BeiGene

PACKAGE INSERT

zanubrutinib

1. NAME OF THE MEDICINAL PRODUCT

BRUKINSA 80 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 80 mg of zanubrutinib.

For the full list of excipients, see Section 6.1 .

3. PHARMACEUTICAL FORM

Hard capsule.

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

Mantle cell lymphoma (MCL)

Zanubrutinib is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Waldenström's Macroglobulinemia (WM)

Zanubrutinib is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

Marginal Zone Lymphoma

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.

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

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

Follicular Lymphoma (FL)

Zanubrutinib in combination with obinutuzumab is indicated for the treatment of adult patients with follicular lymphoma (FL) who have received at least 2 prior therapies.

4.2. Posology and Method of Administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

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	First	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting >10 consecutive days)	Second	Interrupt zanubrutinib Once toxicity has resolved to ≤ Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
Grade 4 thrombocytopenia (lasting > 10 consecutive days)	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.

Dose modifications for concomitant therapy

Dose Modification for use with CYP3A inhibitors or inducers:

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 of strong CYP3A inducers. Avoid concomitant use of moderate inducers. If these inducers cannot be avoided,

CYP3A	Co-administered Drug	Recommended Dose
		increase zanubrutinib dose up to 320 mg twice daily.

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

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.

Special populations

Elderly

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

Renal impairment

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*).

Hepatic impairment

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*).

Paediatric population

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

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.

4.3. 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. 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.

Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal infections, or sepsis) and opportunistic infections (e.g., herpes viral, cryptococcal, aspergillus, and *pneumocystis jirovecii*

infections) have occurred in patients with hematological malignancies treated with zanubrutinib. 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.

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. 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, 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.

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

Effect of Other Drugs on Zanubrutinib

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 coadministration of zanubrutinib with strong CYP3A inducers. • Avoid coadministration of zanubrutinib with moderate CYP3A inducers. If these inducers cannot be avoided, increase zanubrutinib dosage up to 320 mg twice daily *[see Posology and Method of Administration (4.2)]*.

4.6. Fertility, Pregnancy and Lactation

Women will be advised to avoid pregnancy 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 zanubrutinib.

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 stopping 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. Pregnancy testing is recommended for women of reproductive potential prior to initiating therapy.

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.

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 monotherapy 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, and BGB-3111-210, BGB-3111-214), three Phase 3 clinical studies (BGB-3111-302, BGB -3111-304, BGB-3111-305), and a longterm 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.

Discontinuation and dose reduction

Of the 1550 patients treated with zanubrutinib monotherapy, 59 (3.9%) 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 4.8% and 19.8% 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 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
	Contusion	Very common (19.4)	0
	Petechiae	Common (6.6)	0.1
	Purpura	Common (5.4)	0.2

MedDRA SOC	Group Terms/PTs	Zanubrutinib N=1550	
		All grades* (%)	Grade ≥3 (%)
	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	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
	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
Blood and lymphatic system disorders	Thrombocytopenia§	Very common (35.2)	14
	Neutropenia§	Very common (28.5)	24
	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.
§ 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*)

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.

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.

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).

Clinical Efficacy and Safety

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). and 74.4 percent of patients had prior 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 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 was 1 (range 1 to 4). and 93.5 percent of patients had 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%.

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.

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 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. 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)	
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.

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.

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 10.

Table 10: 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			

	Cohort 1* Patients without Del(17p)		Cohort 2 Patients with Del(17p)
Endpoint	**Zanubrutinib (N=241)**	**Bendamustine + Rituximab (N=238)**	**Zanubrutinib (N=110)**
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)	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.

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 11.

Table 11: 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.

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 12.

Table 12: 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 (%) (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[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 13.

Table 13: 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)
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 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.

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

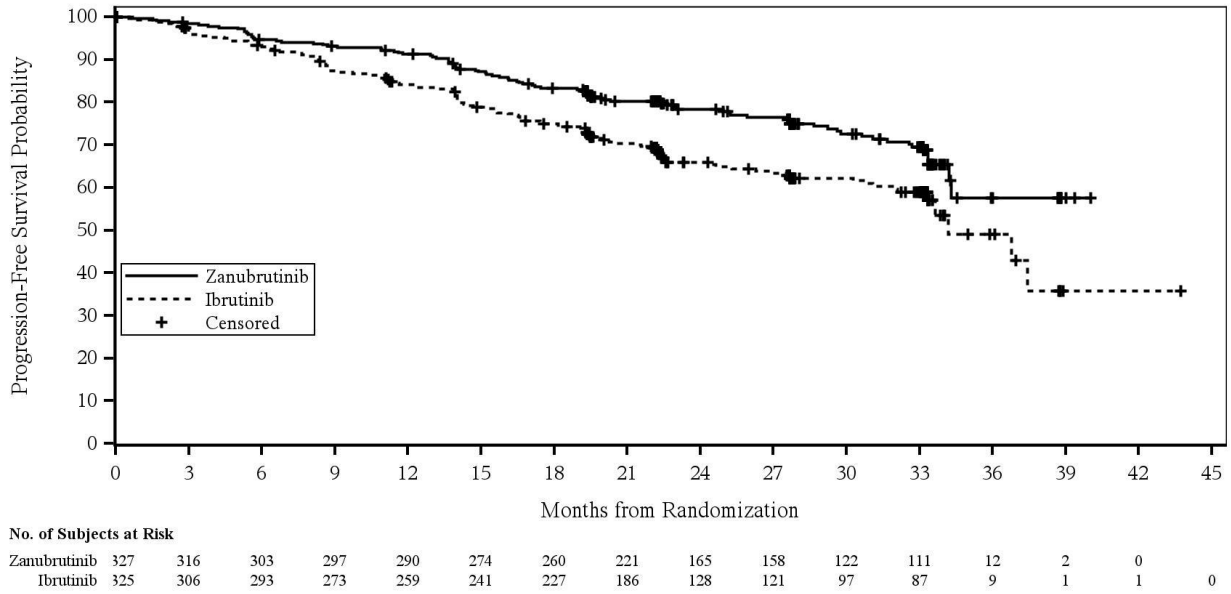
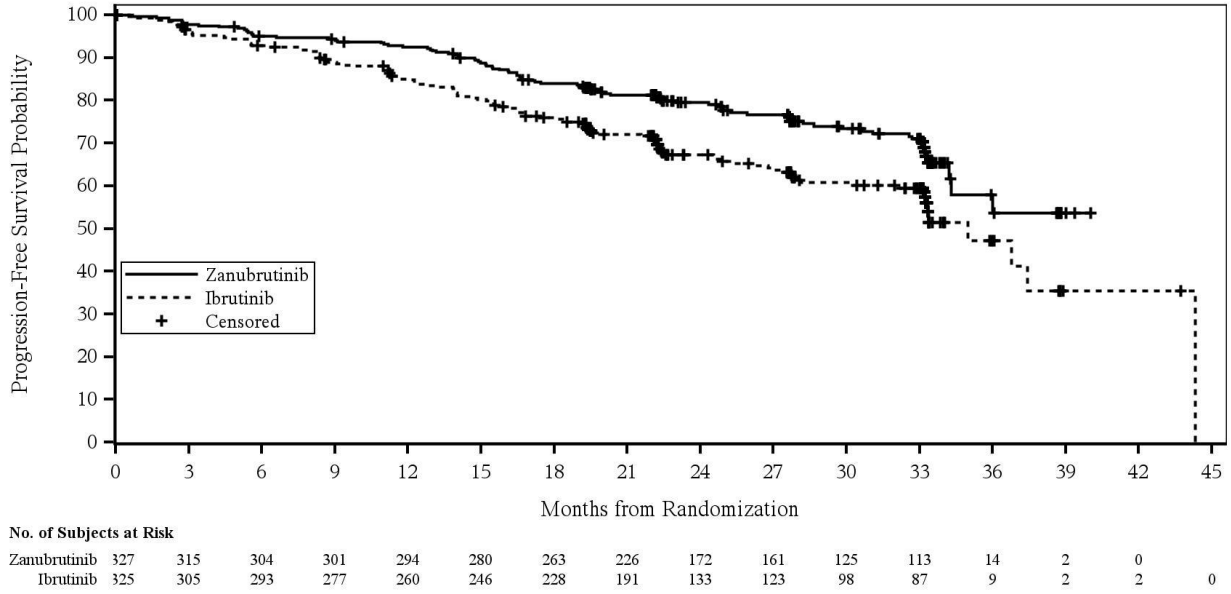


Figure 2: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review (ITT)



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)

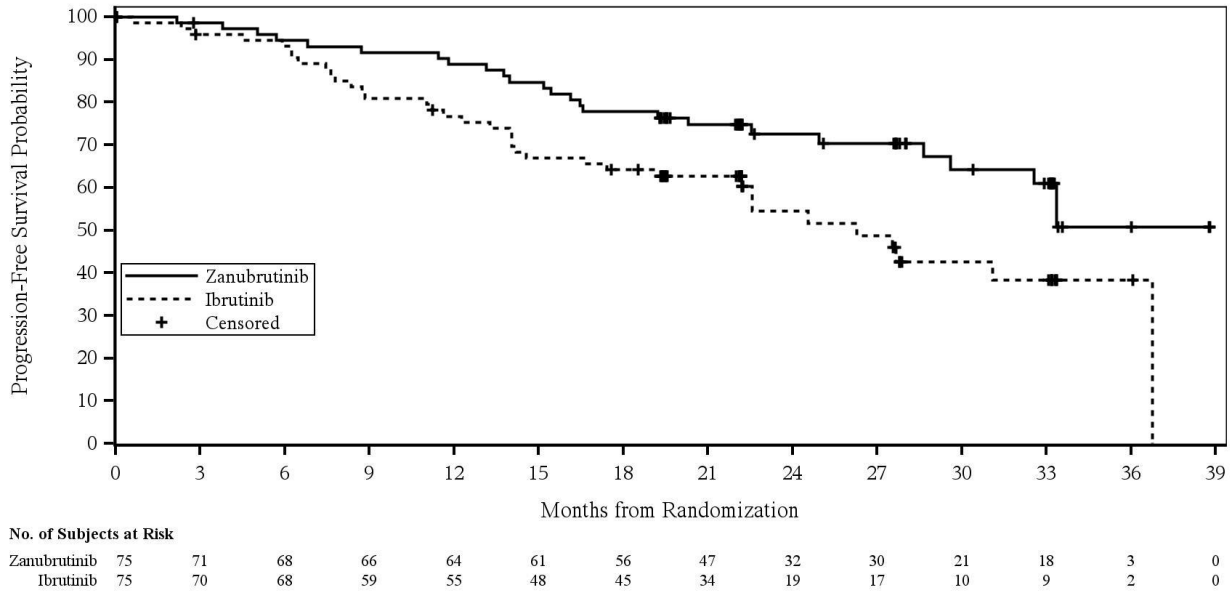
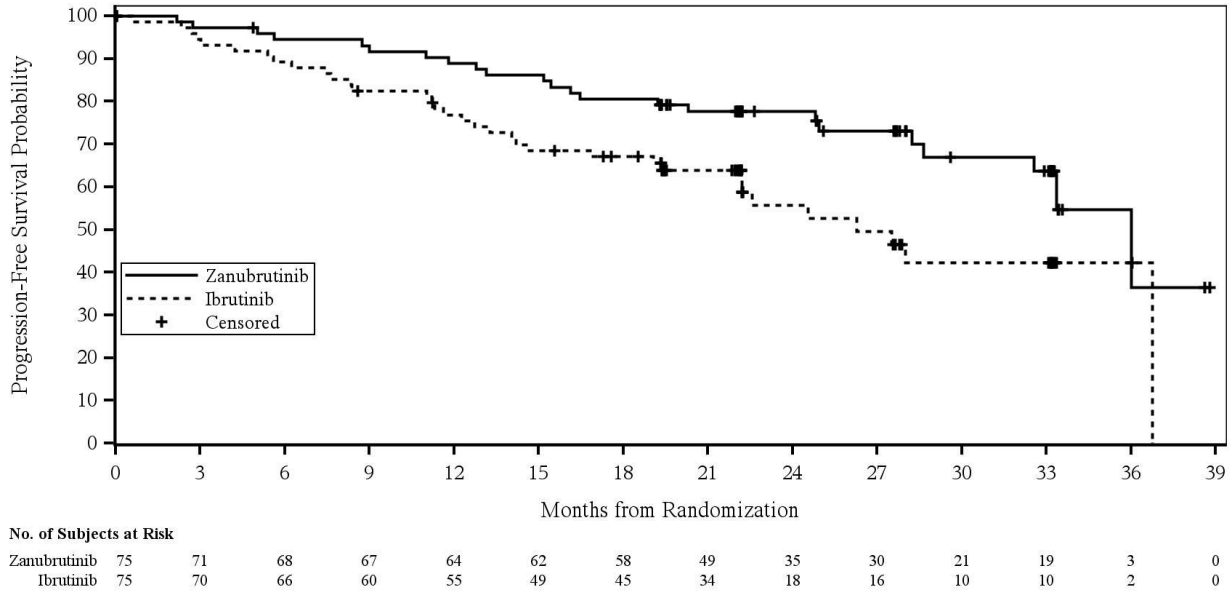


Figure 4: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review for Patients with Del 17P or TP53 (ITT)



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.

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 14: 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.

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).

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 56.3% (95% CI: 46.7, 64.8) in the combination arm and 29.7% (95% CI: 17.6, 42.7) in the obinutuzumab arm; and at 24 months, the PFS rate was 54.8% (95% CI: 45.1, 63.6) in the combination arm and 24.7% (95% CI: 13.5,37.7) in the obinutuzumab arm.

Efficacy results are summarized in Table 15 and Figure 5.

Table 15: 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, 80.9)	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]	56.3 (46.7, 64.8)	29.7 (17.6, 42.7)

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

[a] Estimated using the Clopper-Pearson method.

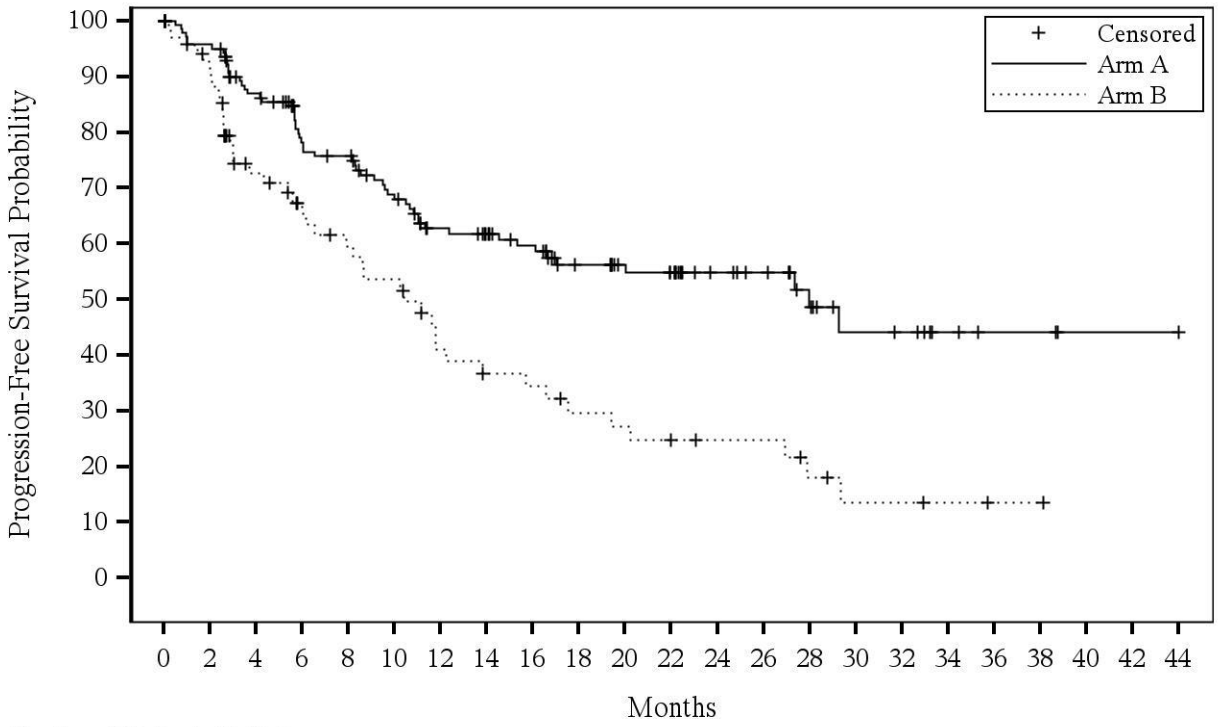
[b] Cochran-Mantel-Haenszel method stratified by rituximab-refractory status, number of prior lines of therapy, and geographic region per IRT.

[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.

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



Number of Patients At Risk:

Arm A	145	135	116	96	92	79	67	62	56	45	38	35	25	22	15	10	9	5	3	3	1	1	0
Arm B	72	63	42	34	30	27	19	16	15	12	11	9	8	8	5	3	3	2	1	1	0		

Arm A, Zanubrutinib + Obinutuzumab; Arm B, Obinutuzumab

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 (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 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 in healthy volunteers (strong CYP3A inhibitor) 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 (in patients 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 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 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. 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.

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 (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.

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

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 33 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose

groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Capsule content

Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate
Colloidal silicon dioxide
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide

Printing ink

Shellac glaze
Iron oxide black
N-butyl alcohol
Purified water
Propylene glycol
Dehydrated ethanol
Isopropyl alcohol
Ammonium hydroxide 28%

6.2. Incompatibilities

N/A

6.3. Shelf Life

36 months.

6.4. Special Precautions for Storage

Do not store above 30°C.

6.5. Nature and Content of Container

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

6.6. Special Precautions for Disposal

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

7. Marketing Authorization holder

Zuellig Pharma Ltd.

Bangkok, Thailand

Manufacturer

Catalent CTS, LLC

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

8. Date of revision of the text

The Date should be up to date