19 June 2025
EMA/CHMP/130759/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Brukinsa

International non-proprietary name: Zanubrutinib

Procedure No. EMEA/H/C/004978/X/0023

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation or Specialist Term	Definition
ARA	acid-reducing agents
AS	active substance
AUC	area under the plasma concentration-time curve
BE	bioequivalence
BGB-3111	zanubrutinib (BRUKINSA™)
BSE	Bovine spongiform encephalopathy
BTK	Bruton tyrosine kinase
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration after administration of study drug
CQA	Critical Quality Attributes
CSR	clinical study report
GM	geometric mean
FDA	Food and Drug Administration
FP	finished product
HDPE	high-density polyethylene
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPC	in-process controls
KF	Karl-Fischer titration
MCL	mantle cell lymphoma
PBPK	physiologically based pharmacokinetic
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PP	polypropylene
QC	Quality control
QTPP	Quality Target Product Profile
RH	Relative humidity

Abbreviation or Specialist Term	Definition
R/R	relapsed/refractory
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
TSE	Transmissible spongiform encephalopathy
USP	United States Pharmacopoeia
UV	Ultra violet spectrometry
WM	Waldenström macroglobulinemia

1. Background information on the procedure

1.1. Submission of the dossier

BeOne Medicines Ireland Ltd submitted on 3 June 2024 an extension application to introduce a new pharmaceutical form associated with new strength (160 mg film-coated tablets).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 and Annex I (2) point (c) and (d) of Commission Regulation (EC) No 1234/2008 - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0205/2022 granting a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: <N/A>

PRAC Rapporteur: Bianca Mulder

The application was received by the EMA on	3 June 2024
The procedure started on	18 July 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	14 November 2024

The MAH submitted the responses to the CHMP consolidated List of Questions on	24 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 October 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	25 April 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	16 May 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	2 June 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Brukinsa on	19 June 2025
The CHMP adopted a report on similarity of Brukinsa with Gazyvaro, Lunsumio, Kymriah and Yescarta on (see Appendix on similarity)	19 June 2025

2. Scientific discussion

2.1. Problem statement

This is a line extension application concerning a new zanubrutinib oral tablet formulation – comprising of quality data and pharmacology results from 2 Phase 1 clinical studies (Studies BGB-3111-115 and BGB-3111-114) in healthy volunteers. The new formulation applies to all approved indications for Brukinsa.

2.1.1. Disease or condition

Brukinsa as monotherapy is indicated for the treatment of adult patients with

- Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.
- marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.
- Chronic lymphocytic leukemia (CLL).

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

2.2. About the product

Zanubrutinib, (Brukinsa), is a second-generation inhibitor of Bruton's tyrosine kinase (BTK). Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.

It is intended for monotherapy for adult patients with Waldenström's macroglobulinaemia (WM), marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL) or in combination with obinutuzumab for adult patients with FL.

Zanubrutinib is formulated as oral capsules of 80mg. The recommended total daily dose of zanubrutinib is 320 mg. The daily dose may be taken either once daily (four 80 mg capsules) or divided into two doses of 160 mg twice daily (two 80 mg capsules).

2.3. Type of Application and aspects on development

This application concerns a new zanubrutinib oral tablet formulation based on data from 2 Phase 1 clinical studies (Studies BGB-3111-115 and BGB-3111-114) in healthy volunteers.

Study BGB-3111-115 consisted of an initial assessment of the relative bioavailability of the tablet compared to the capsule formulation and a food effect evaluation on the tablet.

Subsequently, based on the results of Study BGB-3111-115, Study BGB-3111-114 was conducted to assess bioequivalence between the tablet and capsule formulations.

The submitted clinical studies Studies BGB-3111-115 and BGB-3111-114 were conducted according to GCP.

2.4. Quality aspects

2.4.1. Introduction

This extension application concerns the introduction of a new pharmaceutical form at a higher strength of 160 mg film-coated tablets (scored) in addition to the existing 80 mg hard capsule. The new pharmaceutical form and strength was developed to reduce the overall pill burden considering the maximum daily dose of 320 mg.

The finished product is presented as a film-coated tablet containing 160 mg of zanubrutinib as active substance.

Other ingredients are:

tablet core: lactose monohydrate, croscarmellose sodium, sodium lauryl sulfate (E487), colloidal silicon dioxide, povidone, microcrystalline cellulose, magnesium stearate;

*film coating: h*ypromellose, titanium dioxide (E171), triacetin, brilliant blue FCF aluminium lake (E133), indigo carmine aluminium lake (E132).

The product is available in high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) closure, as stated in the SmPC section 6.5.

2.4.2. Active Substance

No new information regarding the active substance (AS) zanubrutinib has been presented with this application; this is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is an oval blue film-coated tablet with letters "zanu" debossed on one side and a functional score line in the middle on the other side. The approximate dimensions of the film-coated tablets are 16 mm x 7.8 mm. The finished product comes in one strength, i.e. 160 mg.

The finished product is a conventional immediate release film-coated tablet for oral administration.

The choice of pharmaceutical form and strength adequately addresses the proposed dosing regime, i.e. 320 mg zanubrutinib daily, taken either once daily (two 160 mg tablets) or divided into two doses of 160 mg twice daily (one 160 mg tablet).

During development, the following physicochemical properties of the active substance, zanubrutinib, which may influence the performance and manufacturability of the finished product were adequately discussed: polymorphic form, thermal profile, moisture sorption profile, particle size, solid-state stability, solubility, permeability and compatibility with excipients.

The Quality Target Product Profile (QTPP) of zanubrutinib 160 mg film-coated tablets was considered for identification of the FP Critical Quality Attributes (CQAs).

The choice and function of the excipients used in the finished product are considered sufficiently described. Only compendial and well-known excipients are used. No novel excipients are used. Where relevant, functionality-related characteristics are specified for the excipients.

The proposed manufacturing process consists of a standard wet granulation followed by blending, tableting and coating. An initial risk assessment of the manufacturing process was conducted identifying the variables and unit operations which could impact the product quality. Based on this initial risk assessment, development studies of each unit operation were performed on laboratory, pilot and commercial scale batches in order to investigate the process parameters' impact on the product quality and manufacturability. A final risk assessment was made based on the development studies where all risks to CQAs and manufacturability were reduced to low. Process parameters and in-process controls (IPCs) have been specified for the proposed commercial manufacturing process based on the development studies.

The development of the chosen dissolution method and the discriminative properties of the method have been sufficiently discussed and evaluated.

Zanubrutinib tablets, 160 mg, manufactured at a different site using the proposed commercial formulation and manufacturing process, was used for the relative bioavailabilty study. To confirm that the final zanubrutinib tablets, 160 mg, formulation has similar product performance to the commercially available zanubrutinib capsules, 80 mg, a pivotal bioequivalence (BE) study was conducted to compare 1 Brukinsa tablet, 160 mg, with 2 commercial Brukinsa capsules, 80 mg. One of the primary stability batches of Brukinsa 160 mg tablets manufactured at the proposed commercial site, using the proposed commercial formulation, was used for the BE study.

In support of the clinical studies, an in-vitro comparison of the currently approved Zanubrutinib 80 mg hard capsules and the proposed Zanubrutinib 160 mg film-coated tablets with regard to dissolution profile and impurity profile has been investigated and presented. The comparison showed similar dissolution and impurity profiles.

The proposed primary packaging of the finished product is white HDPE bottles with PP child resistant closures, with an induction heat seal liner. Descriptions, technical drawings and specifications are provided for the bottle and closure. Compliance with relevant Ph. Eur. monographs and Commission Regulation (EU) No 10/2011 is confirmed. The suitability of the proposed container closure system is considered adequately described and demonstrated through development and stability studies.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at the same batch release site as already approved for the zanubrutinib 80 mg hard capsules.

The manufacturing process is a standard process consisting of wet granulation followed by blending, tableting coating and packaging.

The description of the manufacturing process is acceptable and is described in sufficient detail. The critical process parameters have been identified and appropriate in-process controls during the manufacture have been established in line with pharmaceutical development. Relevant process parameters are laid down in the description with target values and ranges, which are considered justified by pharmaceutical development.

A batch formula presenting manufacture of batches with the proposed batch size is presented. The batch formula is acceptable.

The hold time is supported by bulk stability data and is found acceptable.

A process validation scheme is provided. Since the proposed manufacturing process is considered a standard process, it is acceptable not to provide any process validation data, but only a process validation scheme. The scheme is found acceptable.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UV, HPLC), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC, Ph. Eur.), water content (KF) and microbial limits (Ph. Eur.).

The product specifications cover appropriate parameters for this dosage form.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 FP pilot scale batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based

on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

All analytical procedures used for testing the finished product have been properly described and sufficiently validated in accordance with the EU/ICH validation guidelines.

Batch analysis data are provided for 3 pilot and 3 commercial scale batches manufactured at the proposed commercial manufacturing site, and for 1 batch manufactured at a different site. All results comply with the specifications and confirm consistency and uniformity of the finished product.

2.4.3.4. Stability of the product

Stability data from 3 pilot scale batches (primary stability) of Brukinsa 160 mg film coated tablets manufactured at proposed commercial site and stored for up to 18 months under long term conditions (30°C/75% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Further, supportive stability data for 24 months under long term conditions were provided from a single batch manufactured at a different site using the same formulation and packed in the same HDPE bottle with child-resistant closure as proposed for the primary stability batches. The primary batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. It is noted that the stability studies are performed with slightly different long term storage conditions than specified in ICH Q1A (i.e. 30°C/65% RH). This is considered acceptable as long as all results comply with specification at both 40°C/75% RH and 30°C/75% RH.

Stability samples were tested for: appearance, assay, related substances, dissolution, water content and microbial limits. All results from the stability batches comply with the specifications at all tested conditions.

A photostability study was performed on a single batch of Brukinsa 160 mg film-coated tablets in line with ICH Q1B. The study included an exposed sample placed in glass dishes and a dark control. No change was observed in appearance, assay, related substances, dissolution, and water content after tablets were exposed to ICH Q1B light conditions. The photostability study sufficiently demonstrates that the finished product is not sensitive towards light.

An in-use stability study on two batches of Brukinsa 160 mg film-coated tablets stored at 30°C/75% RH has been performed with up to 120 days data available. All results complied with the specifications and no trends were observed. Given the results from stability studies (formal and in-use), stress studies performed as part of method validation, packaging size and posology as well as the storage conditions used during the stability studies (30°C/75% RH), an in-use shelf-life of the finished product is not deemed necessary in the SmPC.

Based on available stability data, the proposed shelf-life of 2 years without special storage conditions as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

With the exception of the lactose monohydrate 200, no animal or human derived raw materials are used in the manufacturing process of Brukinsa tablets, 160 mg.

It is confirmed that the lactose is produced from bovine milk from healthy animals in the same conditions as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and

veterinary medicinal products. . A TSE/BSE-free statement has been provided by the manufacturer of lactose monohydrate 200.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the new strength and pharmaceutical form Brukinsa 160 mg film-coated tablets has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

No new information on non-clinical aspects is submitted with this application.

2.5.2. Pharmacology

Not applicable.

2.5.3. Pharmacokinetics

Not applicable.

2.5.4. Toxicology

Not applicable.

2.5.5. Ecotoxicity/environmental risk assessment

The present variation application comprises solely a change in formulation. Therefore, the assessment of the environmental risk of zanubrutinib, from previous procedures, remain applicable.

2.5.6. Discussion on non-clinical aspects

Zanubrutinib is already used in existing marketed products and no significant increase in environmental exposure is anticipated as the additional formulation is an alternative option for the same use of the product

Therefore, zanubrutinib is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

No new information on non-clinical aspects is included in this line extension procedure which is considered acceptable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1: Clinical Pharmacology Studies of Zanubrutinib (BGB-3111)

Region	Study Number	Title	Phase	Primary Objective and Clinical Pharmacology Analyses	Oral Dose Regimen	Evaluable Subjects
US	BGB-3111-115	A Single-dose, Open-label, Randomized, Crossover Study in Healthy Adult Subjects to Assess the Relative Bioavailability of a Zanubrutinib 160-mg Tablet Compared to Two BRUKINSA® (Zanubrutinib) 80-mg Capsules and to Evaluate the Effects of Food on the Pharmacokinetics of the Zanubrutinib Tablet	1	RBA & FE	160 mg 320 mg	19 (PK) – 160 mg 24 (PK) – 320 mg
US	BGB-3111-114	A Single-dose, Open-label, Randomized, Replicate Crossover Study in Healthy Adult Subjects to Assess the Bioequivalence of a Zanubrutinib 160-mg Tablet Compared to Two BRUKINSA® (Zanubrutinib) 80-mg Capsules	1	BE	160 mg	57 (PK)

Abbreviations: BE; bioequivalence; BGB-3111, zanubrutinib; FE, food effect; PK, pharmacokinetic(s); RBA, relative bioavailability; US, United States of America

Study BGB-3111-114 is considered the pivotal study for the evaluation of bioequivalence between the new zanubrutinib 160 mg film-coated tablet and the currently approved zanubrutinib 80 mg capsule.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Study BGB-3111-115

The study was a 2-center, Phase 1, single-dose, open-label, 3-period, 6-sequence crossover study to assess the rBA of the 160 mg zanubrutinib tablet at doses of 160 mg and 320 mg compared to equal doses of the Brukinsa (zanubrutinib) capsules and to evaluate the effects of food on the PK of the zanubrutinib 160 mg tablets at single dose of 160 mg and 320 mg.

Zanubrutinib was administered as a single dose on 3 separate occasions (Days 1, 4, and 7) in a randomized design. All subjects received each of the following treatments (in 1 of 6 treatment sequences):

• A single oral dose of 160 mg (1 x 160 mg) or 320 mg (2 x 160 mg) zanubrutinib tablets administered in the fasted state (T-Fasted [Test-Fasted])

• A single oral dose of 160 mg (1 x 160 mg) or 320 mg (2 x 160 mg) zanubrutinib tablets administered in the fed state (T-HF [Test-High-Fat])

• A single oral dose of 160 mg (2 x 80 mg) or 320 mg (4 x 80 mg) zanubrutinib capsules administered in the fasted state (R-Fasted [Reference Fasted])

The study included 19 healthy male and female subjects at the 160 mg dose level and 24 healthy male and female subjects at the 320 mg dose level. All subjects completed the study and were included in the statistical analysis.

The primary PK parameters were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for assessment of bioequivalence between the 160 mg tablet formulation and the currently approved 80 mg capsule formulation and for the evaluation of the food effect on the tablet formulation at dose levels of 160 mg and 320 mg.

Results (Relative Bioavailability):

160 mg Dose

The statistical analysis of primary PK parameters comparing 160 mg zanubrutinib tablet (fasted) and 2 × 80 mg Brukinsa (zanubrutinib) capsules (fasted) is presented in Table 2.

Table 2: Statistical Analysis of Pharmacokinetic Parameters Following Single 160 mg Oral Dose of Zanubrutinib Tablets in the Fasted State and BRUKINSA® (Zanubrutinib) Capsules in the Fasted State (Relative Bioavailability Assessment) for Protocol BGB-3111-115

				Test versus Reference	
Parameter	**Treatment**	**n**	**GLSM**	**Ratio of GLSMs (90% CI)**	**Within-subject CV**
$AUC_{(0-T)}$ (h•ng/mL)	2 × 80 mg zanubrutinib capsules (fasted) [Reference]	19	1330	---	---
	160 mg zanubrutinib tablet (fasted) [Test]	19	1300	0.980 (0.92, 1.04)	10.5

AUC0-∞ (h•ng/mL)	2 × 80 mg zanubrutinib capsules (fasted) [Reference]	19	1350	---	---
	160 mg zanubrutinib tablet (fasted) [Test]	19	1320	0.976 (0.92, 1.04)	10.5
C_{max} (ng/mL)	2 × 80 mg zanubrutinib capsules (fasted) [Reference]	19	239	---	---
	160 mg zanubrutinib tablet (fasted) [Test]	19	259	1.08 (0.95, 1.23)	23.7

320 mg Dose

The statistical analysis of primary PK parameters comparing a single oral dose of 2 × 160 mg zanubrutinib tablets (fasted) and 4 × 80 mg Brukinsa (zanubrutinib) capsules (fasted) is presented in Table 3.

Table 3: Statistical Analysis of Pharmacokinetic Parameters Following Single 320 mg Oral Dose of Zanubrutinib Tablets in the Fasted State and BRUKINSA® (Zanubrutinib) Capsules in the Fasted State (Relative Bioavailability Assessment) for Protocol BGB-3111-115

				Test versus Reference	
Parameter	**Treatment**	**n**	**GLSM**	**Ratio of GLSMs (90% CI)**	**Within-subject CV**
$AUC_{(0-T)}$ (h•ng/mL)	4 × 80 mg zanubrutinib capsules (fasted) [Reference]	24	2320	---	---
	2 × 160 mg zanubrutinib tablets (fasted) [Test]	24	2570	1.11 (1.04, 1.18)	13.2
$AUC_{0-\infty}$ (h•ng/mL)	4 × 80 mg zanubrutinib capsules (fasted) [Reference]	20	2390	---	---
	2 × 160 mg zanubrutinib tablets (fasted) [Test]	20	2630	1.10 (1.02, 1.19)	13.7
C_{max} (ng/mL)	4 × 80 mg zanubrutinib capsules (fasted) [Reference]	24	332	---	---
	2 × 160 mg zanubrutinib tablets (fasted) [Test]	24	401	1.21 (1.07, 1.37)	25.3

At the 160 mg dose level, for the primary parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} the 90% CIs of the GLSM ratios were within the bioequivalence acceptance criteria of 80.00-125.00% indicating that the 160 mg zanubrutinib tablets are bioequivalent to 2×80 mg zanubrutinib capsules administered in the

fasted state. At the 320 mg dose level, for AUC_{0-t} and $AUC_{0-\infty}$ the 90% CIs of the GLSM ratios were within the bioequivalence acceptance criteria of 80.00-125.00%.

The upper limit of 90% CIs of the GLSM ratios for C_{max} was outside of the bioequivalence acceptance range (107-137%).

Results

Food Effect

160 mg Dose Cohort

The statistical analysis of primary PK parameters comparing 160 mg zanubrutinib tablet (fasted) and 160 mg zanubrutinib tablet with a high-fat meal (fed) is presented in Table 4.

Table 4: Statistical Analysis of Pharmacokinetic Parameters Following Single 160 mg Oral dose of Zanubrutinib Tablets Fasted and Fed State (Food Effect Assessment) for Protocol BGB-3111-115

				Test versus Reference	
Parameter	**Treatment**	**n**	**GLSM**	**Ratio of GLSMs (90% CI)**	**Within-subject CV**
$AUC_{(0-T)}$ (h•ng/mL)	160 mg zanubrutinib tablet (fasted) [Reference]	19	1310	---	---
	160 mg zanubrutinib tablet (fed) [Test]	19	1540	1.18 (1.08, 1.29)	15.9
AUC0-∞ (h•ng/mL)	160 mg zanubrutinib tablet (fasted) [Reference]	19	1330	---	---
	160 mg zanubrutinib tablet (fed) [Test]	19	1550	1.17 (1.07, 1.28)	15.7
C_{max} (ng/mL)	160 mg zanubrutinib tablet (fasted) [Reference]	19	259	---	---
	160 mg zanubrutinib tablet (fed) [Test]	19	382	1.47 (1.29, 1.67)	23.1

320 mg Dose

The statistical analysis of primary PK parameters comparing 2 × 160 mg zanubrutinib tablets (fasted) and 2 × 160 mg zanubrutinib tablets with a high-fat meal (fed) is presented in Table 5.

Table 5: Statistical Analysis of Pharmacokinetic Parameters Following Single 320 mg Oral dose of Zanubrutinib Tablets Fasted and Fed State (Food Effect Assessment) for Protocol BGB-3111-115

				Test versus Reference	
Parameter	**Treatment**	**n**	**GLSM**	**Ratio of GLSMs (90% CI)**	**Within-subject CV**
$AUC_{(0-\tau)}$ (h•ng/mL)	2 × 160 mg zanubrutinib tablets (fasted) [Reference]	24	2570	---	---
	2 × 160 mg zanubrutinib tablets (fed) [Test]	24	3000	1.17 (1.09, 1.25)	14.1
AUC0-∞ (h•ng/mL)	2 × 160 mg zanubrutinib tablets (fasted) [Reference]	23	2590	---	---
	2 × 160 mg zanubrutinib tablets (fed) [Test]	23	2960	1.14 (1.06, 1.23)	14.1
C_{max} (ng/mL)	2 × 160 mg zanubrutinib tablets (fasted) [Reference]	24	401	---	---
	2 × 160 mg zanubrutinib tablets (fed) [Test]	24	716	1.79 (1.50, 2.12)	35.9

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration after administration of study drug; CV, coefficient of variation (%); GLSM, geometric least squares mean; LSM, least square mean; n, number of subjects with valid observations.

Following administration of 1x160 mg tablets after a high-fat meal, the upper limits of the 90% Cis of the GLSM ratios of AUC_{0-t} and $AUC_{0-\infty}$ were outside of the boundaries of 0.8 to 1.25 (1.29 and 1.28, respectively) and for C_{max} both lower and upper limits were outside these boundaries (1.29-1.67). AUC0-t and AUC0-∞ were 17% to 18% higher and Cmax was 47% higher in the fed state.

Following administration of 2x160 mg tablets after a high-fat meal, the upper limits of the 90% Cis of the GLSM ratios of AUC_{0-t} and $AUC_{0-\infty}$ were within the boundaries of 0.8 to 1.25, whereas for C_{max} both lower and upper limits were outside these boundaries (1.50-2.12). AUC_{0-t} and $AUC_{0-\infty}$ were 14% to 17% higher and C_{max} was 79% higher in the fed state.

Study BGB-3111-114

The study was a 2-center, Phase 1, single-dose, open-label, randomized, 4-period, 2 sequence replicate crossover study to determine the BE of zanubrutinib tablets 160 mg to Brukinsa capsules 2 x 80 mg under fasting conditions.

A 160 mg film-coated tablet (test product) or two 80 mg capsules (reference product) was administered at day 1, 4, 7 and 10 in each study period.

The study included 58 healthy male and female subjects of which 57 were included in the statistical analysis.

The primary PK parameters for assessment of bioequivalence were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Results

Table 6: Statistical Analysis of Pharmacokinetic Parameters (Bioequivalence Assessment in BGB-3111-114)

				Test versus Reference	
Parameter	**Treatment**	**n**	**GLSM**	**Ratio of GLSMs (90% CI)**	**Within-subject CV**
$AUC_{(0-\tau)}$ (h•ng/mL)	2 × 80 mg zanubrutinib capsules (Reference)	109	1230	---	15.0
	160 mg zanubrutinib tablet (Test)	112	1230	1.00 (0.95, 1.054)	29.9
AUC0-∞ (h•ng/mL)	2 × 80 mg zanubrutinib capsules (Reference)	108	1270	---	11.8
	160 mg zanubrutinib tablet (Test)	111	1250	0.99 (0.94, 1.036)	29.4
C_{max} (ng/mL)	2 × 80 mg zanubrutinib capsules (Reference)	109	213	---	28.5
	160 mg zanubrutinib tablet (Test)	112	259	1.22 (1.14, 1.30)	31.4

Absorption

Food effect

A therapeutic window was not defined for Brukinsa in the original marketing authorisation. However, a relationship between exposure and safety (proabability of grade >= 3 neutropenia) was found showing that Cmax above 500 ng/mL slightly increases the probability of neutropenia, while Cmax values above approximately 700 ng/mL was not included in the analysis.

A 51% increase in Cmax between a Lo-fat (LF) meal (672 ng/mL) and fasted state (444 ng/mL) for the capsule was accepted as without any safety concerns in the initialmarketing authorisation. In this case, the food effect of a High-fat (HF) meal on the exposure after ingesting the capsules presented no significant difference in Cmax and only 14-17% increase in AUC (data not shown).

Median Cmax values of the tablet in 320 mg strength in the HF fed state resulted in 79% increase in concentration as compared to Cmax in the fasted state (716 ng/ml versus 401 ng/mL).

An evaluation of the no-effect boundary (NEB) for increases in C_{max}, from fasted to fed state was performed based on extensive clinical data and exposure-response analysis for safety endpoints. The NEB was defined as 904 ng/mL, representing the median of the top 5% of C_{max} values derived from safety data (i.e. exposure-safety from zanubrutinib in follicular lymphoma) in clinical studies. The extent of mean C_{max} (716 ng/mL) increase with high-fat meal for tablets (~79%) was well below the NEB of 904 ng/mL, supporting lack of clinically meaningful impact with food.

Distribution

Elimination

Dose proportionality and time dependencies

Dose proportionality from 160 to 320 mg applies with regard to AUC_t and AUC_{inf}. However, C_{max} is slightly below dose proportionality in the fasting state (1.54) and higher than dose-proportional after a

HF meal (2.18). Moreover, the relative increase in C_{max} between fasting and HF is higher for the 320 mg dose (1.79) than for the 160 mg dose (1.26). As the HF meal show higher C_{max} than in the fasting state and even more so for the high dose, this could indicate that peak concentrations obtained after a high fat meal of the high dose may reach into a non-linear (supra-proportional) range of the dose-peak concentration relationship.

Therapeutic window

In the original submission, a mean increase in C_{max} of 51% between prandial states during a LF meal and fasting had no clinical relevance.

Pharmacokinetic interaction studies

No new data submitted in the context of this procedure

Pharmacokinetics using human biomaterials

No new data submitted in the context of this procedure

2.6.2.2. Pharmacodynamics

No new data submitted in the context of this procedure.

2.6.3. Discussion on clinical pharmacology

Two clinical/bioequivalence studies were submitted in support of a new tablet formulation for zanubrutinib.

The pharmacokinetics of BRUKINSA tablets and capsules were evaluated in comparative bioavailability (BGB-3111-115) and bioequivalence (BGB-3111-114) studies. Overall, study design, number of subjects and dose levels appear appropriate.

In the bioequivalence study, the geometric least squares mean (GLSM) ratio (90% confidence interval [CI]) of one 160-mg tablet versus two 80-mg zanubrutinib capsules was 0.99 (0.94 to 1.04) for $AUC_{0-\infty}$, meeting the bioequivalence criteria. The GLSM ratio (90% CI) for C_{max} was 1.22 (1.14 to 1.30), the upper limit of 90% CIs of the GLSM ratios for C_{max} was outside of the bioequivalence acceptance range (107-137%) slightly exceeding the 125.0% upper boundary for bioequivalence. However, this is not expected to have a clinically meaningful impact on safety, as supported by established exposure-response safety relationships (as per the original MAA, see EPAR); the higher peak exposure for the tablet formulation is not expected to have a clinically relevant impact on safety based on the established exposure-response relationship.

At the 160 mg dose level, for the primary parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} the 90% CIs of the GLSM ratios were within the bioequivalence acceptance criteria of 80.00-125.00% indicating that the 160 mg zanubrutinib tablets are bioequivalent to 2×80 mg zanubrutinib capsules administered in the fasted state. At the 320 mg dose level, for AUC_{0-t} and $AUC_{0-\infty}$ the 90% CIs of the GLSM ratios were within the bioequivalence acceptance criteria of 80.00-125.00%.

The pilot study BGB-3111-115 supports the bioequivalence conclusion in the fasted state.

The applied formulation, 160 mg zanubrutinib film-coated tables can be considered bioequivalent to the currently registered 80 mg capsules (2x80mg) with regard to the extent of absorption of zanubrutinib after single dose exposure under fasting conditions, whereas the rate of exposure, Cmax was slightly higher for the tablet formulation than the original capsule formulation.

No clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal in healthy subjects and the film-coated tablets can be taken with or without food (see SmPC section 5.2).

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology information submitted is sufficient to support the additional formulation of 160 mg zanubrutinib film-coated tables. The results demonstrated that zanubrutinib exposures (C_{max} and AUC) were comparable across both formulations. Relevant information has been included in the SmPC sections 4.2 and 5.2.

2.6.5. Clinical efficacy

No new efficacy data were submitted with this application, which is considered acceptable.

2.6.6. Clinical safety

2.6.6.1. Safety Overview

Pharmacokinetic study (BGB-3111-115)

A total of 6 TEAEs were reported by 6 (14.0%) of 43 subjects. These TEAEs were: dermatitis contact (2), constipation (2), ear pain (1) and headache (1). All TEAEs were mild in intensity, and 3 TEAEs were considered by the investigator to be treatment-related, all of which were reported in the 320 mg dose cohort. There were no deaths or SAEs during the study and no subjects were discontinued due to AEs.

Pharmacokinetic studies (BGB-3111-114)

A total of 32 TEAEs were reported by 18 (31.0%) of 58 subjects. 14 (24.1%) AEs were reported after administration of the test product (tablet) and 6 (10.3%) after administration of the reference product (capsule). Most TEAEs were mild with the exception of one moderate event of headache, two moderate events of neutropenia, and one severe event of neutropenia. Two subjects had TEAEs of SARS-CoV-2 test positive, which led to discontinuation of study treatment.

The most commonly reported TEAEs by PT were headache (4 [6.9%] subjects), neutropenia (4 [6.9%] subjects), platelet count decreased (4 [6.9%] subjects), SARS-CoV-2 test positive (2 [3.4%] subjects), and nausea (2 [3.4%] subjects); all other TEAEs were reported once only.

Several subjects developed transient haematological AEs of platelet count decreased and neutropenia, which are known risks with zanubrutinib. All were asymptomatic laboratory values. Notably, 5 of 6 subjects who developed decreased neutrophil count were African, American or Black. This is a population known to have lower neutrophil levels in healthy individuals with no increased risk of infection.

There were no deaths or serious AEs during the study, and no subjects were discontinued due to AEs that were considered related to study treatments.

2.6.7. Discussion on Clinical Safety

Overall, no unexpected safety issues or significant safety findings were identified during the study and the safety outcome were consistent with the existing safety profile of zanubrutinib.

2.6.8. Conclusions on the clinical safety

The clinical safety findings in the submitted clinical trials were consistent with the existing safety profile of zanubrutinib.

2.7. Risk Management Plan

2.7.1. Safety concerns

No new safety concerns have been identified from the submitted data supporting the sought variation. Therefore, the list of the safety specifications remains unchanged.

2.7.2. Pharmacovigilance plan

No amendments in the pharmacovigilance plan are proposed.

2.7.3. Risk minimisation measures

No amendments in the risk minimisation measures are proposed.

2.7.4. Conclusion

The MAH submitted the updated RMP version 5.1, dated 30 April 2024 that included addition of film-coated tablets. The main proposed RMP changes were the following: Addition of film-coated tablet

The CHMP considered that the risk management plan version 5.1. is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the PI for the additional tablet formulation is in line with the currently approved PI for the capsule formulation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Brukinsa is currently available as hard capsules for the following indications:

- Brukinsa as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.
- Brukinsa as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.
- Brukinsa as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL).
- Brukinsa in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

This application concerns the introduction of a new pharmaceutical form and additional strength (160 mg film-coated tablets) encompassing all of the above indications.

3.1.2. Available therapies and unmet medical need

As per the original MAA and subsequent extensions of the indication.

3.1.3. Main clinical studies

Two bioavailability/bioequivalence studies in healthy volunteers, were performed to support the registration of the zanubrutinib IR tablet dosage form.

Study BGB-3111-115 was a 2-center, Phase 1, open-label, 3-period, 6-sequence crossover study to assess the rBA of the 160 mg zanubrutinib tablet at doses of 160 mg and 320 mg compared to equal doses of the BRUKINSA® (zanubrutinib) capsules in the fasted state and to evaluate the effects of food on the PK of the zanubrutinib 160 mg tablets at single dose of 160 mg and 320 mg as primary objectives. The secondary objective was to assess the safety and tolerability of zanubrutinib as a tablet administered in a fasted and fed state.

Study BGB-3111-114 was the pivotal bioequivalence study. It was a 2-center, Phase 1, single-dose, open-label, randomized, 4-period, 2-sequence replicate crossover study to determine the BE of a 160 mg zanubrutinib tablet to 2 × 80 mg BRUKINSA (zanubrutinib) capsules under fasting conditions as primary objective and to assess the safety and tolerability of zanubrutinib as a tablet given in a fasted state as a secondary objective.

3.2. Favourable effects

Since the new tablet formulation is bioequivalent to the capsule formulation, the efficacy is considered demonstrated as per the presently approved capsule formulation.

Additionally the 160 mg zanubrutinib tablet dosage form allows for improved ease of swallowing due to reduced unit size (16 mm tablets versus 22 mm capsules) and overall reduced unit burden (2x160 mg tablets daily versus 4x80 mg capsules daily). The functional scoring further enables the tablet to be split to accommodate a reduced dose of 80 mg of zanubrutinib.

3.3. Uncertainties and limitations about favourable effects

No uncertainties are identified.

3.4. Unfavourable effects

No new safety issues have emerged in the bioequivalence studies.

3.5. Uncertainties and limitations about unfavourable effects

No uncertainties identified.

3.6. Effects Table

N/A

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Since the new tablet formulation is equivalent to the capsule formulation, the efficacy is considered similar to the presently approved capsule formulation.

No new safety issues have emerged in the bioequivalence studies.

Patient convenience is assumed given the potential benefit of easiness to administer and possibility to split the tablet to accommodate 80 mg dose.

3.7.2. Balance of benefits and risks

Given the bioequivalence to the existing formulation, potential additional benefit of easiness to administer, and the identical safety profile to the capsule formulation, the benefit -risk balance remains positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Brukinsa is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Brukinsa is not similar to Gazyvaro, Lunsumio, Kymriah and Yescarta within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Brukinsa 160 mg tablet is favourable in the following indications:

- Brukinsa as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.
- Brukinsa as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.
- Brukinsa as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL).
- Brukinsa in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

The CHMP therefore recommends the extension of the marketing authorisation for Brukinsa subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and

any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES):	
In order to further confirm the efficacy and safety of zanubrutinib in patients with R/R MZL, the MAH will submit the final study report of the post-authorisation efficacy study (PAES): Study BGB-3111-308: a global, multicenter, phase 3, open-label, randomized study of zanubrutinib plus rituximab versus lenalidomide plus rituximab in patients with relapsed/refractory marginal zone lymphoma (NCT05100862).	Q4 2028
The MAH will submit updated efficacy (ORR, DoR, PFS) and safety data from the ROSEWOOD study (BGB-3111-212) as a post-authorisation commitment	Q2 2025

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.