swissmedic

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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 01.02.2024

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.

Table of contents

1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
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)

2 Background information on the procedure

2.1 Applicant's request(s)

Work-sharing procedure
The applicant requested a work-sharing procedure with Health Canada (HC).
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

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

2.2.2 Approved indication

Brukinsa in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed grade 1-3a follicular lymphoma (FL) who have received at least two prior lines of therapy, including anti-CD20 antibody therapy.

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	15 March 2023
Formal objection	12 April 2023
List of Questions (LoQ)	10 August 2023
Response to LoQ	9 October 2023
Preliminary decision	21 November 2023
Response to preliminary decision	14 December 2023
Final decision	1 February 2024
Decision	approval

3 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology and method of administration.
Based on a previously submitted ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

4 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant’s request / Work-sharing procedure).

5 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.

6 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.

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.

NAME OF THE MEDICINAL PRODUCT

Brukinsa 80 mg hard capsules

Composition

Active substances

Zanubrutinib

Excipients

Capsule contents
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)

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 received one or more prior therapies (see “Properties/Effects”).

BRUKINSA in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed grade 1-3a follicular lymphoma (FL) who have received at least two prior lines of therapy, including anti-CD20 antibody therapy.

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 (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80 mg once daily Treatment interruption according to recommendations in case of side effects.
	Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80 mg twice daily Dose adjustment according to recommendations in case of side effects.
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use of strong CYP3A4 inducers.
	Moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use of moderate inducers. If these inducers cannot be avoided, increase dose to 320 mg twice daily.

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

Patients with hepatic disorders

No dose 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 dose 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. Grade 3 or higher bleeding events, including intracranial and gastrointestinal bleeding, haematuria, and haemothorax, were observed in 5% of patients treated with BRUKINSA monotherapy and in less than 1% of patients treated with BRUKINSA in combination with obinutuzumab, respectively. Bleeding events of any grade, including purpura and petechiae, occurred in 51% of patients with haematologic malignancies treated with BRUKINSA monotherapy and in 32% of patients treated with BRUKINSA in combination with obinutuzumab.

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 3 to 7 days before and after surgery.

Infections

Fatal and non-fatal, (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 with haematologic malignancies treated with BRUKINSA. Infections of any grade occurred in 71% of the patients treated with BRUKINSA monotherapy. Infections of grade 3 or higher

occurred in 26% of these patients. Infections of any grade occurred in 58% of patients who were treated with BRUKINSA in combination with obinutuzumab. Infections of grade 3 or higher occurred in 26% of these patients. 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. Case of progressive multifocal leukoencephalopathy (PML) were reported following 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 with increased risk of infections. Patients should be monitored for signs and symptoms of infections and treated appropriately.

Second primary malignancies

Second primary malignancies, including carcinomas other than skin cancers, occurred in 15% of patients with haematologic malignancies treated with BRUKINSA monotherapy and in 8% of patients treated with BRUKINSA in combination with obinutuzumab. The most common second primary malignancy was non-melanoma skin cancer (basal cell and squamous cell carcinoma of the skin), which occurred in 8% of patients treated with BRUKINSA monotherapy and 5% of patients treated with BRUKINSA in combination with obinutuzumab, respectively. Patients should be monitored for the occurrence of skin tumours. Use of sunscreen should be instructed.

Atrial fibrillation and flutter

Atrial fibrillation and flutter occurred in 5% of patients with haematological malignancies treated with BRUKINSA monotherapy and in 2% of patients treated with BRUKINSA in combination with obinutuzumab, particularly in patients with cardiac risk factors, hypertension, and acute infections. Grade 3 or higher atrial fibrillation and flutter occurred in 2% of patients treated with BRUKINSA monotherapy and 1% of patients treated with BRUKINSA in combination with obinutuzumab.
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 (TLS) has been reported with BRUKINSA therapy. The risk of a TLS exists particularly in patients with high tumour burden prior to therapy. Patients are to be monitored closely and appropriate precautions should be taken.

Cytopenia

Grade 3 or 4 cytopenia, including neutropenia (21%), thrombocytopenia (8%), and anaemia (4%) based on laboratory measurements, occurred in patients with haematologic malignancies treated with BRUKINSA monotherapy, and neutropenia (20%), thrombocytopenia (11%) and anaemia (2%) in patients treated with BRUKINSA in combination with obinutuzumab (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 3% of patients with haematologic malignancies treated with BRUKINSA monotherapy and in 2% treated with BRUKINSA in combination with obinutuzumab. 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 transformation, clinically significant cardiovascular disease, uncontrolled active systemic fungal, bacterial, viral, or other infections, including active hepatitis B or C infection, or known history of infection with human immunodeficiency virus (HIV), severe or debilitating pulmonary disease, 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 anaemia and/or autoimmune thrombocytopenia requiring ongoing treatment with corticosteroid were not included in zanubrutinib clinical trials to date for patients with CLL.

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).

Active substances that may increase zanubrutinib plasma concentration

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

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.

Active substances that may increase zanubrutinib plasma concentration

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

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.

The coadministration of zanubrutinib with multiple doses of strong CYP3A inhibitors voriconazole and clarithromycin in patients with B-cell malignancies resulted in increased zanubrutinib levels by 3.30-fold and 1.92-fold for dose-normalized $AUC_{0\text{-}24h}$ and 3.29-fold and 2.01-fold for dose-normalized C_{max}, respectively.

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) daily 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 ”Dosage/Administration”).

Moderate CYP3A inhibitors

The coadministration of zanubrutinib and multiple doses of moderate CYP3A inhibitors fluconazole and diltiazem in patients with B-cell malignancies resulted in increased zanubrutinib levels 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 (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) daily for the period of inhibitor use. Patients should be closely monitored for toxicity and, if necessary, the dose adjustment instructions should be followed (see ”Dosage/Administration”).

Mild 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 ”Dosage/Administration”).

Active substances that may decrease zanubrutinib plasma concentration

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

CYP3 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 CYP3A inducers (carbamazepine, phenytoin, rifampin, St. John’s Wort) should be avoided.

Concomitant use of multiple doses of rifabutin (moderate CYP3A inducer) decreased C_{max} by 48% and AUC by 44% in healthy subjects. Avoid concomitant use of moderate inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin). If these inducers cannot be avoided, increase the zanubrutinib dose to 320 mg twice daily (see “Dosage/Administration”).

Mild 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 mild 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) C_{max} 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 C_{max} 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 administration of zanubrutinib 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

Zanubrutinib monotherapy

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 upper respiratory tract infection, bruising§, neutropenia§, haemorrhage/haematoma § including haematuria, musculoskeletal pain§, including arthralgia and back pain, rash§, pneumonia§, diarrhoea, cough§, fatigue§, thrombocytopenia§, anaemia§, hypertension§, constipation, urinary tract infection, and dizziness §.

Overall, serious adverse reactions occurred in 23% of patients. The most common Grade 3 or higher adverse reactions (>5%) were neutropenia§ (19%), pneumonia§ (12%), hypertension§ (8%), thrombocytopenia§ (6%), and anaemia§ (6%).

Of the 1550 patients treated with BRUKINSA, 4% discontinued treatment due to adverse reaction. The most common adverse reaction leading to treatment discontinuation was pneumonia (2%). Adverse reactions that led to a dose reduction occurred in 5% of patients and an interruption of the dosage in 20% of patients, 2% of patients died due to adverse reactions.

Zanubrutinib in combination with obinutuzumab

The most commonly occurring adverse reactions (≥10%) of BRUKINSA in combination with obinutuzumab were thrombocytopenia§ (35%), neutropenia§ (20%), fatigue§ (27%), musculoskeletal pain§ (21%), upper respiratory tract infection§ (20%), bruising§ (20%), pneumonia§ (18%), diarrhoea (18%), cough§ (17%), haemorrhage/haematoma§ (16%), constipation (13%), rash§ (13%) and anaemia§ (11%).

Overall, serious adverse reactions occurred in 16% of patients. The most common Grade 3 or higher adverse reactions (>5%) of BRUKINSA in combination with obinutuzumab were neutropenia§ (24%), thrombocytopenia§ (14%), and pneumonia§ (11%).

Of the 179 patients treated with BRUKINSA in combination with obinutuzumab, 4% of patients discontinued treatment due to adverse reactions. The adverse reaction leading to treatment discontinuation most frequently was pneumonia§ (3%). Adverse reactions resulted in dose reductions in 6% of patients and an interruption of the dose in 23% of patients, 1% 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: Adverse reactions reported in patients with B-cell malignancies in clinical studies with BRUKINSA monotherapy[≠]

MedDRA system organ classes	MedDRATerms	All Grades* (%)	Grade ≥3 (%) (%)
Infections and infestations	Upper respiratory tract infection[§]	Very common (34)	2
	Pneumonia[§#]	Very common (22)	12
	Urinary tract infection[§]	Very common (13)	2
	Bronchitis	Common (4)	<1
	Hepatitis B reactivation	Uncommon (<1)	<1
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	Non-melanoma skin cancer[‡]	Common (8)	1
Blood and lymphatic system disorders	Neutropenia[§]	Very common (30)	20
	Febrile neutropenia	Common (2)	2
	Thrombocytopenia[§]	Very common (17)	6
	Anaemia[§]	Very common (15)	6
	Absolute neutrophil count decreased[†±]	Very common (51)	21
	Platelet decreased[†±]	Very common (38)	8
	Haemoglobin decreased[†±]	Very common (25)	4
Immune system disorders	Interstitial lung disease[§‡]	Common (3)	<1
Metabolism and nutrition disorders	Tumour lysis syndrom[§#]	Uncommon (<1)	<1
Nervous system disorders	Dizziness[§]	Very common (11)	<1
Cardiac disorders	Atrial fibrillation and flutter[§]	Common (5)	2
Vascular disorders	Bruising[§]	Very common (32)	<1
	Contusion	Very common (19)	0
	Petechia	Common (7)	<1
	Purpura	Common (5)	<1
	Ecchymosis	Common (3)	<1
	Haemorrhage/ Haematoma[§#]	Very common (29)	3
	Haematuria	Very common (10)	<1
	Epistaxis	Common (8)	<1
	Gastrointestinal haemorrhage	Uncommon (<1)	<1
	Hypertension[§]	Very common (15)	8

Respiratory, thoracic and mediastinal disorders	Cough§	Very common (20)	<1
Gastrointestinal disorders	Diarrhoea	Very common (20)	2
	Constipation	Very common (13)	<1
Hepatobiliary disorders	Alanine aminotransferase increased†‡	Very common (25)	1
	Aspartate aminotransferase increased†‡	Very common (17)	1
	Blood bilirubine increased†‡	Very common (19)	<1
Renal and urinary disorders	Blood creatinine increased†‡	Very common (26)	<1
	Blood uric acid increased†‡	Very common (23)	3
Skin and subcutaneous tissue disorders	Rash§	Very common (25)	<1
	Pruritus	Common (8)	<1
	Toxic epidermal necrolysis#‡	Uncommon (<1)	<1
	Dermatitis exfoliative generalised‡	Unknown	Unknown
Musculoskeletal and connective tissue disorders	Musculoskeletal pain §	Very common (26)	2
	Arthralgia	Very common (15)	<1
	Back pain	Very common (11)	<1
General disorders and administration site conditions	Fatigue§	Very common (17)	1
	Fatigue	Very common (13)	<1
	Asthenia	Common (4)	<1
	Oedema peripheral	Common (9)	<1

≠ Includes all patients (N=1550)
* 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.

Table 4: Adverse reactions of BRUKINSA in combination with obinutuzumab reported in clinical studies in patients with follicular lymphoma (n=179)

MedDRA SOC	MedDRA Terms		
		All grades* (%)	Grade ≥3 (%)
Infections and infestations	Upper respiratory tract infection[§]	Very common (20)	<1
	Pneumonia[§#]	Very common (18)	11
	Urinary tract infection[§]	Common (8)	1
	Bronchitis	Common (3)	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps	Non-melanoma skin cancer[‡]	Common (5)	2
Blood and lymphatic system disorders	Neutropenia[§]	Very common (29)	24
	Febrile neutropenia	Common (2)	2
	Thrombocytopenia[§]	Very common (35)	14
	Anaemia[§]	Very common (11)	4
	Neutrophil count decreased[†±]	Very common (48)	20
	Platelets decreased[†±]	Very common (65)	11
	Haemoglobin decreased[†±]	Very common (30)	2
Immune system disorders	Interstitial lung disease[§‡]	Common (2)	0
Nervous system disorder	Dizziness[§]	Common (6)	0
Cardiac disorders	Atrial fibrillation and flutter	Common (2)	1
Vascular disorders	Bruising[§]	Very common (20)	0
	Contusion	Very common (12)	0
	Petechiae	Common (8)	0
	Ecchymosis	Common (1)	0
	Haemorrhage/ haematoma[§]	Very common (16)	<1
	Haematuria	Common (1)	0
	Epistaxis	Common (5)	0
	Hypertension[§]	Common (5)	2
Respiratory, thoracic and mediastinal disorders	Cough[§]	Very common (17)	0
Gastrointestinal disorders	Diarrhoea	Very common (18)	2
	Constipation	Very common (13)	0
Hepatobiliary disorders*	Alanine aminotransferase increased[† ±]	Very common (25)	0
	Aspartate aminotransferase increased[† ±]	Very common (18)	0
	Blood bilirubin increased[† ±]	Common (9)	0
Renal and urinary disorders*	Blood creatinine increased[†±]	Very common (18)	0
	Blood uric acid increased[†±]	Very common (14)	3
	Rash[§]	Very common (13)	0

Skin and subcutaneous tissue disorders	Pruritus	Common (6)	0
	Toxic epidermal necrolysis‡	Unknown	Frequency unknown
Musculoskeletal and connective tissue disorders	Musculoskeletal Pain§	Very common (21)	2
	Arthralgia	Common (7)	0
	Back pain	Very common (11	<1
General disorders and administration site conditions	Fatigue§	Very common (27)	2
	Fatigue	Very common (17)	0
	Asthenia	Very common (10)	<1
	Oedema peripheral	Common (3)	0

* 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 post-baseline assessment available.
‡ Causal relationship unclear

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 evaluated 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 (ASPEN study, BGB-3111-302) 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) (Table 5).

Eligible patients were at least 18 years of age with a clinical and definitive histological diagnosis of relapsed/refractory (R/R) Waldenström's disease WD 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 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 5). Consequently, all other endpoints are considered descriptive. Efficacy outcomes assessed by investigators were consistent with the primary efficacy analysis.

Table 5: 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)
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 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 requiring treatment as per iwCLL 2008 criteria and ECOG performance status of ≤2. Patients were not eligible among others with a known prolymphocytic leukaemia or history of, currently suspected, Richter's transformation, or known CNS involvement by leukaemia or lymphoma. Patients were not eligible 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).

Randomization 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 demographics and disease 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 the ALPINE study (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%).

Patients with Follicular Lymphoma (FL)

The efficacy of zanubrutinib in combination with obinutuzumab versus obinutuzumab monotherapy was assessed in a Phase 2 randomized, open-label, multicentre, study (ROSEWOOD study, BGB-3111-212). Overall, 217 patients with relapsed/refractory grade 1-3A follicular lymphoma (FL) who had previously received at least two prior anti-CD20 therapies and an appropriate alkylator-based combination therapy, were enrolled. Patients were randomized 2:1 to either zanubrutinib 160 mg twice daily in combination with obinutuzumab 1000 mg intravenously (arm A) or obinutuzumab alone (arm B).

Randomization was stratified by the number of prior lines of therapy (2 to 3 versus >3), rituximab-refractory status (yes versus no), and geographic region (China versus not China).

The mean age was 64 years (range: 31 to 88), 49.8% were male, and 64.1% white. Forty-seven percent of patients were ≥65 years old. The majority of patients had a ECOG performance status of 0 or 1.

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

The mean number of prior anticancer therapy was 3 lines (range: 2 to 11 lines). All 217 patients received ≥2 prior lines of therapy that included rituximab therapy, and 59 of the 217 patients (27.2%) received >3 prior lines of therapy. More than half of all patients (114 patients [52.5%]) were refractory to rituximab (defined as failure to respond to, or progression during, any previous rituximab-containing

regimen [monotherapy or combined with chemotherapy], or progression within 6 months of the last rituximab dose, in the induction or maintenance phase).

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

The primary efficacy endpoint was the overall response rate (defined as partial response or complete response) as determined by an independent central review committee (IRC) using the Lugano Classification for NHL. The mean duration of response assessed by the ITC was not reached (95% CI: 25.3, NE) in the zanubrutinib-obinutuzumab combination arm and 14.0 months (95% CI: 9.2, 25.1) in the obinutuzumab monotherapy arm.

The PFS assessed by the IRC was 28.0 months (95% CI: 16.1, NE) in the zanubrutinib-obinutuzumab combination arm and 10.4 months (95% CI: 6.5, 13.8) in the obinutuzumab arm. The median overall survival was not reached in the zanubrutinib-obinutuzumab combination arm and was 34.6 months (95% CI: 29.3, NE) in the obinutuzumab arm. The overall survival rates at 24 months were 77.3% (95% CI: 68.0, 84.2) in the zanubrutinib-obinutuzumab combination arm and 71.4% (95% CI: 58.3, 81.1) in the obinutuzumab monotherapy arm. As multiplicity adjustments were not applied for PFS and OS, these are descriptive results.

Efficacy results are summarized in Table 7.

Table 7: Efficacy Results Per Independent Central Review Committee (ITT)

	Zanubrutinib + Obinutuzumab (N=145) n (%)	**Obinutuzumab (N=72) n (%)**
Overall Response Rate, n (%) (95% CI[a])	100 (69.0) (60.8, 76.4)	33 (45.8) (34.0, 58.0)
CR	57 (39.3)	14 (19.4)
PR	43 (29.7)	19 (26.4)
P value[b]	0.0012	

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.

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 populations

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.

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

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.

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.

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 a dose of 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 also 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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