swissmedic

Date: 3 November 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Brukinsa

International non-proprietary name: zanubrutinib
Pharmaceutical form: hard capsules
Dosage strength(s): 80 mg
Route(s) of administration: oral
Marketing authorisation holder: BeiGene Switzerland GmbH
Marketing authorisation no.: 67998
Decision and decision date: approved on 29 August 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCL-2	B-cell lymphoma 2
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CL/F	Apparent clearance
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum observed plasma/serum concentration of drug
C_{min}	Minimal observed plasma/serum concentration of drug
CrCL	Creatinine clearance
DCO	Data cut-off
EP	Endpoint
ERA	Environmental risk assessment
HR	Hazard ratio
IA	Interim analysis
IRC	Independent Review Committee
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
ORR	Objective response rate
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
RMP	Risk management plan
SAE	Serious adverse event
SLL	Small lymphocytic lymphoma
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Vc/F	Apparent central volume

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2 Background information on the procedure

2.1 Applicant's request(s)

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a[decies] no. 2 of the TPA.
Orphan drug status was granted on 7 August 2020.

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

BRUKINSA is indicated as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received one or more prior therapies (see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
No change to the dosage recommendation was requested with the application for extension of indication.
The dosage recommendation is the same as for the initial marketing authorisation application.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	25 May 2022
Formal control completed	23 June 2022
List of Questions (LoQ)	21 October 2022
Response to LoQ	20 December 2022
Preliminary decision	1 March 2023
Response to preliminary decision	26 April 2023
Labelling corrections	19 June 2023
Response to labelling corrections	12 July 2023
Final decision	29 August 2023
Decision	approval

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3 Medical context

Chronic lymphocytic leukaemia (CLL), a neoplastic malignancy characterised by the clonal proliferation of mature B-lymphocytes, is the most common leukaemia in the Western world, with an estimated incidence of approximately 5-10 cases per 100 000 individuals annually in Switzerland. Small lymphocytic lymphoma (SLL) is a specific subtype of CLL without the leukaemic component.
The course of CLL varies widely, with some patients experiencing an indolent, slow-progressing disease, while others face a more aggressive form of the illness. Several factors influence the prognosis, including clinical stage at diagnosis, genomic abnormalities such as del(17p) and TP53 mutations, and the presence of comorbidities.
While the overall 5-year survival rate of CLL/SLL is high in most cases, CLL remains an incurable disease. In the highest-risk subset of CLL patients, fewer than 25% of the patients survive at 5 years.

In the first-line treatment of CLL, a paradigm shift has occurred in recent years due to the introduction of novel agents. While traditional chemoimmunotherapy, such as fludarabine, cyclophosphamide, and rituximab (FCR), remains a viable option for selected patients, targeted agents like ibrutinib and acalabrutinib, Bruton's tyrosine kinase (BTK) inhibitors, and venetoclax, a BCL-2 inhibitor, in combination with anti-CD20 antibodies, have demonstrated a clinical benefit over the chemoimmunotherapy and currently represent the preferred options.

Despite advances in first-line treatments, CLL often follows a relapsing-remitting course, necessitating robust therapeutical strategies for relapsed patients. The BTK inhibitors ibrutinib or acalabrutinib, and the BCL-2 inhibitor venetoclax either as monotherapy or in combination with anti-CD20 antibodies, are highly effective regimens for relapsed CLL.

Zanubrutinib is an irreversible second-generation BTK inhibitor.

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4 Nonclinical aspects

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Brukinsa in the proposed extension of indication.

No additional preclinical data were provided for this application in addition to the ones submitted for the initial marketing authorisation application, which is accepted.

Efficacy for the proposed indication was assessed clinically.

According to the updated ERA provided, the risk of zanubrutinib to the environment is assumed to be low.

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5 Clinical aspects

5.1 Clinical pharmacology

Sparse PK data were collected in the two ongoing Phase 3 studies BGB-3111-304 and BGB-3111-305 in patients with treatment-naïve and relapsed/refractory CLL/SLL, respectively.
Using the data from 660 patients with treatment-naïve or relapsed/refractory CLL/SLL enrolled in these 2 studies, a previous population PK analysis based on data from 632 subjects enrolled in 9 clinical studies was updated. The PK of zanubrutinib was well described by a two-compartment model with sequential zero-order then first-order absorption as well as first-order elimination. In line with the previous analysis, baseline alanine aminotransferase (ALT) and health status, i.e. patients with B-cell malignancies versus healthy subjects, were identified as significant covariates on the apparent oral clearance (CL/F). Age was identified as an additional significant covariate on CL/F and the apparent central volume (Vc/F) using the new dataset. A sensitivity analysis showed that health status had the highest impact on the PK of zanubrutinib. AUC_{ss} and $C_{max,ss}$ increases of 61.2% and 41.2%, respectively, were predicted for healthy subjects as compared to patients with B-cell malignancies. In contrast, the impact of ALT and age was comparatively small. No relevant PK differences were observed between patient populations. Overall, no dose adjustments are required based on any of the evaluated covariates including those mentioned before as well as body weight, race, albumin, AST, bilirubin, CrCL (renal impairment), sex, tumour type, and use of acid-reducing agents.

Exposures derived from the population PK analysis and efficacy and safety data collected from the Phase 3 studies BGB-3111-304 and BGB-3111-305 were used for an exposure-response analysis. There was no relationship between model-predicted AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ and progression-free survival (PFS) or objective response rate (ORR). Furthermore, no relationships between exposure metrics and adverse events (AEs) leading to treatment discontinuation and AEs of interest (Grade ≥3 neutropenia, thrombocytopenia, anaemia, infections/infestations, secondary primary malignancies, atrial fibrillation/flutter, major bleeding events, and any bleeding events) were observed.
Of note, only the proposed dose of 160 mg twice daily was administered in studies BGB-3111-304 and BGB-3111-305. Moreover, the control arms were not included in the analysis.
Overall, these findings are in line with previous analyses for patients with B-cell malignancies indicating no association between zanubrutinib exposure and efficacy/safety endpoints across dose levels from 40 mg to 320 mg.

5.2 Dose finding and dose recommendation

BGB-311-AU-003 was a Phase 1/2 international study which consisted of two parts. Part 1 was a dose escalation study. The initial dose regimen of zanubrutinib was 40 mg once-daily orally. A total of 17 patients with various B-cell malignancies were enrolled in Part 1. No dose-limiting toxicities were reported in Part 1 at doses up to 320 mg/day (the highest dose tested), and thus, the maximum tolerated dose was not reached. Part 2 was a dose expansion study: The recommended dose selected for Phase 2 studies was 320 mg, to be administered as either 320 mg once daily or 160 mg twice daily orally. In Parts 1 and 2 combined, 385 patients were enrolled in the study; among patients with relapsed/refractory CLL/SLL, the ORR was 94.2%.

5.3 Efficacy

Study BGB-3111-305 is an international Phase 3, open-label, randomised study of zanubrutinib versus ibrutinib in patients with relapsed/refractory CLL. Refractory disease is defined as either no objective response to or disease progression within 6 months of the last treatment, and relapsed disease is defined as patients whose disease relapsed more than 6 months after the last treatment and subsequently progressed. Patients were enrolled in 14 countries and one region in North America, Europe, Asia and Oceania and were randomised in a 1:1 ratio to zanubrutinib at a dosage of 160 mg orally twice daily or to ibrutinib at a dosage of 420 mg once daily. Patients were eligible if they were affected by CLL/SLL requiring treatment, had received at least one prior systemic therapy for CLL/SLL and were not previously treated with a BTK inhibitor.

Randomisation was stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes or no), and del17p/TP53 mutation status (present or absent).

The primary endpoint (EP) was investigator-assessed overall response rate (ORR). The key secondary alpha controlled EPs were progression-free survival (PFS) per investigator assessment and incidence of atrial fibrillation/flutter. PFS per Independent Review Committee (IRC) was submitted as additional preplanned analysis. Overall survival (OS) was included among non-alpha controlled other secondary EPs.

An interim analysis (IA) for the primary EP ORR was planned approximately 12 months after the randomisation of 415 patients (64% information fraction). Both the interim analysis and the final analysis for ORR and the analysis for PFS were planned for non-inferiority, and superiority was to be tested if non-inferiority was met. Secondary EP PFS was to be tested only at the time of the final ORR analysis and only if the superiority for the primary EP was demonstrated. A descriptive analysis of PFS results at the time of the ORR IA was preplanned.

A total of 652 patients were randomised between 1 November 2018 and 14 December 2020 (327 to the zanubrutinib arm and 325 to the ibrutinib arm).

In the intention-to-treat (ITT) population the median age was 67.0 years in the zanubrutinib arm and 68.0 years in the ibrutinib arm. The majority of patients were enrolled in Europe and North America. Patients with either del17p and/or TP53 mutation accounted for less than 25% of the ITT population. Demographic and baseline characteristics were generally balanced between the zanubrutinib and ibrutinib arms, except for a higher proportion of female patients in the zanubrutinib arm (34.9%) compared with the ibrutinib arm (28.6%). Characteristics of the first 415 enrolled patients are consistent with those of the ITT population.

At the data cut-off (DCO) for the IA for ORR of 31 December 2020, approximately 12 months after the randomisation of the 415th patient, the median follow-up was 15.31 months for the zanubrutinib arm and 15.43 months for the ibrutinib arm.
ORR was higher for patients in the zanubrutinib arm (78.3%) compared with the ibrutinib arm (62.5%). Zanubrutinib demonstrated non-inferiority to ibrutinib with a response ratio of 1.25 (95% CI: 1.10, 1.41), with a statistically significant 1-sided p-value < 0.0001 versus the prespecified 1-sided alpha of 0.005. Furthermore, zanubrutinib demonstrated superiority to ibrutinib with a statistically significant 2-sided p-value of 0.0006 versus the prespecified 2-sided alpha of 0.0099. ORR results across subgroups were overall consistent although regarded as exploratory.

At the DCO of the ORR IA, the secondary EP investigator-assessed PFS under familywise type I error control was not planned to be analysed. However, a descriptive analysis was still performed. At that time, 8.3% PFS events have occurred in the zanubrutinib arm and 15.3% in the ibrutinib arm. The median PFS was NE (NE; NE) months in the zanubrutinib arm and 22.3 (19.4-NE) months in the ibrutinib arm. The hazard ratio (HR) was 0.47 (0.29- 0.76), which crossed the non-inferiority and the superiority boundaries at nominal 5% significance level.

At the DCO of 8 August 2022 with a median follow-up of 29.6 months, 26.9% PFS events by IRC had occurred in the zanubrutinib arm and 36.9% in the ibrutinib arm. The median PFS was NE (34.3; NE) in the zanubrutinib arm and 35.0 (33.2-44.3) months in the ibrutinib arm. The hazard ratio (HR) was 0.65 (0.49-0.86), which crossed the non-inferiority and the superiority boundaries at nominal 5% significance level. Of note, PFS by IRC was an exploratory endpoint. Results were consistent in all subgroups.

At the same DCO at a median follow-up of 33 months, 14.75% deaths had occurred in the zanubrutinib arm and 18.5% in the ibrutinib arm. The HR for OS was 0.76 (0.51-1.11), with a median OS NE (NE;

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NE) in both arms. Kaplan-Meier curves separate at about 3 months and never cross. However, the results for OS are immature and not controlled for type I error. Of note, when looking at the reasons for events, about two-thirds of OS events in each arm were due to adverse events; this observation suggests that the OS results are not only immature but also currently reflect more the toxicity of the drugs than their effect on the progression of the disease.

5.4 Safety

The safety assessment is based on n=234 patients with zanubrutinib at the dosage of 160 mg orally twice daily in study BGB-3111-305, with a median exposure to zanubrutinib of 28.4 months at the DCO of 8 August 2022.

In the zanubrutinib arm, a lower number of patients had dose reduction, dose interruption, serious adverse events (SAE), adverse events leading to treatment discontinuation, adverse events leading to dose modification than in the ibrutinib arm. The proportions of patients with Grade 3 or higher treatment-emergent adverse events (TEAE) and adverse events leading to death were comparable between the two arms.

The most frequent adverse events that occurred in the zanubrutinib arm were COVID-19 (23.1%), neutropenia (22.8%), upper respiratory tract infection (21.0%) hypertension (21.9%), and diarrhoea (16.0%).
The most frequent adverse events of Grade 3 or higher in the zanubrutinib arm were neutropenia (16.0%) and hypertension (14.8%).
The most frequent SAE in the zanubrutinib arm by system organ class were infections and infestations.
TEAE leading to death occurred in 10.2% of patients in the zanubrutinib arm and in 11% of patients in the ibrutinib arm. The adverse event “Infections” was the most frequent cause of death due to TEAE in both arms.

Overall, a lower incidence of cardiac disorders was reported in the zanubrutinib arm (21.3%) than in the ibrutinib arm (29.6%), including atrial fibrillation (5.2% vs 13.3%, respectively).

When comparing the toxicity profile observed in the BGB-3111-305 trial with the toxicity profile from the pooled data of all trials with zanubrutinib, the frequencies of TEAE, Grade 3 or higher TEAE, SAE, TEAE leading to death, and TEAE leading to dose interruption were less frequent in the BGB-3111-305 trial; TEAE leading to dose reduction were comparable in the two populations.

5.5 Final clinical benefit risk assessment

Chronic lymphocytic leukaemia (CLL), is the most common leukaemia in the Western world, with an estimated incidence of approximately 5-10 cases per 100 000 individuals annually in Switzerland.
While considerable progress has been made in the treatment of CLL, it remains an incurable disease and there is an important medical need for safe and efficacious treatment options.

Zanubrutinib is an irreversible second-generation BTK inhibitor. The applicant requested regular approval in Switzerland and provided efficacy data from the pivotal Phase 3 BGB-3111-305 trial, supported by efficacy results from the dose finding study BGB-311-AU-003.

The updated population analysis using the sparse PK data from 660 patients with treatment-naïve or relapsed/refractory CLL/SLL enrolled in the studies BGB-3111-304 and BGB-3111-305 was in line with the findings from previous analyses in patients with B-cell malignancies and healthy volunteers.
Overall, no dose adjustments are required based on any of the evaluated covariates.

Zanubrutinib showed clinically meaningful efficacy in the treatment of relapsed CLL patients. The trial met its primary EP at the DCO of 31 December 2020, demonstrating statistically significant non-

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inferiority and superiority of ORR by investigator in favour of zanubrutinib over ibrutinib (78.3% vs 62.5%).
The results of the descriptive analysis of the secondary EP PFS by investigator and of the non-alpha controlled secondary EP PFS by IRC are consistent with the primary EP. At the most updated DCO of 8 August 2022, 26.9% PFS events had occurred in the zanubrutinib arm as assessed by IRC and 36.9% in the ibrutinib arm. The median PFS was NE (34.3; NE) in the zanubrutinib arm and 35.0 (33.2-44.3) months in the ibrutinib arm, with an HR of 0.65 (0.49-0.86).
At the most updated DCO of 8 August 2022, 14.7% of deaths had occurred in the zanubrutinib arm and 18.5% in the ibrutinib arm, with an HR of 0.76 (0.51-1.11).

There was no relationship between model-predicted exposure metrics and clinical efficacy/safety endpoints.

The combination of an open-label trial design of the BGB-3111-305 study with an investigator-assessed primary EP results in uncertainty regarding the reliability of the results, as an assessment bias cannot be excluded.

The primary endpoint ORR is not established as a valid surrogate endpoint for OS in the setting of relapsed CLL. Updated PFS results are more mature and showed an improved efficacy of zanubrutinib compared to ibrutinib. The OS results are still immature for the prognosis of the investigated disease and include a significant proportion of deaths due to adverse events, reflecting more the toxicity of the drugs than their effect on the progression of the disease.

The safety assessment is based on n=234 patients with zanubrutinib at the dosage of 160 mg orally twice daily in study BGB-3111-305, with a median exposure to zanubrutinib of 28.4 months at the DCO of 8 August 2022.

The safety profile of zanubrutinib was overall comparable or better than the safety profile of ibrutinib, including the rate of SAE, Grade 3 or higher TEAE, and TEAE leading to death.

The most common and relevant toxicity related to the treatment with zanubrutinib is the risk of neutropenia and infection, including serious and fatal cases.
Overall, a lower incidence of cardiac disorders, including atrial fibrillation, was reported in the zanubrutinib arm than in the ibrutinib arm.

Uncertainty exists due to the open-label nature of the study, which is susceptible to the introduction of reporting bias.
In addition, there are uncertainties regarding long-term toxicity due to the limited duration of exposure and the proposed long-term use. Moreover, the safety population is of limited size.

There is an unmet medical need in the treatment of relapsed/refractory CLL.
Study BGB-3111-305 met its primary EP demonstrating an ORR benefit of zanubrutinib over ibrutinib. Updated PFS results showed an improved efficacy of zanubrutinib compared to ibrutinib. ORR and PFS results must be evaluated in conjunction with OS data, the desirable EP in this setting. The updated OS results are still immature; nevertheless, the data at hand show a benefit of zanubrutinib over ibrutinib. However, uncertainties remain and therefore an update of the OS results has to be submitted as post-authorisation requirement.
The safety profile on zanubrutinib is consistent with other indications and is comparable with the safety profile of the control arm ibrutinib, with a lower rate of atrial fibrillation.
Overall, the benefit-risk is considered positive. Therefore, the approval for zanubrutinib for the treatment of adult patients with CLL after a previous therapy was granted. The updated OS results of the study BGB-3111-305 are expected within approximately the next two years.

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6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Brukinsa was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Brukinsa

Composition

Active substances

Zanubrutinib

Excipients

Capsule content
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Sodium lauryl sulphate
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac glaze (E904)
Iron oxide black (E172)
Propylene glycol (E1520)
~~Ammonium hydroxide (E527)~~

1 hard capsule contains 1.17 mg sodium.

Pharmaceutical form and active substance quantity per unit

Each hard capsule contains 80 mg zanubrutinib

Indications/Uses

BRUKINSA (zanubrutinib) is used as monotherapy for the treatment of adult patients with Waldenström’s macroglobulinemia (WM) who have received at least one prior therapy or as first-line therapy in adult patients who are not eligible for chemoimmunotherapy.

BRUKINSA is indicated as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received one or more prior therapies (see “Properties/Effects”).

Dosage/Administration

Treatment with BRUKINSA should be prescribed and supervised by a physician experienced in cancer therapy.
In clinical studies, treatment with BRUKINSA was continued until disease progression or unacceptable toxicity.

Usual dosage

The usual dose is 320 mg daily, either once (four capsules) or twice daily (two capsules each in the morning and in the evening).

Dose adjustment following undesirable effects/interactions

Recommended dose adjustments of BRUKINSA for grade 3 or higher adverse reactions are listed in **Table** 1

Table 1: Recommended dose adjustment for adverse reactions

Event	**Occurrence of adverse reactions**	**Dose adjustment (Initial dose: 320 mg once or 160 mg twice daily)**
Grade 3 or higher non-haematologic toxicities Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia (lasting longer than 10 consecutive days) Grade 4 thrombocytopenia (lasting longer than 10 consecutive days)	once	Interrupt BRUKINSA. Once toxicity resolves to grade 1 or less or baseline: Resume treatment with 160 mg twice daily or 320 mg once daily.
	twice	Interrupt BRUKINSA. Once toxicity resolves to grade 1 or less or baseline: Continue with 80 mg twice daily or 160 mg once daily.
	three times	Interrupt BRUKINSA. Once toxicity resolves to grade 1 or less or baseline: Continue with 80 mg once daily.
	four times	Definitively discontinue BRUKINSA.

Asymptomatic lymphocytosis is not considered a side effect; these patients may continue to take zanubrutinib.

Special dosage instructions

Recommended dose adjustments for use with CYP3A inhibitors or inducers are listed in **Table** 2.

Table 2: Use with CYP3A inhibitors or inducers

CYP3A	**Concomitant medication**	**Recommended dose**
Inhibition	Strong CYP3A inhibitor	80 mg once daily

CYP3A	Concomitant medication	Recommended dose
		Treatment interruption according to recommendations in case of side effects.
	Moderate CYP3A inhibitor	80 mg twice daily Dose adjustment according to recommendations in case of side effects.
Induction	Strong and moderate CYP3A inducer	Avoid concomitant use; consider alternative active substances with lower CYP3A induction.

After discontinuation of a CYP3A inhibitor, the previous BRUKINSA dosage must be resumed.

Patients with hepatic disorders

No dosage adjustment is recommended in patients with mild or moderate hepatic impairment. The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg twice daily. The safety of BRUKINSA has not been studied in patients with severe hepatic impairment. These patients should be closely monitored for side effects of BRUKINSA.

Patients with renal disorders

No dose adjustment is recommended in patients with mild to moderate renal impairment (CrCl ≥30 ml/min, estimated per Cockcroft-Gault). Patients with severe renal impairment (CrCl <30 ml/min) or on dialysis should be monitored for BRUKINSA side effects.

Elderly patients

No age-dependent dosage adjustment is required.

Children and adolescents

The safety and efficacy of zanubrutinib in paediatric patients has not been demonstrated.

Mode of administration

BRUKINSA hard capsules should be swallowed whole with water. BRUKINSA can be taken with or without food. Do not chew, dissolve or open the capsules. BRUKINSA must not be taken with grapefruit juice, grapefruit or Seville oranges (see “Interactions”).

Contraindications

BRUKINSA is contraindicated in patients who are hypersensitive to zanubrutinib or an excipient of the medicinal product. See section “Excipients” for complete list.

Warnings and precautions

Haemorrhage

Serious and fatal haemorrhagic events occurred in patients with haematologic malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events, including intracranial and gastrointestinal bleeding, haematuria, and haemothorax, were observed in 4% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 48% of patients with haematologic malignancies treated with BRUKINSA monotherapy.
BRUKINSA may increase the risk of bleeding in patients receiving antiplatelet agents or anticoagulants. Patients who recently had a stroke or intracranial haemorrhage or required warfarin or other vitamin K antagonists were excluded from the BRUKINSA clinical studies.
Warfarin or other Vitamin K antagonists should not be given concomitantly with BRUKINSA.
Patients should be monitored for signs of bleeding. Bleeding events should be managed with supportive care, including transfusions, and specialised care as needed. Dosage should be reduced or treatment interrupted or discontinued if needed (see Dosage/Administration). Treatment should be discontinued for any intracranial haemorrhage.
Consideration in operations
Depending on the type of surgery and the patient's risk of bleeding, consideration should be given of whether to pause BRUKINSA administration for three to seven days before and after surgery.

Infections

Fatal and non-fatal infections, (including bacterial viral, or fungal infections or sepsis) and opportunistic infections (e.g. herpes viral, cryptococcal, aspergillus and pneumocystis jirovecii infections) have occurred in patients with haematologic malignancies treated with BRUKINSA monotherapy. Infections occurred in 66% of the patients, grade 3 or higher infections occurred in 22% of patients treated with BRUKINSA monotherapy. The most common grade 3 or higher infection was pneumonia. Infections due to reactivation of the hepatitis B virus (HBV) have also occurred. Hepatitis B virus (HBV) status should be obtained before initiating treatment with Brukinsa. If patients have a positive hepatitis B serology, it is recommended to consult a liver disease expert before starting therapy. Patients shall be monitored and treated for the prevention of hepatitis B reactivation.
Cases of progressive multifocal leukoencephalopathy (PML) were reported with the use of Bruton tyrosine kinase inhibitors., including fatal cases in patients with prior or concurrent immunosuppressive therapy.
Prophylaxis according to standard of care should be considered in patients at increased risk of infection. Patients should be monitored for signs and symptoms of infection and treated appropriately.

Second primary malignancies

Second primary malignancies, including carcinomas other than skin cancers, occurred in 15,2% of patients with haematologic malignancies treated with BRUKINSA monotherapy. The most common second primary malignancy was non-melanoma skin cancer (basal cell and squamous cell carcinoma of the skin), which occurred in 8.1% of patients. Patients should be monitored for the occurrence of skin tumours. Use of sunscreen should be advised.

Atrial fibrillation and flutter

Atrial fibrillation and flutter occurred in 3,2% of patients with haematological malignancies treated with BRUKINSA monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections. Grade 3 or higher atrial fibrillation and flutter occurred in 1.4% of patients treated with BRUKINSA monotherapy The signs and symptoms of atrial fibrillation and flutter should be monitored and treated as needed. Patients with clinically significant cardiovascular disease (NYHA ≥ 3) were excluded from the pivotal studies.

Tumour Lysis Syndrome

Tumour lysis syndrome has been reported with BRUKINSA therapy. The risk of tumour lysis syndrome exists particularly in patients with high tumour burden prior to therapy. Patients must be monitored closely and appropriate precautions should be taken.

Cytopenia

Grade 3 or 4 cytopenia, including neutropenia (21%), thrombocytopenia (7%), and anaemia (4%) based on laboratory measurements, occurred in patients with haematologic malignancies treated with BRUKINSA monotherapy (see Undesirable effects). The complete blood count should be monitored regularly during treatment (see “Monitoring and laboratory tests”).

Interstitial lung disease

Suspected cases of interstitial lung disease, but not confirmed by biopsies, occurred in 0.8% of patients with haematologic malignancies treated with BRUKINSA monotherapy. Patients should be monitored for signs and symptoms of interstitial lung disease. If interstitial lung disease is suspected, treatment with BRUKINSA should be interrupted. If the suspected case is confirmed, treatment with BRUKINSA should be discontinued.

Potential at-risk populations that have not been investigated

Patients with central nervous system (CNS) lymphoma or leukaemia, known prolymphocytic leukaemia or history of or currently suspected Richter’s syndrome; clinically significant cardiovascular disease; uncontrolled active systemic fungal, bacterial, viral, or other infection, including active

hepatitis B or C infection, or known history of infection with human immunodeficiency virus (HIV); drug induced pneumonitis, history of stroke or intracranial haemorrhage within 6 months before first dose of study drug; history of severe bleeding disorder; active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia and ongoing treatment with corticosteroid were excluded from clinical trials with CLL/SLL patients.

Teratogenic risk

BRUKINSA may cause foetal harm or termination of pregnancy. Women should be advised of the potential risk to the foetus and should not become pregnant for one week after discontinuing BRUKINSA. Before starting treatment with BRUKINSA, women of childbearing potential should have a pregnancy test.

Use during pregnancy and breastfeeding

Women of childbearing potential or patients with a female partner of childbearing potential should use a very reliable method of contraception (see “Pregnancy, lactation”).

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, so it is “essentially sodium free”.

Interactions

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

In-vitro studies

CYP enzymes

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

Co-administration with transporter 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.

Active substances that may increase zanubrutinib plasma concentrations

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

Strong CYP3A inhibitors

Concomitant use of multiple doses of itraconazole (a strong CYP3A inhibitor) increased zanubrutinib C_{max} 2.6-fold and AUC 3.8-fold in healthy subjects.

If a strong CYP3A inhibitor (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir) has to be used, the dose of BRUKINSA should be reduced to 80 mg (one capsule) for the period of use of the inhibitor. Patients should be closely monitored for toxicity and, if necessary, the dose adjustment instructions should be followed (see section 4.2).

Moderate CYP3A inhibitors

Simulations of physiologically based PK (PBPK) suggest that concomitant use of multiple doses of a moderate CYP3A inhibitor may result in an approximately 2-fold increase in zanubrutinib C_{max} and AUC. If a moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges) has to be used, the dose of BRUKINSA should be reduced to 160 mg (two capsules) for the period of inhibitor use. Patients should be closely monitored for toxicity and, if necessary, the dose adjustment instructions should be followed (see section 4.2).

Weak CYP3A inhibitors

Fasting simulations indicated that the weak 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 weak inhibitors. Patients should be closely monitored for toxicity and dose adjustment instructions should be followed as needed.

Grapefruit and Seville oranges should be used with caution during treatment with BRUKINSA as they contain moderate CYP3A4 inhibitors (see section 4.2).

Active substances that may decrease zanubrutinib plasma concentrations

Concomitant use of zanubrutinib with strong or moderate CYP3A inducers may decrease zanubrutinib plasma concentrations.

CYP3A inducers

Concomitant use of multiple doses of rifampin (a strong CYP3A inducer) reduced zanubrutinib C_{max} by 92% and AUC by 93% in healthy subjects. Concomitant use with strong (carbamazepine, phenytoin, rifampin, St. John’s Wort) and moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and should be avoided (see section 4.2).(Concomitant use of multiple doses of rifabutin (moderate CYP3A inducer) decreased C_{max} by 48% and AUC by 44% in healthy subjects. Weak CYP3A inducers may be used with caution during BRUKINSA treatment.

Gastric acid-reducing active substances

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

Active substances whose plasma concentrations may be altered by zanubrutinib.

Zanubrutinib is a weak inducer of CYP3A and CYP2C19. Concomitant use of zanubrutinib may reduce the plasma concentrations of these substrates.

CYP3A substrate

Concomitant use of multiple doses of zanubrutinib decreased midazolam (a CYP3A substrate) Cmax by 30% and midazolam AUC by 47%. Medicinal products with a narrow therapeutic index 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 reduce the plasma exposure of these medicines.

CYP2C19 substrate

Concomitant use of multiple doses of zanubrutinib reduced the Cmax of omeprazole (a CYP2C19 substrate) by 20% and the AUC of omeprazole by 36%. Medicinal products with a narrow therapeutic index that are metabolised by CYP2C19 (e.g. S-mephenytoin), should be used with caution, as zanubrutinib may reduce the plasma exposure of these medicines.

Other CYP substrates

No clinically significant differences in the pharmacokinetics of S-warfarin (a CYP2C9 substrate) were observed with concomitant use with zanubrutinib.

Concomitant use with transporter substrates/inhibitors

Concomitant use of multiple doses of zanubrutinib increased the C_{max} of digoxin (a P-gp substrate) by 34% and the AUC of digoxin by 11%. No clinically significant differences in the pharmacokinetics of rosuvastatin (a BCRP substrate) were observed with concomitant use with zanubrutinib.

Concomitant use with oral P-gp substrates with a narrow therapeutic index (e.g. digoxin) should be used with caution, as zanubrutinib may increase their concentrations.

Pharmacodynamic interactions

An *in 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.

Pregnancy, lactation

Pregnancy

There are no clinical studies with BRUKINSA in pregnant women. Observations from animal studies suggest that BRUKINSA may cause foetal harm when administered to pregnant women. In animal reproductive studies, oral zanubrutinib administration to pregnant rats during the period of organogenesis was associated with foetal cardiac malformation (see “Preclinical data”).

BRUKINSA should not be used during pregnancy. Women of childbearing potential must use effective contraception while taking BRUKINSA and for at least one week after stopping BRUKINSA. A barrier method must also be used when using hormonal methods of contraception.

Male patients should use a highly effective method of contraception during treatment with BRUKINSA and for at least three months after the last treatment if their partner can become pregnant.

If the patient becomes pregnant while taking the drug, she must be informed of the possible risk to the foetus.

Lactation

It is not known whether BRUKINSA is excreted in human milk. Because many medicinal products are excreted in human milk, as well as the potential risk of serious adverse events with zanubrutinib in breastfed infants, breastfeeding should be discontinued during BRUKINSA treatment and breastfeeding should be avoided for two weeks after the last treatment

Fertility

There are no data on the effects of BRUKINSA on fertility in humans. No effects of zanubrutinib on fertility were observed in male or female rats, with morphological abnormalities in sperm and increased post-implantation loss at the highest dose tested (see Preclinical data).

Effects on ability to drive and use machines

No specific studies have been conducted to evaluate the effect of BRUKINSA treatment on the ability to drive or use heavy machinery. Fatigue, dizziness and asthenia have been reported in some patients taking BRUKINSA and should be considered when assessing the ability to drive or use machines.

Undesirable effects

Summary of side effects

The overall safety profile of BRUKINSA is based on pooled data from 1550 patients with B-cell malignancies treated with BRUKINSA in clinical studies.

The most common adverse reactions (≥10%) were neutropenia, thrombocytopenia, upper respiratory tract infection, haemorrhage/haematoma including bruising, skin rash, anaemia, musculoskeletal pain including back pain and arthralgia, diarrhoea, pneumonia, cough, fatigue, urinary tract infection, constipation and dizziness.

Overall, serious adverse reactions occurred in 18.6% of patients. The most commonly reported adverse reactions (>5%) were neutropenia (20.5%), pneumonia (9.4%) and thrombocytopenia (6.9%)..

Of the 1550 patients treated with BRUKINSA, 2.6 % discontinued treatment due to adverse reactions. The most common adverse reaction leading to treatment discontinuation was pneumonia (1.4%). Adverse reactions that led to a dose reduction occurred in 5.1% and an interruption of the dosage in 23.1% of patients. 1.2% of patients died due to adverse reactions.

Tabulated list of adverse reactions

Adverse reactions in patients treated with BRUKINSA for B-cell malignancies are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (frequency cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented by decreasing severity.

Table 3: Side effects reported in patients with B-cell malignancies in clinical studies≠

MedDRA system organ classes	MedDRA terms	All grades* (%)	Grade 3 or higher (%)
Infections and infestations	Upper respiratory tract infection§	Very common (32.8)	1.9
	Pneumonia§#	Very common (17.8)	9.4
	Urinary tract infection	Very common (11.5)	1.7
	Bronchitis	Common (3.5)	0.6
	Hepatitis B reactivation	Uncommon (0.9)	0.5
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps	Non-melanoma skin cancer‡	Common (6.9)	1.2
Blood and lymphatic system disorders	Neutropenia	Very common (28)	19
	Febrile neutropenia†	Common (2.0)	2.0
	Thrombocytopenia	Very common (16)	6
	Anaemia	Very common (14)	5

	Absolute neutrophil count decreased†±	Very common (49)	21
	Platelets decreased†±	Very common (36)	7
	Haemoglobin decreased†±	Very common (23)	4
Immune system disorders	Interstitial lung disease‡	Uncommon (0.8)	0.8
Metabolism and nutrition disorders	Tumour lysis syndrome#	Uncommon (0.4)	Uncommon (0.4)
Nervous system disorders	Dizziness§	Very common (10.7)	0.3
Cardiac disorders	Atrial fibrillation and flutter	Common (3.2)	1.4
Vascular disorders			
	Bruising§	Very common (26.3)	0.3
	Contusion	Very common (18.1)	0.0
	Petechiae	Common (6.5)	0.1
	Ecchymosis	Common (2.4)	0.1
	Bleeding/Haematoma§#	Very common" (27.0)	2.8
	Haematuria	Very common (9.5)	0.6
	Epistaxis	Common (7.4)	0.1
	Gastrointestinal bleeding	Uncommon (0.3)	0.1
	Hypertension	Very common (13.0)	6.5
Respiratory, thoracic and mediastinal disorders	Cough	Very common (18.6)	0.1
Gastrointestinal disorders	Diarrhoea	Very common (18.8)	1.5
	Constipation	Very common (12.3)	0.3
Hepatobiliary disordersx	Alanine aminotransferase increased	Very common (21.5)	1.1
	Aspartate aminotransferase increased	Very common (14.0)	1.0
	Blood bilirubin increased	Very common (17.1)	0.6
Renal and urinary disordersx	Blood creatinine increased	Very common (24.0)	0.7
	Blood uric acid increased	Very common (22.4)	2.9
Skin and subcutaneous tissue disorders	Rash§	Very common (23.2)	0.5
	Toxic epidermal necrolysis#	Uncommon (0.1)	0.1
	Dermatitis exfoliative generalised‡	Unknown	Unknown
Musculoskeletal and connective tissue disorders	Musculoskeletal pain§	Very common (22.6)	1.6

	Arthralgia	Very common (12.8)	0.7
	Back pain	Common (9.5)	0.5
General disorders and administration site conditions	Fatigue§	Very common (16.2)	1.2
	Fatigue	Very common (11.9)	0.8
	Asthenia	Common (3.5)	0.3

≠ Includes all patients (N=1550)
⁎ Laboratory deviations (>10%) in patients from Cohort 1 of Study BGB-3111-302 (N=101)
* Grade was assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (NCI-CTCAE) Version 4.03.
† Based on laboratory values
‡ Causal relationship unclear
§ Includes multiple terms for these side effects.
# Includes events with fatal outcome.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for BRUKINSA overdose. Patients who experience an overdose should be closely monitored and receive appropriate supportive care.

Properties/Effects

ATC code

Pharmacotherapeutic group: Antineoplastic agents, Bruton’s tyrosine kinase (BTK) inhibitors, ATC code: L01EL03.

Mechanism of action

Zanubrutinib is a BTK inhibitor. It forms a covalent bond with a cysteine residue in the active centre of the BTK, resulting in inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signal transduction leads to activation of signalling pathways required for B-cell proliferation, trafficking, chemotaxis, and adhesion.
In non-clinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumour growth.

Pharmacodynamics

BTK occupancy in peripheral blood mononuclear cells and lymph node biopsies

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

Cardiac electrophysiology

The QT interval prolongation potential of zanubrutinib was examined in a TQT study in healthy male and female subjects (N=40). 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 (≥10 ms). The maximum plasma exposure of zanubrutinib in this study was close to the maximum plasma exposure observed in patients following the recommended dose of 320 mg once daily.

The effect of BRUKINSA on the QTc interval above therapeutic exposure has not been studied.

Clinical efficacy

Waldenström macroglobulinemia

The safety and efficacy of BRUKINSA were studied in a randomised, open-label, multi-centre, comparative study of ibrutinib in 201 patients with Waldenström's disease (WD) carrying a MYD88 mutation (*MYD88*^{MUT}) (Cohort 1). In addition, a group of WD patients with the non-mutated *MYD88* gene (*MYD88*^{WT}) by gene sequencing (N=26) or with missing or unclear mutation status (N=2) was enrolled in a third, non-randomised study arm (Cohort 2).

Eligible patients were at least 18 years of age with a clinical and definitive histological diagnosis of relapsed/refractory (R/R) Waldenström's Macroglobulinemia (WM) or first diagnosed who were considered unsuitable for standard chemoimmunotherapy. Patients had to meet at least one treatment criterion according to consensus panel criteria of the 7th International Workshop on Waldenström's Macroglobulinaemia (IWWM-7) and have measurable disease defined by a serum IgM level above 0.5 g/dl. Patients with *MYD88* mutation (*MYD88*^{MUT}) were assigned to Cohort 1 (N=201) and randomised 1:1 to receive either BRUKINSA 160 mg twice daily (Arm A) or ibrutinib 420 mg once daily (Arm B) until disease progression or unacceptable toxicity. Patients with a wild-type *MYD88* gene (*MYD88*^{WT}) by centrally confirmed gene sequencing (estimated presence in approximately 10% of enrolled patients) were enrolled in Cohort 2 (N=26) and received BRUKINSA 160 mg twice daily in

a third non-randomised study arm (Arm C). In addition, those patients whose MYD88 mutation status was missing or inconclusive (N=2) were also assigned to Cohort 2, Arm C.

In Cohort 1, the median age was 70 years (range: 38 to 90 years), 28% were over 75 years of age (22% in the ibrutinib arm, 33% in the BRUKINSA arm), 67% were male, and 91% were Caucasian. At study entry, patients had a high International Prognostic Scoring System (IPSS) score derived from serum protein electrophoresis (SPEP) M-protein as follows: 44% of patients in the ibrutinib arm and 46% of patients in the BRUKINSA arm. 94% of patients had an ECOG performance status of 0 or 1 at baseline and 6% had an ECOG performance status of 2 at baseline. The median time from initial diagnosis was 4.6 years. Overall, 74 patients (37%) had IgM levels of at least 40 g/l. 164 patients (82%) had R/R WD. The median number of prior therapies was 1 (range: 1 to 8) and the median time from initial diagnosis was 5.6 years. The patient disposition and demographics of patients with R/R WD in Cohort 1 were generally comparable between the BRUKINSA and ibrutinib arms except for age. Compared with the ibrutinib treatment arm, the BRUKINSA treatment arm had a higher proportion of patients aged 75 years or older (32.5% vs. 19.8%) and under 65 years (43.4% vs. 32.1%).

In Cohort 2, the median age was 72 years (range: 39 to 87), 43% were over 75 years, 50% were male, and 96% were Caucasian. At study entry, 43% of patients had high IPSS score (derived by M-protein in the SPEP). The ECOG performance status score at baseline was 0 or 1 in 86% of patients and 14% of patients had a baseline ECOG performance status of 2. Median times from initial diagnosis were slightly shorter than in Cohort 1 (median 3.7 years vs. 4.6 years). 8 patients (29%) in Cohort 2 had IgM levels of at least 40 g/l. 23 of the 28 patients (82%) in Cohort 2 had R/R disease, with a median number of prior therapies of 1 (range: 1 to 5). Patient disposition and demographics of R/R WD *MYD88*^{WT} patients were similar to those of R/R WD *MYD88*^{MUT} patients in Cohort 1; only wild-type patients (R/R WD *MYD88*^{WT}) had a median of 4.0 years from first diagnosis whereas the median first diagnosis in mutant patients in Cohort 1 (R/R MW *MYD88*^{MUT}) was 5.6 years.

The primary endpoint was the rate of complete response (CR) or very good partial response (VGPR) in R/R *MYD88*^{MUT} WD patients, as assessed by an Independent Review Committee (IRC), adjusting for response criteria updated at the 6th IWWM. Secondary endpoints for Cohort 1 included investigator-assessed major response rate (MRR), duration of response, CR or VGPR rate, and progression-free survival (PFS).

Study results

The primary efficacy analysis for patients with R/R WD with *MYD88* mutation (*MYD88*^{MUT}), Cohort 1, was performed at a median treatment duration of 18.8 months in the ASPEN study. According to IRC

assessment, the primary study results did not reach statistical significance in the R/R analysis set (two-sided, p=0.12), so the study did not meet the primary efficacy endpoint (Table 4). Consequently, all other endpoints are considered descriptive. Efficacy outcomes assessed by investigators were consistent with the primary efficacy analysis.

Table 4: Efficacy outcomes based on IRC in patients with Waldenström macroglobulinaemia (ASPEN study; Cohort 1)

Response category	Initially treated		Relapsed/Refractory		Total (ITT)	
	BRUKINSA (N=19)	**Ibrutinib (N=18)**	**BRUKINSA (N=83)**	**Ibrutinib (N=81)**	**BRUKINSA (N=102)**	**Ibrutinib (N=99)**
VGPR or CR rate, n (%)	**5 (26.3)**	**3 (16.7)**	**24 (28.9)**	**16 (19.8)**	**29 (28.4)**	**19 (19.2)**
95% CI[c]	(9, 51)	(4, 41)	(20, 40)	(12, 30)	(20, 38)	(12, 28)
Risk difference, %[d]	-		10.7		10.2	
95% CI	(-, -)		(-3, 24)		(-2, 22)	
P value[e]	0.12					

Abbreviations: CR: complete response, IRT: interactive response technology, ITT: intent-to-treat, MR: low response, MRR: higher response rate, NE: non-evaluable, ORR: overall response rate, PD: progressive disease, PR: partial response, SD: stable disease, VGPR: very good partial response
Cohort 1 includes patients with activating mutations in MYD88.
Percentages are based on N.
[a] The 95% CI was calculated using the Clopper-Pearson method.
[b] The common risk difference according to the Mantel-Haenszel method with 95% CI was calculated using normal approximation and Sato standard error stratified by stratification factors as per IRT (Strata CXCR4 WT and unknown will be combined) and age group (up to and over 65 years). Ibrutinib is the reference group.
[c] Based on the Cochran-Mantel-Haenszel test stratified by stratification factors as per IRT (Strata CXCR4 WT and unknown will be combined) and age group (up to and over 65 years). The p-value is two-sided.

MRRs were 78% (95% CI: 68, 87) and 80% (95% CI: 70, 88) in the BRUKINSA and ibrutinib arm of the primary efficacy set (R/R *WM MYD88^{MUT}*patients). MRRs for first-treated patients were 74% (95% CI: 49, 91) and 67% (95% CI: 41, 87) in the BRUKINSA and ibrutinib arm.
Median duration of response (DoR) of CR or VGPR and PFS were not reached in any arm of the primary efficacy set of R/R *MYD88^{MUT}* WD patients.

In the non-randomised exploratory subgroup of *MYD88^{WT}* WD patients treated with BRUKINSA (Cohort 2), the IRC-assessed rates of VGPR or CR were 20% (95% CI: 1, 72) for treatment-naïve patients (n=5) and 29% (95% CI: 11, 52) for R/R patients (n=21). No CRs were observed.

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

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

BGB-3111-305 is an international, multicenter, randomized, open-label, Phase 3 study of 652 patients (ITT population) randomized 1:1 to receive either zanubrutinib 160 mg orally twice daily or ibrutinib 420 mg orally once daily, until disease progression or unacceptable toxicity.

Eligible patients were adult patients (≥18 years old) with relapsed or refractory CLL/SLL, after at least one prior systemic Therapy, requiring treatment as per iwCLL 2008 criteria and ECOG performance status of ≤2. Patients were with a known prolymphocytic leukaemia or history of, currently suspected, Richter's transformation, or known CNS involvement by leukaemia or lymphoma were excluded.

Patients were not eligible for participation if they received warfarin or K-vitamin antagonist prior to study entry; however, if the patient was randomized to zanubrutinib arm, warfarin or K-vitamin antagonist was allowed. Patients were also excluded if they had received prior treatment with other Bruton Tyrosine Kinase inhibitors (BTKi).

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

Baseline characteristics were generally balanced between treatment arms in the ITT analysis set of 327 patients in the zanubrutinib arm and 325 patients in the ibrutinib arm: 13 SLL patients in the zanubrutinib arm, and 16 SLL patients in the ibrutinib arm. The zanubrutinib arm had 65.1% male patients and 71.4% in the ibrutinib arm. The median age was 67.0 years in the zanubrutinib arm and 68.0 years in the ibrutinib arm. In both arms, 61.5% of patients were ≥ 65 years old. ECOG 0 or 1 was in 97.9% patients in the zanubrutinib arm and 96.0% in the ibrutinib arm. The median number of prior lines of systemic therapy is 1.0 in both arms. The median time from initial diagnosis to randomization was 7.5 years in the zanubrutinib arm and 7.8 years in the ibrutinib arm.

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.

The primary endpoint was overall response rate (ORR, defined as partial response or better) as determined by investigator assessment, using iwCLL 2008 criteria with additional of treatment related lymphocytosis for CLL and the Lugano criteria for SLL. Efficacy results are presented in Table 6.

Table 6: Efficacy Results in BGB-3111-305 (Pre-specified Interim Analysis of the First 415 randomized Patients)

	Investigator Assessed		IRC Assessed	
Endpoint	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**	**Zanubrutinib (N=207)**	**Ibrutinib (N=208)**
Overall Response Rate n (%)	162 (78.3)	130 (62.5)	158 (76.3)	134 (64.4)
(95% CI)	(72.0, 83.7)	(55.5, 69.1)	(69.9, 81.9)	(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	

Data based on Data cutoff date of 31 December 2020.
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
[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. Pre-specified 1-sided alpha of 0.005
[c] Stratified Cochran-Mantel-Haenszel test. Pre-specified 2-sided alpha of 0.0099

At the time of the PFS final analysis (DCO 08 August 2022) with median study follow-up time of 29.6 months on ITT population (n=652), zanubrutinib demonstrated PFS superiority (2-sided P =0.0024) and non-inferiority (1-sided P = <0.0001) over ibrutinib with HR of 0.65 (95%CI: 0.49, 0.86) by Independent Review Committee. Median overall survival (OS) was not reached in either arm. There were 48 deaths reported in the zanubrutinib arm (14.7%) and 60 deaths reported in the ibrutinib arm (18.5%).

Pharmacokinetics

The pharmacokinetics (PK) of zanubrutinib have been studied in healthy subjects and patients with B-cell lymphomas. The maximum zanubrutinib plasma concentration (C_{max}) and the area under the plasma drug concentration curve over time (AUC) increase proportionally over a dose range of 40 mg to 320 mg (0.13 to 1 times the total recommended daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated use.

The geometric mean (% CV) daily AUC for zanubrutinib at steady state is 2099 (42%) ng·h/ml after a dose of 160 mg twice daily and 1917 (59%) ng·h/ml after a dose of 320 mg once daily. The geometric mean (% CV) C_{max} for zanubrutinib at steady state is 299 (56%) ng/ml after a dose of 160 mg twice daily and 533 (55%) ng/ml after a dose of 320 mg once daily.

Absorption

Food effect: No clinically significant differences in the AUC or C_{max} of zanubrutinib were observed in healthy subjects following a high-fat meal (approx. 1,000 calories with 50% of total calorie content from fat).

Distribution

The geometric mean (% CV) apparent volume of zanubrutinib distribution at steady state during the terminal phase (Vz/F) was 537 l (73%) after a dose of 160 mg twice daily. Plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio is 0.7 to 0.8.

Metabolism

In vitro, zanubrutinib is primarily metabolised by cytochrome P450(CYP)3A.

Elimination

The mean half-life ($t_{½}$) of zanubrutinib is approximately two to four hours after a single oral zanubrutinib dose of 160 mg and 320 mg. The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib was 128 (58%) l/hr.

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

Special patient groups

Elderly

Age (19 to 90 years; mean age 65±12.5) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis (N=1291).

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.

Ethnicity

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

Body weight

Body weight (36 to 149 kg, mean weight 76.5±16.9 kg) had no clinically meaningful effect on zanubrutinib pharmacokinetics based on population PK analysis (N=1291).

Patients with hepatic disorders

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

Patients with renal disorders

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.

Preclinical data

Repeated dose toxicity

The general toxicological profiles of zanubrutinib were characterised by oral treatment in Sprague-Dawley rats for up to six months and in Beagle dogs for up to nine months.

In the six-month study, rats received a dose of 30, 100 or 300 mg/kg/day for 182 days or 1,000 mg/kg/day for up to 8 days. Mortality associated with the test item was only observed at a dose of 1,000 mg/kg/day after 5 days of treatment, and the most important toxicological findings were gastrointestinal toxicities associated with histopathological changes. Histopathological changes in surviving animals related to the test item were found in the pancreas, lungs, and skeletal muscles, most were completely or partially reversible. The NOAEL was 300 mg/kg/day, with systemic exposure (AUC) in males approximately 25 times and in females 42 times the human exposure at the recommended dose.

In the nine-month study, dogs received 10, 30, or 100 mg/kg/day for 273 days. No mortalities occurred throughout the study. Toxicological findings or changes were minimal or mild and resolved during recovery, including abnormal stool, conjunctival hyperaemia, lymphoid depletion, or erythrophagocytosis in intestinal-associated lymphoid tissue. The NOAEL was 100 mg/kg/day, with systemic exposure (AUC) in males approximately 20 times and in females 18 times the human exposure at the recommended dose.

Genotoxicity

Zanubrutinib was non-mutagenic in a bacterial mutagenic test (Ames), non-clastogenic in a mammalian cell (CHO) chromosomal aberration test, and non-clastogenic in an *in vivo* bone marrow micronucleus test in rats.

Carcinogenicity

No carcinogenicity studies have been conducted with zanubrutinib.

Reproductive toxicity

A combined study of male and female fertility and early embryonic development was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed four weeks before mating and during mating and female rats were dosed two weeks before mating and up to gestation day seven. No effects on male or female fertility were noted, but at the high dose of 300 mg/kg/day, morphological abnormalities in sperm and increased post-implantation loss were noted. The 300 mg/kg/day dose is approximately 9 times the recommended human dose based on body surface area.

Embryo-foetal developmental toxicity studies have been 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. Cardiac malformations (two or three heart chambers) were noted at all dose levels (incidence between 0.3 and 1.5%) without maternal toxicity. The lowest dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose.

Administration of zanubrutinib to pregnant rabbits in the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss and maternal toxicity at the highest dose. The dose of 70 mg/kg/day is approximately 25 times the exposure (AUC) of patients at the recommended dose.

In a pre- and post-natal development toxicity study in rats, zanubrutinib was administered orally at a dose of 30, 75, and 150 mg/kg/day from implantation until weaning. Offspring from the 75 mg/kg/day and 150 mg/kg/day groups had decreased body weight before weaning and all dose groups had adverse ocular findings (cataract, protruding eye, etc.). The dose of 30 mg/kg/day is approximately 4 times the exposure (AUC) in patients receiving the recommended dose.

Other information

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.
36 months

Special precautions for storage

Store at 15-30°C.
Store in the original packaging.
Keep the container tightly closed.
Keep out of the reach of children.

Authorisation number

67998

Packs

White high-density polyethylene (HDPE) plastic bottle with a child resistant polypropylene cap.
Package size
Bottle with 120 hard capsules (A)

Marketing authorisation holder

BeiGene Switzerland GmbH
Aeschengraben 27
4051 Basel

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