Zanubrutinib

Brukinsa
80mg capsule

1.0 PHARMACOLOGIC CATEGORY

Bruton's tyrosine kinase inhibitor

2.0 DESCRIPTION

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

3.0 FORMULATION/COMPOSITION

Each hard capsule contains 80 mg of zanubrutinib.

4.0 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).

4.2 Dosage and Method of Administration

4.2.1 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.

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:

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.

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.

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 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.

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.

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 is based on pooled data from 779 patients with B-cell malignancies treated with zanubrutinib in 6 clinical trials, including one Phase 1 clinical study (BGB-3111-1002), one Phase 1/2 clinical study (BGB-3111-AU-003), three Phase 2 studies (BGB-3111-205, BGB-3111-206, and BGB-3111-210), and one Phase 3 clinical study (BGB-3111-302).

The most commonly occurring adverse reactions in the 6 studies combined (≥ 20%) were neutropenia, thrombocytopenia, upper respiratory tract infection, anemia, rash, musculoskeletal

pain, and diarrhea. The most common Grade 3 or higher adverse reactions (≥ 5%) were neutropenia, thrombocytopenia, pneumonia, and anemia.

Discontinuation and dose reduction

Of the 779 patients treated with zanubrutinib, 47 (6.0%) patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (1.3%). Adverse reactions leading to dose reduction occurred in 5.3% of patients.

Presented in Table 4 below are adverse reactions that have been reported in association with the use of zanubrutinib monotherapy in the 6 clinical studies.

Table 4: Adverse Reactions in Patients Treated with Zanubrutinib

Body System Adverse Reaction	**Zanubrutinib (N = 779)**	
	All Grades* (%)	**Grade 3 or Higher (%)**
Blood and lymphatic system disorders		
Neutropenia†	53.6	27.4
Thrombocytopenia†	40.6	11.3
Anemia†	28.7	8.4
Infections and infestations		
Upper respiratory tract infection	36.2	2.3
Pneumonia§	18.6	10.1
Urinary tract infection	14.2	1.8
Skin and subcutaneous tissue disorders		
Rash§	26.2	0.4
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain§	22.8	2.2
Gastrointestinal disorders		
Diarrhea	22.3	1.7
Respiratory, thoracic and mediastinal disorders		
Cough	19.9	0.1
Injury, poisoning and procedural complications		
Contusion	19.8	0.0
Vascular disorders		
Hemorrhage§	13.2	2.1
Renal and urinary disorders		

Body System Adverse Reaction	**Zanubrutinib (N = 779)**	
	All Grades* (%)	**Grade 3 or Higher (%)**
Hematuria	13.2	0.4

* Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

† Based on laboratory measurements.

§ Includes multiple adverse reaction terms.

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.

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

<u>BTK occupancy in peripheral blood mononuclear cells and lymph node biopsies</u>

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 5: 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). 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 6: 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 7.

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

Table 7: 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 8.

Table 8: 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.

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 (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.

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%. PBPK simulations indicate that a moderate CYP3A inducer (e.g. efavirenz) may decrease zanubrutinib C_{max} by 58% and AUC by 60%.

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.

5.2.1 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.

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 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

24 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 Instructions for Disposal

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

7. FDA REGISTRATION NUMBER

DR-XY 48345

8. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

08092022

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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