BRUKINSA

Zanubrutinib 80 mg

1. NAME OF THE MEDICINAL PRODUCT

BRUKINSA® 80 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: zanubrutinib

Each hard capsule contains 80 mg of zanubrutinib.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

White to off-white opaque hardcapsule of 22 mm in length (size 0), marked with "ZANU 80" in black ink.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Mantle cell lymphoma (MCL)

Zanubrutinib is indicated for the treatment of adult's patients with relapsed/refractory mantle cell lymphoma (MCL).

Waldenström's Macroglobulinemia (WM)

Zanubrutinib is indicated for the treatment of adult patients with relapsed/refractory Waldenström's Macroglobulinemia (WM) and for treatment naïve (TN) unsuitable for standard immunochemotherapy based on documented comorbidities or risk factors.

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

Zanubrutinib is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL),

Marginal Zone Lymphoma (MZL)

Zanubrutinib is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one-prior anti–CD20-based therapy.

Follicular Lymphoma (FL)

Zanubrutinib in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

4.2. Posology and Method of Administration

4.2.1. Posology

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.

Dose Modification for Adverse Reactions:

Recommended dose modifications of zanubrutinib for Grade 3 or greater adverse reactions are provided in Table 1:

Table 1: Recommended Dose Modification for Adverse Reactions

Event	**Adverse Reaction Occurrence**	**Dose Modification (Starting Dose: 320 mg once daily or 160 mg twice daily)**
≥ Grade 3 non-hematological 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 zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
	Third	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue zanubrutinib

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

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

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:

Zanubrutinib capsules should be administered orally 320 mg taken orally once daily or 160 mg twice daily approximately every twelve hours. Zanubrutinib 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.

4.2.2. Use in Children

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

4.2.3. Use in the Elderly

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

4.2.4. 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 zanubrutinib adverse reactions in patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis (see Section 5.2 Pharmacokinetic Properties).

4.2.5. 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 zanubrutinib clinical studies. The recommended dose of zanubrutinib for patients with severe hepatic impairment is 80 mg orally twice daily. The safety of zanubrutinib has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse reactions of zanubrutinib (see Section 5.2 Pharmacokinetic Properties).

4.2.6. Interactions Requiring Dose Adjustments

Dose Modification for use with CYP3A inhibitors or inducers:

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Table 2: Recommended Dose Modifications [see Drug Interactions] and [Pharmacokinetics]:

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 Posology and Method of Administration (4.2)]*.
	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 Posology and Method of Administration (4.2)]*.
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) and moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use; Consider alternative agents with less CYP3A induction

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

4.3. Contraindications

None.

4.4. Special Warnings and Special Precautions for Use

Hemorrhage

Serious and fatal hemorrhagic events have occurred in patients with hematological malignancies treated with zanubrutinib monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in patients. Bleeding events of any grade, including purpura and petechiae, occurred in patients with hematological malignancies.

The mechanism for the bleeding events is not well understood.

Zanubrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding zanubrutinib for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred in patients with hematological 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) 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.

Cytopenias

Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia, based on laboratory measurements, were reported in patients with hematologic malignancies treated with zanubrutinib monotherapy.

Monitor complete blood counts during treatment.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma have occurred in patients with hematological malignancies treated with zanubrutinib monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin). Advise patients to use sun protection.

Atrial Fibrillation and Flutter

Atrial fibrillation and atrial flutter have occurred in patients with hematological malignancies treated with zanubrutinib monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Hepatotoxicity, including DILI

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors (BTKIs).

Evaluate bilirubin and transaminases at baseline and throughout treatment with zanubrutinib. For patients who develop abnormal liver tests after zanubrutinib, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold zanubrutinib. Upon confirmation of DILI, discontinue zanubrutinib.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Effect of Other Drugs on Zanubrutinib :

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Table 3: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Pharmacokinetic Properties (*5.2*)]* which may increase the risk of zanubrutinib toxicities.
Prevention or management	• Reduce zanubrutinib dosage when co-administered with moderate or strong CYP3A inhibitors *[see Posology and Method of Administration (*4.2*)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Pharmacokinetic Properties (*5.2*)]* which may reduce zanubrutinib efficacy.
Prevention or management	• Avoid co-administration of zanubrutinib with moderate or strong CYP3A inducers *[see Posology and Method of Administration (*4.2*)]*.

4.6. Use During Pregnancy and Lactation

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

Males with female sexual partners of reproductive potential should avoid fathering a child or be advised to use effective contraception during BRUKINSA treatment and for 1 week after the last dose of BRUKINSA.

Based on findings in animals, zanubrutinib may cause fetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking zanubrutinib and for at least one week after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking zanubrutinib and for at least one week after stopping treatment.

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 zanubrutinib and for at least two weeks following the last dose.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

4.7. Effects on Ability to Drive and Use Other Machinery

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

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

4.8. Undesirable Effects

The safety profile of zanubrutinib monotheraphy is based on pooled data from 1550 patients with B-cell malignancies treated with zanubrutinib monotherapy in 10 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 and BGB-3111-214), and three Phase 3 clinical studies (BGB-3111-302 BGB -3111-304, BGB-3111-305), and a long-term extension study (BGB-3111-LTE1). The long-term extension study consists of patients rolling over from studies BGB-3111-AU-003, BGB-3111-205, BGB-3111-206, BGB-3111-210, and BGB-3111-1002. Subjects enrolled in BGB-3111-LTE1 are combined with data from their respective parent studies. Among 1550 patients receiving zanubrutinib, the median duration of exposure was 28.58 months. Among the patients, 81% were exposed to zanubrutinib for at least 1 year, 63.2% were exposed for at least 2 years, and 31.2% were exposed for at least 3 years.

The most commonly occurring adverse reactions in the 10 monotherapy studies combined (≥ 20%) were neutropenia,† thrombocytopenia,† upper respiratory tract infection,§ bruising,§ hemorrhage/hematoma,§ musculoskeletal pain,§ rash,§ anemia,† and pneumonia.§ The most common Grade 3 or higher adverse reactions (≥5%) were neutropenia,† pneumonia,§ thrombocytopenia,† and hypertension.§

The safety of zanubrutinib in combination with obinutuzumab is based on pooled data from 179 patients with B-cell malignancies treated with zanubrutinib combination with obinutuzumab in 2 clinical trials, including 143 patients from study BGB-3111-212 and 36 patients from study BGB-3111-GA101. Among the 179 patients, the median duration of exposure was 13.27 months. Among the patients, 51.96% were exposed to zanubrutinib in combination with obinutuzumab for at least 1 year, 29.6% were exposed for at least 2 years, and 10.1% were exposed for at least 3 years. The most commonly occurring adverse reactions in the 2 studies combined (≥20%) were thrombocytopenia,† neutropenia,† anemia,† fatigue,§ musculoskeletal pain,§ and upper respiratory tract infection.§ The most common Grade 3 or higher adverse reactions (≥5%) were neutropenia,† pneumonia,§ and thrombocytopenia.†

<u>Discontinuation and dose reduction</u>

Of the 1550 patients treated with zanubrutinib monotheraphy, 59 (3.8%) patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia§ (1.9%). Adverse reactions leading to dose reduction and dose interruption occurred in 4.3% and 19.3% of patients, respectively.

Of the 179 follicular lymphoma patients treated with zanubrutinib in combination with obinutuzumab, 7 (3.9%) patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia§ (2.8%). Adverse

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

reactions leading to dose reduction and dose interruption occurred in 5.6% and 22.9% of patients, respectively.

Table 4 presents adverse reactions that have been reported in association with the use of zanubrutinib monotherapy in the 10 clinical studies. Table 5 presents adverse reactions that have been reported in association with the use of zanubrutinib in combination with obinutuzumab in the 2 clinical studies.

Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10, 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 4: Adverse Reactions in Patients Treated with Zanubrutinib Monotherapy

MedDRA SOC	**Group Terms/PTs**	**Zanubrutinib N=1550**	
		All grades* (%)	**Grade ≥3 (%)**
Infections and infestations	Upper respiratory tract infection[§]	Very common (34.3)	2.1
	Pneumonia[§,#]	Very common (21.5)	11.8
	Pneumonia	Very common (13.5)	7.9
	Lower respiratory tract infection	Common (5.4)	0.7
	Urinary tract infection[§]	Very common (13.1)	2.2
	Bronchitis	Common (3.9)	0.7
	Hepatitis B reactivation	Uncommon (0.9)	0.5
Blood and lymphatic system disorders	Neutropenia[§]	Very common (29.5)	20
	Thrombocytopenia[§]	Very common (17.1)	6.2
	Anemia[§]	Very common (15.2)	5.7
Nervous system disorder	Dizziness[§]	Very common (11.4)	0.4
Vascular disorders	Bruising[§]	Very common (31.6)	0.5

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

MedDRA SOC	Group Terms/PTs	Zanubrutinib N=1550	
		All grades* (%)	Grade ≥3 (%)
	Contusion	Very common (19.4)	0
	Petechiae	Common (6.6)	0.1
	Purpura	Common (5.4)	0.2
	Ecchymosis	Common (2.6)	0.1
	Hemorrhage/hematoma[§#]	Very common (29)	3.4
	Hematuria	Very common (10.3)	0.8
	Epistaxis	Common (7.8)	0.1
	Gastrointestinal Hemorrhage	Uncommon (0.3)	0.2
	Hypertension	Very common (15.2)	7.5
Gastrointestinal disorders	Diarrhea	Very common (19.9)	1.7
	Constipation	Very common (13.1)	0.3
Skin and subcutaneous tissue disorders	Rash[§]	Very common (24.8)	0.6
	Pruritus	Common (7.7)	0.2
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain[§]	Very common (25.9)	1.7
	Arthralgia	Very common (14.6)	0.7
	Back pain	Very common (11.2)	0.7
General disorders and administration site conditions	Fatigue[§]	Very common (17.3)	1.3
	Fatigue	Very common (12.8)	0.9
	Asthenia	Common (3.8)	0.3

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

MedDRA SOC	Group Terms/PTs	Zanubrutinib N=1550	
		All grades* (%)	Grade ≥3 (%)
	Edema peripheral	Common (8.5)	0.3
Respiratory, thoracic and mediastinal disorders	Cough§	Very common (19.7)	0.1
Investigations	Neutrophil count decreased†	Very common (50.8)	21.4
	Platelets decreased†	Very common (37.8)	7.7
	Hemoglobin decreased†	Very common (24.6)	4.1

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

† Based on laboratory measurements.

§ Includes multiple adverse reaction terms.

Includes events with fatal outcome.

Table 5: Adverse Reactions in Patients Treated with Zanubrutinib in Combination with Obinutuzumab

MedDRA SOC	Group Terms/PTs	Zanubrutinib + Obinutuzumab N=179	
		All grades* (%)	Grade ≥3 (%)
Infections and infestations	Upper respiratory tract infection§	Very common (20.1)	0.6
	Pneumonia§#	Very common (18.4)	11.2
	Pneumonia	Very common (11.2)	8.4
	Lower respiratory tract infection	Common (4.5)	0.6
	Urinary tract infection§	Common (8.4)	1.1
	Bronchitis	Common (2.8)	0.0
	Thrombocytopenia§	Very common (35.2)	14
	Neutropenia§	Very common (28.5)	24

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Blood and lymphatic system disorders	Anemia§	Very common (10.6)	3.9
Nervous system disorder	Dizziness§	Common (5.6)	0.0
Vascular disorders	Bruising§	Very common (19.6)	0.0
	Contusion	Very common (12.3)	0.0
	Petechiae	Common (8.4)	0.0
	Purpura	Common (1.7)	0.0
	Ecchymosis	Common (1.1)	0.0
	Hemorrhage/hematoma§	Very common (16.2)	0.6
	Epistaxis	Common (5)	0.0
	Hematuria	Common (1.1)	0.0
	Hypertension§	Common (5)	2.2
Gastrointestinal disorders	Diarrhea	Very common (18.4)	2.2
	Constipation	Very common (12.8)	0.0
Skin and subcutaneous tissue disorders	Rash§	Very common (12.8)	0.0
	Pruritus	Common (6.1)	0.0
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain§	Very common (20.7)	1.7
	Back pain	Very common (11.2)	0.6
	Arthralgia	Common (6.7)	0.0
General disorders and administration site conditions	Fatigue§	Very common (27.4)	1.7
	Fatigue	Very common (17.3)	0.0
	Asthenia	Common (9.5)	0.6
	Edema peripheral	Common (3.4)	0.0
Respiratory, thoracic and mediastinal disorders	Cough§	Very common (17.3)	0.0
Investigations	Platelets decreased†	Very common (65.2)	10.8
	Neutrophil count decreased†	Very common (45.5)	17.9
	Hemoglobin decreased†	Very common (30.4)	1.3

* Adverse events were graded by NCI-CTCAE (v5.0).

† Based on laboratory measurements.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

§ 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*)

Hepatotoxicity, including DILI (See Section 4.4 Special Warnings and Special Precautions for Use)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 via the national reporting system.

Pharmaceutical Industry Reporting Contact

PT ETANA BIOTECHNOLOGIES INDONESIA

Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav.11-13, Jakarta

Email: pv@id.etanabiotech.com

Web-site: https://ebi-pharmacovigilance.azurewebsites.net/

Pusat Farmakovigilans/MESO Nasional

Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekursor, dan Zat Aktif

Badan Pengawas Obat dan Makanan Republik Indonesia

Address: Jl. Percetakan Negara 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

Website: http://e-meso.pom.go.id/

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

5.1.1. 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 signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling 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 tumor growth.

5.1.2. Pharmacodynamics

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).

5.1.3. Clinical Efficacy and Safety

5.1.3.1. 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, multicenter, 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). The most common prior regimens were CHOP-based (90.7%) followed by rituximab-based (74.4%). 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 6: 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.

24.8-month Follow-up

With an overall follow-up of 24.8 months, the investigator-assessed overall response rate was 83.7% with 95% CI of 74.2% to 90.8%. The CR rate was 77.9% (95% CI 67.7% to 86.1%). The median duration of response was 24.9 months (95% CI 23.1, NE).

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, multicenter, 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

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

was 1 (range 1 to 4). The most common prior regimens were rituximab-based (93.8%) followed by CHOP-based regimen (59.4%). 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%.

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. PET scans were not required per protocol, and most responses were assessed using CT imaging.

Table 7: 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.

5.1.3.2. Waldenström's Macroglobulinemia (WM)

BGB-3111-302: 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 randomized, open-label, multicenter 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 randomized 1:1 to receive either zanubrutinib 160 mg twice daily (Arm A) or ibrutinib 420 mg once daily (Arm B) until disease progression or unacceptable toxicity. Subjects found to have MYD88 wildtype ($MYD88^{WT}$) by gene sequencing (estimated to be present in approximately 10% of enrolled subjects), were enrolled to Cohort 2 (N = 26) and received zanubrutinib 160 mg twice

daily on a third, non-randomized, 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, 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 ≥ 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 (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 ≥ 40 g/L.

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, anti-lymphoma effects. 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. Results are shown in Table 8.

Responses were observed with zanubrutinib across subgroups, including $MYD88^{WT}$ patients.

Table 8: Analysis of Disease Response Per Overall Combined Assessment (Study BGB-3111-302; Cohort 1) (Overall WM Population)

	By Independent Review Committee		**By Investigator**	
Response Category	**Ibrutinib N = 99**	**Zanubrutinib N = 102**	**Ibrutinib N = 99**	**Zanubrutinib N = 102**
VGPR or CR rate, n (%)	**19 (19.2)**	**29 (28.4)**	**17 (17.2)**	**29 (28.4)**
95% CI [a]	(12.0, 28.3)	(19.9, 38.2)	(10.3, 26.1)	(19.9, 38.2)
Risk difference (%) [b]	10.2		12.1	
95% CI [a]	(-1.5, 22.0)		(0.5, 23.7)	
p-value [c]	**0.0921**		**0.0437**	
MRR (PR or better), n (%)	77 (77.8)	79 (77.5)	76 (76.8)	78 (76.5)
95% CI [a]	(68.3, 85.5)	(68.1, 85.1)	(67.2, 84.7)	(67.0, 84.3)
Risk difference (%) [b]	-0.5		-0.7	
95% CI	(-12.2, 11.1)		(-12.5, 11.1)	

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Response Category	By Independent Review Committee		By Investigator	
	Ibrutinib N = 99	Zanubrutinib N = 102	Ibrutinib N = 99	Zanubrutinib N = 102
ORR (MR or better), n (%)	**92 (92.9)**	**96 (94.1)**	**93 (93.9)**	**97 (95.1)**
95% CI [a]	(86.0, 97.1)	(87.6, 97.8)	(87.3, 97.7)	(88.9, 98.4)

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, directionally favoring zanubrutinib.

In the overall population in Cohort 2, response as assessed by either the IRC or by investigator, demonstrated a best overall response of VGPR or CR of 26.9%. 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, multicenter, 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 ≥ 40 g/L.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

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 9.

Table 9: 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 ≥ 1 dose of zanubrutinib, had baseline IgM or M-protein ≥ 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.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

BGB-3111-210: A Phase 2, Single-Arm, Open-Label, Multicenter Study of Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 in Chinese Subjects with Relapsed/Refractory Waldenström's Macroglobulinemia (WM)

BGB-3111-210 is a, single-arm, open-label, multicenter Phase 2 study in patients with relapsed or refractory Waldenström's macroglobulinemia (WM). The study is comprised of an initial screening phase (up to 28 days), a single-arm treatment phase, and a follow-up phase. Patients received zanubrutinib 160 mg orally twice daily for up to 3 years or until disease progression, unacceptable toxicity, death, or withdrawal of consent. The median follow-up time was 14.9 months (range: 3.2 to 20.2 months).

The median age was 65 years (range: 41 to 83 years); 43.2% of the overall study population was >65 years. Most patients (61.4%) were male and patients had received a median of 2 prior anticancer regimens for their disease. All patients were Chinese in this study. The median time from progression to first study drug was relatively short at 1.22 years and 45.5% of patients were high-risk by IPSS. Furthermore 70% (31/44) of patients enrolled had a best response of stable disease or PD to the last regimen, including 25% with best response of PD to last therapy.

The efficacy resulted was evaluated by IRC based on modified Owen 2013.

Table 10: Efficacy results in Patients with R/R WM (BGB-3111-210)

Endpoints	Total (N=44)
Major response rate [95% CI] (%)	70.5 [54.8, 83.2]
VGPR or CR (%)	34.1
PR (%)	36.4
Median duration of major response [95% CI] (month)	NR

5.1.3.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

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

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

BGB-3111-304 is a randomized multicenter, open-label, active controlled Phase 3 trial of zanubrutinib monotherapy (arm A) and bendamustine in combination with rituximab (arm B) in 479 patients with previously untreated CLL and SLL *without* 17p deletion (del(17p)) (Cohort 1). BGB-3111-304 arm C (Cohort 2) is a multicenter single-arm trial of zanubrutinib monotherapy in 110 patients with previously untreated CLL and SLL *with* centrally confirmed del(17p).

Both Cohorts enrolled patients 65 years of age or older as well as patients between 18 and 65 years of age that were unsuitable for chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR).

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 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 to 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 arm C was 70 years. The proportion of patients 65 to 75 years old was 55.2% in arm A and 61.3% in arm C. Arm A included 13.7% and arm C included 42.3% patients from the Asia Pacific region.

In Cohort 1, randomization was stratified by age (<65 years vs ≥65 years), Binet stage (stage C versus stages A or B), immunoglobulin variable region heavy chain (IGHV) mutational status (mutated vs unmutated), and geographic region (North America versus Europe versus Asia-Pacific). A total of 479 patients were randomized (intent-to-treat [ITT] analysis set), 241 to zanubrutinib continuous monotherapy and 238 to 6 cycles of therapy with bendamustine and rituximab.

In Cohort 1, patients in the zanubrutinib arm (A) received 160 mg twice daily until disease progression or unacceptable toxicity. In arm B, patients received bendamustine at a dose of 90 mg/m^2/day on the first 2 days of each cycle for 6 cycles and rituximab at a dose of 375 mg/m^2 for Cycle 1, and at a dose of 500 mg/m^2 for Cycles 2 to 6. Each treatment cycle consisted of approximately 28 days.

In Cohort 2 (arm C), patients received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity.

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

In Cohort 1, the median duration of follow-up was 25 months (range: 0 to 41.4). The event-free rate at 24 months was 85.5% (95% CI 80.1, 89.6) for zanubrutinib 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 to 38.8) and the event-free rate at 24 months 88.9% (95% CI 81.3, 93.6).

Additional efficacy results are presented in Table 11.

Table 11: Efficacy Results in BGB-3111-304

	Cohort 1* Patients without Del(17p)		**Cohort 2** Patients with Del(17p)
Endpoint	**Zanubrutinib (N=241)**	**Bendamustine + Rituximab (N=238)**	**Zanubrutinib (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)

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

	Cohort 1* Patients without Del(17p)		**Cohort 2** Patients with Del(17p)
Endpoint	**Zanubrutinib (N=241)**	**Bendamustine + Rituximab (N=238)**	**Zanubrutinib (N=110)**
Death, n (%)	9 (3.7)	12 (5)	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, 97.1)	85.3% (80.1, 89.5)	90% (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

Interim Analysis for ORR

BGB-3111-305 is a randomized, multicenter, 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 randomized to either zanubrutinib 160 mg orally twice daily or ibrutinib 420 mg orally once daily, continued until disease progression or unacceptable toxicity.

Randomization 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).

Of 652 patients total, 327 were assigned to zanubrutinib monotherapy, 325 to ibrutinib monotherapy. The efficacy evaluation is based on the prespecified interim analysis of the first 415 randomized patients of the ITT population. Of these, 207 were randomized to zanubrutinib monotherapy, 208 to ibrutinib monotherapy.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Baseline demographics and disease characteristics were generally balanced between treatment arms in the intent-to-treat (ITT) analysis set and in the first 415 randomized patients. The zanubrutinib 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% in the first 415 randomized patients). In the ITT analysis set, the median age was 67 years in the zanubrutinib arm and 68 years in the ibrutinib arm, and 67 in both arms of the first 415 randomized 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 zanubrutinib arm and 61.5% in the ibrutinib arm were ≥65 years old. In the ITT analysis set 97.9% of patients in the zanubrutinib arm and 96% in the ibrutinib arm had an ECOG PS of 0 or 1, and 98.1% and 95.7%, respectively, in the first 415 randomized 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 12.

Table 12: Efficacy Results in BGB-3111-305 (Prespecified Interim Analysis of the First 415 Randomized Patients)

	Investigator Assessed		**Independently Assessed***	
Endpoint	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**
Overall Response Rate n (%) (95% CI)	162 (78.3) (72, 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)	
Noninferiority[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 (66.1, 86.2)

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

* By independent central review committee.

[a] Response ratio: estimated ratio of the overall response rate in the zanubrutinib 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.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Zanubrutinib demonstrated noninferiority and superiority to ibrutinib in overall response to ibrutinib in investigator-assessed overall response rate and noninferiority to ibrutinib in independently assessed overall response rate.

In patients with del(17p) mutation in the first 415 randomized patients, the overall response rates were, based on investigator assessment, 80.5% (95% CI 65.1, 91.2; 33 of 41 patients) in the zanubrutinib group and 50.0% (95% CI 33.4, 66.6; 19 of 38 patients) in the ibrutinib group. Based on independent review, the overall response rates were 80.5% (95% CI 65.1, 91.2; 33 of 41 patients) in the zanubrutinib group and 55.3% (95% CI 38.3, 71.4; 21 of 38 patients) in the ibrutinib group.

In the first 415 randomized patients, the rate of atrial fibrillation and flutter was 2.5% in the zanubrutinib arm and 10.1% in the ibrutinib arm (difference -7.7%; 95% CI: -12.3%, -3.1%).

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 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 10). 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, 81.3% (95% CI 70.7, 89.4; 61 of 75 patients) in the zanubrutinib group and 65.3% (95% CI 53.5, 76.0; 49 of 75 patients) in the ibrutinib group. Based on independent review, the overall response rates were 80.0% (95% CI 69.2, 88.4; 60 of 75 patients) in the zanubrutinib group and 58.7% (95% CI 46.7, 69.9; 44 of 75 patients) in the ibrutinib group.

Efficacy results at final analysis are shown in Table 13.

Table 13: Efficacy Results in BGB-3111-305

	Investigator Assessed		**Independently Assessed[a]**	
Endpoint	**Zanubrutinib (N=327)**	**Ibrutinib (N=325)**	**Zanubrutinib** (N=327)	**Ibrutinib** (N=325)
Overall response rate[b]				
n (%)	260 (79.5)	231 (71.1)	263 (80.4)	237 (72.9)
(95% CI, %)	(74.7, 83.8)	(65.8, 75.9)	(75.7, 84.6)	(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[e]: 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)

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, HR=hazard ratio.

[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 zanubrutinib 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 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 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 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 14.

Table 14: Efficacy Results in BGB-3111-305

Endpoint	Investigator Assessed		Independently Assessed*	
	Zanubrutinib (N=327)	**Ibrutinib (N=325)**	**Zanubrutinib (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		0.00007	
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)

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

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.

* By independent central review committee.

[a] Response ratio: estimated ratio of the overall response rate in the zanubrutinib 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.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

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

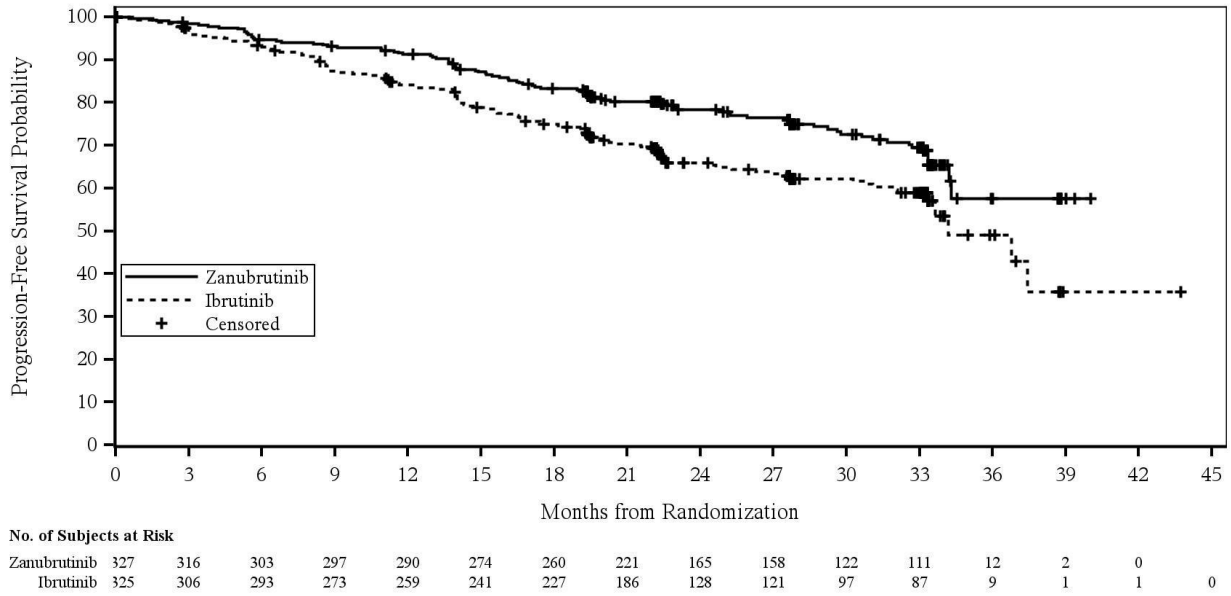
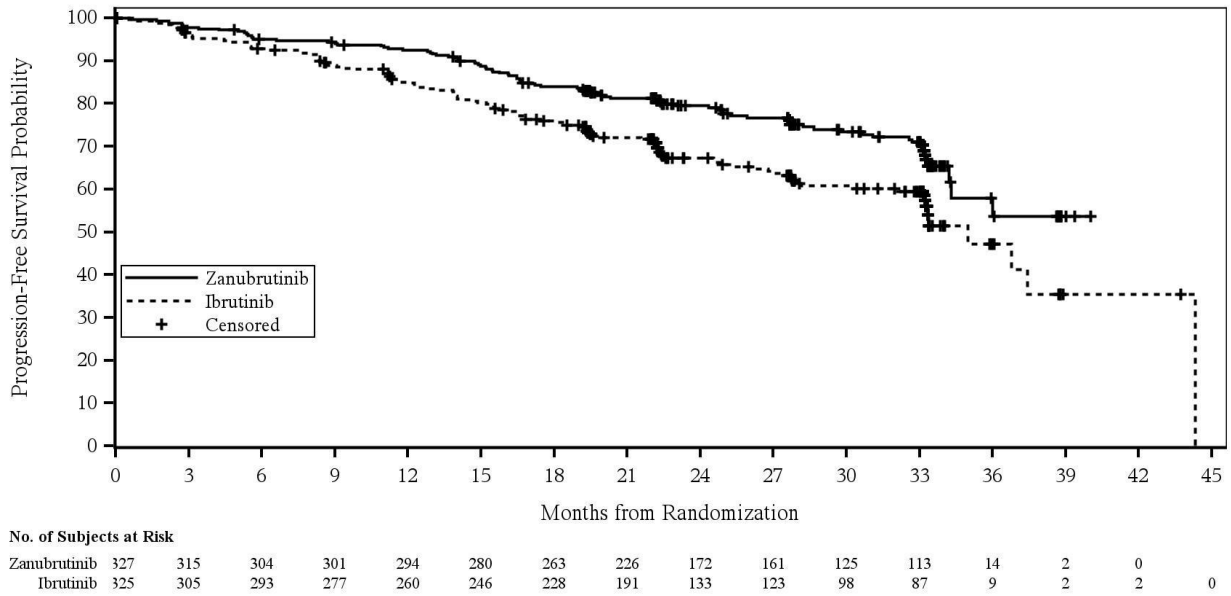


Figure 2: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review (ITT)



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)

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

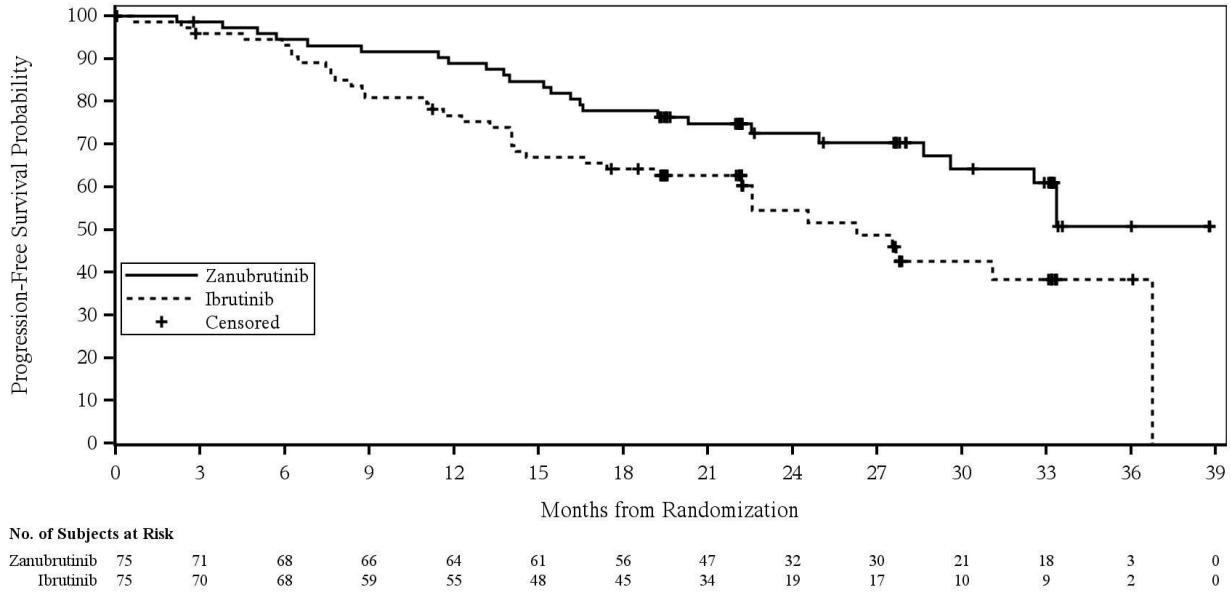
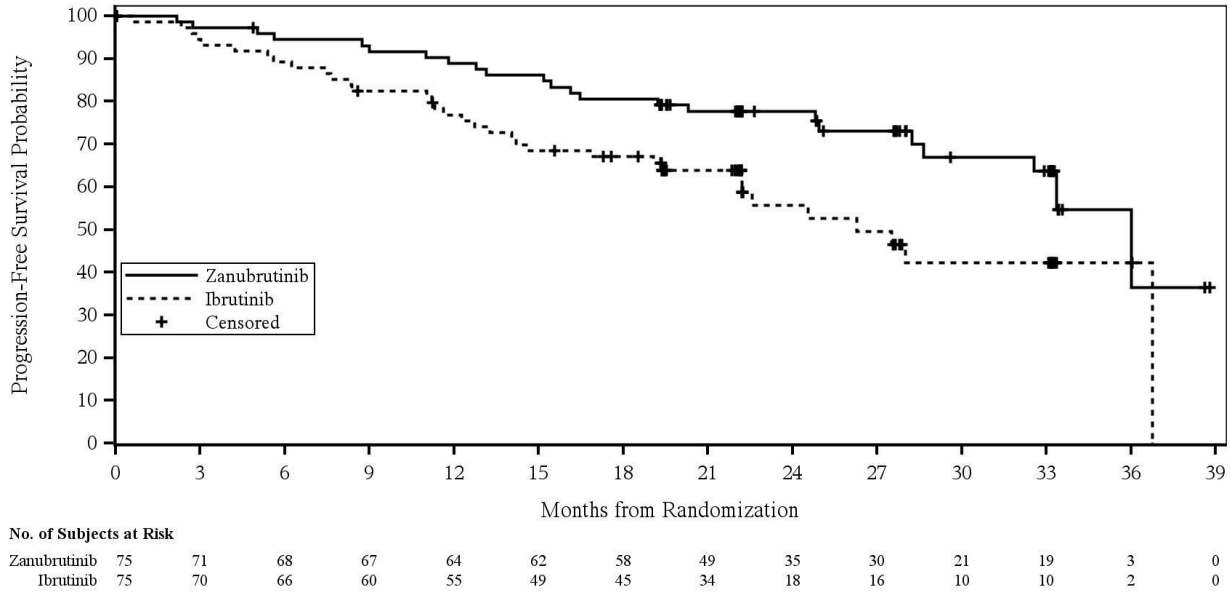


Figure 4: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review for Patients with Del 17P or TP53 (ITT)



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.

<u>BGB-3111-205:</u> A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Safety and Efficacy of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor in Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

BGB-3111-205 is an open-label, multicenter, single-arm trial (BGB-3111-205) conducted in China. Ninety-one patients with confirmed diagnosis of R/R CLL/SLL, including of 22 patients with 17p deletion or TP53 mutation, enrolled in total, including CLL (82 [90.1%] patients) and SLL (9 [9.9%] patients). The median age was 61 years (range: 35 to 87 years) with more than one third (34.1%) of patients were 65 years of age or older. Male patients composed 57.1% of the overall population. Most patients had a baseline ECOG score of 0 or 1 (46.2% and 50.5%, respectively). At baseline, 40 (44%) and 9 (9.9%) patients had bulky disease defined as having at least 1 lesion with longest transverse diameter ≥5 cm and ≥10 cm, respectively. The molecular characteristics with poor prognostic included del(11q) (22% of patients), del(17p) or TP53 mutation (24.2%), and unmutated IGHV (56%). Approximately half of all patients had received 2 or more lines of prior anticancer drug therapy. Most patients (79.1%) were refractory to the most recent systemic therapy.

Zanubrutinib was administered orally at 160 mg twice daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the modified iwCLL Guidelines (2008) in patients with CLL and the Revised Criteria for Response for Malignant Lymphoma in patients with SLL. The primary endpoint in this study was overall response rate (ORR) assessed by an Independent Review Committee (IRC). With median follow-up time of 15.08 months (range: 0.8 to 21.2 months), responses to zanubrutinib are shown in Table 15.

Table 15: Overall Response Rate (ORR) Based on Assessment by IRC in Patients with R/R CLL/SLL

	Total (N=91)
Best Overall Response (BOR), n (%)	
Complete Response	3 (3.3)
Partial Response	54 (59.3)
Partial Response with Lymphocytosis	20 (22)
Stable Disease	4 (4.4)
Progressive Disease	4 (4.4)
Not evaluable[a]	3 (3.3)
Discontinued prior to first assessment	3 (3.3)
ORR (%)[b]	77 (84.6)
95% CI (%)[c] for ORR	75.54, 91.33
P value(1-sided)[d]	<0.0001

CI = confidence interval; CR = complete response; CRi= complete response with incomplete bone marrow recovery; PR= partial response; nPR= nodular partial response; PR-L= partial response with lymphocytosis.
[a] Not evaluable due to insufficient imaging and clinical information.
[b] ORR defined as: CLL who achieved CR, CRi, PR, nPR, PR-L; SLL who achieved CR or PR.
[c] 2-sided Clopper-Pearson 95% CIs.
[d] p-value (1-sided) was based on the binomial exact test against the null hypothesis H0: ORR=0.32.

Patients with del(17p) or TP53 mutation, achieved ORR at 86.4%, which is comparable to the study population as a whole (84.6%).

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

5.1.3.4 Marginal Zone Lymphoma (MZL)

BGB-3111-214: A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma

The efficacy of zanubrutinib was assessed in Study BGB-3111-214 [NCT03846427], a Phase 2 open-label, multicenter, single-arm trial of 68 previously treated patients with MZL who had received at least one prior anti–CD20-based therapy. Twenty-six (38.2%) patients had extranodal MZL, 26 (38.2%) had nodal MZL, 12 (17.6%) had splenic MZL, and 4 (6%) patients had unknown subtype. Zanubrutinib was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity. The median age of patients was 70 years (range: 37 to 95) and 53% were male. The median time since initial diagnosis was 61.5 months (range: 2 to 353.6). The median number of prior treatments was 2 (range: 1 to 6). Twenty-two (32.4%) patients had refractory disease at study entry.

BGB-3111-AU-003: A Phase 1/2, open-label, dose-expansion, global, multicenter, single-arm trial of B-cell malignancies

The efficacy of zanubrutinib was also assessed in BGB-3111-AU-003 [NCT02343120], a Phase 1/2, open-label, dose-expansion, global, multicenter, single-arm trial of B-cell malignancies including 20 previously treated MZL patients. Majority of patients (n=9 [45%]) had extranodal MZL, 6 (30%) had splenic, and 5 (25%) had nodal subtype. Zanubrutinib was given orally at doses of 160 mg twice daily or 320 mg daily. The median age of patients was 69.5 years (range: 52 to 85). There was equal distribution of male (50%) and female (50%) patients. The median number of prior therapies was 2 (range: 1 to 5).

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

Table 16: Efficacy Results in Patients with MZL by Independent Review Committee

	Study BGB-3111-214 (N=66)*	**Study BGB-3111-AU-003 (N=20)**
ORR (95% CI)	68% (55.6, 79.1)	80% (56.3, 94.3)
CR	26%	20%
PR	42%	60%
Median DoR in months (95% CI)	NE (NE, NE)	NE (8.4, NE)

*Two patients in BGB-3111-214 were not evaluable for efficacy due to central confirmation of MZL transformation to diffuse large B-cell lymphoma.

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: not estimable.

In BGB-3111-214, the median time to response was 2.8 months (range: 1.7 to 11.1 months). The overall response rates were 64%, 76%, 67%, and 50% for the MZL subtypes (extranodal, nodal, splenic, unknown subtype), respectively.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

In BGB-3111-AU-003, the median time to response was 2.8 months (range: 2.6 to 23.1 months). The overall response rates by MZL subtypes were 89% (extranodal), 100% (nodal), and 50% (splenic).

5.1.3.5. Follicular Lymphoma (FL)

BGB-3111-212: An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined with Obinutuzumab Compared with Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma

BGB-3111-212 is a Phase 2, open-label, randomized study of zanubrutinib in combination with obinutuzumab versus obinutuzumab monotherapy in patients with relapsed/refractory follicular lymphoma (FL) who had previously received at least two prior systemic therapies including an anti-CD20 antibody and an appropriate alkylator-based combination therapy. Patients were randomized 2:1 to either zanubrutinib 160 mg orally twice daily in combination with obinutuzumab 1000 mg intravenously (arm A) or obinutuzumab alone (arm B).

Randomization was stratified by the number of prior lines of therapy (2 to 3 versus >3), rituximab-refractory status (yes versus no), and geographic region (China versus ex-China).

Baseline demographics and disease characteristics were generally balanced between the zanubrutinib combination arm and the obinutuzumab monotherapy arm in the 217 randomized patients. The median age was 64 years (range: 31 to 88), 49.8% were male, and 64.1% White. Forty-seven percent of patients were ≥65 years old. Most (97.2%) of the patients had a baseline ECOG performance status of 0 or 1.

Most patients had a Follicular Lymphoma International Prognostic Index (FLIPI) risk of intermediate or high (172 patients [79.3%]) and were Ann Arbor Stage III or IV (179 patients [82.5%]). Eighty-eight patients (40.6%) had bulky disease (defined as ≥1 baseline target lesion measuring ≥5 cm diameter).

The median number of prior anticancer therapy was 3 lines (range: 2 to 11 lines). All 217 patients received ≥2 prior lines of therapy that included rituximab therapy, and 59 of the 217 patients (27.2%) received >3 prior lines of therapy. More than half of all patients (114 patients [52.5%]) were refractory to rituximab (defined as failure to respond to, or progression during, any previous rituximab-containing regimen [monotherapy or combined with chemotherapy], or progression within 6 months of the last rituximab dose, in the induction or maintenance treatment settings).

Of 217 patients total, 145 were randomized to the zanubrutinib combination arm and 72 were randomized to the obinutuzumab monotherapy arm. The median follow-up time on was 20.21 months (range: 0.1 to 46.6 months) in the zanubrutinib obinutuzumab combination arm and 20.40 months (range: 0.1 to 46.2 months) in the obinutuzumab monotherapy arm.

The primary efficacy endpoint was overall response rate (defined partial response or better) as determined by independent central review using the Lugano Classification for NHL. The overall response rate as assessed by independent central review was 69% (95% CI: 60.8, 76.4) in the zanubrutinib combination arm and 45.8% (95% CI: 34, 58) in the obinutuzumab monotherapy arm. The overall response rate as assessed by the investigator was 68.3% (95% CI: 60, 75.7) in the combination arm and 43.1% (95% CI: 31.4, 55.3) in the obinutuzumab monotherapy arm, which were comparable to the results assessed by independent central review. The median duration of response assessed by independent central review was not reached (95% CI: 25.3, NE) in the zanubrutinib combination arm with a median follow-up time of 16.9 months (range: 0 to 41.2

months). The median duration of response in the obinutuzumab monotherapy arm, was 14 months (95% CI: 9.2, 25.1) with a median follow-up time of 23.3 months (range: 0 to 32.7 months). Duration of response rates at 18 months were 69.3% (95% CI: 57.8, 78.2) in the zanubrutinib combination arm and 41.9% (95% CI: 22.6, 60.1) in the obinutuzumab arm.

The median PFS assessed by independent central review was 28 months (95% CI: 16.1, NE) in the zanubrutinib combination arm and 10.4 months (95% CI: 6.5, 13.8) in the obinutuzumab arm.

Landmark analyses were measured at 18 and 24 months. At 18 months, the PFS rate was 56.4% (95% CI: 46.9, 64.9) in the combination arm and 29.7% (95% CI: 17.7, 42.8) in the obinutuzumab arm; and at 24 months, the PFS rate was 55.0% (95% CI: 45.2, 63.7) in the combination arm and 24.8% (95% CI: 13.6,37.7) in the obinutuzumab arm.

Efficacy results are summarized in Table 17 and Figure 5.

Table 17: Efficacy Results Per Independent Central Review (ITT)

	Zanubrutinib + Obinutuzumab (N=145) n (%)	**Obinutuzumab (N=72) n (%)**
Overall Response Rate, n (%) (95% CI[a])	100 (69) (60.8, 76.4)	33 (45.8) (34.0, 58)
CR	57 (39.3)	14 (19.4)
PR	43 (29.7)	19 (26.4)
P value[b]	0.0012	
Duration of Response (Months)		
Median (95% CI)[c]	NE (25.3, NE)	14 (9.2, 25.1)
DOR Rate at 12-months (95% CI)[e]	72.8 (62.1, 81.0)	55.1 (34.4, 71.6)
DOR Rate at 18-months (95% CI)[e]	69.3 (57.8, 78.2)	41.9 (22.6, 60.1)
Progression-free Survival (Months)		
Median (95% CI)[c]	28 (16.1, NE)	10.4 (6.5, 13.8)
PFS Rate at 18 Months (95% CI)[d]	56.4 (46.9, 64.9)	29.7 (17.7, 42.8)

Overall Response Rate: CR + PR, CR: complete response, PR: partial response

[a] Estimated using the Clopper-Pearson method.

[b] Cochran-Mantel-Haenszel method stratified by rituximab-refractory status, number of prior lines of therapy, and geographic region per IRT.

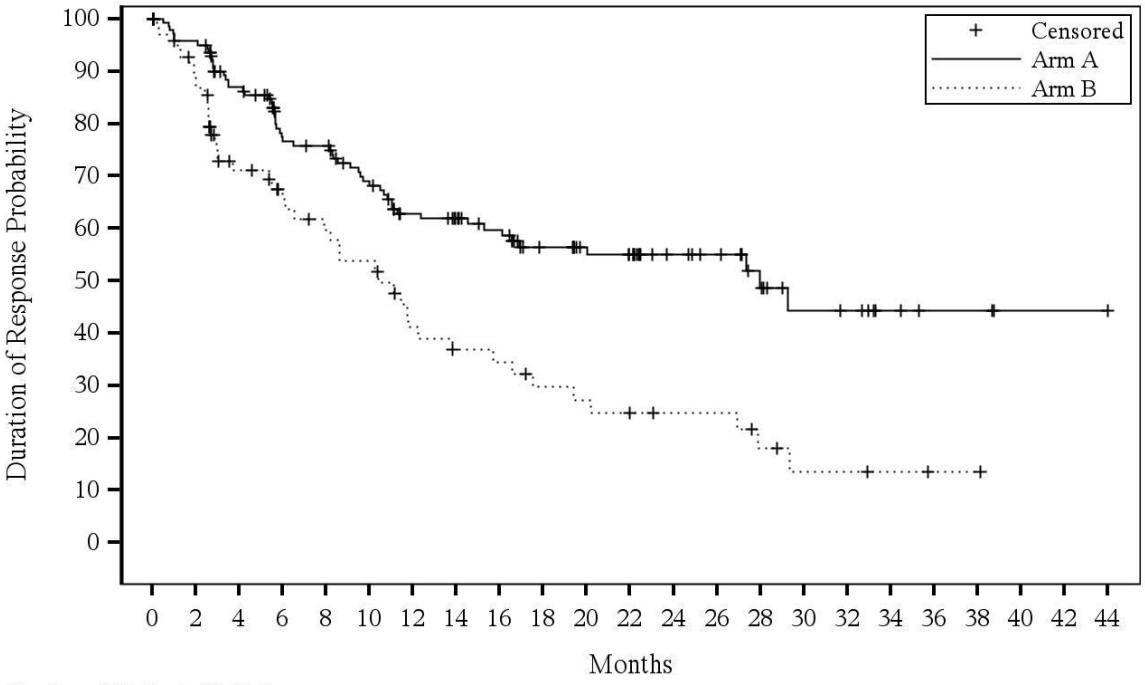
[c] Medians estimated by Kaplan-Meier method; 95% CIs estimated by Brookmeyer and Crowley method.

[d] PFS rates estimated by Kaplan-Meier method; 95% CIs estimated using the Greenwood's formula.

[e] DOR rates estimated by Kaplan-Meier method; 95% CIs estimated using the Greenwood's formula.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Figure 5: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review (ITT)



Number of Patients At Risk:

Arm A	145	135	116	94	92	79	67	62	56	45	38	35	25	22	15	10	9	5	3	3	1	1	0
Arm B	72	61	41	34	30	27	19	16	15	12	11	9	8	8	5	3	3	2	1	1	0		

Source: ADSL, ADTTEIRC. Data cutoff: 25JUN2022. Data extraction: 12SEP2022.
Arm A, Zanubrutinib + Obinutuzumab; Arm B, Obinutuzumab.
/bgb_3111/bgb_3111_212/irc_impact_analysis_fup_12m_csr20220625/dev/pgm/tfls/f-ef-km-updtd-i.sas 14MAY2024 09:24 f-3-1-1--ef-km-pfs-updtd-irc-itt-i.rtf

Overall Survival

Twenty-nine patients (20.0%) in the combination arm and 22 patients (30.6%) in the obinutuzumab monotherapy arm died. At 18 months, overall survival rates were 84.6% (95% CI: 77.1, 89.8) in the combination arm and 73.5% (95% CI: 60.7, 82.7) in the obinutuzumab monotherapy arm. At 24 months, the overall survival rates were 77.3% (95% CI: 68.0, 84.2) in the combination arm and 71.4% (95% CI: 58.3, 81.1) in the obinutuzumab monotherapy arm.

5.2 Pharmacokinetic Properties

Zanubrutinib maximum plasma concentration (Cmax) 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.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

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 (Vz/F) was 522 L (71%) following a 160 mg twice daily dose. The plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio is 0.7 to 0.8.

Metabolism

Zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A.

Elimination

The mean half-life (t½) 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 radiolabeled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in feces (38% unchanged) and 8% in urine (less than 1% unchanged).

Drug Interaction Studies

Agents that may increase zanubrutinib plasma concentrations

CYP3A Inhibitors: The coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the C_{max} of zanubrutinib by 2.6-fold and AUC by 3.8-fold. 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.

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}.

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 rifampin (strong CYP3A inducer) decreased the zanubrutinib C_{max} by 92% and AUC by 93%. Coadministration of multiple doses of rifabutin (moderate CYP3A inducer) decreased the zanubrutinib Cmax 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%.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

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. Based on in vitro data and PBPK modeling, no interaction with CYP2B6 substrates is expected at clinically relevant concentrations.

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.

5.1.1. Special Populations

5.2.1.1 Age

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

5.2.1.2 Gender

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

5.2.1.3 Race

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

5.2.1.4 Body Weight

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

5.2.1.5 Renal Insufficiency

Zanubrutinib undergoes minimal renal elimination. Based on population PK analysis, mild and moderate renal impairment (CrCl ≥ 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 (CrCl < 30 mL/min) or in patients requiring dialysis.

5.2.1.6 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.

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

5.3 Preclinical Safety Data

Carcinogenicity

Carcinogenicity studies have not been conducted with zanubrutinib.

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 doses up to 2000 mg/kg.

Developmental and Reproductive Toxicity

A combined male and female fertility and early embryonic development study was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed 4 weeks prior to mating and through mating and female rats were dosed 2 weeks prior to mating and to gestation day 7. No effect on male or female fertility was noted but at the high dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 10 times the human recommended dose, based on body surface area.

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts with the incidence between 0.3% and 1.5%) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a prenatal and postnatal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

6. PHARMACEUTICAL PARTICULARS

1.1 List of Excipients

Capsule content

Microcrystalline cellulose

Croscarmellose sodium

Sodium lauryl sulfate

Colloidal silicon dioxide

Magnesium stearate

Capsule shell

Gelatin

Titanium dioxide

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

Printing ink

Shellac glaze

Iron oxide black

N-butyl alcohol

Purified water

Propylene glycol
Dehydrated ethanol

Isopropyl alcohol

Ammonium hydroxide 28%

1.2 Incompatibilities

N/A

1.3 Shelf Life

24 months.

1.4 Special Precautions for Storage

Do not store above 30° C.

1.5 Nature and Content of Container

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

1.6 Instructions for Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRESENTATION

BRUKINSA, box of 1 bottle @ 120 capsules. Reg. No.: DKI2468000201A1

HARUS DENGAN RESEP DOKTER

Discard within 120 days after opening.

Manufactured by:

Catalent CTS, LLC

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10245 Hickman Mills Dr, Kansas City, MO 64137, USA

Packed by:
AndersonBrecon Incorporated.
4545 Assembly Drive, Rockford, IL 61109, USA

Released by:
Millmount Healthcare Limited
Block-7, City North Business Campus, Stamullen, Co. Meath, K32 YD60 Ireland

Registered by:

PT Etana Biotechnologies Indonesia
Jl. Rawa Gelam V Blok L, Kav. 11-13, Kawasan Industri Pulo Gadung, Jakarta Timur, DKI Jakarta, Indonesia

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INFORMASI PRODUK UNTUK PASIEN

BRUKINSA

Zanubrutinib 80 mg Kapsul

Bacalah seluruh leaflet ini dengan seksama sebelum anda menggunakan obat ini karena leaflet ini berisi informasi yang penting mengenai obat ini. Leaflet ini merupakan ringkasan informasi mengenai BRUKINSA dan tidak berisikan semua informasi terkait obat ini. Dokter, perawat atau apoteker anda memiliki leaflet mengenai BRUKINSA khusus untuk tenaga kesehatan professional. Silakan bertanya kepada dokter, perawat atau apoteker jika anda memiliki pertanyaan lebih lanjut.

Simpan leaflet ini sebagai referensi

Apa itu BRUKINSA dan apa kegunaannya?
BRUKINSA adalah obat anti kanker yang digunakan pada pengobatan pasien dewasa dengan kondisi :
***Mantle cell lymphoma* (MCL)**
BRUKINSA diindikasikan pada pengobatan pasien dewasa dengan kondisi *Relapsed/refractory Mantle cell lymphoma* (MCL)
***Waldenström's Macroglobulinemia* (WM)**
BRUKINSA diindikasikan pada pengobatan pasien dewasa dengan kondisi *Relapsed/refractory Waldenström's Macroglobulinemia* (WM) dan untuk *Treatment Naïve* (TN) yang tidak cocok dengan imunokemoterapi standar berdasarkan komorbiditas dan faktor resiko.
Chronic Lymphocytic Leukima (CLL) or Small Lymphoma (SLL)
BRUKINSA diindikasikan pada pengobatan pasien dewasa dengan *Chronic Lymphocytic Leukemia (CLL) atau Small Lymphocytic Lymphoma (SLL)*
Marginal Zone Lymphoma (MZL)
BRUKINSA diindikasikan pada pengobatan pasien dewasa dengan *Marginal Zone Lymphoma* (MZL) dan telah menerima setidaknya satu jenis pengobatan tertentu (*anti-CD20based therapy*)
Follicular Lymphoma (FL)
BRUKINSA diindikasikan pada pengobatan pasien dewasa dengan kondisi *Relapsed/refractory* Follicular lymphoma (FL) dalam kombinasi dengan obat Obinutuzumab dan telah menerima setidaknya dua jenis pengobatan sistematis tertentu.

BRUKINSA bekerja dengan memblok *Bruton's tyrosine kinase,* protein yang berperan penting dalam pertumbuhan dan pertahanan sel kanker. BRUKINSA memblok protein tersebut, yang berakibat pada berkurangnya jumlah sel kanker dan memperlambat perparahan penyakit kanker. BRUKINSA dapat diresepkan untuk pengobatan kondisi selain yang dijelaskan pada leaflet ini. Jika anda memiliki pertanyaan lebih lanjut, silakan konsultasikan dengan dokter anda.

Apa informasi terpenting yang harus saya ketahui tentang BRUKINSA?
BRUKINSA dapat menyebabkan efek samping yang serius, meliputi:

- **Masalah pendarahan** yang dapat menjadi serius dan dapat menyebabkan kematian. Resiko pendarahan anda dapat meningkat jika anda juga mengkonsumsi obat pengencer darah. Beritahu dokter anda jika anda mengalami gejala pendarahan, termasuk:
    - Terdapat darah pada feses atau feses berwarna hitam
    - Urin berwarna coklat atau merah muda
    - Pendarahan tidak terduga atau pendarahan berat atau pendarahan yang tidak dapat

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

anda kontrol
    - Muntah darah atau muntah yang terlihat seperti ampas kopi
    - Batuk darah atau terdapat gumpalan darah
    - Muncul banyak memar atau tanda merah atau ungu pada kulit
    - Pusing
    - Lemah
    - Kebingungan
    - Perubahan kemampuan berbicara
    - Sakit kepala berkepanjangan
- **Infeksi** yang dapat menjadi serius dan dapat menyebabkan kematian. Segera beritahu dokter anda jika anda mengalami gejala infeksi, termasuk:
    - Demam
    - Menggigil
    - Gejala seperti flu
- **Penurunan jumlah sel darah** (sel darah putih, sel darah merah dan platelet) adalah keadaan yang umum terjadi pada penggunaan BRUKINSA namun dapat juga menjadi berat. Dokter anda harus melakukan tes darah secara reguler untuk memeriksa jumlah sel darah anda selama pengobatan dengan BRUKINSA
- **Permasalahan ritme jantung (fibrilasi atrium**, ***atrial flutter,*** dan aritmia ventrikel*)* yang bersifat serius dan dapat menyebabkan kematian. Beritahu dokter anda jika anda mengalami gejala dari masalah ritme jantung, termasuk :
    - Detak jantung cepat atau tidak beraturan**.**
    - Pusing
    - Sensasi seperti kehilangan keseimbangan (*Lightheadedness*)
    - Perasaan akan pingsan/tidak sadarkan diri
    - Rasa tidak nyaman di dada
    - Nafas pendek
- ***Second primary cancers***. Penyakit kanker baru dapat muncul pada pasien selama terapi menggunakan BRUKINSA, termasuk kanker kulit. Gunakan tabir surya saat anda berada di luar ruangan dan terpapar sinar matahari.
- **Masalah hati.** Masalah hati, yang mungkin parah atau mengancam jiwa, atau menyebabkan kematian, dapat terjadi pada orang yang diobati dengan BRUKINSA. Penyedia layanan kesehatan anda akan melakukan tes darah untuk memeriksa hati anda sebelum dan selama pengobatan dengan BRUKINSA. Beritahukan penyedia layanan kesehatan Anda atau dapatkan bantuan media segera jika anda memiliki tanda-tanda masalah hati, termasuk:
    - Sakit perut atau rasa tidak nyaman
    - Air seni berwarna gelap
    - Kulit dan mata berwarna kuning

Siapa yang tidak diperbolehkan mengkonsumsi BRUKINSA?
Hindari penggunaan BRUKINSA jika anda alergi terhadap zanubrutinib atau kandungan lain dari obat ini (Lihat bagian akhir Panduan Obat ini untuk daftar lengkap bahan dalam BRUKINSA)
Keamanan dan efektivitas BRUKINSA pada anak tidak diketahui.

Konsultasikan dengan dokter anda jika anda mengalami beberapa kondisi seperti disebutkan berikut. BRUKINSA tidak dapat anda gunakan, jika :
- Baru saja atau akan menjalani pembedahan. Dokter anda akan menghentikan penggunaan BRUKINSA pada rencana pengobatan, pembedahan atau prosedur dental.
- Memiliki masalah pendarahan

- Memiliki masalah ritme jantung
- Memiliki tekanan darah tinggi
- Memiliki infeksi
- Memiliki masalah pada organ hati, termasuk infeksi virus Hepatitis B (HBV)
- Hamil atau sedang berupaya untuk hamil. BRUKINSA dapat membahayakan kesehatan janin. Jika anda menduga anda sedang hamil, dokter anda akan melakukan tes kehamilan sebelum memulai terapi anda dengan BRUKINSA
    - **Wanita** tidak diperbolehkan hamil selama pengobatan dan selama 1 (satu) minggu setelah dosis terakhir BRUKINSA. Anda harus menggunakan alat kontrasepsi yang efektif selama pengobatan dan selama 1 (satu) minggu setelah dosis terakhir BRUKINSA
    - **Laki-laki** harus menghindari kehamilan pada pasangan wanita selama pengobatan dan selama 1 (satu) minggu setelah dosis terakhir BRUKINSA. Anda harus menggunakan alat kontrasepsi yang efektif selama pengobatan dan selama 1 (satu) minggu setelah dosis terakhir BRUKINSA
- Sedang menyusui atau berencana menyusui. Tidak diketahui apakah BRUKINSA dapat masuk ke dalam air susu ibu. Jangan menyusui selama pengobatan dengan BRUKINSA dan selama kurang lebih 2 minggu setelah kosumsi dosis terakhir BRUKINSA

Beritahu dokter anda semua obat yang sedang anda konsumsi, termasuk obat resep, produk obat bebas dan obat bebas terbatas, vitamin, suplemen dan produk herbal. Penggunaan BRUKINSA bersamaan dengan obat lain dapat mempengaruhi kerja BRUKINSA dan dapat menyebabkan efek samping. Ketahui obat-obatan yang anda konsumsi. Buat daftar obat yang anda konsumsi dan beritahu dokter serta apoteker jika anda mendapatkan pengobatan baru.

Bagaimana saya harus menggunakan BRUKINSA?

- Ikuti instruksi dokter anda mengenai cara penggunaan BRUKINSA
- Dosis yang direkomendasikan adalah total dosis 320 mg per hari secara oral; baik 320 mg (4 kapsul) per hari atau 160 mg (2 kapsul) dua kali sehari. Dokter anda akan menyesuaikan dosis penggunaan obat.Telan kapsul seutuhnya dengan 1 gelas air minum. Jangan membuka, memecahkan atau mengunyah kapsul BRUKINSA
- Konsumsi kapsul seutuhnya pada waktu yang sama setiap harinya. BRUKINSA dapat diminum dengan atau tanpa makanan.
- Jika anda melewatkan 1 (satu) dosis, segera minum saat anda mengingatnya di hari yang sama. Minum dosis BRUKINSA selanjutnya pada waktu yang biasa anda konsumsi di hari selanjutnya.
- Jika anda mengira anda atau orang lain mungkin mengkonsumsi BRUKINSA melebihi dosis yang disarankan, segera hubungi dokter, pusat kontrol keracunan, atau layanan gawat darurat
- Jangan mengganti dosis atau menghentikan penggunaan BRUKINSA kecuali diinstruksikan oleh dokter anda.
- Dokter anda mungkin akan meminta anda untuk mengurangi dosis anda, berhenti sementara, atau berhenti sama sekali mengonsumi BRUKINSA jika anda mengalami efek samping tertentu.

Apa yang harus saya hindari selama penggunaan BRUKINSA

- Hindari mengemudikan kendaraan atau mengoperasikan mesin selama penggunaan BRUKINSA. BRUKINSA dapat membuat anda merasa lelah atau pusing yang dapat mempengaruhi kemampuan anda mengemudi atau mengoperasikan mesin.
- Hindari penggunaan CYP3A *inhibitors* kuat atau sedang (misalnya itraconazole, fluconazole, diltiazem) selama penggunaan BRUKINSA. Obat-obatan tersebut dapat

DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078

meningkatkan kadar BRUKINSA dalam darah anda.
- Hindari penggunaan CYP3A *inducers* (misalnya rifampisin) selama penggunaan BRUKINSA. Obat-obatan tersebut dapat menurunkan kadar BRUKINSA dalam darah anda.

Apa efek samping yang mungkin terjadi dari penggunaan BRUKINSA?
Efek samping yang sering terjadi, yaitu :
- Ruam
- Diare
- Batuk
- Memar
- Penurunan jumlah sel darah putih
- Penurunan jumlah sel darah merah (anemia)
- Penurunan jumlah platelet
- Infeksi saluran pernapasan atas
- Pendarahan
- Nyeri otot, tulang, atau sendi

Gejala yang disebutkan diatas belum mencakupkan semua efek samping yang mungkin terjadi dari penggunaan BRUKINSA. **Hubungi dokter jika anda merasa terganggu dengan efek samping yang disebutkan atau jika efek tersebut tidak menghilang, atau jika anda mengalami efek selain yang disebutkan diatas.** Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak di bawah ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamaan obat ini.

Kontak untuk Pelaporan ke Industri Farmasi
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Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav. 11-13, Jakarta
Email: pv@id.etanabiotech.com
Web-site: https://ebi-pharmacovigilance.azurewebsites.net/

Bagaimana saya menyimpan BRUKINSA?
- Simpan BRUKINSA dan obat-obatan lainnya diluar pandangan dan jangkauan anak-anak
- Jangan menyimpan BRUKINSA diatas suhu 30°C
- Buang BRUKINSA yang tidak digunakan setelah tanggal kadaluarsanya. Jangan membuang BRUKINSA yang tidak digunakan ke saluran air atau tempat pembuangan sampah rumah tangga. Tanyakan apoteker anda bagaimana cara membuang obat yang sudah tidak anda gunakan. Perilaku ini akan membantu perlindungan sumber air dan lingkungan

Obat ini hanya diresepkan kepada anda hanya untuk kondisi tertentu. Jangan konsumsi obat ini untuk kondisi kesehatan yang lain. Jangan diberikan kepada orang lain meskipun mereka memiliki gejala atau tanda yang sama karena hal itu dapat membahayakan mereka.

Seperti apakah bentuk BRUKINSA?
BRUKINSA berupa kapsul gelatin berwarna putih hingga putih buram dengan Panjang 22 mm, dengan tulisan “ZANU 80” berwarna hitam. Kapsul tersedia dalam kemasan botol plastic yang dilengkapi dengan tutup botol *child-resistant* berisikan 120 kapsul.

Apa kandungan BRUKINSA?
Zat aktif : zanubrutib
Komposisi lainnya : mikrokristaline selulosa, natrium kroskarmelosa, natrium lauril sulfat, silicon dioksida koloidal, magnesium stearat, gelatin, titanium dioksida, *shellac glaze*, besi oksida hitam, *N-butyl alcohol*, air, etanol terdehidrasi, isopropil alkohol, ammonium hidroksida 28% dan propilen glikol.

BRUKINSA, 1 box isi 1 botol @ 120 kapsul. Reg. No.: DKI2468000201A1

HARUS DENGAN RESEP DOKTER

Jangan digunakan jika sudah melebihi 120 hari setelah kemasan dibuka

Diproduksi oleh:
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AndersonBrecon Incorporated.
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DISETUJUI OLEH BPOM : 29/12/2025 ID : EREG10000712500078