Disease Progression, n (%)	27 (11.2)	59 (24.8)	14 (12.7)
Death, n (%)	9 (3.7)	12 (5.0)	1 (0.9)
Median (95% CI), months ^a	NE (NE, NE)	33.7 (28.1, NE)	NE (NE, NE)
Hazard Ratio (95% CI) ^b	0.42 (0.28, 0.63)		N/A
P value ^c	< 0.0001		N/A
Overall Response Rate % (95% CI)	94.6% (91.0, 97.1)	85.3% (80.1, 89.5)	90.0% (82.8, 94.9)

Overall Response Rate: CR+CRi+nPR+PR, CR: complete response, CRi: complete response with incomplete hematopoietic recovery, nPR: nodular partial response, PR: partial response, CI: confidence interval, NE: not estimable

* ITT analysis set

^a Based on Kaplan-Meier estimation.

^b Based on a stratified Cox-regression model with bendamustine + rituximab as the reference group.

^c Based on a stratified log-rank test.

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

BGB-3111-305 is a randomised, multicentre, open-label, Phase 3, active controlled trial. It enrolled 652 patients with relapsed or refractory CLL/SLL after at least one prior systemic therapy. The patients were randomised to either BRUKINSA 160 mg orally twice daily or ibrutinib 420 mg orally once daily, continued until disease progression or unacceptable toxicity.

Randomisation was stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del(17p)/TP53 mutation status (present or absent).

Interim Analysis for ORR

Of 652 patients total, 327 were assigned to BRUKINSA monotherapy, 325 to ibrutinib monotherapy. The efficacy evaluation is based on the pre-specified interim analysis of the first 415 randomised patients of the ITT population. Of these, 207 were randomised to BRUKINSA monotherapy, 208 to ibrutinib monotherapy.

Baseline demographics and disease characteristics were generally balanced between treatment arms in the intent-to-treat (ITT) analysis set and in the first 415 randomised patients. The BRUKINSA arm had a higher proportion of female patients compared with the ibrutinib arm (34.9% versus 28.6% in the ITT analysis set and 31.4% versus 25.0% in the first 415 randomised patients). In the ITT analysis set, the median age was 67.0 years in the BRUKINSA arm and 68.0 years in the ibrutinib arm, and 67.0 in both arms of the first 415 randomised patients. In both arms of the ITT analysis set 61.5% of patients were ≥ 65 years old. In the first 415 randomized patients, 62.3% of patients in the BRUKINSA arm and 61.5% in the ibrutinib arm were ≥ 65 years old. In the ITT analysis set 97.9% of patients in the BRUKINSA arm and 96.0% in the ibrutinib arm had an ECOG PS of 0 or 1, and 98.1% and 95.7%, respectively, in the first 415 randomised patients 98.1%.

The primary endpoint was overall response rate (defined as partial response or better) as determined by investigator assessment, using the 2008 iwCLL guidelines for CLL and the Lugano criteria for SLL.

Efficacy results are shown in Table 20.

Table 20: Efficacy Results in BGB-3111-305 (ALPINE) (Pre-specified Interim Analysis of the First 415 Randomised Patients)

Endpoint	Investigator Assessed		Independently Assessed*	
	BRUKINSA (N = 207)	Ibrutinib (N = 208)	BRUKINSA (N = 207)	Ibrutinib (N = 208)
Overall Response Rate n (%) (95% CI)	162 (78.3) (72.0, 83.7)	130 (62.5) (55.5, 69.1)	158 (76.3) (69.9, 81.9)	134 (64.4) (57.5, 70.9)
Response ratio ^a (95% CI)	1.25 (1.10, 1.41)		1.17 (1.04, 1.33)	
Non-inferiority ^b	1-sided p-value < 0.0001		1-sided p-value < 0.0001	
Superiority ^c	2-sided p-value 0.0006		2-sided p-value 0.0121	

Duration of Response ^d : 12-months event-free rate % (95% CI)	89.8 (78.1, 95.4)	77.9 (64.7, 86.7)	90.3 (82.3, 94.8)	78.0 (66.1, 86.2)
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Overall Response Rate: CR + Cri + nPR + PR, CR: complete response, CRi: complete response with incomplete haematopoietic recovery, nPR: nodular partial response, PR: partial response, CI: confidence interval

* By independent central review committee

^a Response ratio: estimated ratio of the overall response rate in the BRUKINSA arm divided by that in the ibrutinib arm.

^b Stratified test against a null response ratio of 0.8558.

^c Stratified Cochran-Mantel-Haenszel test.

^d Kaplan-Meier estimate.

BRUKINSA demonstrated non-inferiority (1-sided $p < 0.0001$) and superiority (2-sided $p = 0.0006$) to ibrutinib in the protocol-specified primary endpoint, overall response rate assessed by investigator and noninferiority to ibrutinib in independently assessed overall response rate (1-sided $p < 0.0001$).

In the total of 652 enrolled patients, the 12-months event-free rates, assessed by independent central review, were 90.4% (95% CI, 85.7, 93.6) for the BRUKINSA arm and 81.7% (95% CI, 75.8, 86.4) for the ibrutinib arm.

In patients with del(17p) mutation in the first 415 randomised patients, the overall response rates were, based on investigator assessment, 83.3% (95% CI 62.5, 95.3; 20 of 24 patients) in the BRUKINSA group and 53.8% (95% CI 33.4, 73.4; 14 of 26 patients) in the ibrutinib group. Based on independent review, the overall response rates were 79.2% (95% CI 57.8, 92.9; 19 of 24 patients) in the BRUKINSA group and 61.5% (95% CI 40.6, 79.8; 16 of 26 patients) in the ibrutinib group.

Final Analysis for ORR

As of the data cutoff date of December 01, 2021, the overall response rate by investigator assessment was higher for patients in the ~~zanubrutinib~~ BRUKINSA arm (79.5% [95% CI: 74.7% to 83.8%]) compared with the ibrutinib arm (71.1% [95% CI: 65.8% to 75.9%]) (ITT Analysis Set) (Table 24). The response ratio for the two arms was 1.12 (95% CI: 1.02 to 1.22).

In patients with del(17p)/TP53 mutation, the overall response rates were, based on investigator assessment, 80.0% (95% CI 69.2, 88.4; 60 of 75 patients) in the BRUKINSA group and 58.7% (95% CI 46.7, 69.9; 44 of 75 patients) in the ibrutinib group. Based on independent review, the overall response rates were 81.3% (95% CI 70.7, 89.4; 61 of 75 patients) in the BRUKINSA group and 65.3% (95% CI 53.5, 76.0; 49 of 75 patients) in the ibrutinib group.

Efficacy results at final analysis are shown in Table 21.

Table 21: Efficacy Results in BGB-3111-305 (ALPINE)

Endpoint	Investigator Assessed		Independently Assessed ^a	
	Zanubrutinib BRUKINSA (N=327)	Ibrutinib (N=325)	Zanubrutinib BRUKINSA (N=327)	Ibrutinib (N=325)
Overall response rate ^b n (%) (95% CI, %)	260 (79.5) (74.7, 83.8)	231 (71.1) (65.8, 75.9)	263 (80.4) (75.7, 84.6)	237 (72.9) (67.7, 77.7)
Response Rate Ratio (95% CI) ^c	1.12 (1.02, 1.22)		1.1 (1.01, 1.2)	
2-sided p-value ^d	0.0133		0.0264	

Duration of response ^c : Rate at 12 months, % (95% CI)	92.2 (87.7, 95.1)	85.8 (79.5, 90.2)	91.6 (87, 94.6)	86.4 (80.5, 90.7)
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Overall Response Rate: CR + Cri + nPR + PR, CR: complete response, CRi: complete response with incomplete hematopoietic recovery, nPR: nodular partial response, PR: partial response, CI=Confidence interval.

^a By independent central review committee.

^b Responders are defined as patients with a best overall response of partial response or higher.

^c Response ratio is the estimated ratio of the overall response rate of the BRUKINSA arm divided by that of the ibrutinib arm.

^d 2-sided p-value is calculated via stratified Cochran-Mantel-Haenszel test statistic.

^e Based on Kaplan-Meier estimate method with 95% CIs estimated using the Greenwood's formula.

With an estimated median follow-up for progression-free survival of 22.1 months, the 12-month progression-free survival rates by investigator assessment were 91.5% (95% CI, 87.8, 94.1) for the ~~zanubrutinib~~ BRUKINSA arm and 84.5% (95% CI, 79.9, 88.1) for the ibrutinib arm. The 12-month progression-free survival rates, assessed by independent review, were 91.4% (95% CI, 87.8, 94.1) for the ~~zanubrutinib~~ BRUKINSA arm and 84.7% (95% CI, 80.2, 88.3) for the ibrutinib arm.

Final Analysis for PFS

At the prespecified final analysis, the median PFS follow-up time was 30.7 months. ~~Zanubrutinib~~ BRUKINSA demonstrated superiority in PFS over ibrutinib.

The median PFS follow-up assessed by investigator was 28.1 months overall.

Efficacy results for ORR and PFS are shown in Table 22.

Table 22: Efficacy Results in BGB-3111-305 (ALPINE)

Endpoint	Investigator Assessed		Independently Assessed*	
	BRUKINSA (N=327)	Ibrutinib (N=325)	BRUKINSA (N=327)	Ibrutinib (N=325)
Overall Response Rate n (%) (95% CI)	273 (83.5) (79.0, 87.3)	241 (74.2) (69.0, 78.8)	282 (86.2) (82.0, 89.8)	246 (75.7) (70.7, 80.3)
Response ratio ^a (95% CI)	1.12 (1.04, 1.22)		1.14 (1.05, 1.22)	
2-sided p-value ^b	0.0035		0.0007	
Progression-Free Survival				
Events, n (%)	87 (26.6)	118 (36.3)	88 (26.9)	120 (36.9)
Hazard Ratio ^c (95% CI)	0.65 (0.49, 0.86)		0.65 (0.49, 0.86)	
2-sided p-value ^d	0.0024		0.0024	
PFS rate at 12-months % (95% CI) ^e	91.3 (87.6, 93.9)	84.1 (79.6, 87.7)	92.5 (89.0, 94.9)	84.8 (80.3, 88.3)
PFS rate at 24-months % (95% CI) ^e	78.4 (73.3, 82.7)	65.9 (60.1, 71.1)	79.5 (74.5, 83.6)	67.3 (61.5, 72.4)

Overall Response Rate: CR + Cri + nPR + PR, CR: complete response, CRi: complete response with incomplete hematopoietic recovery, nPR: nodular partial response, PR: partial response, CI: confidence interval.

^a Response ratio: estimated ratio of the overall response rate in the BRUKINSA arm divided by that in the ibrutinib arm.

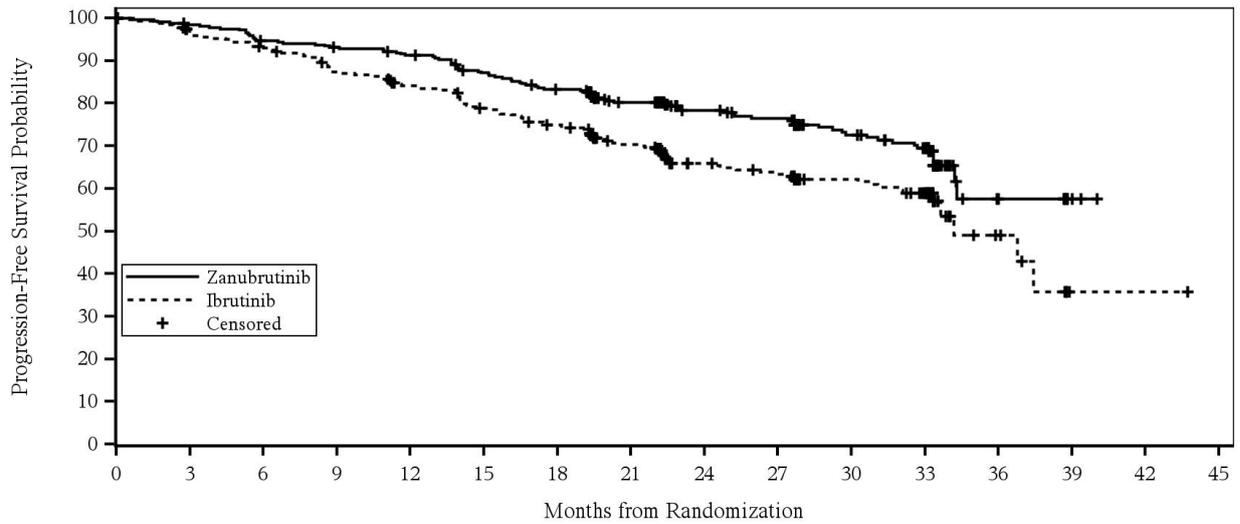
^b Stratified Cochran-Mantel-Haenszel test; descriptive p-value as superiority met at prior planned analysis.

^c Based on a stratified Cox-regression model with ibrutinib as the reference group.

^d Based on a stratified log-rank test.

^e Based on Kaplan-Meier estimation.

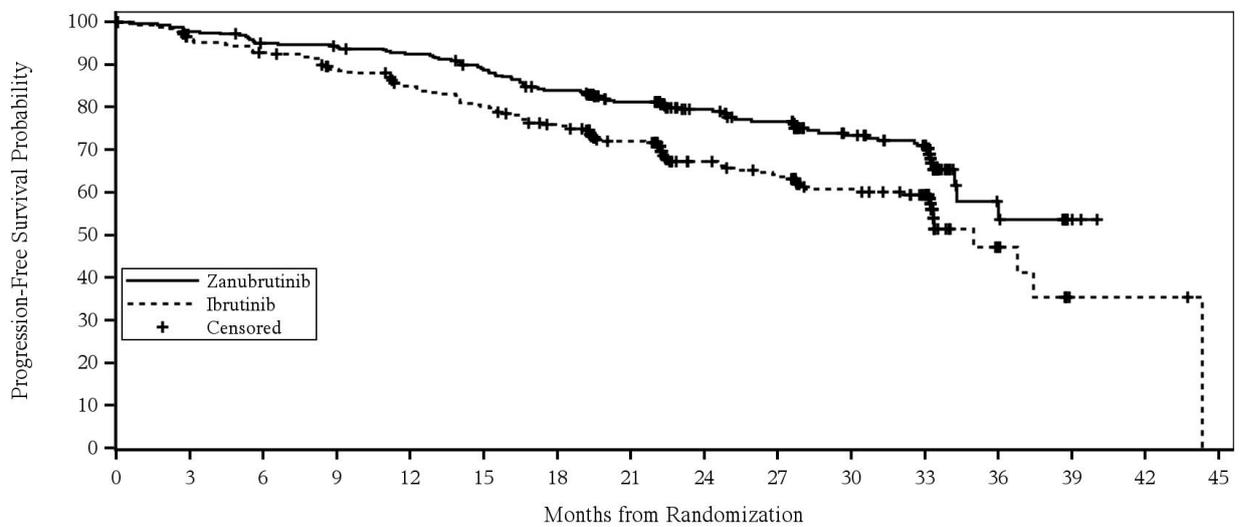
Figure 1: Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment (ITT)



No. of Subjects at Risk

Zanubrutinib	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1

Figure 2: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review (ITT)



No. of Subjects at Risk

Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2

In patients with del(17p)/TP53 mutation, the hazard ratio for progression-free survival by investigator assessment was 0.53 (95% CI 0.31, 0.88). Based on independent review, the hazard ratio was 0.52 (95% CI 0.30, 0.88).

Figure 3: Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment for Patients with Del 17P or TP53 (ITT)

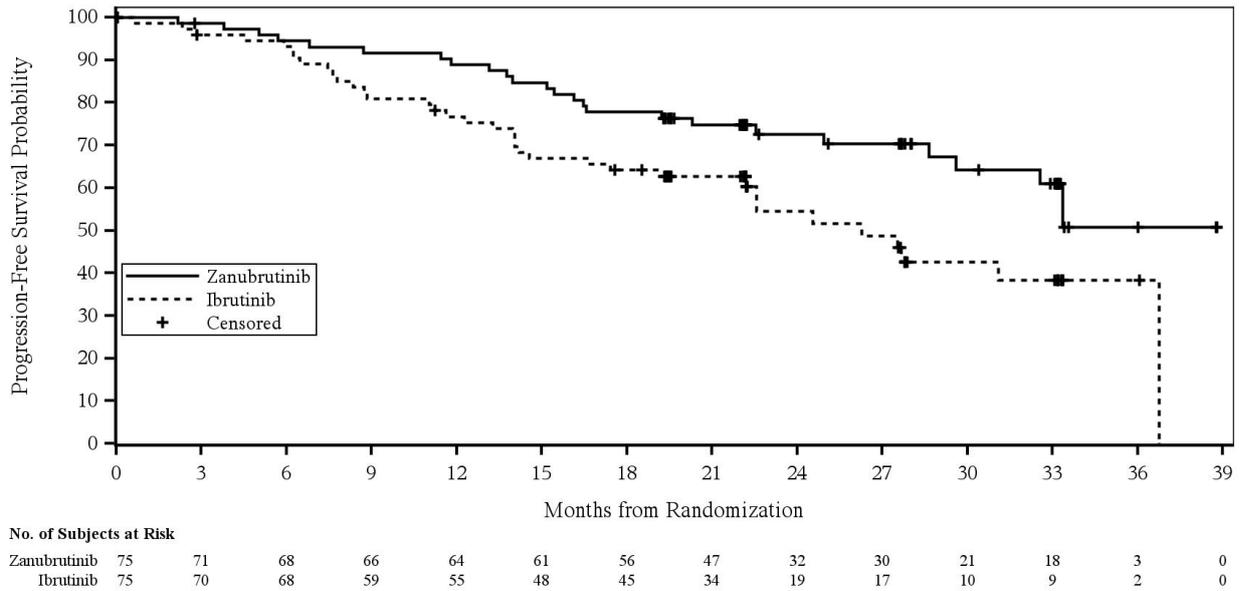
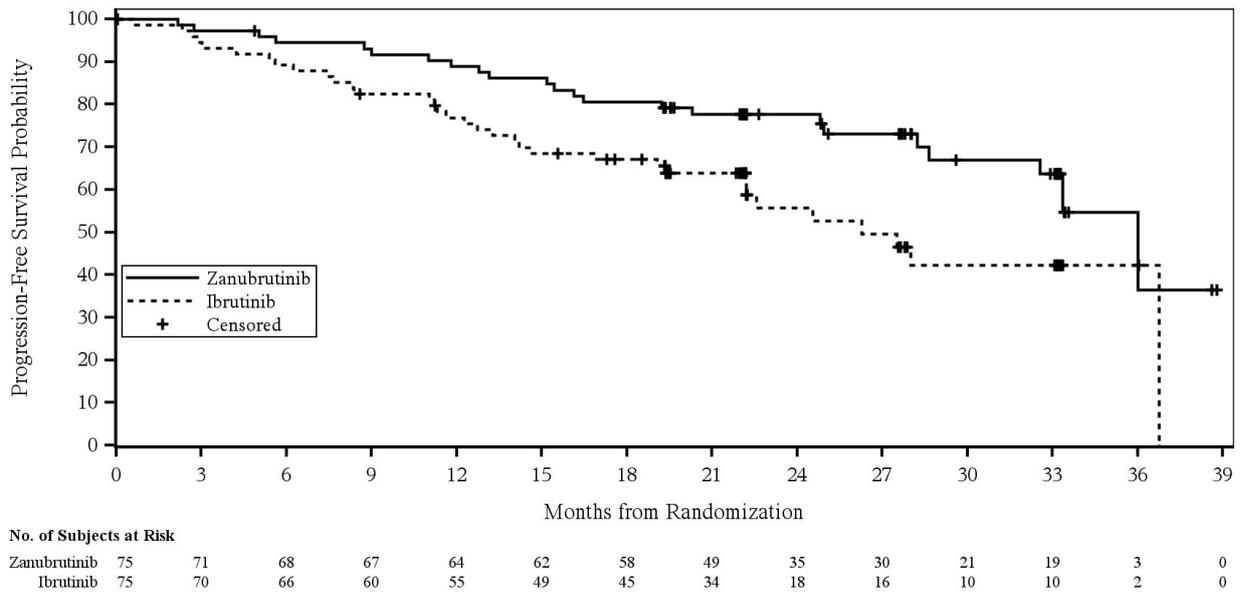


Figure 4: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review for Patients with Del 17P or TP53 (ITT)



With an estimated median follow-up of 32.8 months, the median overall survival was not reached in either arm with 17% of patients experiencing an event.

5.2 PHARMACOKINETIC PROPERTIES

Zanubrutinib maximum plasma concentration (C_{\max}) and area under the plasma drug concentration over time curve (AUC) increase proportionally over a dosage range from 40 mg to 320 mg (0.13 to 1 time the recommended total daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated administration.

The geometric mean (%CV) zanubrutinib steady-state daily AUC is 2,099 (42%) ng·h/mL following a 160 mg twice daily dose and 1,917 (59%) ng·h/mL following a 320 mg once daily dose. The geometric mean (%CV) zanubrutinib steady-state C_{\max} is 299 (56%) ng/mL following a 160 mg twice daily dose and 533 (55%) ng/mL following a 320 mg once daily dose.

Absorption

The median T_{\max} of zanubrutinib is 2 hours. No clinically significant differences in zanubrutinib AUC or C_{\max} were observed following administration of a high-fat meal (approximately 1,000 calories with 50% of total caloric content from fat) in healthy subjects.

Distribution

The geometric mean (%CV) apparent steady-state volume of distribution of zanubrutinib during the terminal phase (V_z/F) was 522 (71%) L. The plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio was 0.7-0.8.

Metabolism

Zanubrutinib is primarily metabolised by cytochrome P450(CYP)3A. None of these metabolites are considered to contribute significantly to the safety and efficacy profile of zanubrutinib.

Excretion

The mean half-life ($t_{1/2}$) of zanubrutinib is approximately 2 to 4 hours following a single oral zanubrutinib dose of 160 mg or 320 mg. The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib during the terminal phase was 128 (61%) L/h.

Following a single radio-labelled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in faeces (38% unchanged) and 8% in urine (less than 1% unchanged).

Special Populations

Age

Age (19 to 90 years) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Gender

Gender had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Race

Ethnicity (Asian, Caucasian, and Other) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Body Weight

Body weight (36 to 140 kg) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Renal Insufficiency

Zanubrutinib undergoes minimal renal elimination. Based on population PK analysis, mild and moderate renal impairment ($\text{CrCl} \geq 30$ mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of zanubrutinib. Limited PK data is available in patients with severe renal impairment ($\text{CrCl} < 30$ mL/min) or in patients requiring dialysis.

Hepatic Insufficiency

The total AUC of zanubrutinib increased by 11% in subjects with mild hepatic impairment (Child-Pugh class A), by 21% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 60% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The unbound AUC of zanubrutinib increased by 23% in subjects with mild hepatic impairment (Child-Pugh class A), by 43% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 194% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in rats at oral doses up to 2000 mg/kg.

Carcinogenicity

Carcinogenicity studies have not been conducted with zanubrutinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content

Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate
Colloidal anhydrous silica
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide

Printable ink

OPACODE monogramming ink S-1-277002 BLACK

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE bottles with a child-resistant polypropylene closure. Each carton contains one bottle. Each bottle contains 120 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

BeiGene NZ Unlimited
c/o TMF Group
Level 11, 41 Shortland Street
Auckland 1010
New Zealand

9 DATE OF FIRST APPROVAL

08 June 2023

10 DATE OF REVISION

25 January 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	New indication - Chronic Lymphocytic Leukaemia (CLL)/Small Lymphocytic Lymphoma (SLL)
4.2	Editorial changes
4.4	Updated information regarding haemorrhage, infections and second primary malignancies
4.5	Updated information about use of BRUKINSA with CYP3A inducers and inhibitors
4.6	Editorial changes
4.8	Updated safety information with additional studies, number of patients, including CLL/SLL studies
5.1	Added clinical studies in treatment-naïve and relapsed/refractory CLL/SLL patients