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, marked with "ZANU 80" in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRUKINSA as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

BRUKINSA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20- based therapy.

BRUKINSA as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL).

BRUKINSA as monotherapy is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved based on overall response rate. Continued approval for this indication is contingent upon verification and description of clinical benefit in a confirmatory trial.

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

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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 dose of zanubrutinib is 320 mg. The daily dose may be taken either once daily (four 80 mg capsules) or divided into two doses of 160 mg twice daily (two 80 mg capsules). Treatment with Brukinsa should be continued until disease progression or unacceptable toxicity.

BRUKINSA in combination with obinutuzumab

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Zanubrutinib must be administered orally before obinutuzumab infusion. The recommended dose is obinutuzumab 1,000 mg intravenously on Days 1, 8, and 15 of Cycle 1, and on Day 1 of every 28-day cycle from Cycles 2 to 6. At the discretion of the physician, obinutuzumab may be administered 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1. Obinutuzumab maintenance (one infusion every two months for up to two years) may be prescribed. Refer to the obinutuzumab SmPC for additional dosing information, including premedication before each infusion.

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Dose modifications for adverse reactions

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

Table 1: Recommended dose modifications for adverse reactions

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

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

For dose modification of obinutuzumab for adverse reactions, refer to the SmPC of obinutuzumab.

Dose modifications for concomitant therapy

Dose modifications for use with CYP3A inhibitors or inducers (see sections 4.4, 4.5 and 5.2):

Table 2: Recommended dose modifications when co-administered with other medicinal products

CYP3A	**co-administered medicinal product**	**recommended dose**
Inhibition	Strong CYP3A inhibitor (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily
	Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) Moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use; Consider alternative agents with less CYP3A induction

Missed dose

A double dose should not be taken to make up for a forgotten dose. If a dose is not taken at the scheduled time, the next dose should be taken according to the normal schedule.

Special populations

Elderly

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

Renal impairment

No dose modification is recommended in patients with mild to moderate renal impairment (creatinine clearance (CrCl) ≥30 mL/min, estimated by Cockcroft-Gault). There is limited data on patients with severe renal impairment and end-stage renal disease (n=5). Patients with severe renal impairment (CrCl <30 mL/min) or on dialysis should be monitored for adverse reactions (see section 5.2).

Hepatic impairment

Dose modifications are not needed in patients with mild (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). Patients with mild or moderate hepatic impairment were treated in BRUKINSA clinical studies. The recommended dose of BRUKINSA for patients with severe hepatic impairment (Child-Pugh class C) is 80 mg orally twice daily. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse events of BRUKINSA (see section 5.2).

Paediatric population

The safety and efficacy of BRUKINSA in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

BRUKINSA is for oral use. The hard capsules can be taken with or without food. Patients should be instructed to swallow the capsules whole with water, and not to open, break or chew the capsules.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haemorrhage

Serious and fatal haemorrhagic events have occurred in patients treated with BRUKINSA ~~monotherapy~~. Grade 3 or higher bleeding events including intracranial and gastrointestinal haemorrhage, haematuria and haemothorax have been reported in patients (see section 4.8). Bleeding events of any grade including purpura and petechiae occurred in patients with haematological malignancies. The mechanism for the bleeding events is not well understood.

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BRUKINSA may increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Dose modification may be necessary for Grade 3 or greater adverse reactions as recommended (see section 4.2). Warfarin or other vitamin K antagonists should not be administered concomitantly with BRUKINSA. Patients should be monitored for signs and symptoms of bleeding and monitor complete blood counts. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with BRUKINSA. Consider the benefit-risk of withholding zanubrutinib for 3 to 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 jiroveci infections) have occurred in patients treated with BRUKINSA ~~monotherapy~~. Grade 3 or higher infections occurred in patients (see section 4.8). The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have also occurred. Before initiating treatment with BRUKINSA, patients's HBV status should be established. Consultation with a liver disease expert physician is recommended for patients who test positive for HBV or have positive hepatitis B serology, before initiating treatment. Patients should be monitored and managed according to the medical standards to prevent hepatitis B reactivation. Consider prophylaxis according to standard of care in patients who are at increased risk for infections. Patients should be monitored for signs and symptoms of infection and treat appropriately.

Cytopenia

Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia, and anaemia based on laboratory measurements were reported in patients treated with BRUKINSA ~~monotherapy~~ (see section 4.8). Monitor complete blood counts monthly during treatment (see section 4.2).

Second primary malignancies

Second primary malignancies, including non-skin carcinoma have occurred in patients treated with BRUKINSA ~~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 treated with BRUKINSA ~~monotherapy~~, particularly in patients with cardiac risk factors, hypertension, ~~and~~ acute infections and elderly (≥ 65 years). ~~Monitor~~ ~~S~~signs and symptoms for atrial fibrillation and atrial flutter should be monitored and ~~and~~ managed as appropriate.

Tumour Lysis Syndrome

Tumour lysis syndrome has been infrequently reported with zanubrutinib monotherapy therapy, particularly in patients who were treated for chronic lymphocytic leukaemia (CLL). Assess relevant risks (e.g., high tumour burden or blood uric acid level) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Women of childbearing potential

Women of childbearing potential must use a highly effective method of contraception while taking BRUKINSA(see section 4.6).

BRUKINSA contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

Zanubrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A).

Agents that may increase zanubrutinib plasma concentrations

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

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Strong CYP3A inhibitors

The coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) in healthy volunteers increased the C_{max} of zanubrutinib by 2.6-fold and AUC by 3.8-fold. The coadministration of multiple doses of strong CYP3A inhibitors voriconazole and clarithromycin 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}, respectively.

If a strong CYP3A inhibitor must be used (e.g., voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir), reduce the BRUKINSA dose to 80 mg (one capsule) for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed (see section 4.2).

Moderate CYP3A inhibitors

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}, respectively.

If a moderate CYP3A inhibitor must be used (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges), reduce the BRUKINSA dose to 160 mg (two capsules) for the duration of the inhibitor use. Monitor patients closely for toxicity and follow dose modification guidance as needed (see section 4.2).

Mild CYP3A inhibitors

Simulations using fasted conditions suggested that the mild CYP3A inhibitors (e.g., cyclosporine and fluvoxamine) may increase the AUC of zanubrutinib by <1.5-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patients closely for toxicity and follow dose modification guidance as needed.

Grapefruit and Seville oranges should be used with caution during BRUKINSA treatment, as these contain moderate inhibitors of CYP3A (see section 4.2).

Agents that may decrease zanubrutinib plasma concentrations

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

CYP3A inducers

Co-administration of multiple doses of rifampin (strong CYP3A inducer) decreased zanubrutinib C_{max} by 92% and AUC by 93% in healthy subjects. Co-administration of multiple doses of rifabutin (moderate CYP3A inducer) decreased zanubrutinib C_{max} by 48% and AUC by 44% in healthy subjects. Mild CYP3A inducers may be used with caution during BRUKINSA treatment.

Gastric acid reducing agents

No clinically significant differences in zanubrutinib pharmacokinetics were observed whenco-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists).

Agents that may have their plasma concentrations altered by zanubrutinib

Zanubrutinib is a mild inducer of CYP3A and CYP2C19. Concomitant use of zanubrutinib can decrease the plasma concentrations of these substrate medicinal products.

CYP3A substrates

Co-administration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) C_{max} by 30% and AUC by 47%. Narrow therapeutic index medicinal products that are metabolised by CYP3A (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be used with caution, as zanubrutinib may decrease the plasma exposures of these medicinal products.

CYP2C19 substrates

Co-administration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} by 20% and AUC by 36%. Narrow therapeutic index medicinal products that are metabolized by CYP2C19 (e.g., S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these medicinal products.

Other CYP substrates

No clinically significant differences were observed with S-warfarin (CYP2C9 substrate) pharmacokinetics when co-administered with zanubrutinib.

Co-administration with transport substrates/inhibitors

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.

The coadministration of oral P-gp substrates with a narrow therapeutic index (e.g., digoxin) should be done with caution as zanubrutinib may increase their concentrations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Based on findings in animals, BRUKINSA may cause foetal harm when administered to pregnant women (see section 5.3). Women should avoid becoming pregnant while taking BRUKINSA and for up to 1 month after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking BRUKINSA and for up to 1 month after stopping treatment. It is currently unknown whether zanubrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. Pregnancy testing is recommended for women of reproductive potential prior to initiating therapy.

Pregnancy

BRUKINSA should not be used during pregnancy. There are no data from the use of BRUKINSA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

It is not known whether zanubrutinib or its metabolites are excreted in human milk and no non-clinical studies were conducted. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with Brukinsa.

Fertility

No effect on male or female fertility was noted in rats but morphological abnormalities in sperm and increased post-implantation loss were noted at 300 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

Brukinsa has no or negligible influence in the ability to drive and use machines. Fatigue, dizziness, and asthenia have been reported in some patients taking BRUKINSA and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

Zanubrutinib monotherapy

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The most commonly occurring adverse reactions (≥20%) of zanubrutinib monotherapy were upper respiratory tract infection§ (36%), bruising§ (32%), haemorrhage/haematoma§ (30%), neutropenia§ (30%), musculoskeletal pain§ (27%), rash§ (25%), pneumonia§ (24%), diarrhoea (21%) and cough§ (21%) (Table 3).

The most common Grade 3 or higher adverse reactions (>3%) of zanubrutinib monotherapy were neutropenia§ (21%), pneumonia§ (14%), hypertension§ (8%), thrombocytopenia§ (6%), anaemia (6%) and haemorrhage /haematoma§ (4%).

Of the 1550 patients treated with zanubrutinib, 4.8% of patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia§ (2.6%). Adverse reactions leading to dose reduction occurred in 5.0% of patients.

Zanubrutinib in combination with obinutuzumab

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The most commonly occurring adverse reactions (≥20%) of zanubrutinib in combination with obinutuzumab were thrombocytopenia§ (37%), neutropenia§ (31%) and fatigue§ (27%) (Table 4).

The most common Grade 3 or higher adverse reactions (>3%) of zanubrutinib in combination with obinutuzumab were neutropenia§ (25%), thrombocytopenia§ (16%), pneumonia§ (15%) and anaemia (5%).

Of the 143 patients treated with zanubrutinib in combination with obinutuzumab, 4.9% of patients discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was pneumonia§ (4.2%). Adverse reactions leading to dose reduction occurred in 7.0% of patients.

Platelet count decreased† (based on laboratory values) was observed in 65% (all grade) and 12% (grade 3 or 4) patients receiving zanubrutinib in combination with obinutuzumab compared to 43% (all grade) and 11% (grade 3 or 4) in patients receiving obinutuzumab. All grade and grade 3 or 4 platelet counts decreased were reported for 39% and 7.8% patients who received Zanubrutinib monotherapy.

Tabulated list of adverse reactions

The safety profile of zanubrutinib monotherapy is based on pooled data from 1550 patients with B-cell malignancies, including patients with chronic lymphocytic leukaemia (N = 938), Waldenström macroglobulinemia (N = 249), mantle cell lymphoma (N = 140), marginal zone lymphoma (N = 93), follicular lymphoma (N = 59) and other types of B-cell malignancies (N = 71), treated with BRUKINSA in clinical studies with a median duration of exposure of 34.41 months.

The safety profile of zanubrutinib in combination with obinutuzumab is based on ROSEWOOD study data from 143 patients with FL treated with BRUKINSA in combination with obinutuzumab in two clinical studies with a median duration of exposure of 12.35 months.

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Adverse reactions in patients treated with BRUKINSA as monotherapy or in combination with Obinutuzumab for B-cell malignancies are listed in Table 3 and Table 4, by system organ class and frequency grouping. 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 the order of decreasing seriousness.

Table 3: Adverse reactions of zanubrutinib monotherapy reported in clinical studies in patients with B-cell malignancies (n=1550)

MedDRA SOC	MedDRA Terms	All Grades* (%)	Grade 3 or higher (%)
Infections and infestations	Upper respiratory tract infection[§]	Very Common (36)	2
	Pneumonia[§#]	Very Common (24)	14
	Pneumonia	Very Common (15)	8
	Lower respiratory tract infection	Common (5)	<1
	Urinary tract infection[§]	Very Common (14)	2
	Bronchitis	Common (4)	<1
	Hepatitis B reactivation	Uncommon (<1)	<1
Blood and lymphatic system disorders	Neutropenia[§]	Very Common (30)	21
	Febrile neutropenia	Common (2)	2
	Thrombocytopenia[§]	Very Common (18)	6
	Anaemia[§]	Very Common (16)	6
Nervous system disorder	Dizziness[§]	Very Common (12)	<1
Cardiac disorders	Atrial fibrillation and flutter	Common (5)	2
Vascular disorders	Bruising[§]	Very Common (32)	<1
	Contusion	Very Common (20)	0
	Petechiae	Common (7)	<1
	Purpura	Common (5)	<1
	Ecchymosis	Common (3)	<1
	Haemorrhage/Haematoma[§ #]	Very Common (30)	4
	Haematuria	Very common (11)	<1
	Epistaxis	Common (8)	<1
	Gastrointestinal haemorrhage	Uncommon (<1)	<1
	Hypertension[§]	Very Common (17)	8
Gastrointestinal disorders	Diarrhoea	Very Common (21)	2
	Constipation	Very Common (14)	<1
Skin and subcutaneous tissue disorders	Rash[§]	Very Common (25)	<1
	Pruritus	Common (8)	<1
	Dermatitis exfoliative generalized	Unknown	Unknown
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[§]	Very Common (27)	2
	Arthralgia	Very Common (15)	<1
	Back pain	Very common (12)	<1
General disorders and administration site conditions	Fatigue[§]	Very common (18)	1
	Fatigue	Very common (14)	1
	Asthenia	Common (4)	<1

	Oedema peripheral	Common (9)	<1
Respiratory, thoracic and mediastinal disorders	Cough[§]	Very Common (21)	<1
Metabolism and nutrition disorders	Tumour lysis syndrome[§#]	Uncommon (<1)	<1
Investigations[†]	Neutrophil count decreased[†±]	Very common (52)	22
	Platelets decreased[†±]	Very common (39)	8
	Haemoglobin decreased[†±]	Very common (26)	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.
± Percentages are based on number of patients with both baseline and at least one postbaseline assessment available.
§ Includes multiple adverse reaction terms
# Includes events with fatal outcome.

Table 1: Adverse reactions of zanubrutinib in combination with obinutuzumab reported in clinical study BGB-3111-212 in patients with follicular lymphoma (n=143)

MedDRA SOC	MedDRA Terms		
		All grades* (%)	Grade ≥3 (%)
Infections and infestations	Upper respiratory tract infection[§]	Very common (14)	<1
	Pneumonia[§#]	Very common (20)	15
	Pneumonia	Very common (13)	11
	Lower respiratory tract infection	Common (4)	<1
	Urinary tract infection§	Common (10)	2
	Bronchitis	Common (2)	0
Blood and lymphatic system disorders	Thrombocytopenia[§]	Very common (37)	16
	Neutropenia§	Very common (31)	25
	Anaemia§	Very common (12)	5
Nervous system disorder	Dizziness[§]	Common (4)	0
Cardiac disorders	Atrial fibrillation and flutter[§]	Common (3)	1
Vascular disorders	Haemorrhage/hematoma[§]	Very common (16)	<1
	Epistaxis	Common (5)	0
	Hematuria	Common (<1)	0
	Bruising[§]	Very common (15)	0
	Contusion	Very common (8)	0
	Petechiae	Common (6)	0
	Purpura	Common (2)	0
	Ecchymosis	Common (1)	0
	Hypertension[§]	Common (4)	<1
Respiratory, thoracic and mediastinal disorders	Cough[§]	Very common (13)	0
Gastrointestinal disorders	Diarrhoea	Very common (19)	3
	Constipation	Very common (13)	0
Skin and subcutaneous tissue disorders	Rash[§]	Very common (10)	0
	Pruritus	Common (7)	0

	Dermatitis exfoliative generalized	Unknown	Unknown
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain[§]	Very common (18)	2
	Back pain	Very common (11)	<1
	Arthralgia	Common (4)	0
General disorders and administration site conditions	Fatigue[§]	Very common (27)	1
	Fatigue	Very common (15)	0
	Asthenia	Common (12)	<1
	Oedema peripheral	Common (2)	0
Investigations[†±]	Platelets decreased[†±]	Very common (65)	12
	Neutrophil count decreased[†±]	Very common (48)	18
	Haemoglobin decreased[†±]	Very common (31)	<1

[*] Adverse events were graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0.)
[†] Based on laboratory measurements.
[§] Includes multiple adverse reaction terms.
[#] Includes events with fatal outcome.
[±] Percentages are based on number of patients with both baseline and at least one postbaseline assessment available.

Other special population

Elderly

Of the 1550 patients treated with BRUKINSA monotherapy, 61.3% were 65 years of age or older. The incidence of Grade 3 or higher adverse events was slightly higher among elderly patients treated with zanubrutinib (69.6% of patients age ≥65 versus 62.7% of patients <65 years of age). No clinically relevant differences in safety were observed between patients ≥65 years and younger.

Of the 143 patients treated with BRUKINSA in combination with obinutuzumab, 42.0% were 65 years of age or older. The incidence of Grade 3 or higher adverse events was slightly higher among elderly patients treated with zanubrutinib in combination with obinutuzumab (70.0% of patients age ≥65 versus 62.7% of patients <65 years of age). No clinically relevant differences in safety were observed between patients ≥65 years and younger.

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Paediatric population

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

4.9 Overdose

There is no specific antidote for BRUKINSA. 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 an inhibitor of Bruton's tyrosine kinase (BTK). Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.

Pharmacodynamic effects

BTK occupancy in PBMCs 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% to 100% following the recommended dose.

Effect on QT/QTc interval and cardiac electrophysiology

At the 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

Patients with Waldenström Macroglobulinemia (WM)
The safety and efficacy of BRUKINSA in WM were evaluated in a randomized, open-label, multicentre study comparing zanubrutinib and ibrutinib (ASPEN study) in patients who were BTK inhibitor naive. 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 unsuitable for standard chemo-immunotherapy regimens by their treating physician. 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 = 28) and received zanubrutinib 160 mg twice daily on a third, non-randomized, study arm (Arm C).

In Cohort 1 ($MYD88^{MUT}$), the median age was 70 years (range, 38 to 90 years), with 71% and 60% of patients treated with ibrutinib and zanubrutinib respectively being >65 years old. 33% of patients in the zanubrutinib arm and 22% in the ibrutinib were >75 years. 67% were male, and 91% were Caucasian. At study entry, 44% of patients in the ibrutinib arm and 46% of patients in the zanubrutinib arm had an International Prognostic Scoring System (IPSS) high. One hundred and sixty-four patients had relapsed or refractory disease; the median number of prior therapies was 1 (range, 1 to 8).

The primary outcome measure was rate of Complete Response (CR) or Very Good Partial Response (VGPR), as assessed by an independent review committee (IRC) with adaptation of the response criteria updated at the Sixth IWWM. The secondary endpoints for Cohort 1 include major response rate (MRR),

duration of response, rate of CR or VGPR determined by investigator, and progression-free survival (PFS).

The testing for the superiority of the primary endpoint of VGPR or CR rate required testing in the Relapsed/Refractory Analysis Set prior to testing in the ITT Analysis Set. Median follow-up was 19.4 months. In the relapsed/refractory patients, 19.8% and 28.9% achieved VGPR or CR on the ibrutinib and zanubrutinib arms, respectively. The primary efficacy endpoint was not significant in the Relapsed/Refractory Analysis Set (2-sided p=0.1160). Table 54 summarizes the responses as assessed by IRC for the Relapsed/Refractory and intent-to-treat (ITT) Analysis Set. Responses were observed with zanubrutinib across subgroups, including MYD88^{WT} patients (Cohort 2) who had a VGPR or CR rate of 26.9% and an MRR of 50%.

Table 54: Primary analysis of disease response by independent review committee (ASPEN Study)

	Relapsed/Refractory		**ITT**	
Response Category	**Ibrutinib N = 81**	**Zanubrutinib N = 83**	**Ibrutinib N = 99**	**Zanubrutinib N = 102**
Median follow-up time, months (range)	18.79 (0.5, 30.0)	18.73 (0.4, 28.7)	19.38 (0.5, 31.1)	19.47 (0.4, 31.2)
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VGPR	16 (19.8)	24 (28.9)	19 (19.2)	29 (28.4)
PR	49 (60.5)	41 (49.4)	58 (58.6)	50 (49.0)
VGPR or CR rate, n (%)	**16 (19.8)**	**24 (28.9)**	19 (19.2)	29 (28.4)
95% CI [a]	(11.7, 30.1)	(19.5, 39.9)	(12.0, 28.3)	(19.9, 38.2)
Risk difference (%) [b]	10.7		10.2	
95% CI [a]	(-2.5, 23.9)		(-1.5, 22.0)	
p-value [c]	**0.1160**			
MRR (PR or better), n (%)	65 (80.2)	65 (78.3)	77 (77.8)	79 (77.5)
95% CI [a]	(69.9, 88.3)	(67.9, 86.6)	(68.3, 85.5)	(68.1, 85.1)
Risk difference (%) [b]	-3.5		-0.5	
95% CI	(-16.0, 9.0)		(-12.2, 11.1)	
Duration of major response				
Event-free rate at, % (95% CI)[d] 18 months	85.6 (73.1, 92.6)	87.0 (72.5, 94.1)	87.9 (77.0, 93.8)	85.2 (71.7, 92.6)

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)
[d] Event-free rates are estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

Based on an updated data cut-off the progression free-survival event-free rate by investigator assessment was 77.6% vs 84.9% at 30 months (ibrutinib vs zanubrutinib), with an estimated overall hazard ratio of 0.734 (95% CI: 0.380, 1.415).

Patients with Marginal Zone Lymphoma (MZL)

The efficacy of zanubrutinib was assessed in a Phase 2 open-label, multicentre, single-arm trial of 68 patients with MZL who had received at least one prior anti-CD20-based therapy (MAGNOLIA study, BGB-3111-214). Twenty-six (38.2%) patients had extranodal MZL, 26 (38.2%) had nodal MZL, 12 (17.6%) had splenic MZL, and in 4 (6%) patients, the subtype was unknown. 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: 2.0 to 353.6). The median number of prior treatments was 2

(range: 1 to 6), with 27.9 % patients having 3 or more lines of systemic therapy; 98.5% (n=67) patients had received prior rituximab-based chemotherapy and 85.3% (n=58) patients had received prior treatment with alkylating agents; 5.9% patients (n=4) had prior stem cell transplantation. Sixty-three (92.6%) patients had a baseline ECOG performance status of 0 or 1. Twenty-two (32.4%) patients had refractory disease at study entry.

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~~5~~).

Table 6~~5~~: Efficacy Results in Patients with MZL by Independent Review Committee (MAGNOLIA study)

	Study BGB-3111-214 (N=66) [a]
ORR (95% CI)	68% (55.6,79.1)
CR	26%
PR	42%
Median DoR in months (95% CI)	NE (25.0, NE)
DOR Event Free Rate [b] at 24 months, % (95% CI)	72.9 (54.4, 84.9)
Median study follow-up in months (Min, Max)	28.04 (1.64, 32.89)

A Two patients in BGB-3111-214 were not evaluable for efficacy due to central confirmation of MZL transformation to diffuse large B-cell lymphoma.
b Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
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 2.79 months (range: 1.7 to 11.1 months). After a median study follow-up time of 28.04 months (range: 1.64 to 32.89 months), the median duration of response (DOR) as assessed by the IRC has not been reached (95% CI 25.0 months to NE), and a total of 72.9 % (95% CI 54.4 to 84.9) of responders were estimated to be event-free at 24 months after initial response.

The overall response rates observed were similar across three different MZL subtypes (extranodal, nodal and splenic).

Patients with Chronic Lymphocytic Leukaemia (CLL)

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

SEQUOIA study (BGB-3111-304): An International, Phase 3, Open-label, Randomized Study of Zanubrutinib Compared with Bendamustine plus Rituximab (BR) in Patients with Previously Untreated CLL.

The SEQUOIA study (BGB-3111-304) is a randomized multicenter, open-label, active controlled Phase 3 trial of zanubrutinib monotherapy and bendamustine in combination with rituximab in 479 patients with previously untreated CLL without 17p deletion (del(17p)) (arms A and B; Cohort 1). Arm C (Cohort 2) is a multicenter single-arm trial of zanubrutinib monotherapy in 110 patients with previously untreated CLL 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 (zanubrutinib) and arm B (BR) of Cohort 1. In both arms, the median age was 70.0 years, with a slightly higher proportion of patients of ≥ 75 years (26.1%) in arm A compared with arm B (22.3%) and a slightly lower proportion of

patients 65-75 years old (55.2%) in arm A compared with arm B (58.4%). In Cohort 1, 92.7% patients had a baseline ECOG performance status of 0 or 1 (93.7% in arm A and 91.6% in arm B). In Cohort 2 (arm C zanubrutinib), 87.3% patients had a baseline ECOG performance status of 0 or 1.

Demographic and baseline characteristics were also generally similar between arm A (zanubrutinib) in Cohort 1 and arm C (zanubrutinib) in Cohort 2.

In Cohort 1, randomisation was stratified by age (< 65 years vs ≥ 65 years), Binet stage (C versus 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 (BR).

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/m2/day on the first 2 days of each cycle for 6 cycles and rituximab at a dose of 375 mg/m2 for Cycle 1, and at a dose of 500 mg/m2 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 (PFS), assessed by an independent central review committee (IRC). Secondary endpoints included the overall response rate based on IRC assessment.

In Cohort 1, the median duration of follow-up for PFS was 25.0 months (range: 0.0 to 41.4). The PFS 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 BR. In Cohort 2, the median duration of follow up for PFS was 27.9 months (range: 1.0 to 38.8) and the PFS rate at 24 months 88.9% (95% CI: 81.3, 93.6). The ORR assessed by IRC in Cohort 2 was 90.0% (95% CI: 82.8, 94.9). The median time to partial response or higher as assessed by IRC was 2.89 months (range: 1.8, 14.2) and 2.86 months (range: 1.9, 13.9) in the zanubrutinib arm of Cohort 1 and Cohort 2, respectively.

Efficacy results for cohort 1 is presented in Table 7: Efficacy Results in the~~Table 7. he~~~~Table 6: Efficacy Results in the~~. The Kaplan-Meier curves for PFS for both arms in Cohort 1 are shown in Figure 1.

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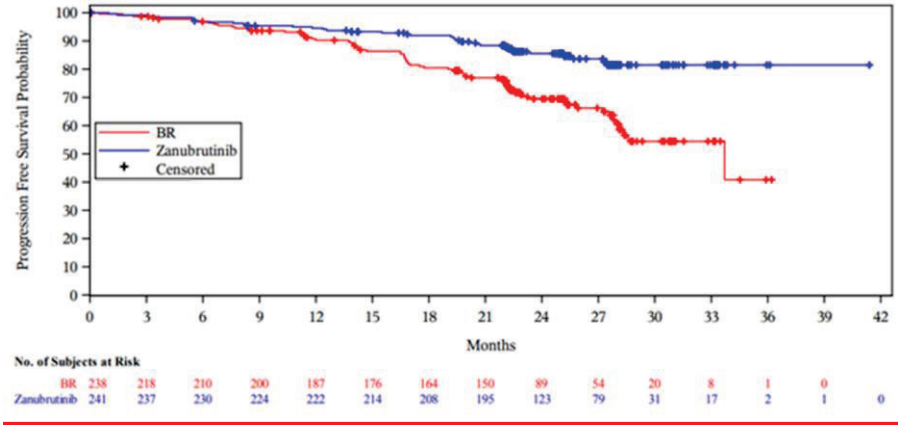
Table 76: Efficacy Results in the SEQUOIA study

	Cohort 1* Patients without Del(17p)	
Endpoint	**Zanubrutinib (N=241)**	**Bendamustine + Rituximab (N=238)**
Progression-Free Survival†		
Number of Events, n (%)	36 (14.9)	71 (29.8)
Disease Progression, n (%)	27 (11.2)	59 (24.8)
Death, n (%)	9 (3.7)	12 (5.0)
Median (95% CI), months [a]	NE (NE, NE)	33.7 (28.1, NE)
Hazard Ratio (95% CI) [b]	0.42 (0.28, 0.63)	
P value [c]	<0.0001	
Overall Response Rate† % (95% CI)	94.6% (91.0, 97.1)	85.3% (80.1, 89.5)

Overall Response Rate: CR+CRi+nPR+PR+PR-L, CR: complete response, CRi: complete response with incomplete haematopoietic recovery, nPR: nodular partial response, PR: partial response, PR-L: partial response with lymphocytoma, CI: confidence interval, NE: not estimable, median follow-up time for PFS was 25.0 months (95% CI: 24.6, 25.2).
* ITT analysis set
† Assessed by independent central review committee.
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.

At an updated ad hoc analysis with a median follow-up of 33.5 months for PFS, the investigator-assessed PFS remained consistent with the primary analysis with a HR of 0.33 (95% CI: 0.22 to 0.48, descriptive P<0.0001) in the zanubrutinib arm over the BR arm. Median PFS was not reached with zanubrutinib arm and was 39.2 months for BR arm. At 36 months after randomization, 83.6% of patients treated with zanubrutinib and 55.1% with BR were estimated to be progression-free and alive. With a median follow-up of 35.8 months, the median OS was not reached for both arms; the 36-month OS rate estimate was 90.9% (95% CI: 86.3 to 94.0) in the zanubrutinib arm and 89.5% (95% CI: 84.2 to 93,1) in the BR arm, respectively.

Figure 1: Kaplan-Meier Curve of IRC-assessed PFS in the SEQUOIA study Cohort 1 (ITT population)



ALPINE study (BGB-3111-305): A Phase 3, Randomized Study of Zanubrutinib Compared with Ibrutinib in Patients with Relapsed/Refractory (R/R) CLL

The ALPINE study (BGB-3111-305) is a randomized, multicenter, open-label, Phase 3, active controlled trial. It enrolled 652 patients with relapsed or refractory CLL 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).

Baseline demographics and disease characteristics were generally balanced between treatment arms in ITT analysis set and in the first 415 randomized patients.

In the ITT analysis set, the median age was 67.0 years in the zanubrutinib arm and 68.0 years in the ibrutinib arm. The majority of patients in both arms had an ECOG PS of 0 or 1 (97.9% in the zanubrutinib arm; 96.0% in the ibrutinib arm). Similar demographics and baseline characteristics were observed in the first 415 randomized patients. The median number of prior lines of systemic therapy is 1.0 the zanubrutinib arm (range, 1 to 6) and 1.0 in the ibrutinib arm (range, 1 to 8) in both the ITT analysis set and the first 415 randomized patients.

Patients previously treated with a BTK inhibitor were excluded from study 305 and limited data for zanubrutinib after prior BCL 2 inhibitor treatment is available.

Of 652 patients total, 327 were assigned to zanubrutinib monotherapy, 325 to ibrutinib monotherapy. The efficacy evaluation is based on the pre-specified interim analysis of the first 415 randomized patients of the ITT population. Of these, 207 were randomized to zanubrutinib monotherapy, 208 to ibrutinib monotherapy. Efficacy results are presented in Table 8~~7~~.

The primary endpoint was overall response rate (ORR, defined as partial response or better).

At the pre-specified ORR interim analysis in the first 415 randomised patients, zanubrutinib demonstrated non-inferiority (1-sided p <0.0001) and superiority (2-sided p = 0.0006) to ibrutinib in the protocol-specified primary endpoint ORR assessed by investigator. Response as determined by IRC also demonstrated non-inferiority of zanubrutinib to ibrutinib (1-sided p < 0.0001). At the ORR final analysis, ORR assessed by the investigator continues to be higher (79.5% versus 71.1%) in the zanubrutinib arm compared with the ibrutinib arm (descriptive p = 0.0133); ORR determined by IRC was also significantly higher in the zanubrutinib arm compared with the ibrutinib arm, demonstrating superiority (80.4% versus 72.9%, respectively; 2-sided p = 0.0264).

Table 8~~7~~: Efficacy Results in the ALPINE study (Pre-specified Interim Analysis of the First 415 randomized Patients) by Investigator (protocol defined primary endpoint) and IRC Assessment

	Investigator Assessed (protocol-define primary endpoint)		**IRC Assessed**	
Endpoint	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**
Overall Response Rate[§] n (%) (95% CI)	162 (78.3) (72.0, 83.7)	130 (62.5) (55.5, 69.1)	158 (76.3) (69.9, 81.9)	134 (64.4) (57.5, 70.9)
Response ratio [a] (95% CI)	1.25 (1.10, 1.41)		1.17 (1.04, 1.33)	
Non-inferiority [b]	1-sided p-value <0.0001		1-sided p-value <0.0001	
Superiority [c]	2-sided p-value 0.0006		2-sided p-value 0.0121	
Duration of Response [d]: 12-months event-free rate % (95% CI)	89.8 (78.1, 95.4)	77.9 (64.7, 86.7)	90.3 (82.3, 94.8)	78.0 (66.1, 86.2)

Overall Response Rate : CR + CRi + nPR + PR, CR: complete response, CRi: complete response with incomplete haematopoietic recovery, nPR: nodular partial response, PR: partial response, CI: confidence interval
Median duration of response as assessed by investigator was not reached in the zanubrutinib arm at interim analysis, median study follow-up time was 15.31 months (range: 0.1, 23.1) in zanubrutinib arm and 15.43 months (range: 0.1, 26.0) in ibrutinib arm.

§ Hypothesis testing for the noninferiority of ORR at the interim analysis is based on the first 415 randomized patients only with a 1-sided significance level of 0.005.

[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.

The median time to response as assessed by the investigator at the ORR interim analysis in first 415 randomised patients was 5.59 months (range: 2.7, 14.1) in zanubrutinib arm and 5.65 months (range: 2.8, 16.7) in ibrutinib arm. The results assessed by IRC were consistent (5.55 months vs. 5.63 months in zanubrutinib and ibrutinib arms respectively). At the ORR final analysis in all 652 randomised patients, the median time to response remained unchanged (5.59 months vs. 5.65 months as assessed by investigator and 5.52 months vs. 5.62 months as assessed by IRC in zanubrutinib and ibrutinib arms respectively).

In patients with del(17p) mutation in the first 415 randomized patients, the ORR assessed by investigator were 83.3% (95% CI 62.5, 95.3; 20 of 24 patients) in the zanubrutinib arm and 53.8% (95% CI 33.4, 73.4; 14 of 26 patients) in the ibrutinib arm. Based on IRC assessment, the ORR were 79.2% (95% CI 57.8, 92.9; 19 of 24 patients) in the zanubrutinib arm and 61.5% (95% CI 40.6, 79.8; 16 of 26 patients) in the ibrutinib arm. At the ORR final analysis in all 652 randomized patients, the ORR assessed by investigator were 86.7% (95% CI 73.2, 94.9; 39 of 45 patients with del(17p) mutation) in the zanubrutinib arm and 56.0% (95% CI 41.3, 70.0; 28 of 50 patients with del(17p) mutation) in the

ibrutinib arm. Based on IRC assessment, the ORR were 86.7% (95% CI 73.2, 94.9; 39 of 45 patients with del(17p) mutation) in the zanubrutinib arm and 64.0% (95% CI 49.2, 77.1; 32 of 50 patients with del(17p) mutation) in the ibrutinib arm.

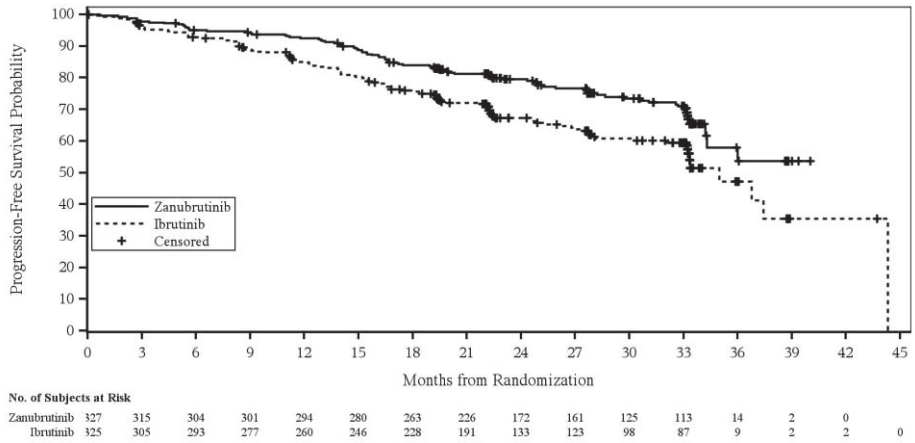
A total of 652 patients were enrolled at the prespecified time of final PFS analysis (cut-off date 8 August 2022). The median PFS follow-up time was 28.1 months as assessed by investigator and 30.7 months as assessed by IRC Zanubrutinib showed superiority in PFS over ibrutinib as assessed by both investigator and IRC. The efficacy results for PFS are presented in Table 98, and a Kaplan Meier Plot as assessed by IRC is provided in Figure 2.

Table 98: Efficacy Results in the ALPINE study (prespecified final PFS analysis of all 652 randomized patients) by Investigator and IRC assessment (cut-off date 8 August 2022)

Endpoint	Investigator Assessed		Independently Assessed	
	Zanubrutinib (N=327)	Ibrutinib (N=325)	Zanubrutinib (N=327)	Ibrutinib (N=325)
Progression-Free Survival				
Events, n (%)	87 (26.6)	118 (36.3)	88 (26.9)	120 (36.9)
Hazard Ratio[a] (95% CI)	0.65 (0.49, 0.86)		0.65 (0.49, 0.86)	
2-sided p-value[b]	0.0024		0.0024	

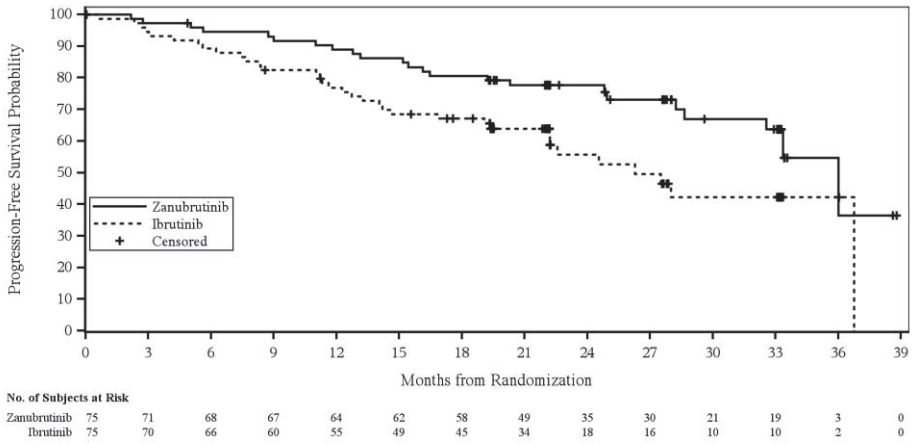
[a] Based on a stratified Cox-regression model with ibrutinib as the reference group.
[b] Based on a stratified log-rank test.

Figure 2: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review (ITT) (cut-off date 8 August 2022)



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).

Figure 3: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review for Patients with Del 17P or TP53 (ITT) (cut-off date 8 August 2022)



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.

Patients with Mantle Cell Lymphoma (MCL)

The safety and efficacy of BRUKINSA in patients with MCL were evaluated in an open-label, multicentre, single-arm Phase 2 study (BGB-3111-206) of 86 previously treated patients, and an open-label, dose escalation and expansion, global, multicentre, single arm Phase 1/2 study (BGB-3111-AU-003) of 32 previously treated patients.

In Study BGB-3111-206, 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 2.5 years (range: 0.3, 8.5) 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 study excluded patients with prior allogeneic hematopoietic stem cell transplant or prior exposure to a BTK inhibitor. 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 MIPI score (which includes age, ECOG score, baseline lactate dehydrogenase, and WBC count) was intermediate in 29% and high risk in 13%.

Tumour response was according to the 2014 Lugano Classification and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee. Duration of response (DoR) was a secondary endpoint.

In Study BGB-3111-AU-003, the median age of patients was 70.5 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 (range: 0.3, 14.5) 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%). MCL patients who received prior treatment with a BTK inhibitor or who received allogeneic stem cell transplantation within 6 months prior to enrolment were excluded from this study. The majority of patients had extranodal involvement (78.1%), and 25% had refractory disease. The MIPI score (which includes age,

ECOG score, baseline lactate dehydrogenase and WBC count) was intermediate in 40.6% and high risk in 31.3%.

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

For BGB-3111-206 the efficacy analysis was conducted at a median follow-up of 18.5 months. At the time of analysis, 70% of patients remained on study. The independent review committee (IRC) assessed overall response rate (ORR) was 83.7% with a median duration of response (DoR) of 19.5 months (Table 10). The efficacy analysis was also conducted at a median follow-up of 24.8 months. At time of analysis, 66.3% of patients remained on study. The investigator assessed ORR was 83.7% (95% CI: 74.2, 90.8) with a CR rate of 77.9% and a PR rate of 5.8%. The median DoR was 24.9 months (95%CI: 23.1, NE).

Table 10~~9~~: Efficacy Results Based on IRC in MCL Patients Who Have Received At Least One Prior Therapy (Study BGB-3111-206, Study BGB-3111-AU-003)

	Study BGB-3111-206 (N=86)	**Study BGB-3111-AU-003 (N=32)**
ORR n (%) (95% CI)	**72 (83.7)** (74.2, 90.8)	**27 (84.4)** (67.2, 94.7)
CR	59 (68.6)	8 (25)[a]
PR	13 (15.1)	19 (59.4)
Median DoR in months (95% CI)	**19.5 (16.6, NE)**	**18.5 (12.6, NE)**

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

[a] FDG-PET scans were not required for response assessment

For BGB-3111-AU-003 the efficacy analysis was conducted at a median follow-up of 18.8 months. At time of analysis, 53.1% of patients remained on study. The IRC assessed ORR was 84.4% with a median DoR of 18.5 months (Table 9).

Patients with Follicular Lymphoma (FL)

The efficacy of zanubrutinib in combination with obinutuzumab versus obinutuzumab was assessed in the ROSEWOOD study (BGB-3111-212), a phase 2 randomized, open-label, multicentre study. Overall, 217 patients with relapsed (defined by disease progression after completion of the most recent therapy) or refractory (defined as failure to achieve CR or PR to most recent therapy), Grade 1- 3a 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, were enrolled. Patients were randomized 2:1 to either zanubrutinib 160 mg orally twice daily until progressive disease or unacceptable toxicity, in combination with obinutuzumab 1000 mg intravenously (arm A) or obinutuzumab alone (arm B). Obinutuzumab was given on Day 1, 8, and 15 of the first cycle, then at Day 1 of cycles 2-6. Each cycle was 28 days long. Patients received optional obinutuzumab maintenance, one infusion every other cycle, for a maximum of 20 doses.

Patients randomized in obinutuzumab arm were allowed to crossover and to receive the combination of zanubrutinib plus obinutuzumab in case of progressive disease or absence of response (defined by stable disease as best response) after 12 cycles. Randomization was stratified by the number of prior lines of

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therapy (2 to 3 versus >3), rituximab- refractory status (yes versus no), and geographic region (China versus other countries).

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% were White. Most (97.2%) of the patients had a baseline ECOG performance status of 0 or 1.

At screening, most patients 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). One hundred and twenty-three patients (56.7%) met the GELF criteria.

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 (as a monotherapy or in combination with chemotherapy), and 59 of the 217 patients (27.2%) received >3 prior lines of therapy. Of the 217 patients, 114 (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). Twelve (5.5%) patients received prior obinutuzumab.

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 is shown in Table 10. Median duration of zanubrutinib exposure was 12.4 months at data cutoff date 31 December 2024.

Of 72 patients randomized in the obinutuzumab monotherapy arm, 36 did crossover to combination therapy.

The primary efficacy endpoint was overall response rate (defined as partial response or complete response) as determined by independent central review using the Lugano Classification for NHL. Main secondary endpoints included duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

Efficacy results are summarized in Table 11 and Figure 4

Table 11: Efficacy Results Per Independent Central Review (ITT) (ROSEWOOD study)

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	Zanubrutinib + Obinutuzumab (N=145) n (%)	**Obinutuzumab (N=72) n (%)**	**Zanubrutinib + Obinutuzumab (N=145) n (%)**	**Obinutuzumab (N=72) n (%)**
Data cut-off date	31DEC2024		25JUN2022	
median follow-up time (Months)	36.83	31.52	20.21	20.40
Overall Response Rate, n (%) (95% CI[a])	102 (70.3) (62.2, 77.6)	32 (44.4) (32.7, 56.6)	100 (69.0) (60.8, 76.4)	33 (45.8) (34.0, 58.0)
P value[b]	0.0003		0.0012	
CR	61 (42.1)	14 (19.4)	57 (39.3)	14 (19.4)
PR	41 (28.3)	18 (25.0)	43 (29.7)	19 (26.4)
Duration of Response (Months)				
Median (95% CI)[c]	32.9 (19.6, 43.1)	14.0 (9.2, 26.5)	NE (25.3, NE)	14.0 (9.2, 25.1)
Progression-free Survival (Months)				
Median (95% CI)[c]	22.1 (16.1, 34.0)	10.3 (6.5, 13.8)	28.0 (16.1, NE)	10.4 (6.5, 13.8)

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

[a] Estimated using the Clopper-Pearson method.

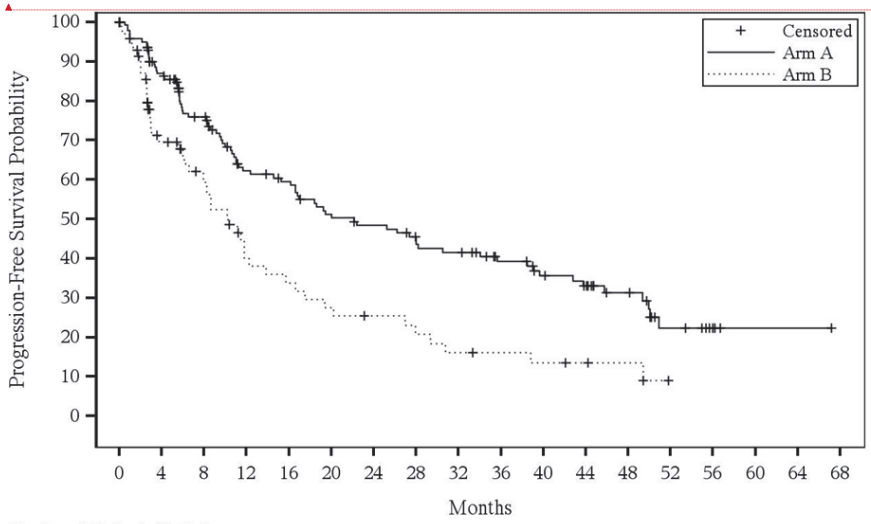
[b] Cochran-Mantel-Haenszel method stratified by rituximab-refractory status, number of prior lines of

therapy, and geographic region per IRT.

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

[d] DOR rates estimated by Kaplan-Meier method; 95% CIs estimated using the Greenwood's formula. DOR was not type I error controlled and the CIs are nominal in nature.

Figure 4: Kaplan-Meier Plot of Progression-Free Survival by Independent Central Review (ITT)



Number of Patients At Risk:

Arm A	145	135	117	95	93	80	70	68	65	59	55	54	51	50	44	43	42	39	34	34	28	27	24	17	17	13	8	7	3	1	1	1	1	1	0
Arm B	72	61	41	35	31	27	19	17	16	14	13	12	11	11	9	8	7	6	6	6	5	5	4	3	3	1	0								

Arm A, Zanubrutinib + Obinutuzumab; Arm B, Obinutuzumab

Overall Survival

As of 31 December 2024, 51 patients (35.2%) in the combination arm and 33 patients (45.8%) in the obinutuzumab monotherapy arm died. At 18 months, overall survival rates were 84.1% (95%CI: 76.6, 89.3) in the combination arm and 71.5% (95%CI: 59.0, 80.8) in the obinutuzumab monotherapy arm. OS analysis may be confounded by 36 patients (50.0%) who crossed over from obinutuzumab monotherapy arm to combination 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 dose 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 for one week.

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

Absorption

The median t_{max} of zanubrutinib is 2 hours. No clinically significant differences in zanubrutinib AUC

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or C_{max} were observed following administration of a high-fat meal (approximately 1,000 calories with 50% of total caloric content from fat) in healthy subjects.

Distribution

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

Metabolism

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

Elimination

The mean half-life ($t_{½}$) 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 radiolabelled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in faeces (38% unchanged) and 8% in urine (less than 1% unchanged).

Special populations

Elderly

Age (19 to 90 years; mean age 62±14.5) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis (N=632).

Paediatric population

No pharmacokinetic studies were performed with zanubrutinib in patients under 18 years of age.

Gender

Gender (872 males and 419 females) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Race

Race (964 White, 237 Asian, 30 Black, and 25 categorized as Other) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis.

Body weight

Body weight (36 to 144 kg, mean weight 76.5±16.9 kg) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis (N=1291).

Renal impairment

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. The analysis was based on 362 patients with normal renal function, 523 with mild renal impairment, 303 with moderate renal impairment, 11 with severe renal impairment, and one with ESRD. The effects of severe renal impairment (CrCl <30 mL/min) and dialysis on zanubrutinib pharmacokinetics is unknown.

Hepatic impairment

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. A significant correlation was observed between the Child-Pugh score, baseline serum albumin, baseline serum bilirubin and baseline prothrombin time with unbound zanubrutinib AUC.

In vitro studies

CYP enzymes

Zanubrutinib is a weak inducer of CYP2B6 and CYP2C8. Zanubrutinib is not an inducer of CYP1A2.

Co-administration with transport substrates/inhibitors

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

Pharmacodynamic interactions

An i*n vitro* study showed that the potential pharmacodynamic interaction between zanubrutinib and rituximab is low and zanubrutinib is unlikely to interfere with the anti-CD20 antibody-induced antibody-dependent cellular cytotoxicity (ADCC) effect.
In vitro, *ex vivo*, and animal studies showed that zanubrutinib had no or minimal effects on platelet activation, glycoprotein expression, and thrombus formation.

5.3 Preclinical safety data

General toxicity

The general toxicologic profiles of zanubrutinib were characterized orally in Sprague-Dawley rats for up to 6-month treatment and in beagle dogs for up to 9-month treatment.

In rat repeat dose studies up to 6-month treatment, test article related mortality was noted at the dose of 1,000 mg/kg/day (81x clinical AUC) with histopathologic findings in the gastrointestinal tract. Other findings were mainly noted in the pancreas (atrophy, fibroplasia, haemorrhage, and/or inflammatory cell infiltration) at the doses ≥ 30 mg/kg/day (3x clinical AUC), in the skin around the nose/mouth/eyes (inflammatory cell infiltration, erosion/ulcer) from the dose of 300 mg/kg/day (16x clinical AUC), and in the lung (presence of macrophages in the alveolar) at the dose of 300 mg/kg/day. All these findings were fully or partially reversed after a 6-week recovery except for the pancreatic findings which were not considered clinically relevant.

In dog repeat dose studies up to 9-month treatment, test article related findings were mainly noted in the gastrointestinal tract (soft/watery/mucoid stool), skin (rash, red discoloration, and thickened/ scaling), and in the mesenteric, mandibular, and gut associated lymph nodes and spleen (lymphoid depletion or erythrophagocytosis) at the doses from 10 mg/kg/day (3x clinical AUC) to 100 mg/kg/day (18x clinical AUC). All these findings were fully or partially reversed after a 6-week recovery.

Carcinogenicity/genotoxicity

Carcinogenicity studies have not been conducted with zanubrutinib.
Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (Chinese hamster ovary) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in rats.

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, 100 and 300 mg/kg/day. No effect on male or female fertility was noted but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The dose of 100 mg/kg/day is approximately 13-fold higher than the human therapeutic exposure.

Embryo-foetal 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 of 0.3%-1.5%) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5-fold higher than the human therapeutic exposure.

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 70 mg/kg is approximately 25-fold higher than the human therapeutic exposure 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-fold higher than the human therapeutic exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate (E487)
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide (E171)

Printing ink

Shellac glaze (E904)
Iron oxide black (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

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

7. MANUFACTURER

Catalent CTS LLC
10245 Hickman Mills Dr.,
Kansas City, MO
64137, USA

8. DATE OF REVISION

9 February ~~10 November 2025~~2026

Commented [CO9]: Updated.