Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende zanubrutinib til behandling af Waldenstrøms makroglobulinæmi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. zanubrutinib
2. Forhandlingsnotat fra Amgros vedr. zanubrutinib
3. Ansøgers endelige ansøgning vedr. zanubrutinib

Medicinrådet
Dampfærgevej 21-23, 3. sal
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Basel, March 25, 2022

Medicinrådets udkast til rapporten for zanubrutinib til Waldenströms macroglobulinæmi

Document number 136172

Dear Medicinrådet,

On behalf of BeiGene, I would like to thank you for the fast assessment of our drug Brukinsa® in the indication of Waldenstrom's macroglobulincemia.

Your assessment is well received and appreciated by us and we have no objections regarding your evaluation.

Please allow me to just comment on your uncertainties with regards to the safety profile of Brukinsa® compared to Ibrutinib.

Like in most RCTs, the study population is intended to optimally reflect the overall patient population in most countries. However, there can be of course country-specific differences in real-life.

Nevertheless, the baseline characteristics in the ASPEN study are aligned between the two arms and results demonstrated that the treatment with zanubrutinib was associated with toxicity and tolerability advantages, particularly notable for cardiovascular complications which is of special importance for this vulnerable patient population due to their age and co-morbidities.

Overall, the comparisons of the incidence and type of AEs, including grade 3 or higher, serious, treatment-related, and AEs leading to treatment discontinuation, suggest that the safety profile for zanubrutinib among patients with WM is trending towards less toxicity compared to ibrutinib. AEs leading to death occurred in 4 (4.1%) patients in the ibrutinib arm and 1 (1.0%) patient in the zanubrutinib arm. Treatment discontinuation due to AEs was reported in 9.2% of the patients from the ibrutinib arm and 4.0% from the zanubrutinib arm[1].

We believe that with our demonstrated superiority of zanubrutinib compared to ibrutinib due to being at least as effective with a more favourable safety profile, we can be a cost-saving treatment and therefore valuable treament option for Waldenström patients in Denmark.

[1] Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: The ASPEN study. Blood. 2020;136(18):2038–50.

We are looking forward to your final decision.

Yours sincerely,

Beigene Switzerland GmbH

Cathrin Schäfer
Sr. Director Market Access Sub-Region Europe

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28.03.2022
MGK/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	20.04.2022
Leverandør	BeiGene
Lægemiddel	Brukinsa (zanubrutinib)
Ansøgt indikation	Voksne patienter med Waldenstrøms makroglobulinæmi, som har modtaget mindst én tidligere behandling, eller til førstelinjebehandling af patienter, som er uegnede til kemo-immunterapi,

Forhandlingsresultat

Amgros har opnået følgende pris på Brukinsa (zanubrutinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Brukinsa (zanubrutinib)	80mg / 320mg dagligt	120 stk. kapsler	43.116,68	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Amgros har forhandlet en aftale med leverandøren. Leverandøren har mulighed for at sætte prisen yderligere ned i hele aftaleperioden.

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Brukinsa (zanubrutinib)	80mg/320mg dagligt	120 stk.	[redacted]	12*	[redacted]
Imbruvica (ibrutinib)	420mg/420mg dagligt	28 stk.	[redacted]	13	[redacted]

*12,2

Status fra andre lande

Brukinsa (zanubrutinib) er på nuværende tidspunkt under vurdering i [redacted]

Konklusion

Det er Amgros vurdering, at der er opnået den bedst mulige pris på Brukinsa (zanubrutinib), som det er muligt at opnå på nuværende tidspunkt.

Application for the assessment of zanubrutinib for Waldenström's Macroglobulinemia

Instructions for companies

This is the template for submission of evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new pharmaceutical or new indication for an existing pharmaceutical. The template is not exhaustive; companies must adhere to the current version of the guidelines alongside using this template when preparing their submission.

[redacted]

In addition to this template, the company must submit a health economic model in Excel, with full access to the programming code. All the information requested in this template and described in the guidelines must be presented in the application. The model can be accompanied by a technical document. The information in the technical document will, however, not be considered as part of the application. Hence, all relevant information for the application must also be described in the application (including appendices) itself. This can be done by copying the relevant information from the technical document into the application, and by presenting it as described in this template and in the guidelines. Companies are encouraged to provide the European Public Assessment Report (EPAR) including the scientific discussion as an appendix to the submission (draft versions will be accepted).
When making an evidence submission, companies must ensure that all confidential information is highlighted in yellow and provide the expected date of publication. If confidential appendices are provided, these must be watermarked as "confidential".

Version 1.0

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1. Basic information

Contact information	
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Name	**Sara Vinther (Zealth)**
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Overview of the pharmaceutical	
Proprietary name	BRUKINSA (1)
Generic name	Zanubrutinib (1)
Marketing authorization holder in Denmark	BeiGene Ireland Ltd. 10 Earlsfort Terrace, Dublin, D02 T380, Ireland D02 T380
ATC code	L01EL03 (1)
Pharmacotherapeutic group	Antineoplastic agents, Bruton's tyrosine kinase inhibitors (1)
Active substance(s)	Zanubrutinib (1)
Pharmaceutical form(s)	Hard capsule. White to off-white opaque hard capsule of 22 mm in length, marked with "ZANU 80" in black ink. (1)
Mechanism of action	Zanubrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. (1)

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Overview of the pharmaceutical	
Dosage regimen	The recommended dose of zanubrutinib is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity. Each hard capsule contains 80 mg of zanubrutinib. (1)
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	BRUKINSA as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia who have received at least one prior therapy, or in 1st line treatment for patients unsuitable for chemo-immunotherapy. (1)
Other approved therapeutic indications	No (1)
Will dispensing be restricted to hospitals?	No (1)
Combination therapy and/or co-medication	No (1)
Packaging – types, sizes/number of units, and concentrations	Hard capsules provided in a plastic bottle containing 120 capsules. Each capsule contains 80 mg of zanubrutinib (1)
Orphan drug designation	No

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2. Abbrevations

AE	Adverse event
AEIs	Adverse events of interest
AESI	Adverse event of special interest
BCR	B-cell antigen receptor
BTK	Bruton's tyrosine kinase
DLBCL	Diffuse large B-cell lymphoma
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
CrCl	Creatine clearance
DMC	Danish Medicines Council
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
IgM	Immunoglobulin M
ILD	Interstitial Lung Disease
IPSS	International Prognostic Scoring System
IRC	Independent Review Committee
ITT	Intention-to-treat
IWWM	International Workshop on Waldenström Macroglobulinemia
K-M	Kaplan-Meier
LVEF	Left ventricular ejection fraction
LPL	Lymphoplasmacytic lymphoma
MCL	Mantle cell lymphoma
MGUS	Monoclonal gammopathy of undetermined significance
MRR	Major response rate
MUGA	Multigated Acquistion Scan
MYD88^{WT}	MYD88 wild-type
NCI-CTCAE	the National Cancer Institute Common Toxicity Criteria
NE	Not estimable
N/A	Not available
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PN	Peripheral neuropathy
PR	Partial response
QoL	Quality of life
SPD	Sum of the product of diameter
TEAE	Treatment-emergent adverse event
TN	Treatment naïve
TRAE	Treatment-related adverse event
TTNT	Time to next treatment
VGPR	Very good partial response
WHIM	Warts Hypogammaglobulinemia Immunodeficiency Myelokathexis
WM	Waldenström's macroglobulinemia

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3. Tables and Figures

Tables:

Tables in appendices are not included in the list above.

Figures:

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4. Summary

This submission to the Danish Medicines Council (DMC) is focusing on Waldenström's macroglobulinemia (WM), which is a rare, malignant, slow-growing (indolent) lymphoproliferative B-cell disorder characterized by infiltration of lymphoplasmacytic lymphoma (LPL) into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy (2,3). In Denmark, the prevalence of WM is estimated to be approximately 1000 patients and the incidence is approximately 160 patients per year and higher among men. The median age of Danish patients with WM is 70 years. (4–7)

Most Waldenström's macroglobulinemia patients show activating (gain-of-function) mutations in the MYD88 gene in their tumor cells, in particular MYD88^{L265P}, which can be noted in more than 90% of patients. Other MYD88 activating mutations in WM patients have been described, albeit at low frequency (1-2%). These mutations result in constitutive activation of downstream pro-survival and proliferative signaling through Bruton's tyrosine kinase (BTK) and transcription factor NF-κB. 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. (1,8–10)

The intervention that is going to be assessed by the DMC is zanubrutinib which will be indicated for adult patients who have received at least one prior therapy, or those in 1st line treatment unsuitable for chemoimmunotherapy (1). Zanubrutinib is a next-generation inhibitor of BTK. BTK is a signalling molecule of the B-cell antigen receptor and cytokine receptor pathways. In B cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Zanubrutinib forms a covalent bond with a cysteine residue in the BTK's active site, leading to inhibition of BTK activity. (1)

In Denmark, it is expected that zanubrutinib can be a valuable alternative to treatment with ibrutinib, a first-generation BTK inhibitor, which is currently implemented in the national clinical guideline for patients with WM and indicated for the same patient population as zanubrutinib. Ibrutinib is currently used as 1st line therapy for treating patients who are unfit for chemotherapy and for patients experiencing relapse where the time to next treatment (TTNT) is <1 year. (4)
In this submission, it is expected that eligible patients for treatment with zanubrutinib are patients who are currently treated with ibrutinib according to the clinical guidelines, and based on clinical expert input it is assumed to be approximately 207 patients per year in Denmark.

Zanubrutinib has been compared directly to ibrutinib in the pivotal phase 3 trial (ASPEN study) and this is the first comparative phase 3 study exclusively recruiting WM. The study is a randomised, open-label, multicentre study to compare the efficacy and safety of zanubrutinib and ibrutinib in patients with WM who required therapy according to the consensus panel criteria from the Seventh International Workshop on Waldenström Macroglobulinemia (IWWM). (11)
In the study, WM patients with mutation MYD88^{L265P} (Cohort 1) were randomized 1:1 to receive treatment with ibrutinib or zanubrutinib. In total, 201 patients were randomized whereof 101 patients received zanubrutinib and 98 patients received ibrutinib. The primary endpoint for in the study was the proportion of patients achieving a complete response (CR) or very good partial response (VGPR) assessed by an Independent Review Committee (IRC) assessment based on the Sixth IWWM consensus criteria. Secondary endpoints were major response rate (MRR), duration of response (DOR), progression-free survival (PFS), anti-lymphoma effect, and resolution of treatment-precipitating symptoms. Exploratory endpoints were overall survival (OS) and quality of life (QoL). (11,12)
Safety was demonstrated by adverse event (AE) assessments including type, incidence, outcome, and severity. Severity of AE was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 4.03. (11)

The trial demonstrated zanubrutinib to be at least equally effective treatment choice to ibrutinib, trending towards higher activity. Zanubrutinib demonstrated superiority compared to ibrutinib in relation to response and tendency for

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improved PFS and OS rates. Findings were comparable for anti-lymphoma effect and resolution of treatment-precipitating symptoms, and patients who achieved VGPR trended toward a greater QoL improvement. (11)

Treatment with zanubrutinib was further associated with toxicity and tolerability advantages, particularly notable for cardiovascular complications. Overall, the comparisons of the incidence and type of AEs, including grade 3 or higher, serious, treatment-related, and AEs leading to treatment discontinuation, suggest that the safety profile for zanubrutinib among patients with WM is trending towards less toxicity compared to ibrutinib. AEs leading to death occurred in 4 (4.1%) patients in the ibrutinib arm and 1 (1.0%) patient in the zanubrutinib arm. Treatment discontinuation due to AEs was reported in 9.2% of the patients from the ibrutinib arm and 4.0% from the zanubrutinib arm. As the patient group is vulnerable due to age and co-morbidities, the demonstration of less discontinuation due to AEs favors the zanubrutinib treatment arm. (11)

Given that zanubrutinib demonstrated tendency to be at least as effective as ibrutinib with a more favourable safety profile and favourable drug interaction properties, it has been agreed with DMC on the 21st of September that the submission will include a cost-minimization analysis as the economic part.
The patient journey and associated relevant costs have been validated by the clinical expert, and the relevant costs that should be reflected in the cost-minimization analysis are those related to drug, AEs, and patient-related costs due to AEs. [redacted], and AEs are based on those reported as grade 3 or above where the clinical expect elaborated if outpatient visits or hospital admissions were required. Therefore, costs excluded in the economic analysis are those related to GP and other health care specialists, diagnostics and testing, and administration and monitoring.

In conclusion, it is believed that the submission demonstrate superiority of zanubrutinib compared to ibrutinib due to being at least as effective with a more favourable safety profile and being a cost-saving treatment in Denmark. The budget impact analysis indicates that recommendation of zanubrutinib will result in a negative budget impact from year 1 with ≥ 5 patients being expected to receive zanubrutinib, thus favoring zanubrutinib. The negative budget impact will gradually continue the subsequent years as more patients will receive zanubrutinib.

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5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

5.1.1 Pathophysiology and clinical presentation

5.1.1.1 Pathophysiology

Waldenström's Macroglobulinaemia (WM) is a rare, malignant, slow growing (indolent) lympho-proliferative B-cell disorder characterized by infiltration of lymphoplasmacytic lymphoma (LPL) into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy (11,13).

The etiology of WM is still not completely understood. LPL is a neoplasm of small B-lymphocytes, plasmacytoid lymphocytes, and plasma cells. Tumor cells in WM are thought to originate from a memory-like B cell that has undergone somatic hypermutation, possibly under the influence of antigen stimulation, but not isotype switching. It thus continues to produce IgM. These WM cells differentiate into lymphoplasmacytic cells and plasma cells in the bone marrow. (14)

About 20% of patients have at least one first-degree relative with WM or other B-cell disorder (15,16), however, most cases of WM appear sporadic. Studies have found an elevated risk of developing WM in patients with personal or familial history of autoimmune disease, including Sjögren's syndrome, systemic lupus erythematosus, autoimmune hemolytic anemia, Guillain-Barré syndrome, polymyalgia rheumatica, and giant cell arteritis as well as prior history of infectious disease (17,18).

WM is often preceded by a pre-malignant condition called monoclonal gammopathy of undetermined significance (MGUS) characterized by the presence of monoclonal IgM but without LPL infiltration into the bone marrow. Patients diagnosed with MGUS have a 46-fold increased risk of progression to WM than patients not diagnosed with MGUS. (8) About 10% of patients with MGUS develop WM in a time frame of five years (19).

5.1.1.2 Genetic landscape

Most WM patients show activating (gain-of-function) mutations in the MYD88 gene in their tumor cells, in particular $MYD88^{L265P}$, which can be noted in more than 90% of patients. Other MYD88 activating mutations in WM patients have been described, albeit at low frequency (1-2%). These mutations result in constitutive activation of downstream pro-survival and proliferative signaling through Bruton's tyrosine kinase (BTK) and transcription factor NF-κB. (8–10)

Mutated MYD88 can also be detected in 50-80% of patients with MGUS, suggesting an early oncogenic role for MYD88 in the pathogenesis of WM (20). Less than 5% of WM patients appear to not harbor any activating MYD88 mutations and are classified as MYD88 wild-type ($MYD88^{WT}$). (8,9)

Somatic mutations in the C-terminal domain of chemokine receptor CXCR4 are present in 30 to 40% of patients with WM. Most observed mutations are similar to those seen in patients with a rare germline mutation that results in a syndrome referred to as the Warts Hypogammaglobulinemia Immunodeficiency Myelokathexis (WHIM) syndrome. (8,9,21) CXCR4 mutations promote WM cell survival through stimulation of proliferation, migration, and homing of WM cells to bone marrow niches (8). Patients with CXCR4 WHIM-like mutations may have a more aggressive disease as defined by higher IgM levels, higher risk of hyperviscosity syndrome, and higher bone marrow involvement (8).

5.1.1.3 Clinical presentation

Early stages of WM are often indolent and asymptomatic and only progress slowly to symptomatic disease and therefore may remain undetected for several years. About 75% of patients are symptomatic at the time of diagnosis and indicated

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for treatment. (22,23) About 70% of patients with asymptomatic WM at diagnosis ultimately develop symptomatic WM over a time frame of five to ten years (19).

WM presents with a variety of symptoms, which are mostly related to the tumor's main characteristics, infiltration of the bone marrow by LPL, and elevated levels of serum IgM paraprotein (3,8). Common symptoms presenting at diagnosis are constitutional B symptoms such as fever, fatigue, night sweat, and weight loss. More than half of WM patients present with these symptoms at diagnosis. (8,24)

Impairment of hematopoiesis due to tumor infiltration into the BM, in combination with iron deficiency due to overproduction of hepcidin by lymphoplasmacytic cells, commonly results in anemia (3,21). Anemia represents the most common reason for WM patients to require treatment, being present in 72% of patients at the start of treatment in clinical practice (24). More extensive bone marrow tumor infiltration can cause other cytopenias (i.e., thrombocytopenia, leukopenia) (3,21), which can aggravate the symptomatic burden of WM (21).

Increased IgM production can result in progressive symmetrical sensorimotor peripheral neuropathy (PN). It is estimated that PN is present in about 20% of patients with WM at diagnosis (25–29). Other IgM-related problems include coagulation disorders, cryoglobulinemia, Raynaud's syndrome, vasculitis, and cold agglutinin hemolytic anemia. Approximately 3% of patients with WM have amyloidosis (commonly light-chain type) due to paraprotein deposits that result in organ dysfunction: bullae or papules in the skin; bleeding, diarrhea, and malabsorption in the GI tract; proteinuria and renal failure when involving the kidney (3,21,30).

The most common IgM-related complication is hyperviscosity syndrome, which affects up to 35% of patients (31). Hyperviscosity syndrome manifests by the skin and mucosal bleeding and neurological symptoms (e.g., headache, diplopia, vertigo, ataxia, tinnitus, confusion, and epistaxis) and requires immediate treatment with plasmapheresis (30,31). Currently, how good or how long a response will be for an individual patient cannot be accurately predicted. The response is assessed using the quantitative IgM level through complete response (CR)/very good partial response (VGPR), as the IgM level correlates well with the overall disease activity (32,33).

About 20% of patients show extramedullary infiltration at the time of diagnosis, most commonly in lymphatic tissues. Upon disease relapse after frontline treatment, lymphadenopathy or hepatosplenomegaly are more common, affecting about 50% of patients. Other extramedullary sites of involvement are rare (4.4% of patients) and can involve lungs, soft tissue, central nervous system, kidneys, and bones. (3,21) However, with disease progression, extramedullary disease that poses the threat of end-organ damage becomes more and more common. (21)

Involvement of the central nervous system (Bing-Neel syndrome) is a rare, severe complication of WM that manifests with heterogenous neurological symptoms affecting balance, motor control, vision, and cognitive abilities (34,35). Bing-Neel Syndrome is usually presented during relapsed disease but may be present at diagnosis (36).

5.1.1.4 Patient population

The relevant patient population for this application is the population included in the regulatory indication of zanubrutinib, i.e. adult patients with WM who have received at least one prior therapy, or treatment for patients unsuitable for chemoimmunotherapy. In Denmark, the median age is 70 years with the incidence being higher among men (4,5).

5.1.1.5 Prognosis with current treatment

WM generally has a chronic indolent course and remains incurable to this date. During the course of disease, patients experience multiple relapses of symptomatic, more rapidly progressing cancer requiring several lines of therapy before

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death. Asymptomatic WM patients have an overall survival (OS) similar to that of the general population, whereas symptomatic disease is associated with WM-related mortality. (37) About 25% of patients are asymptomatic at the time of diagnosis and do not require treatment (22,23). Patients with symptomatic WM require treatment to resolve symptoms and prevent organ damage.

The median OS of patients in Europe has been estimated to be between five and ten years (38), but may be a bit longer today, and the majority of patients die from WM-related causes, such as disease progression, transformation to high-grade lymphoma, or infections (39).

Gene mutations occurring in WM patients have been shown to affect clinical disease presentation and to influence patients' prognosis. The influence of mutations in MYD88, CXCR4, and TP53 genes is currently best understood. The mutational status of WM patients is emerging as a prognostic factor (20)

WM prognosis is assessed using the International Prognostic Scoring System (IPSS) score. According to IPSS for WM, patients are stratified into low, intermediate, and high-risk groups with respective 5-year survival rates of 87%, 68%, and 36%, based upon age, serum monoclonal protein concentration, β2-microglobulin level, hemoglobin, and platelet count (40). Based on the clinical expert's input, the IPSS score is only used for clarification of differential diagnosis in Denmark and is not used for indication of treatment choice. The prognostic index can be found in Table 1. (40)

Table 1. Prognostic stratification of WM patients (40).

Risk groups[a]	Low	Intermediate	High
Defined criteria for diagnosis	0 or 1 adverse characteristics and advanced age	2 adverse characteristics or only advanced age	> 2 adverse characteristics
5-year OS (%)	87	68	36

[a]Risk groups are based on advanced age>65 years and the following adverse characteristics; hemoglobin ≤11.5 g/dL, platelet count ≤100x10^9/L, β2-mikroglobulin > 3 mg/L, and serum monoclonal protein concentration > 7.0 g/dL.

5.1.1.6 Incidence, prevalence, and eligible candidates for treatment

The Danish Cancer Society reports that the expected incidence of WM in Denmark is approximately 25 patients per year (6). However, The National clinical guideline for LPL/WM reports that the incidence is approximately 170-180 patients per year in Denmark based on registry-based data from the Annual report of Malignant lymphomas and Chronic Lymphocytic Leukemia (CLL) from 2019 (4,5). Based on inputs from the clinical expert, the latter is representative for Danish patients and it can be expected that approximately 90% of the LPL-registered patients are WM patients. Moreover, the clinical expert estimated the prevalence of WM to be 1000 patients in Denmark, as 200 WM patients is registered in Region Zealand, which roughly estimated accounts for one fifth of the Regions in Denmark. The incidence and prevalence of WM patients can be found in Table 2.

Table 2. Incidence and prevalence of WM in the past 5 years.*

Year	2015	2016	2017	2018	2019	Reference(s)
Incidence, total LPL patients	182	180	191	176	176	(5,41)
Incidence, WM patients (90%)	164	162	172	158	158	*Clinical expert*
Estimated WM prevalence in Denmark	1000	1000	1000	1000	1000	*Clinical expert*

* The newest incidence data from the annual report is available until year 2019. But it was confirmed by the clinical expert, that the patient population is stable and therefore the numbers are expected to reflect the current patient population.

The proportion of eligible patients for treatment with zanubrutinib is estimated by the clinical expert to be 20%. However, the number of eligible patients from the incidence population is adjusted to the fact that newly diagnosed patients will only involve treatment-naïve patients, as relapse will first occur after approximately five years from first treatment. This has been validated by the clinical expert. Therefore, the 20% of eligible patients from the incidence population are adjusted to the distribution between treatment-naïve and relapse patients from the ASPEN study. The calculations can be found in Table 3.

Table 3 Estimated number of patients in Denmark who are eligible for treatment with a BTK inhibitor.

Year	2022	2023	2024	2025	2026	Reference(s)
20% of incidence WM population	33	32	34	32	32	*Clinical expert*
Adjustment to treatment-naïve patients	7	7	7	7	7	(11)
20% of prevalence WM population	200	200	200	200	200	*Clinical expert*
Total number of patients in Denmark who are candidates for treatment with zanubrutinib	207	207	207	207	207	-

5.1.2 Patient populations relevant for this application

The relevant patient population for this application is adult patients with WM who received at least one prior therapy or treatment-naïve patients unfit for chemoimmunotherapy. The estimated number of eligible candidates indicated for treatment with a BTK inhibitor is presented in Table 3.

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

The Danish Medicines Council (DMC) has not conducted a Danish national treatment guideline describing the treatment of WM. However, the current standard treatment of WM in Denmark is described in the newly developed and accepted clinical guideline from 2021 made by "Danske Multidisciplinære Cancer Grupper" and "Regionernes Kliniske Kvalitetsudviklingsprogram"(4).

According to the clinical guideline for WM, the current treatment options are divided into patients being biologically fit, patients being biologically unfit, or patients experiencing relapse or transformation. An overview of the treatment options can be found in Figure 1 and has been adapted from the clinical guidelines and clinical expert inputs. The clinical expert mentioned that the disease area does not include comprehensive evidence and large phase 3 trials, why clinicians have several treatments to choose. Thus, treatment is still very individual and treatment algorithm depends on the individual patient's need. However, ibrutinib is always considered when patients are treatment-naïve or in case of relapse as indicated in this treatment flowchart.

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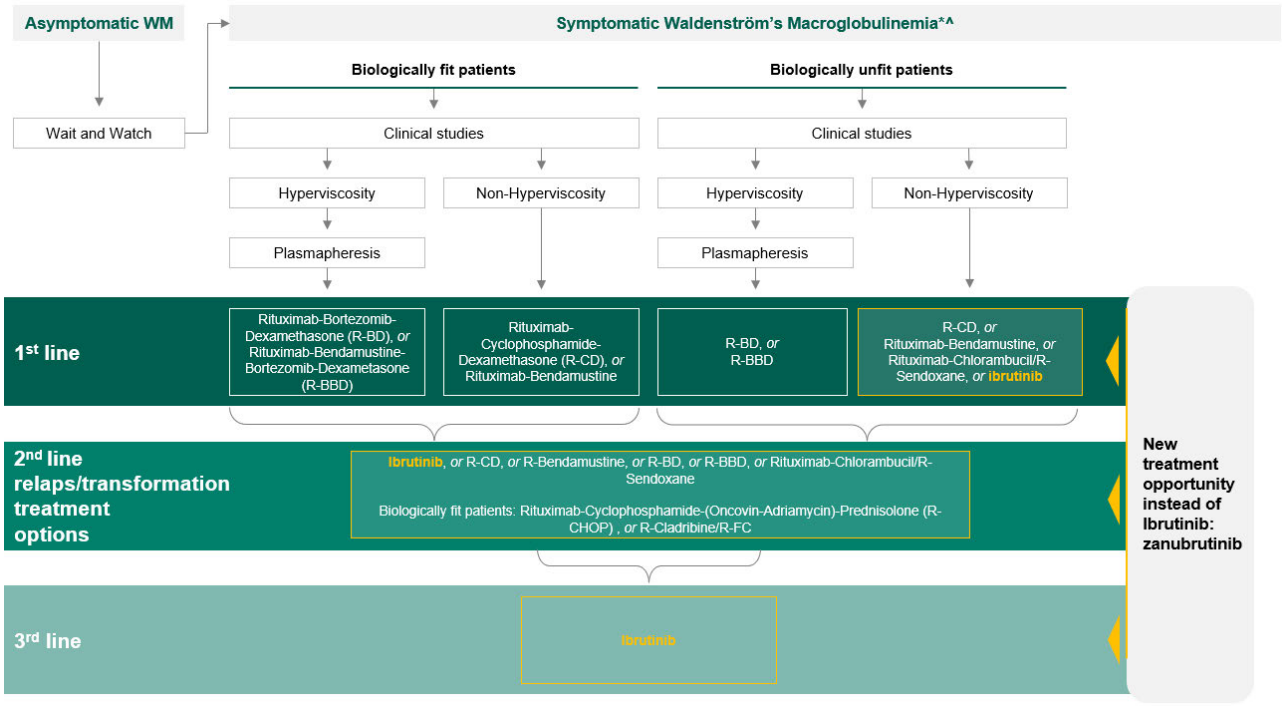

Figure 1. Overview of WM treatment (4). (The yellow marked information is were ibrutinib is considered.)
*Patients with cold agglutinin disease and MAG-neuropathy can be treated with Rituximab monotherapy.
^Rituximab should be excluded from the initial treatment if the patient has a high M-component due to the risk of developing IgM flare

Zanubrutinib will be indicated for the treatment of adult patients with WM who received at least one prior therapy or treatment-naïve patients unfit for chemoimmunotherapy which is the same indication as ibrutinib. Because of this and the similarity in mechanisms of action, ibrutinib is the most relevant current treatment to highlight (1,11).
Ibrutinib is currently used as 1st line therapy for treating treatment-naïve patients who are unfit for chemoimmunotherapy. In patients experiencing relapse, ibrutinib is currently used as 2nd or 3rd line treatment (4)

5.2.2 Choice of comparator

The main alternative treatment expected to be replaced by zanubrutinib is ibrutinib. Ibrutinib is a first-generation BTK inhibitor and hence has a similar main mechanism of action as zanubrutinib. Zanubrutinib has demonstrated a higher bioavailability, less off-target kinase inhibition as well as favorable drug interaction properties compared to ibrutinib (42,43). The choice of ibrutinib as a comparator for zanubrutinib in Denmark has been validated by the clinical expert.
Ibrutinib for WM has not been assessed by the Danish Medicines Council or by RADS; however, ibrutinib was approved for standard use for patients with WM who have received one prior treatment or who are not fit for R-chemotherapy, by KRIS on the 1st of March 2016(44). In the KRIS application, it is specified that ibrutinib for WM can also be used for patients that up until that point did not have any other treatment options; mainly patients with primary or secondary refractory disease, and elder/frail patients who cannot tolerate the side effects of R-chemotherapy. Furthermore, it is stated that treatment with ibrutinib will not include any additional monitoring or tests for patients compared with former usual practice(45). The clinical expert confirmed that there is no difference in monitoring and tests for the two treatments. Moreover, ibrutinib is administered orally as a tablet which can be done at home, whereas R-chemotherapy (R-CD and R-Benda) is administered intravenously or subcutaneously at the hospital, which has been confirmed by a clinician(45). This indicates that ibrutinib potentially requires less resources due to the oral administration. The cost of the drugs is the most relevant factor if cost-effectiveness is considered.

At the time of approval, ibrutinib had in a single arm study shown a 2-year PFS rate of 69% and a OS of 96%, indicating that the treatment is clinically effective(45). In a long-term follow-up study, the median 5-year PFS rate was not reached and the 5-year overall survival was 87%(46). Since ibrutinib made it possible to treat patients who previously could not be treated (mainly patients with primary or secondary disease, and elder/frail patient who cannot tolerate R-chemotherapy), it is considered reasonable to assume that the treatment would be more effective than no treatment.
Ibrutinib is reimbursed in WM in several countries including Austria, Belgium, Netherlands, England, Finland, France, Germany, Italy, Ireland, Northern Ireland, Spain, Switzerland, and Wales, indicating that the drug is deemed cost-effective in these countries. It would be reasonable to assume that ibrutinib could be assessed as clinically effective and cost-effective in Denmark.
Moreover, ibrutinib has been included in the National Treatment Guideline for WM published in 2021, strengthening the argument that ibrutinib is used in the Danish Regions, where the effect and cost is regarded as acceptable(4).

To summarize, ibrutinib requires no additional monitoring or test compared with former usual practice, allows new patients to receive treatment and demonstrated clinical effectiveness. The treatment of ibrutinib was approved by KRIS and has been used in the clinic since 2016. This indicates that the Danish Regions and the clinical departments deem the use and cost of ibrutinib acceptable. Thus, zanubrutinib should be compared with Ibrutinib, as this is the comparator used in a Danish clinical setting and which costs have been evaluated and deemed acceptable. Even if a theoretical comparison between zanubrutinib and placebo were to be made, this would not reflect the Danish clinical setting. Ibrutinib would still be used for patients with WM who have received one prior treatment or who are not fit for R-chemotherapy, and it is therefore only relevant to make a comparison between zanubrutinib and ibrutinib.
A placebo-controlled study has not been performed due to ethical reasons. A supplemental analysis comparing the comparator with placebo, as described in section 2.4.2 in the DMC's method guide (version 1.2) (47), is omitted in this submission.

5.2.3 Description of the comparator

A description of the comparator, ibrutinib, is provided in Table 4.

Table 4. Description of the comparator, ibrutinib.

Comparator: ibrutinib	
Generic name and ATC-code	Ibrutinib (L01EL01) (48)
Mode of action	Ibrutinib is a potent, small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including classical MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and CLL. BTK's pivotal role in signaling through the B-cell surface receptors results in the activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Preclinical studies have shown that ibrutinib effectively inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro. (48)
Pharmaceutical form	Film-coated tablets (48)
Posology	The recommended dose for WM, either as a single agent or in combination, is 420 mg (140 mg x three capsules) once daily. (48)

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Method of administration	Oral (48)
Dosing	420 mg once daily (48)
Should the pharmaceutical be administered with other medicines?	Ibrutinib can be taken in combination with rituximab is indicated for the treatment of adult patients with WM (48)
Treatment duration/criteria for end of treatment	Treatment should continue until disease progression or no longer tolerated by the patient (48)
Necessary monitoring, both during administration and during the treatment period	**Prior to the administration of ibrutinib treatment** (48) • Viral reactivation: Hepatitis B virus (HBV) status should be established before initiating treatment with ibrutinib. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **During the treatment period** (48) • Mild or moderate renal impairment: Hydration should be maintained and serum creatinine levels monitored periodically. • Severe renal impairment: only administered if the benefit outweighs the risk and monitor patients closely for signs of toxicity. • Hepatic impairment: Monitor patients for signs of ibrutinib toxicity and follow dose modification guidance as needed. • Bleeding-related events: Monitor for signs and symptoms of bleeding as anticoagulants or medicinal products that inhibit platelet function (antiplatelet agents) concomitantly with ibrutinib increases the risk of major bleeding. • Leukostasis: Cases of leukostasis have been reported in patients treated with ibrutinib why patients should be closely monitored. • Splenic rupture: Disease status and spleen size should be carefully monitored (e.g. clinical examination, ultrasound) when ibrutinib treatment is interrupted or ceased. • Infections: Patients should be monitored for fever, abnormal liver function tests, neutropenia, and infections and appropriate anti-infective therapy should be instituted as indicated. • Cytopenia: Monitor complete blood counts monthly. • Interstitial Lung Disease (ILD): Monitor patients for pulmonary symptoms indicative of ILD. • Cardiac arrhythmia and cardiac failure: Periodically monitor all patients clinically for cardiac manifestations, including cardiac arrhythmia and cardiac failure. • Cerebrovascular accidents: regular monitoring of patients. • Tumor lysis syndrome: Monitor patients closely and take appropriate precautions. • Non-melanoma skin cancer: Monitor patients for the appearance of non-melanoma skin cancer. • Hypertension: Regularly monitor blood pressure in patients treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.

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	• Hemophagocytic lymphohistiocytosis (HLH): Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. • Drug-drug interactions: Patients should be closely monitored for signs of ibrutinib toxicity if a CYP3A4 inhibitor must be used. If a CYP3A4 inducer must be used, closely monitor patients for signs of ibrutinib lack of efficacy. • Overdose: Patients who ingested more than the recommended dose should be closely monitored and given appropriate supportive treatment.
Need for diagnostics or other tests (i.e. companion diagnostics)	No (48).
Packaging	140 mg x 28 tablets, 280 mg x 28 tablets, 420 mg x 28 tablets, or 560 mg x 28 tablets (48,49)

5.3 The intervention

A description of the intervention, zanubrutinib, is provided in Table 5.

Table 5. Description of the intervention, zanubrutinib.

Intervention : zanubrutinib	
Dosing	Each hard capsule contains 80 mg of zanubrutinib, 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) (1)
Method of administration	Oral / Capsules (1)
Treatment duration/criteria for treatment discontinuation	Treatment should continue until disease progression or unacceptable toxicity. (1)
Should the pharmaceutical be administered with other medicines?	No (1)

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Intervention : zanubrutinib	
Necessary monitoring, during administration, during the treatment period, and after the end of treatment	Patients with severe renal impairment (creatine clearance (CrCl) <30 mL/min) or on dialysis should be monitored for adverse reactions. Patients with hepatic impairment. Patients receiving antiplatelet or anticoagulant therapies should be monitored for signs of bleeding. Before initiating treatment with zanubrutinib, patients' HBV status should be established. Consultation with a liver disease expert physician is recommended for patients who test positive for HBV or have positive hepatitis B serology, before initiating treatment. Patients should be monitored and managed according to the medical standards to prevent hepatitis B reactivation. Monitor complete blood counts monthly during treatment due to the risk of cytopenias. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate. Coadministration of CYP3A inhibitors: Monitor patients closely for toxicity and follow dose modification guidance as needed. Overdose. (1)
Need for diagnostics or other tests (i.e. companion diagnostics)	No (1)

5.3.1 Expected change in clinical practice

Ibrutinib is a first-generation BTK inhibitor and currently the most effective single agent in WM. In Denmark, ibrutinib is used for patients in first line setting who are unfit for chemoimmunotherapy or 2nd/3rd line treatment for patients experiencing relapse (4). However, ibrutinib shows some off-target kinase inhibition, leading to specific cardiovascular adverse events (AE). There is therefore a need for new treatment options in WM, with a demonstrated improvement of the disease, while minimizing the toxicities seen with these treatments.

Zanubrutinib, a next-generation oral competitive irreversible inhibitor of BTK is indicated for the treatment of adult patients with WM who have received at least one prior therapy and experience relapse, or in 1st line treatment for patients unfit for chemoimmunotherapy. Zanubrutinib has shown higher bioavailability, less off-target kinase inhibition as well as favorable drug interaction properties compared to ibrutinib (42,43).
With improved target selectivity and superior pharmacological profile, higher exposure and more complete BTK inhibition from zanubrutinib in patients become possible at lower daily doses. It is therefore validated by the clinical expert, that zanubrutinib can replace ibrutinib given that zanubrutinib demonstrated to be at least as effective as ibrutinib with a more favorable safety profile and favorable drug interaction properties. Based on clinical expert input there is no difference in monitoring and administration, why recommendation of zanubrutinib is not expected to change the clinical practice.

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6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A newly published (dated 29 October 2020) pivotal head-to-head phase 3 trial of zanubrutinib (intervention) versus ibrutinib (comparator) in symptomatic WM already exists, and thus a literature search was omitted in accordance with the guidelines from the DMC (section 3.1, version 1.2, Danish) (11).

Ibrutinib is the only appropriate comparator in the Danish clinical practice for adult patients with WM as both ibrutinib and zanubrutinib are single-agent treatments for WM and have the same indication. With the recent published head-to-head study and since WM is a rare disease, it is not expected that a literature search will provide more recent information on safety and efficacy for both the intervention and comparator (11). Thus, the main source for comparative data of zanubrutinib versus ibrutinib is the pivotal phase 3 trial ASPEN and the summary of product documents for zanubrutinib and ibrutinib, respectively.

In addition, Appendix A is not filled out as a systematic literature search has no added value on the efficacy and safety of zanubrutinib and ibrutinib.

6.2 List of relevant studies

Information on the relevant study that was used for this submission can be found in Table 6. Detailed study characteristics of the included study are provided in Appendix B.

Table 6. Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study, Tam CS. Et al., Blood by the American Society of Hematology, 2020 (11).	BGB-3111-302 (ASPEN)	NCT03053440	January 2017 - January 2022	Zanubrutinib vs. ibrutinib for patients who had R/R WM after ≥1 prior line of therapy or TN WM unsuitable for standard immunochemotherapy

Completed and ongoing trials involving WM patients receiving zanubrutinib that have not been included in the submission are listed in Table 7. The results have been identified on the 25th of August 2021 on ClinicalTrials.gov where the search term for the disease was "Waldenstrom Macroglobulinemia" and the drug name "zanubrutinib".

Table 7. Completed and ongoing trials not included in the assessment.

Trial official title	NCT number	Status	Dates of study (start and expected completion date)	Used in comparison of
A Phase 2 Clinical Trial to Evaluate the Efficacy of Zanubrutinib Plus Ixazomib and Dexamethasone in	NCT04463953	**Recruiting**	May 2020 – May 2025	Zanubrutinib, ixazomib and dexamethasone (ZID regimen) in

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Trial official title	NCT number	Status	Dates of study (start and expected completion date)	Used in comparison of
Newly Diagnosed Symptomatic Waldenström Macroglobulinemia				patients with newly diagnosed WM
A Phase 2, Multicenter, Single-arm Study of Zanubrutinib (BGB-3111) in Patients With Previously Treated B-Cell Lymphoma Intolerant of Prior Treatment With Ibrutinib and/or Acalabrutinib	NCT04116437	Recruiting	October 2019 – July 2025	Zanubrutinib vs. Ibrutinib, acalabrutinib, or acalabrutinib with ibrutinib in patients with chronic lymphocytic leukemia, small lymphocytic lymphoma, waldenström macroglobulinemia, mantle cell lymphoma, or marginal zone lymphoma who have become intolerant of prior ibrutinib and/or acalabrutinib treatment
A Phase 2, Single-Arm, Open-Label, Multicenter Study of Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 in Chinese Subjects With Relapsed/Refractory Waldenström's Macroglobulinemia (WM)	NCT03332173	Completed	August 2017 – January 2021	Zanubrutinib in Chinese Subjects with R/R WM
A Single-Arm, Expanded Access Study of Zanubrutinib (BGB3111) in Participants With B-cell Malignancies	NCT04052854	No longer available	Not available (N/A)	Zanubrutinib in patients with with treatment naïve or R/R WM who are ineligible to enroll into any available zanubrutinib clinical trials

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7. Efficacy and safety

7.1 Efficacy and safety of zanubrutinib compared to ibrutinib for Waldenström's macroglobulinemia

7.1.1 Relevant studies

The main source of data on efficacy and safety of zanubrutinib in the WM indication and also the main source of comparative data with ibrutinib is the pivotal phase 3 study ASPEN (11). This is a randomized open-label phase 3 study comparing zanubrutinib to ibrutinib in patients with WM who required treatment based on consensus criteria outlined in Dimopoulos et al (2014)(50). Eligible patients had relapsed/refractory (R/R) WM after ≥1 prior line of therapy or treatment naïve (TN) WM unsuitable for standard chemoimmunotherapy based on the presence of documented comorbidities or risk factors. (11)

There are two cohorts. Cohort 1 (n=201) are patients with MYD88^{L265P}. These patients were randomized 1:1 to either receive ibrutinib (n=99) or zanubrutinib (n=102). Cohort 2 (n=28) consisted of patients with wild type or unknown MYD88 mutational status. (11) A study schematic is presented in Figure 2.
For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to Appendix C.

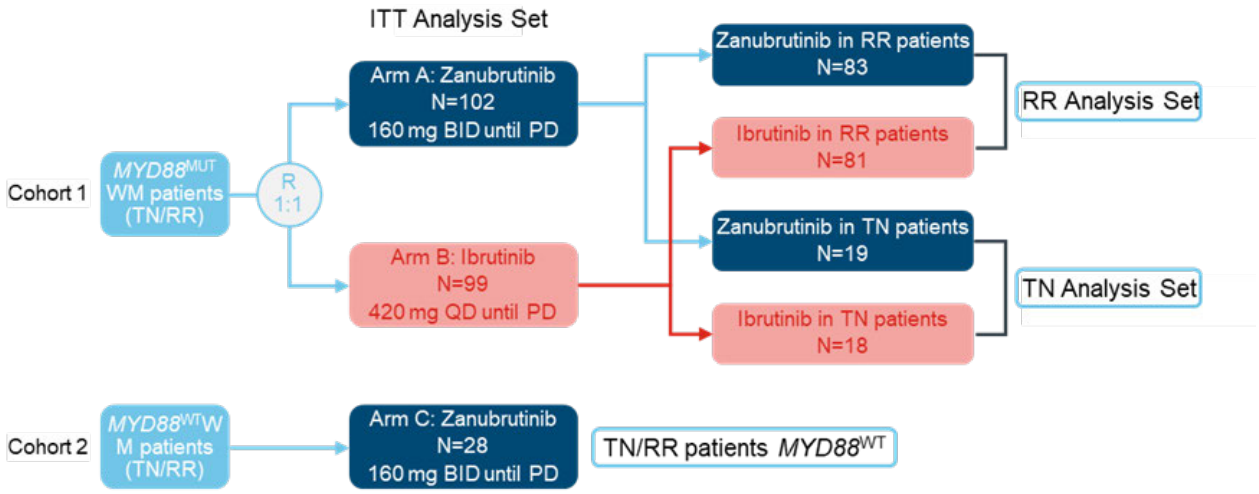

Figure 2. Overview of the study design of the ASPEN study (11).

In Cohort 1, at the date of August 31, 2019 data cut-off, with a median study follow-up time of 19.4 months, 20 patients (19.6%) randomized to zanubrutinib and 21 patients (21.2%) randomized to ibrutinib had discontinued treatment (11). See Table 8 for the patient disposition in Cohort 1 intention-to-treat (ITT) analysis set.

Table 8. Patient disposition (Cohort 1) (11).

	Zanubrutinib, n (%) N=102	Ibrutinib, n (%) N=99
Median follow-up, months	19.4	
Patients treated with study drug	101 (99.0)	98 (99.0)
Patients discontinued from study drug	20 (19.6)	21 (21.2)
Reason for discontinuation of study drug		
Progressive disease (PD)	7 (6.9)	5 (5.1)
AE	4 (3.9)	9 (9.1)
Investigator decision	2 (2.0)	4 (4.0)
Patient decision	5 (4.9)	[redacted]
Other	2 (2.0)	3 (3.0)
Patients remaining on study drug	81 (79.4)	77 (77.8)

*Data on file (51).

7.1.2 Efficacy and safety – results per study

In this submission, only Cohort 1 is discussed due to the majority of WM patients being MYD88^{MUT} patients and Cohort 1 providing comparative evidence of zanubrutinib and ibrutinib. Cohort 2 (TN/RR patients with MYD88^{WT}) constitutes a small part of the WM population and only includes one nonrandomized treatment arm, for which reason the results do not add additional value for the comparison between treatment with zanubrutinib and ibrutinib. (11)

A summary of key efficacy and safety findings can be found in section 7.1.2.1. The efficacy and safety results from the ASPEN study are presented with an initial data cut-off in August 2019, a data cut-off in January 2020, and the latest data cut-off in August 2020. Data cut-off in August 2020 is investigator-assessed data only. Data from August 2019 will primarily be based on the published data from the ASPEN study, and in some circumstances from data on file which will be marked as confidential. Furthermore, the data cut-off from January 2020 will be based on published data presented at the 2020 Annual Meeting of the American Society of Clinical Oncology presentation by the study author Constantine S. Tam (52). The latest data from the data cut-off in August 2020 originates from data on file and is marked as confidential. Primary and secondary endpoints in the published data from the ASPEN study were assessed by an independent review committee (IRC), whereas the data cut-off from August 2020 was based on investigator assessment. (11,51)

7.1.2.1 Summary of key efficacy and safety findings

Overall, the ASPEN study demonstrated at least comparable efficacy between zanubrutinib and ibrutinib, with a trend toward a deeper quality of response and better efficacy favoring zanubrutinib. A summary of clinical efficacy between zanubrutinib and ibrutinib in the ASPEN study can be found in Table 9, and further descriptions for each endpoint can be found in section 7.1.2.2-7.1.2.9. A summary of safety findings can be found in section 7.1.2.10.
For further detailed efficacy and safety results, refer to appendices D and E.

Table 9. Summary of key efficacy findings in the ASPEN study (11,51–53).

Endpoints	Findings
Response	Zanubrutinib demonstrate superiority compared to ibrutinib. VGPR/CR rate for the ITT analysis set was 28.4% compared to 19.2% at the initial data cut-off in August 2019. At the latest data cut-off in August 2020, the VGPR/CR rate continued to be numerically greater in zanubrutinib vs. ibrutinib [redacted]

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	Major response rates (MRR) and duration of response (DOR) also showed tendency to greater response in the zanubrutinib arm.
Progression-free survival and overall survival	Trends for improved PFS at 12, 18, [redacted] months, and for improved OS at 18.
Anti-lymphoma effect	Comparable findings in reductions from baseline for both treatments.
Resolution of treatment-precipitating symptoms	Comparable findings for both treatments.
Quality of Life (QoL)	Patients who achieved VGPR trended toward gaining greater improvement.

7.1.2.2 CR/VGPR

At data cut-off in August 2019, the IRC-assessed VGPR in Cohort 1 for the ITT analysis set was 28.4% (95% CI: 20-38) in the zanubrutinib arm and 19.2% (95% CI: 12-28) in the ibrutinib arm (2-sided p-value = 0.0921). No patient achieved a CR. Investigator-assessed rates of VGPR were 28.4% and 17.2% in the zanubrutinib and ibrutinib arms, respectively (P=0.0437). Concordance rates between IRC- and investigator-assessed best responses were 94% for the zanubrutinib arm and 95% for the ibrutinib arm. (11,52)

For R/R patients the result for VGPR/CR were 29% (95% CI: 20-40) vs 20% (95% CI: 12-30) in favor of zanubrutinib (p= 0.12), and for TN patients 26% (95% CI: 9-51) vs 17% (95% CI: 4-41) in favor of zanubrutinib (p=0.54). Median times to achieve VGPR were skewed in favor of zanubrutinib; for TN patients the median time was 5.6 and 22.1 months for zanubrutinib and ibrutinib, respectively (p=0.35), and for R/R patients the median time was 4.7 and 5.1 months for zanubrutinib and ibrutinib, respectively (p=0.17). (11)
At the more recent data cut-off in August 2020, [redacted]. (51)

In Cohort 1, subgroup differences in the rate of VGPR/CR showed a tendency to favor zanubrutinib compared to ibrutinib in prognostically more difficult to treat populations such as those with higher IgM (≥ 40 g/L), cytopenias (anemia, thrombocytopenia), extramedullary disease, and especially for the subgroups having medium/high IPSS scores (Figure 3.

Subgroup	Response/patients		Rate difference, % (95%, CI)*
	Ibrutinib	Zanubrutinib	
All patients	19/99	29/102	9.2 (-2.5, 20.9)
Age group			
≤65 years	5/29	12/41	12.0 (-7.5, 31.6)
>65 years	14/70	17/61	7.9 (-6.8, 22.5)
Age group			
≤75 years	12/77	22/68	16.8 (3.0, 30.5)
>75 years	7/22	7/34	-11.2 (-35.0, 12.5)
Sex			
Male	11/65	18/69	9.2 (-4.6, 23.0)
Female	8/34	11/33	9.8 (-11.7, 31.3)
Geographic region			
Australia/New Zealand	3/30	13/32	30.6 (10.5, 50.7)
Europe	13/59	16/61	4.2 (-11.1, 19.5)
North America	3/10	0/9	-30.0 (-58.4, -1.6)
Treatment type			
Relapsed/Refractory	16/81	24/83	9.2 (-3.9, 22.2)
Treatment Naive	3/18	5/19	9.6 (-16.6, 35.9)
Prior line of therapy			
0	3/18	5/19	9.6 (-16.6, 35.9)
1-3	13/74	22/76	11.4 (-2.0, 24.8)
>3	3/7	2/7	-14.3 (-63.9, 35.4)
Baseline ECOG-PS			
0	10/42	15/46	8.8 (-9.9, 27.5)
≥1	9/57	14/56	9.2 (-5.6, 24.0)
Baseline CXCR4 mutation status by central lab			
WHIM	1/8	1/11	-3.4 (-31.9, 25.1)
WT/UNKNOWN	18/91	28/91	11.0 (-1.5, 23.5)
Baseline IgM			
<40 g/L	14/60	19/66	5.5 (-9.8, 20.7)
≥40 g/L	5/38	10/36	14.6 (-3.5, 32.8)
Missing	0/1	0/0	NE
Baseline B2 microglobulin			
≤3 mg/L	3/25	6/27	10.2 (-10.0, 30.4)
>3 mg/L	16/74	23/75	9.0 (-5.0, 23.1)
Baseline hemoglobin			
≤110 g/L	9/53	22/67	15.9 (0.7, 31.0)
>110 g/L	10/46	7/35	-1.7 (-19.6, 16.1)
Baseline platelet			
≤110 × 10^9/L	1/12	6/12	41.7 (9.3, 74.0)
>110 × 10^9/L	18/87	23/90	4.9 (-7.5, 17.3)
Baseline presence of extramedullary disease by IRC			
Yes	14/73	26/81	12.9 (-0.7, 26.5)
No	5/26	3/21	-4.9 (-26.2, 16.4)
WM IPSS			
High	9/44	15/47	11.5 (-6.4, 29.3)
Intermediate	8/42	12/38	12.5 (-6.4, 31.5)
Low	2/13	2/17	-3.6 (-28.5, 21.3)

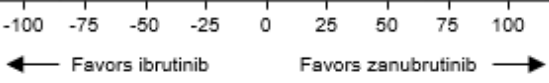


Figure 3. Forest plot of subgroup differences in the rate of CR/VGPR (11).
*Unstratified rate difference and 95% CIs.

7.1.2.3 Major response rate (MRR)

At data cut-off in August 2019, MRRs among zanubrutinib and ibrutinib patients were 77.5% (95% CI: 68-85) and 77.8% (95% CI: 68-86) for the overall ITT analysis set, respectively. MRRs among TN patients were 74% (95% CI: 49-91) and 67% (95% CI: 41-87), and 78% (95% CI: 68-87) and 80% (95% CI: 70-88) among R/R patients, for zanubrutinib and ibrutinib, respectively The noninferiority hypothesis for MRR difference was not tested due to a lack of statistically significant superiority of CR/VGPR rates for zanubrutinib. (11)

At data cut-off in August 2020, [redacted] (51)

7.1.2.4 Duration of response (DOR)

The median duration of CR/VGPR and the major response were not estimable for the overall ITT population. However, the 18-month event-free rates for duration of CR/VGPR were 93% (95% CI: 59-99) in the ITT zanubrutinib arm and 64% (95% CI: 29-85) in the ITT ibrutinib arm. The 18-month event-free rates for duration of CR/VGPR for TN patients were 100% (95% CI: not estimable (NE) for zanubrutinib and NE (95% CI: NE, NE) for ibrutinib. Among R/R patients, this was 90% (95% CI: 47-99) for zanubrutinib and 64% (95% CI: 29-85) for ibrutinib. (11)

The 18-month event-free rates for duration of major response were 85% (95% CI: 72-93) in the overall ITT zanubrutinib arm and 88% (95% CI: 77-94) in the overall ITT ibrutinib arm. The rates for duration of major response were 80% (95% CI: 39-95) and 100% (95% CI: NE,NE) among TN patients, and 87 (95% CI: 73-94) and 86 (95% CI: 73-93) among R/R patients, for the zanubrutinib and ibrutinib arm, respectively. (11)

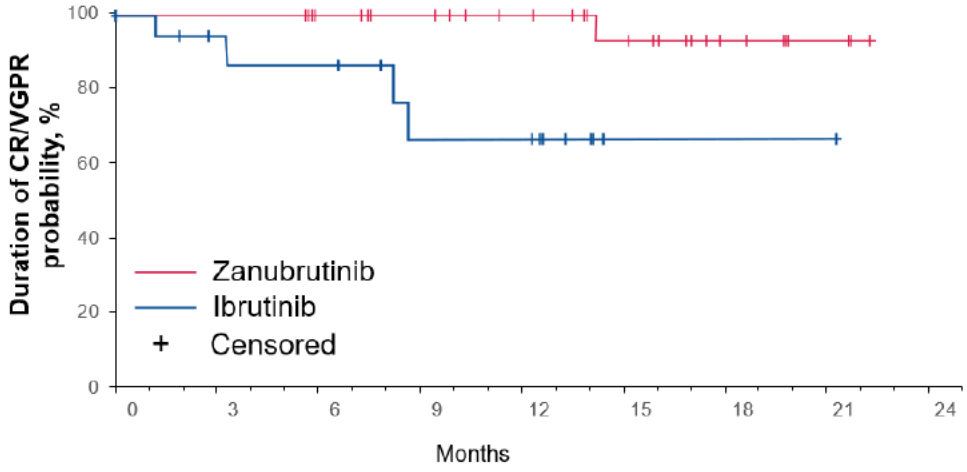
The event-free rates were estimated by Kaplan-Meier (K-M) methodology, where Greenwood's formula was used to estimate 95% CIs. (11)

At data cut-off in August 2020, [redacted] (51)

As of the data cut-off in August 2020, [redacted] (51)

K-M plots of the duration of CR/VGPR and major response from data cut-off in August 2019 and 2020 can be found in Figure 4.

4A. K-M plot for the duration of CR/VGPR – data cut-off in August 2019 (11)



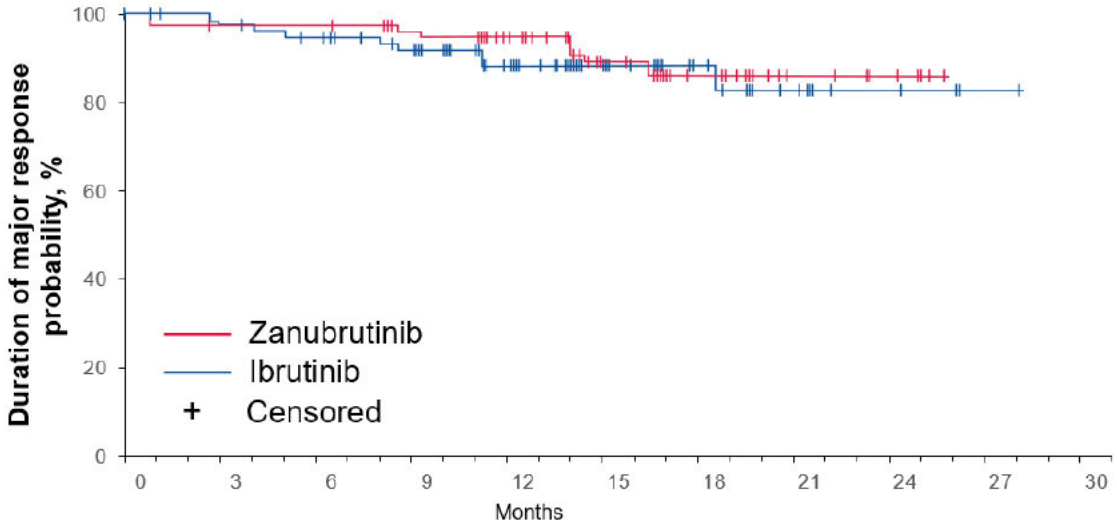
No. of Patients at Risk

Zanubrutinib	29	27	24	22	18	12	5	2	0
Ibrutinib	19	11	10	6	5	1	1	0	

[redacted] (51)

[redacted]

4C. K-M plot for the duration of major response – data cut-off in August 2019 (11)



No. of Patients at Risk

Zanubrutinib	79	72	71	66	52	32	21	10	6	0
Ibrutinib	77	72	67	59	44	29	15	7	3	1	0

[redacted] (51)

[redacted]

Figure 4. K-M plots of the duration of CR/VGPR and major response (11,51). A) and C) is from data cut-off in August 2019, and B) and D) is from data cut-off in August 2020.

7.1.2.5 PFS

Zanubrutinib showed a tendency to improve PFS compared to ibrutinib, with a 15% reduction in hazard rate, HR= 0.846 (95% CI: 0.425, 1.759; Likelihood ratio rest P-value = 0.6874) (11).

After a median follow-up for PFS of 18.0 months, 15% of the overall zanubrutinib arm experienced disease progression or death, and after median follow-up for PFS of 18.5 months, 16% of the overall ibrutinib arm experienced disease progression or death. Median PFS was not reached for zanubrutinib and ibrutinib. The event-free rates at 18 months were comparable for the overall ITT zanubrutinib and ibrutinib arm; 85% (95% CI: 75-91) and 84% (95% CI: 75-90), respectively. The event-free rates at 18 months for R/R patients were 86% (95% CI: 74-93) and 82% (95% CI: 71-89) for the zanubrutinib and ibrutinib arm, respectively, and for TN patients rates were 78% (95% CI: 52-91) and 94% (95% CI: 63-99) for the zanubrutinib and ibrutinib arm, respectively. (11)

At data cut-off, August 2020, [redacted] (51)

[redacted] (51)

The K-M plots of PFS related to the ITT analysis set from data cut-off in 2019 and 2020 can be found in Figure 5.

5A. K-M plot of PFS (ITT Analysis Set)

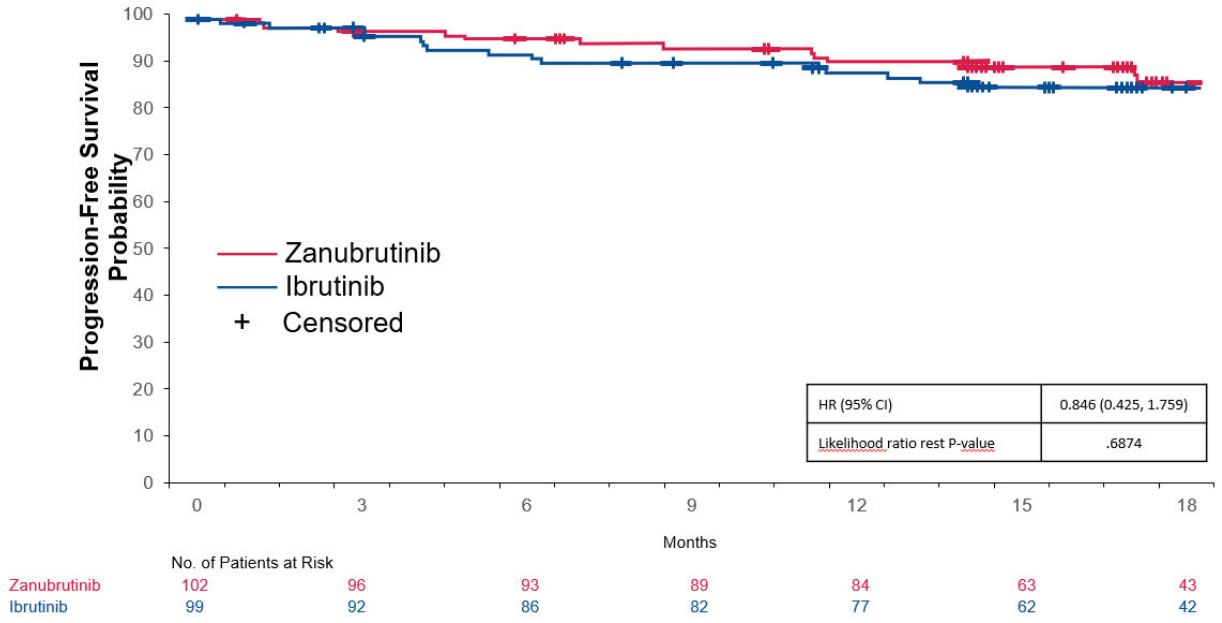


Figure 5: K-M plots for progression-free survival (11,51).

7.1.2.6 Anti-lymphoma effect

[redacted] (see Table 10). (51)

Table 10. Anti-lymphoma effect (Cohort 1) (51).

	TN		R/R		Overall	
	Ibrutinib N=18	Zanubrutinib N=19	Ibrutinib N = 81	Zanubrutinib N=83	Ibrutinib N=99	Zanubrutinib N=102
Patients with positive baseline bone marrow involvement and/or lymphadenopathy and/or splenomegaly by CT scan (IRC) at baseline	[redacted]					
Positive bone marrow involvement at baseline	[redacted]					
Lymphadenopathy and/or splenomegaly at baseline	[redacted]					
Patients with anti-lymphoma effect, n (%)	[redacted]					
Reduction in bone marrow involvement, n (%)	[redacted]					
Reduction in size of lymphadenopathy and/or splenomegaly by CT scan (IRC), n (%)	[redacted]					

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[redacted] (51)

7.1.2.7 Resolution of treatment-precipitating symptoms

[redacted] (see Table 11). (51)

Table 11. Resolution of treatment-precipitating symptoms (Cohort 1) (51).

	TN		R/R		Overall	
	Ibrutinib N=18	Zanubrutinib N=19	Ibrutinib N = 81	Zanubrutinib N=83	Ibrutinib N=99	Zanubrutinib N=102
Patients with any treatment-precipitating symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with resolution of all treatment-precipitating symptoms, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with resolution of any treatment- precipitating symptoms, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.1.2.8 Overall survival

At the August 2019 data cut-off, OS numerically favored zanubrutinib over ibrutinib. Six (3 R/R and 3 TN) patients from the zanubrutinib arm and 8 (8 R/R and 0 TN) patients from the ibrutinib arm died. The OS rates at 18 months were 97% for zanubrutinib and 93% ibrutinib. (11)

At the data cut-off from August 2020, [redacted] (51)

The K-M plot of OS related to the ITT analysis set from data cut-off 2020 can be found in Figure 6 (51).

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7.1.2.9 Quality of life (QoL)

In most QoL assessments, patients treated with zanubrutinib trended toward gaining greater improvement, particularly among patients who achieved VGPR (11). The QoL measures over time can be found in Figure 7.

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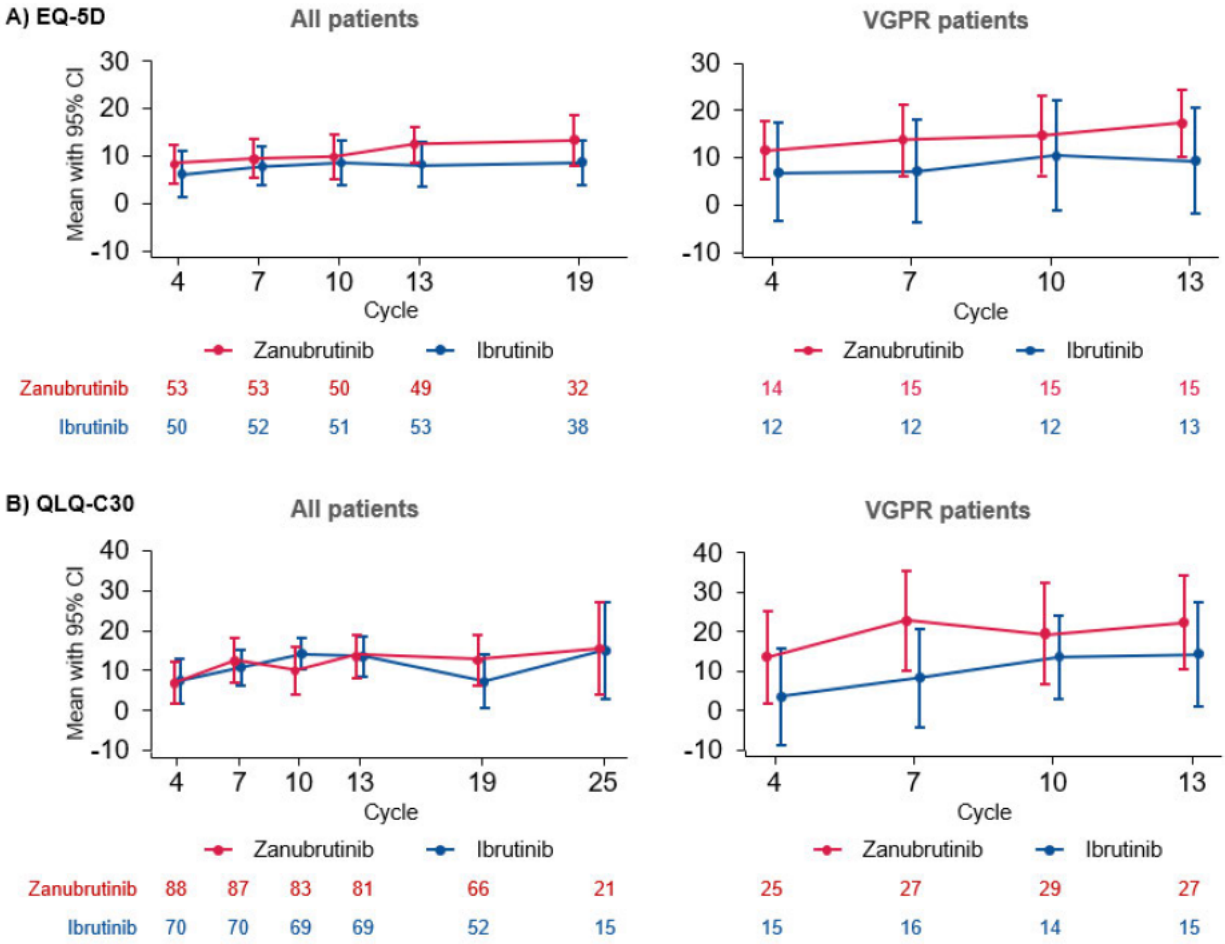

Figure 7. Quality of life: change from baseline over time for all patients and VGPR patients (Cohort 1) (53). A) shows EQ-5D data and B) shows QLQ-C30 data.

7.1.2.10 Key safety findings

Zanubrutinib was designed to be a more selective inhibitor of BTK and its kinase selectivity profile was hypothesized to demonstrate superiority in drug tolerability and safety versus ibrutinib. In line with the hypothesis, from the pivotal phase 3 ASPEN study, patients with WM who were treated with zanubrutinib demonstrated a better toxicity and tolerability profile. Key safety findings are summarized in Table 12, and further details regarding treatment-emergent adverse events (TEAE), serious AEs and adverse event of special interest (AESI) can be found in Appendix E.

Table 12. Summary of comparative assessment of clinical safety between zanubrutinib and ibrutinib in the ASPEN study (11).

AE category	Results
Overall	Zanubrutinib was associated with lower rates of AEs leading to treatment discontinuation, treatment interruption, or fatalities compared with ibrutinib.
Treatment-emergent adverse events (TEAE)	Zanubrutinib was associated with a lower incidence of TEAEs.

Adverse event of special interest (AESI)	Zanubrutinib showed a distinct safety profile compared to ibrutinib. In particular, the risk of developing atrial fibrillation, bleeding, diarrhea, or pneumonia over time was lower in zanubrutinib recipients compared with ibrutinib recipients.
Atrial fibrillation or flutter	Patients treated with zanubrutinib have a ten-fold lower exposure-adjusted risk to experience atrial fibrillation or flutter compared to patients treated with ibrutinib.
Hypertension	Particularly with increased time of exposure, patients treated with zanubrutinib have a two-fold lower risk to experience hypertension compared to patients treated with ibrutinib.
Hemorrhage	Patients treated with zanubrutinib tend to have a lower risk to experience a hemorrhagic or major hemorrhagic event.
Neutropenia	Patients treated with zanubrutinib have a higher risk of neutropenia, but no higher susceptibility to infection when compared to ibrutinib.

The incidence of patients with at least one AE was comparable in two treatment arms (99.0% for the ibrutinib arm and 97.0% for the zanubrutinib arm), and almost all patients experienced at least one AE. In the ibrutinib arm, 40.8% experienced serious AEs and 63.3% experienced AEs of grade 3 or higher, whereas in the zanubrutinib arm 39.6% experienced serious AEs and 58.4% experienced AEs of grade 3 or higher. AEs leading to death occurred in 4 (4.1%) patients in the ibrutinib arm and 1 (1.0%) patient in the zanubrutinib. Treatment discontinuation due to AEs was reported in 9.2% of the patients from the ibrutinib arm and 4.0% from the zanubrutinib arm. As the patient group is vulnerable due to age and co-morbidities, the demonstration of less discontinuation due to AEs favors the zanubrutinib treatment arm. 82.7% of patients in the ibrutinib arm and 85.1% of the patients in the zanubrutinib arm experienced at least one AESI, whereas 79.2% of the patients in the ibrutinib arm and 85.7% of the patients in the zanubrutinib arm experienced at least one treatment-related AE (TRAE), respectively. (52)

Overall, the comparisons of the incidence and type of AEs, including grade 3 or higher, serious, treatment-related, and AEs leading to treatment discontinuation, suggest that the safety profile for zanubrutinib among patients with WM is trending towards less toxicity compared to ibrutinib. The overall summary of AEs for the overall ITT population can be found in Table 13. (52)

Table 13. Overall summary of AEs for the overall ITT population in the ASPEN-study (52).

	Ibrutinib Cohort 1 (N = 98) n (%)	Zanubrutinib Cohort 1 (N = 101) n (%)
Patients with ≥ 1 AE	97 (99.0)	98 (97.0)
Grade ≥ 3	62 (63.3)	59 (58.4)
Serious	40 (40.8)	40 (39.6)
AE leading to death	4 (4.1)[a]	1 (1.0)[b]
AE leading to treatment discontinuation	9 (9.2)[c]	4 (4.0)[d]
AE leading to dose reduction	23 (23.5)	14 (13.9)

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AE leading to dose held	55 (56.1)	47 (46.5)
Patients with ≥ 1 TRAE	84 (85.7)	80 (79.2)
Patients with ≥ 1 AESI	81 (82.7)	86 (85.1)

[a]cardiac failure acute; sepsis (n=2); unexplained death.
[b]cardiac arrest after plasmapheresis.
[c]grade 5 sepsis (n=2); grade 5 unexplained death; grade 3 acute myocardial infarction; grade 3 hepatitis; grade 3 pneumonia; grade 2 drug-induced liver injury; grade 2 pneumonitis, grade 1 pneumonitis.
[d]grade 5 cardiac arrest after plasmapheresis; grade 4 neutropenia; grade 4 subdural hemorrhage; grade 2 plasma cell myeloma.

7.1.3 Comparative analyses of efficacy and safety

Not applicable.

Method of synthesis

Not applicable.

Results from the comparative analysis

Not applicable.

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8. Health economic analysis

Ibrutinib is currently recommended and used in Denmark for adult patients with WM who received at least one prior therapy or treatment-naïve patients unfit for chemoimmunotherapy. This is the same population which zanubrutinib is indicated for. Given the similar mechanisms of action of the two treatments, zanubrutinib is expected to be a valuable alternative to ibrutinib in clinical practice and ibrutinib is therefore the most relevant comparator to assess the clinical benefits and economic consequences of introducing zanubrutinib. The phase 3 study ASPEN was a direct head-to-head study comparing zanubrutinib with ibrutinib which further strengthen the reliability of the value-assessment of zanubrutinib in comparison to ibrutinib.
A cost-minimization approach is applied in this submission as zanubrutinib is shown to be at least as effective and safe as the relevant comparator ibrutinib. This was also confirmed by DMC in pre-submission discussions. In the following health economic section the headings from the DMC template that are not considered relevant for a cost-minimization analysis was removed.

8.1 Model

The ASPEN trial found zanubrutinib to be an at least equally effective treatment choice to ibrutinib, trending towards higher activity (11). Treatment with zanubrutinib was also associated with toxicity and tolerability advantages over ibrutinib, particularly notable for cardiovascular complications. This overall means that zanubrutinib may potentially have clinical benefits compared to ibrutinib and can be concluded to be at least as efficacious with a more favourable safety profile and favourable drug interaction properties compared to ibrutinib.
Besides equal efficacy and safety, a clinical expert has also validated that the patient pathway from diagnosis to treatment, treatment monitoring etc. also is expected to be similar for the two treatments in Danish clinical practice. However, due to the fact that ibrutinib has not previously been assessed by the Danish Medicines Council, as it was introduced to the market prior to year 2017, the model will include costs related to the drugs, monitoring, adverse events and patients' time and transportation due to treatment and adverse events.

Cost-minimization approach
The relevant treatment-related costs to include in the CMA are the drug costs [redacted], AE costs (as there are some differences in adverse event profiles) and monitoring costs (start-up consultations, clinical controls, blood samples and other tests). Patient-related costs reflecting time consumption and transportation are included for start up-consultations, clinical controls, blood samples, tests and adverse events.
Both treatments are orally administrated as tablets at home and consequently administration costs are not relevant. However, it is estimated that each patient will have a start up consultation with a physician, and that the medicine is handed out to the patients by a nurse every three months. Both treatments are assumed to be administered daily until disease progression or no longer tolerated by the patient/unacceptable toxicity, and similar treatment duration and discontinuation is assumed. The clinical expert estimated that the treatment length in clinical practice is approximately 4 years for ibrutinib, and expects the same treatment length if patients receive zanubrutinib. Therefore the time horizon in this CMA model is 4 years to reflect Danish clinical practice.
It is estimated that patients on zanubrutinib and ibrutinib will have the same disease course and monitoring after treatment stop, and this has therefore been omitted in the analysis due to irrelevancy. In accordance to the DMC's Method Guidelines, a discounting rate of 3,5% is used, and costs are coverted to 2021-prices.
Cost-minimization analyses are always surrounded with uncertainty as the patient outcome of two different treatments are rarely the same. In this case, it is shown that zanubrutinib is at least as effective and safe as ibrutinib but with trends towards higher activity and if there is a difference between the treatments, it is likely in favor of zanubrutinib. Therefore, a cost-minimization approach can be in this case considered as conservative for zanubrutinib.

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8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

Population

The patient population assessed is the population according to the expected label on zanubrutinib, i.e. adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy (1). This has been validated by the clinical expert.

Intervention

The intervention is zanubrutinib according to its label and posology described in the Summary of Product Characteristics. 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). The length of treatment is not known as all patients in the phase 3 ASPEN trial had not stopped treatment at the time of analysis, however it is estimated to be the same as for ibrutinib, which has been estimated to be 4 years by the clinical expert. (11).

Comparator

The comparator used is ibrutinib, which has a similar mechanisms of action and is indicated for the same WM patient population as zanubrutinib. Ibrutinib is currently recommended in Danish treatment guidelines and it is expected that zanubrutinib can be a valuable alternative to ibrutinib in clinical practice. Therefore, ibrutinib is seen as the most relevant comparator, which also was confirmed by DMC in pre-submission discussions and the clinical expert. The recommended dose for ibrutinib is 420 mg once daily, with an estimated treatment length of 4 years due to the clinical expert input.

Relative efficacy and adverse reaction outcomes

The outcomes from the ASPEN trial are described in detail in the dossier. In summary, the ASPEN trial found zanubrutinib to be an at least equally effective treatment choice to ibrutinib, trending towards higher activity. Treatment with zanubrutinib was also associated with toxicity and tolerability advantages over ibrutinib, particularly notable for cardiovascular complications, as well as improvements in the possibility to co-administer zanubrutinib with some other commonly used drugs. (11)

8.3 Resource use and costs

Patients with WM incur a wide-range of resource use and costs, within and outside the health care system. The ASPEN study concluded that zanubrutinib may potentially have clinical benefits compared to ibrutinib and is at least as efficacious. If the treatment outcomes are assumed to be at least as good with zanubrutinib as with ibrutinib, a conservative assumption is that there are no differences in WM disease-related costs between the two alternatives, and the only cost aspect to consider in an economic evaluation is related to the drug. However, because ibrutinib has not previously been assessed by the Danish Medicines Council, as it was introduced to the market prior to 2017, it is requested that the cost-minimization analysis includes costs related to the drugs, monitoring, adverse events and patients by the Danish Medicines Council.

The list in Table 14 is an overview of the costs included in the cost-minimization analysis.

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Table 14. Costs included in the cost-minimization analysis.

Type of cost	Expected to differ between treatments (yes/no)	Comments
Drug cost for the treatment	Yes	[redacted]
Hospital costs	No	Oral treatment. Cost for the start-up consultation, distribution of medicine, and monitoring (i.e. clinical controls and blood samples) are assumed to be the same for both treatments after validation by clinical expert.
Adverse event-related costs	Yes	Difference expected due to different AE frequencies for the two treatments. Validated by clinical expert.
Patient costs (Time consumption, transportation etc)	Yes	Due to different adverse event profiles patient cost related hereto will differ. Validated by clinical expert.

In summary, the cost categories that could potentially differ between treatment with zanubrutinib and ibrutinib are the drug costs and AE costs (and indirectly the patient costs).

8.3.1 Drug costs

The acquisition cost and dosing differ between the treatments and the drug costs are therefore relevant to consider. Drug costs are indicated in pharmacy purchase price. The recommended dose of zanubrutinib is 320 mg per day and the recommended dose of ibrutinib is 420 mg per day. Both treatments are assumed to be administered daily until disease progression or no longer tolerated by the patient/unacceptable toxicity. According to the ASPEN study the dose intensity for both zanubturinib and iburtinb are 98%.
Prices for the treatments are based on pharmacy purchase prices and can be found in Table 15.

Table 15. Drug cost.

Costs	Strength and package size		Price per package	Cost per year per patient*	Reference
	Zanubrutinib	Ibrutinib			
Drug cost *(pharmacy purchase price)*	80 mg x 120	420 mg x 28	[redacted]	[redacted]	(54)

*When drug intensity of 98% and 365.25 days per year are taken into account.

8.3.2 Hospital costs

It is estimated that the monitoring approaches of patients receiving zanubrutinib and ibrutinib are equal, and consist in the following; prior to initiation of treatment the patient will have a consultation with an oncologist and get the medicine distributed by a nurse. It is estimated that some patients will need a phone consulation with the oncologist 14 days and 1 month after treatment initiation. In this model, a consevertive estimate is used and it is assumed that all patients will receive both phone consultations. Hereafter, the patients will receive a clinical control by an oncologist every third month, and get the medicine distributed by a nurse as well. The clinical control includes a physical examination and a blood sample. It is furthermore estimated, that the patients will receive an ECG every sixth month. It is estimated that 2% and 5% of the patients will be anually examined for amyloidosis and polyneuropathy respectively and receive the

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necessary testing for these conditions. The clinical expert have validated the model inputs.
See Table 16 for resource use related to hospital costs.

Table 16: Resource use for hospital costs: clinical controls, distribution of medicine, monitoring, and blood samples.

Resource use						
		Month 1	Month 4	Month 7	Month 10	Total
Start up consultation with the physician (only year 1)		1				**1.0**
Nurse visit, distribution of medicine to the patient		1	1	1	1	**4.0**
Phone consultation with the physician (only year 1)		2				**2.0**
Clinical control with the physician* (every third month after treatment initiation)		1	1	1	1	**4.0**
Blood test (number)	Specific blood tests can be seen in the unit cost sheet	1	1	1	1	**4.0**
Amyloidosis screening	Spot urine sample (%)**			2%		**2%**
	Plasma NT-proBNP (%)**					
	Alkaline phosphatase (%)**					
	Abdominal, subcutanous fat aspiration (%)					
	Amyloidosis type determination (%)					
PN control	Serum-anti-myelin associated glycoprotein (S-anti-MAG) (%)			5%		**5%**
	Consultation at neurologist (%)					
	Nerve conduction examination					
ECG (number)		1		1		**2.0**

*During the first year this control is done as the start up consultation
**These tests are performed during visitation

Table 17 is an overview of the related costs for year 1 and the subsequent years (until year 4). Costs are calculated by using 2021 DRG-tariffs found via the interactive DRG database and prices of blood samples collected via The Capitol Region's Lab Portal. The costs accounts for both zanubrutinib and ibrutinib as the resource use for hospital costs are equal based on validation from the clinical expert. Cost are not discounted.

Table 17: Total hospital costs for ibrutinib and zanubrutinib for year 1 and year 2 and beyond.

Year 1	Year 2 and beyond	Incremental cost year 1 and beyond
37.604,2 DKK	35.556,2 DKK	- DKK

8.3.3 Adverse event-related costs

In the ASPEN study, zanubrutinib was generally associated with a more favourable safety profile. Atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia, as well as AE leading to treatment discontinuation, were less common among zanubrutinib recipients. Incidence of neutropenia was higher with zanubrutinib, although grade ≥3 infection rates were similar in both arms. Grade ≥3 AE were reported in 63% and 58% of ibrutinib and zanubrutinib patients, respectively. (11,52)

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TRAEs with grade 3 or above was included in this analysis. The clinical expert confirmed that AEs of grade 3 or above is sufficient to include in a cost analysis. Please note, that in the ASPEN study there are two TRAE categories "bleeding" and "infections" which are not included in the cost minimization analysis. This is due to the categories being to broad for any meaningful DRG-tariff and the risk of double-counting as some related AEs are already included in the analysis – e.g. upper respiratory tract infection, urinary tract infection and hematuria. However, specific TRAEs such as nausea, diarrhea, and neutropenia has been included in the analysis, as these have been specified in the ASPEN study. The TRAEs' frequencies were obtained in the ASPEN study and were converted to a 12 month frequency for use in the model based on the expectation that these would be recurring events rather than one-time events. The clinical expert estimated the frequency of outpatient treatment and treatment via admission per AE. This is demonstrated in Table 18.

Table 18: Resource use for adverse events: frequencies per AE and distribution of hospital visits

Resource					
Treatment-emergent adverse events, Grade ≥3 AE	**Requires contact with the hospital***	**Zanubrutinib AE 12 month frequency %****	**Ibrutinib AE 12 month frequency %****	**% treated as outpatient***	**% treated via admission***
Diarrhea	Yes	1.9%	0.6%	70%	30%
Upper respiratory tract infection	Yes	0.0%	0.6%	5%	95%
Muscle spasms	No	0.0%	0.6%	0%	0%
Hypertension***	No	3.9%	7.5%	0%	0%
Arthralgi	No	1.9%	0.0%	0%	0%
Fatigue	No	0.6%	0.6%	0%	0%
Nausea	Yes	0.0%	0.6%	70%	30%
Vomiting	Yes	0.0%	0.6%	20%	80%
Pyrexia	Yes	1.2%	1.2%	20%	80%
Pneumonia	Yes	0.6%	4.3%	20%	80%
Headache	Yes	0.6%	0.6%	90%	10%
Urinary tract infection	Yes	0.0%	1.2%	10%	90%
Hematuria	Yes	0.0%	1.2%	10%	90%
Extremity pain	Yes	0.6%	0.0%	80%	20%
Back pain	Yes	2.5%	0.0%	70%	30%
Atrial fibrillation/flutter***	Yes	0.0%	3.5%	50%	50%
Neutropenia***	Yes	11.2%	4.0%	90%	10%
Febrile neutropenia	Yes	2.5%	0.0%	0%	100%
Thrombocytopenia	Yes	3.7%	1.9%	80%	20%
Anemia	Yes	3.1%	3.1%	80%	20%
Median follow-up time, months****					
Data cutoff 31 August, 2019			19.4		
Data cutoff 31st January, 2020			24.4		

*Estimated by a clinical expert
**References: (11,52)
*** Additional 5 months follow-up adverse event data (Cutoff date: 31 January 2020)(52)
****The AE frequencies during the study period were converted to 12-month percentages (from median follow-up time of 19,4 months for data cutoff 31st of August, 2019, and median follow-up time of 24,4 months (=19,4+5 months) for data cutoff 31st of January, 2020)

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Using the relevant DRG tariffs for each TRAE, the cost of each TRAE was calculated and added together to get a toal AE cost per year, see Table 19.

Table 19: Total AE costs per year for zanubrutinib and ibrutinib.

	AE cost per year					
	Zanubrutinib			Ibrutinib		
	Outpatient	Admission	Total	Outpatient	Admission	Total
Diarrhea	29,58 DKK	2.183,56 DKK	2.213,14 DKK	9,86 DKK	2.164,52 DKK	2.174,38 DKK
Upper respiratory tract infection	- DKK	- DKK	- DKK	0,58 DKK	89,12 DKK	89,70 DKK
Nausea	- DKK	- DKK	- DKK	9,86 DKK	9,52 DKK	19,38 DKK
Vomiting	- DKK	2.155,00 DKK	2.155,00 DKK	2,82 DKK	2.180,39 DKK	2.183,20 DKK
Pyrexia	4,14 DKK	225,50 DKK	229,64 DKK	4,14 DKK	225,50 DKK	229,64 DKK
Pneumonia	2,14 DKK	127,15 DKK	129,29 DKK	15,00 DKK	890,05 DKK	905,05 DKK
Headache	19,78 DKK	12,09 DKK	31,87 DKK	19,78 DKK	12,09 DKK	31,87 DKK
Urinary tract infection	- DKK	- DKK	- DKK	2,36 DKK	272,02 DKK	274,37 DKK
Hematuria	- DKK	- DKK	- DKK	2,36 DKK	193,31 DKK	195,67 DKK
Extremity pain	8,00 DKK	2.157,05 DKK	2.165,05 DKK	- DKK	2.155,00 DKK	2.155,00 DKK
Back pain	28,01 DKK	143,73 DKK	171,73 DKK	- DKK	- DKK	- DKK
Atrial fibrillation	- DKK	- DKK	- DKK	40,26 DKK	270,41 DKK	310,67 DKK
Neutropenia	628,52 DKK	397,87 DKK	1.026,39 DKK	226,05 DKK	143,10 DKK	369,14 DKK
Febrile neutropenia	- DKK	877,93 DKK	877,93 DKK	- DKK	- DKK	- DKK
Thrombocytopenia	184,91 DKK	263,38 DKK	448,29 DKK	92,46 DKK	131,69 DKK	224,15 DKK
Anemia	154,09 DKK	139,45 DKK	293,55 DKK	154,09 DKK	139,45 DKK	293,55 DKK
Total	**1.059,18 DKK**	**8.682,72 DKK**	**9.741,89 DKK**	**579,61 DKK**	**8.876.16 DKK**	**9.455,77 DKK**

The annual cost for AEs for zanubrutinib and ibrutinib is 9.741,89 DKK and 9.455,77 DKK, respectively, with an incremental total cost of 286,13 DKK in favor of ibrutinib.

8.3.4 Patient-related costs

Patient-related costs involves patients' time consumption and transportation spent on treatment-related hospital visits and AE-related hospital visits.

For patient costs related to treatment, it is estimated that all planned monitoring and tests are conducted on the same day when possible (i.e. clinical control, blood sample, distribution of medicine, and ECG). This results in four annual visits corresponding to every third month. Furthermore, it is assumed that a patient suspected of having amyloidosis and PN will go to the hospital for two visits and one visit, respectively. This results in a further 0.04 and 0.05 visit per year, respectively. Finally, the frequency of AEs and out-patient visits and hospital admissions results in a further 0.43 and 0.33 visits for zanubrutinib and ibrutinib respectively. The total number of visits for zanubrutinib are therefore 4.52 per year, while the total number of annual visits for ibrutinib are 4.42. Amount of visits can be seen in Table 20 below.

Table 20: Total amount of hospital visits due to treatment

	Zanubrutinib	ibrutinib

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Number of visits*	Clinical control, blood test, distribution of medicine, and ECG	4,0	4,0
	Amyloidosis screening	0,04	0,04
	PN screening	0,05	0,05
	Adverse events	0,43	0,33
Total		**4,52**	**4,42**

To estimate the patients' time consumption for the visits, the following assumptions are used, Table 21. This has been validated by the clinical expert.

Table 21: Time spent on resource use for hospital contact and adverse events

Visit description	Resource items	Time used per year, hour(s) (year 1)	Time used per year, hour(s) (year 2 and beyond)
Start-up consultation with physician	-	0.5	0
Phone consultation with a physician	-	0.5	0
Clinical control with physician	-	1.5	2
Nurse, distribution of medicine to patient	-	1	1
Blood test/urin sample	-	0.67	0.67
ECG	-	0.33	0.33
Amyloidosis screening*	Spot urine sample (%) Plasma NT-proBNP (%) Alkaline phosphatase (%)	0.003	0.003
	Abdominal, subcutanous fat aspiration (%)	0.04	0.04
	Amyloidosis type determination (%)	0	0
PN screening**	Serum-anti-myelin associated glycoprotein (S-anti-MAG) (%)	0.0083	0.0083
	Consultation at neurologist (%)	0.025	0.025
	Nerve conduction examination	0.15	0.15
Transport		1	1
Out-patient visit		0.25	0.25
Admission		24 *(per admission day)*	24 *(per admission day)*

The clinical expert also estimated the number of outpatient visit per AE. It was estimated that most of the AEs only required one outpatient visit, while a few required two visits. Moreover, the amount of mean admission days as a consequence of patients experiencing an AE were estimated by the clinical expert. The trim point for long-term DRG

tariffs were identified using the Interactive DRG System. The model inputs for hospital resources can be found in Table 22 below.

Table 22: Hospital visits due to AEs

	Outpatient	Hospital admission	
Adverse event	Number of visits	Length of admission (days)	Long-term DRG tariff added after day (days)
Diarrhea	1	3	2
Upper respiratory tract infection	1	5	5
Nausea	1	2	2
Vomiting	1	3	2
Pyrexia	1	3	5
Pneumonia	1	4	10
Headache	1	2	5
Urinary tract infection	1	3	10
Hematuria	1	3	5
Extremity pain	1	2	1
Back pain	1	2	7
Atrial fibrillation	2	2	5
Febrile neutropenia	-	2	13
Neutropenia	2	4	13
Thrombocytopenia	2	2	13
Anemia	2	2	7

The total cost for patient-related costs can be found in Table 23 below.

Table 23: Total patient-related costs

	Zanubrutinb		Ibrutinib	
	Year 1	Year 2 and beyond	Year 1	Year 2 and beyond
Patient time	2.674,3 DKK	2.584,8 DKK	3.161,5 DKK	3.072,0 DKK
Transportation costs	435,8 DKK	435,8 DKK	425,7 DKK	425,7 DKK
Total	3.110,1 DKK	3.020,6 DKK	3.587,14 DKK	3.497,64 DKK

8.4 Results

Table 24 shows the total annual cost for the two interventions where all costs have been discounted. The cost results are divided into each category; drug costs, hospital costs, AE costs and patient-related costs. Based on the applied assumptions, where only drug cost and adverse event costs are reflected as relevant costs, it was found that zanubrutinib is cost-saving compared to ibrutinib throughout the treatment period.

Table 24: Total costs for zanubrutinib and ibrutinib, and incremental costs.

Zanubrutinib

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	Year 1	Year 2	Year 3	Year 4	Total
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	37.604 DKK	34.354 DKK	33.192 DKK	32.070 DKK	137.220 DKK
Adverse event costs	9.742 DKK	9.412 DKK	9.094 DKK	8.787 DKK	37.035 DKK
Patient costs	3.110 DKK	2.918 DKK	2.820 DKK	2.724 DKK	11.573 DKK
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Total**
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospital costs	37.604 DKK	34.354 DKK	33.192 DKK	32.070 DKK	137.220 DKK
Adverse event costs	9.456 DKK	9.136 DKK	8.827 DKK	8.529 DKK	35.947 DKK
Patient costs	3.587 DKK	3.379 DKK	3.265 DKK	3.155 DKK	13.386 DKK
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Total**
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospital costs	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
Adverse event costs	286 DKK	276 DKK	267 DKK	258 DKK	1.088 DKK
Patient costs	- 477 DKK	- 461 DKK	- 445 DKK	- 430 DKK	- 1.813 DKK
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The cost-minimization analysis results in an incremental cost per patient [redacted] Moreover, minor incremental values are shown in costs related to AEs and patients, whereas hospital costs are equal for both treatments.

8.5 Sensitivity analysis

The factor that could potentially affect the incremental costs in the cost-minimization analysis is assessed as the frequency of AEs (which indirectly have an impact on patient-related costs). To examine the effect of AE frequency, a sensitivity analysis where each AE were changed with 5% point in both a positive and negative direction was performed. The frequency could at minimum reach 0%. As the effect of zanubrutinib is deemed to be the same, the treatment length is also deemed to be the same. This has been validated by a clinician, and confirmed in the ASPEN study where the dose intensity is 98% for both treatments. A sensitivity analysis on treatment length is therefore irrelevant to conduct.

The results of the one-way deterministic sensitivity analysis can be found in the tornado diagram in Figure 8 below. This indicates that changes with +/- 5% in AE frequency do not affect the cost-effectiveness of zanubrutinib, why zanubrutinib is still favoured in a clinical setting.

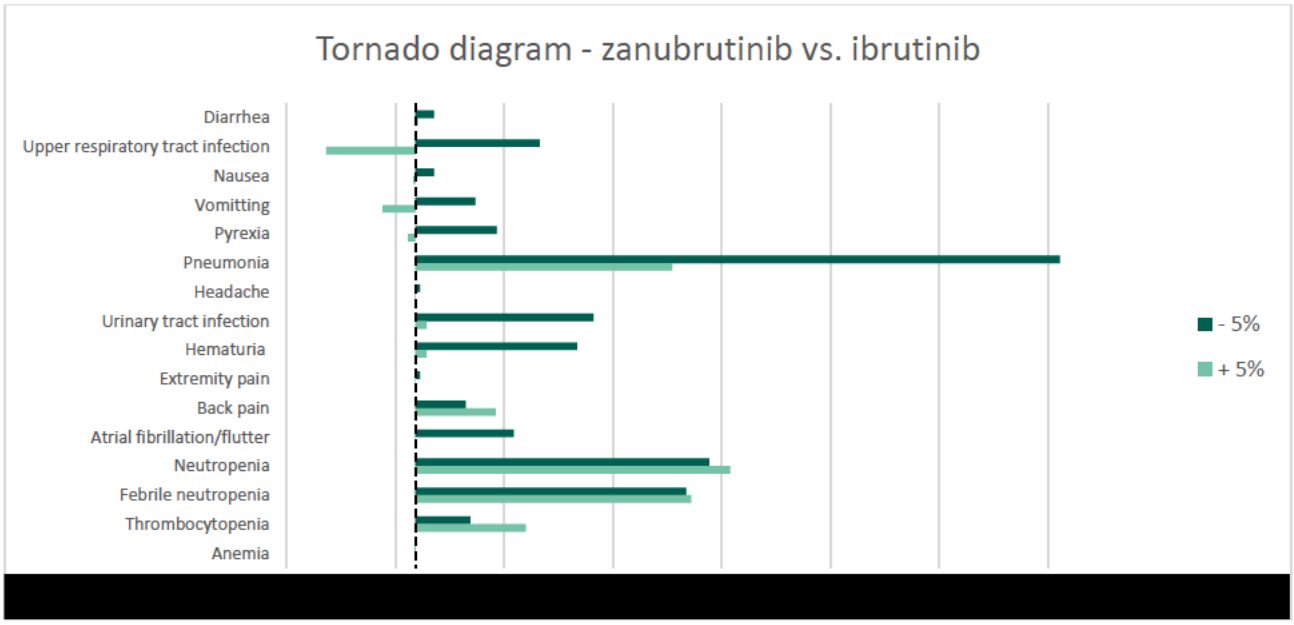

Figure 8. Tornado diagram illustrating the results of the one-way sensitivity analysis of change in AE frequencies. The results are stated as incremental costs of zanubrutinib vs. ibrutinib.

9. Budget impact analysis

A Danish clinical expert estimated that there are about 207 patients in Denmark who would theoretically be eligible for treatment with zanubrutinib or ibrutinib. It is however, not expected that all of these eligible patients will receive treatment, as many patients are in a wait and watch phase. Therefore, the budget calculations assumes that half of them, 104 patients, are currently treated with ibrutinib. This estimation is an assumption made without validation but used in the HTA submission in other countries, and the assumption is associated with uncertainty in regards to Danish practice. The clinical expert was not able to estimate the expected market uptake of zanubrutinib, but stated that new treatments in usual practice will slowly be implemented. The implementation and uptake may however be faster for a new treatment that is priced lower. Based on this input, the market uptake is expected to be the incident patient population corresponsing to approximately 4 patients per year if zanubrutinib is recommended.
Table 25 to Table 29 specify in detail expected budget consequences.

Table 25. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced.

	Year 1	Year 2	Year 3	Year 4	Year 5
Zanubrutinib	4	8	12	16	20
Ibrutinib	100	96	92	88	84
Total number of patients	104	104	104	104	104

Table 26. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced.

	Year 1	Year 2	Year 3	Year 4	Year 5
Zanubrutinib	0	0	0	0	0
Ibrutinib	104	104	104	104	104
Total number of patients	104	104	104	104	104

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Table 27. Costs per patient per year in DKK - if the pharmaceutical is recommended.

	Year 1	Year 2	Year 3	Year 4	Year 5
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28. Costs per patient per year in DKK - if the pharmaceutical is NOT recommended.

	Year 1	Year 2	Year 3	Year 4	Year 5
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 29. Expected budget impact of recommending the pharmaceutical for the current indication.

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact is zanubrutinib is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

It is expected that introduction of zanubrutinib in Denmark will result in [redacted]

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10. Discussion on the submitted documentation

Clinical data from the ASPEN study

The reported data from the ASPEN study reflects the same patient population as zanubrutinib is intended to treat in Denmark. According to the clinical expert, the characteristics of the study population are overall comparable to the Danish setting, thus considered to be transferable. Due to the transferability, it is expected that the efficacy and safety data reported in the ASPEN study can also be achieved in Danish patients (11).

However, the clinical expert pointed out that WM patient population in Denmark often have co-morbidities, and the clinical presentation of WM is therefore complicated and thus the treatment choice is dependent on the individual patient's clinical history. When compared to Danish setting, a potential weakness that can be associated with the ASPEN study is therefore that findings are not stratified in relation to co-morbidities, why the correlation between effect, safety, and co-morbidities is unknown and consequently the treatment outcomes may differ in the Danish patients.

The choice of comparator in the ASPEN study was validated by the clinical expert to be relevant and is widely used as a treatment for WM patients who are treatment-naïve and unfit for chemoimmunotherapy and experiences relapse after at least one prior treatment in Denmark. In conclusion, it is considered a strength that a head-to-head study reflecting the relevant patient population and relevant comparator in Denmark is used in this submission.

Adjustments to Danish setting

The data used for estimating the overall WM patient population and patients eligible for treatment is associated with uncertainties. On cancer.dk the incidence of WM is reported to be 25 patients per year, whereas the clinical guidelines and annual report for malignant lymphomas and CLL report a significantly higher incidence of 170-180 patients per year (4–6). According to the clinical expert, the majority (90%) of the patients reported in the annual report are WM patients and is evaluated to be representative of the population in Denmark. The incidence number reported on cancer.dk, is assessed by the clinical expert to be significantly lower than the clinical practice.

The prevalence was estimated by the clinical expert to be approximately 200 patients in Region Zealand and was assumed to be the same in the other regions of Denmark. Based on this assumption by the clinical expert, the prevalence in Denmark is estimated to be around 1000 WM patients.

As there is a clear discrepancy between literature and clinical practice, and thus an uncertainty surrounding the estimates from the literature, the number of eligible patients for treatment with Zanubrutinib was based on clinical expert input to best reflect the clinical practice. Moreover, the expected patients that are going to receive zanubrutinib is associated with uncertainties, as this number could not be validated by the clinical expert.

Health economic analysis

The cost-minimization analysis is conducted to reflect the relevant cost components subject to change if Zanubrutinib is recommended as standard treatment in Denmark. The relevant cost components include drug costs, hospital cost, AE cost and- and patient-related costs, where relevancy in a cost analysis was assessed by a clinical expert.

The two relevant factors resulting in a different costs, are the drug costs and the frequency of AEs. The drug cost is highly dependent on the treatment length, however as zanubrutinib and ibrutinib are assumed to have the same effect and the dose intensity was equal in the ASPEN study, the treatment length is estimated to be equal. A change in treatment length would therefore apply to both treatments, and not change the incremental cost.

The other factor affecting the incremental cost between the treatments are the frequency of AEs. To accommodate this, a sensitivity analysis was made where the frequency of each AEs was changed with +/- 5% points. The sensitivity analysis demontrated that zanubrutinib was still favourable even when the frequency of AEs changed.

Due to the uncertainty associated with the estimated patient population and unknown market uptake, there is also an uncertainty associated with the BIA. The market uptake of zanubrutinib patients has however been set at a low rate, meaning the BIA is a conservative estimate.

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Therefore it can be concluded that [redacted] and that zanubrutinib is still favoured even when uncertainties regarding AE frequency is taking into account.

11. List of experts

[redacted]

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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

Not applicable. As this submission is based on a pivotal head-to-head phase 3 study comparing zanubrutinib and ibrutinib in patients with WM a systematic literature search has been omitted. Thus, Appendix A has not been filled out.

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Appendix B Main characteristics of included studies

Trial name: BGB-3111-302 (ASPEN)	NCT number: NCT03053440
Objective	To directly compare safety and efficacy of ibrutinib vs zanubrutinib in patients with WM (11).
Publications – title, author, journal, year	A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study, Tam CS. Et al., Blood by the American Society of Hematology, 2020 (11).
Study type and design	Randomized open-label phase 3 study comparing ibrutinib and zanubrutinib in patients with WM who required treatment based on consensus criteria. Patients with $MYD88^{L265P}$ disease were assigned 1:1 to receive ibrutinib at the approved dose of 420 mg once daily or zanubrutinib, 160mg twice daily, in 28-day cycles until progression or intolerance (Cohort 1). Randomization was stratified by WHIM ($CXCR4^{WHIM}$) syndrome-like mutation status and number of prior lines of therapy. Patients with $MYD88^{WT}$ disease or with undetermined MYD88 mutation status were enrolled in Cohort 2 and received zanubrutinib on a third nonrandomized arm. Results from Cohort 2 were reported separately. Treatment interruption for ≤2 consecutive cycles and ≤2 dose reductions were permitted for management of recurring grade 3/4 treatment-related toxicities. Crossover at progression or due to intolerance in Cohort 1 was not permitted. (11)
Sample size (n)	In total, 201 patients were enrolled in Cohort 1 (11).

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Main inclusion and exclusion criteria	**Inclusion criteria** (12)**:** • 18 Years and older • All sexes eligible for study • Clinical and definitive histologic diagnosis of WM • Measurable disease, requiring treatment • Participants with no prior therapy for WM, must be considered inappropriate candidates for treatment with a standard chemoimmunotherapy regimen • Age ≥ 18 years old • ECOG-PS of 0-2 • Adequate bone marrow function • Adequate renal and hepatic function • Echocardiogram (ECHO)/Multigated Acquisition Scan (MUGA) demonstrating left ventricular ejection fraction (LVEF)≥ the lower limit of institutional normal • Subjects may be enrolled who relapse after autologous stem cell transplant if they are at least 3 months after transplant, and after allogeneic transplant if they are at least 6 months post transplant. • Females of childbearing potential must agree to use highly effective forms of birth control throughout the course of the study and at least up to 90 days after last dose of study drug. Males must have undergone sterilization- vasectomy, or utilize a barrier method • Life expectancy of > 4 months **Exclusion criteria** (12)**:** • Prior exposure to a BTK inhibitor • Evidence of disease transformation at the time of study entry • Corticosteroids given with antineoplastic intent within 7 days, or chemotherapy given with antineoplastic intent, targeted therapy, or radiation therapy within 3 weeks, or antibody-based therapy within 4 weeks of the start of study drug • Major surgery within 4 weeks of study treatment • Toxicity of ≥ Grade 2 from prior anticancer therapy • History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in-situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally with curative intent • Currently active, clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease within 6 months of screening • QTcF prolongation (defined as a QTcF > 450 msec) • Active, clinically significant Electrocardiogram (ECG) abnormalities • Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction • Uncontrolled active systemic infection or recent infection requiring parenteral anti-microbial therapy • Known human immunodeficiency virus (HIV), or active hepatitis B or hepatitis C • Pregnant or lactating women • Any life-threatening illness, medical condition, organ system dysfunction, need for profound anticoagulation, or bleeding disorder, which, in the investigator's opinion, could compromise the subject's safety Any medications which are strong or moderate cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or strong CYP3A inducers

Trial name: BGB-3111-302 (ASPEN)	NCT number: NCT03053440
Intervention	Zanubrutinib 160mg PO BID (twice daily) until PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor. 101 patients were enrolled and treated. (11,12)
Comparator(s)	Ibrutinib 420mg PO QD (once daily) until PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor. 98 patients were enrolled and treated. (11,12)
Follow-up time	The following assessments were planned (11): • Bone marrow aspiration and biopsy were collected at baseline, week 48, and as clinically indicated thereafter (including for confirmation of CR). Baseline bone marrow samples were assayed for MYD88 and CXCR4 mutations prior to cohort assignment. • Quantitative serum immunoglobulins (IgM, IgG, IgA), M-paraprotein, β-2 microglobulin levels were measured at baseline, the beginning of each cycle until cycle 12, and every 3 cycles thereafter. • Contrast-enhanced computed tomography or magnetic resonance imaging scans were performed at baseline; patients with extramedullary disease underwent follow-up scans every 3 cycles until cycle 12 and every 6 cycles thereafter until progression. • ECGs were performed on day 1 of cycles 1 and 2, every 4 cycles thereafter, and at the end of treatment. • QoL assessments (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and the European Quality of Life Five Dimensions Questionnaire) were collected at baseline, every 3 cycles until cycle 12, and every 6 cycles thereafter. The following statistical analyses were planned (11): • The primary efficacy analysis was planned to take place ~12 months after the last R/R patient was randomized.
Is the study used in the health economic model?	Yes.

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Trial name: BGB-3111-302 (ASPEN)	NCT number: NCT03053440

Primary, secondary and exploratory endpoints

Primary endpoint (11,12):

- Proportion of participants achieving either a CR or VGPR in Cohort 1 using an adaptation of the response criteria updated at the Sixth IWWM as assessed by an IRC.

Secondary endpoints (11,12):

- Efficacy measured by MRR in Cohort 1
- Efficacy measured by DOR in Cohort 1
- Efficacy measured by PFS in Cohort 1
- Resolution of treatment-precipitating symptoms in Cohort 1, measured by the absence of the symptoms that triggered initiation of study treatment (per the IWWM treatment guidelines) at any point during study treatment
- Anti-lymphoma effect in Cohort 1, measured by any reduction in bone marrow involvement
- Safety measured by the incidence, timing, and severity of treatment-emergent AEs in Cohort 1
- The incidence of AEs of Special Interest in Cohort 1
- New onset of atrial fibrillation and/or ventricular arrhythmia of any NCI-CTCAE v4.03 grade

Exploratory endpoints (11):

- OS
- QoL

Endpoints included in this application:

All the above-mentioned endpoints have been included in this application.

Other endpoints:

All endpoints from the ASPEN study have been included in this application.

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Trial name: BGB-3111-302 (ASPEN)	NCT number: NCT03053440

Method of analysis (11)

All efficacy analyses were ITT analyses.

PFS

PFS by treatment arm was estimated at the time of primary efficacy analysis by K-M methodology with censoring. Two-sided 95% CIs for median PFS were estimated with the Brookmeyer and Crowley method. K-M methodology was used to estimate PFS at selected time points, with corresponding 95% CIs estimated using Greenwood's formula.

DOR

Analysis methods for DOR were similar to those for PFS.

Response

A Cochran-Mantel-Haenszel test for difference in CR/VGPR rates was performed for both comparisons, with the magnitude of difference estimated as the weighted average across the randomization stratification factors, age groups (#65 vs .65 years), and the corresponding 2-sided 95% confidence intervals. Superiority was to be declared if the 2-sided P value from the Cochran-Mantel-Haenszel test was <.05 and the estimated difference was positive. Statistical significance for the first or both response comparisons was to trigger a test of noninferiority in MRRs between zanubrutinib and ibrutinib, using the estimated difference and its 95% CIs. Noninferiority would be declared if the lower limit of the 95% CI for the estimated difference in MRRs between zanubrutinib and ibrutinib excluded the prespecified margin for noninferiority, 28%. If the lower limit of the 95% CI excluded 0%, superiority of zanubrutinib in MRR would be declared. A total of 150 R/R patients randomized 1:1 in cohort 1 would provide 81.4% power to demonstrate superiority under an assumed CR/VGPR rate of 35% for zanubrutinib vs 15% for ibrutinib, using a normal approximation of a binomial test and a 2-sided a of 0.05. Noninferiority was powered to 85.5% under assumed MRRs of 90% and 80% for zanubrutinib and ibrutinib, respectively, and a noninferiority margin of 0.08.

Reduction in IgM levels

Reductions in IgM levels from baseline were assessed with parametric and nonparametric methods. A likelihood-based repeated-measures mixed model was used to estimate the slopes of IgM reduction from baseline and to compare the estimated slopes between arms. IgM reduction was also summarized as area under the (IgM) x time curve, with the treatment arm difference tested using the Mantel-Haenszel test. Logtransformed IgM levels were used in both analyses.

AEs

Crude incidence rates for all AEs and exposure adjusted incidence rates for adverse events of interest (AEIs) included all Cohort 1 patients who received any dose of ibrutinib or zanubrutinib and were summarized using descriptive statistics. The distribution of times to first occurrence of AEIs was summarized using K-M methodology.

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Trial name: BGB-3111-302 (ASPEN)	NCT number: NCT03053440
Subgroup analyses	Rates of CR/VGPR for selected subgroups defined by prespecified characteristics were summarized for each treatment arm in a forest plot. Subgroup characteristics were as follows (11): • Age (≤65 years, >65 years, ≤75 years, >75 years) • Gender (male, female) • Geographic region (Australia/New Zealand, Europe, North America) • Treatment type (R/R, TN) • Prior line of therapy (0, 1-3, >3) • Baseline ECOG-PS (0, ≥1) • Baseline CXCR4 mutation status by central lab (WHIM, WT/UNKNOWN) • Baseline IgM (<40 g/L, ≥40 g/L, missing) • Baseline B2 microglobulin (≤3 mg/L, >3 mg/L) • Baseline hemoglobin (≤110 g/L, >110 g/L) • Baseline platelet (≤100x10^9 /L, >100x10^9 /L) • Baseline presence of extramedullary disease by IRC (yes, no) • WM IPSS (high, intermediate, low)
Other relevant information	No

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Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	BCG-3111-302 (ASPEN)					
	R/R		TN		Overall	
	Ibrutinib (N = 81)	Zanubrutinib (N = 83)	Ibrutinib (N = 18)	Zanubrutinib (N = 19)	Ibrutinib (N = 99)	Zanubrutinib (N = 102)
Age, median (min, max), y	69 (52, 90)	69 (45, 87)	72 (38, 89)	74 (50, 81)	70 (38, 90)	70 (45, 87)
Age > 75 years, no. (%)	16 (20)	27 (33)	6 (33)	7 (37)	22 (22)	34 (33)
Male sex, no. (%)	53 (65)	58 (70)	12 (67)	11 (58)	65 (66)	69 (68)
ECOG-PS, no. (%)						
0/1	76 (94)	78 (94)	16 (89)	18 (95)	92 (93)	96 (94)
2	5 (6)	5 (6)	2 (11)	1(5)	7 (7)	6 (6)
Prognostic category at study entry*						
Low	12 (15)	16 (19)	1 (6)	1 (5)	13 (13)	17 (17)
Intermediate	34 (42)	30 (36)	8 (44)	8 (42)	42 (42)	38 (37)
High	35 (43)	37 (45)	9 (50)	10 (53)	44 (44)	47 (46)
Median (min, max) time from initial diagnosis, years	5.9 (0.1, 25)	5.3 (0.1, 23)	1.7 (0.1, 17)	0.5 (0.1, 9)	4.9 (0.1, 25)	4.4 (0.1, 23)
Prior lines of therapy, median (min, max), no.	1 (1, 6)	1 (1, 8)	0 (0, 0)	0 (0, 0)	1 (0, 6)	1 (0, 8)
0, no. (%)	0	0	18 (100)	19 (100)	18 (18)	19 (19)
1-3, no. (%)	74 (91)	76 (92)	0	0	74 (75)	76 (75)
>3, no. (%)	7 (9)	7 (8)	0	0	7 (7)	7 (7)
Prior stem cell transplant, no. (%)	1 (1)	3 (4)	0	0	1 (1.0)	3 (2.9)
IgM, median (min, max), g/L †	33.4 (2.4, 108)	30.4 (5.8, 73)	36.8 (9.9, 100)	35.7 (8.1, 87)	34.2 (2.4, 108)	31.8 (5.8, 87)
≥ 40 g/L, no. (%)	30 (37)	28 (34)	8 (44)	8 (42)	38 (38)	36 (35)
< 40 g/L, no. (%)	50 (62)	55 (66)	10 (56)	11 (58)	60 (61)	66 (65)
Missing data, no. (%)	1 (1)	0	0	0	1 (1.0)	0
β2-microglobulin, median (min, max), mg/L	4.2 (1.7, 13.6)	4.1 (1.6, 21.7)	4.1 (1.8, 10.3)	4.7 (2.1, 12.1)	4.2 (1.7, 13.6)	4.3 (1.6, 21.7)
>3 mg/L, no. (%)	60 (74)	62 (75)	14 (78)	13 (68)	74 (75)	75 (74)
MYD88‡/CXCR4 genotype, no. (%)						

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MYD88^{L265P}/CXCR4^{WT}	73 (90)	73 (88)	17 (94)	18 (95)	90 (91)	91 (89)
MYD88^{L265P}/CXCR4^{WHIM}	8 (10)	10 (12)	0(0)	1 (5)	8 (8)	11 (11)
MYD88^{L265P}/CXCR4^{UNK}▪	0	0	1 (6)	0	1 (1.0)	0
Bone marrow involvement, no. (%)¶	72 (89)	77 (93)	17 (94)	19 (100)	89 (90)	96 (94)
Tumor cells, median (min, max)	60 (0, 90)	60 (0, 90)	70 (8, 90)	70 (10, 90)	60 (0, 90)	60 (0, 90)
Extramedullary disease, no. (%)	58 (72)	64 (77)	15 (83)	17 (90)	73 (74)	81 (79)
Lymphadenopathy	53 (65)	63 (76)	14 (78)	16 (84)	67 (68)	79 (78)
Splenomegaly	10 (12)	14 (17)	3 (17)	3 (16)	13 (13)	17 (17)
Other‖	3 (4)	0	0	1 (5)	1 (1)	4 (2)
Peripheral blood cytopenias, no. (%)						
Haemoglobin ≤ 110 g/L	43 (53)	51 (61)	10 (56)	16 (84)	53 (54)	67 (66)
Platelet count ≤ 100 x 10^9/L	12 (15)	10 (12)	0	2 (11)	12 (12)	12 (12)
ANC ≤ 1.5 x 10^9/L	7 (9)	8 (10)	0	3 (16)	7 (7)	11 (11)

Percentages may not add to 100% because of rounding.
ECOG-PS, Eastern Cooperative Oncology Group performance status; max, maximum; min, minimum; WHIM, warts, hypogammaglobulinemia, infections, myelokathexis; WT, wild-type.
* Patients were assigned 1 point for each of the following baseline characteristics: age >65 years; hemoglobin ≤11.5 g/dL; platelet count ≤100 x 10^9/L; β-2 microglobulin level > 3 mg/L; and M paraprotein levels >7.0 g/dL. Patients with a score of 0 or 1 (excepting age) were assigned to the low-risk category, those >65 years old or with a score of 2 were assigned to the intermediate-risk category. and those with a score ≥3 were assigned to the high-risk category.[29] M-paraprotein levels were quantitated by serum protein electrophoresis.
† Central laboratory nephelometric assessments.
‡ Three patients (all zanubrutinib treated and all TN) had second missense mutations detected within the Toll/interleukin-1 receptor (TIR) binding domain of MYD88: M232T, V217F, and P182L. Additional mutations were identified in non-TIR binding domains in 4 patients: D165del (R/R zanubrutinib patient); W91ter, G93ter (R/R ibrutinib patient); L72M (RR zanubrutinib patient); and T107S, fs24ter (TN zanubrutinib patient).
§ Mutation testing using a next-generation sequencing method performed in a local laboratory revealed the presence of MYD88^{L265P} in baseline bone marrow aspirate.
¶ Based on imaging studies, as assessed by independent review. Lymphadenopathy was defined as the presence of ≥1 lymph node with a long axis >1.5 cm or other extranodal lesions with a short axis > 1.0 cm. Splenomegaly was defined as a spleen length (cranial to caudal) >13 cm.
‖ Three patients had discrete extranodal splenic lesions; 1 patient had 2 breast lesions.

Comparability of patients across studies

Not applicable as this application only includes one study; a pivotal phase 3 study (ASPEN) directly comparing the intervention and comparator.

Comparability of the study populations with Danish patients eligible for treatment

Overall, the ASPEN study population reflects the Danish patients that are eligible for treatment with zanubrutinib. According to the clinical expert, it should however be mentioned that the median age for R/R patients is 69 years, where the Danish population have a median age of 70 years when receiving a diagnosis. Thus, age is skewed and R/R patients in Denmark are expected to be 4-5 years elder than the study population. Since the economic evaluation does not involve age-related assumptions, this is not expected to affect results.
Moreover, the expert stated that based on usual practice several Danish patients suffer from anemia, why the baseline hemoglobin level does not match Danish setting. At last, Danish patients often have comorbidities, and treatment choice is dependent of this as well.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures.

Outcome measure	Definition	Validity	Clinical relevance
CR	Normal serum IgM values • Disappearance of monoclonal protein by immunofixation • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy/splenomegaly (if present at baseline) (11)	CR is assessed using an adaptation of the response criteria updated at the IWWM-6. *Data cut-off Aug 2019:* CR is assessed by IRC. *Data cut-off Aug 2020:* CR is investigator-assessed.	Superiority was to be declared if the 2-sided P-value from the Cochran-Mantel-Haenszel test was <.05 and the estimated difference was positive. (11) IgM levels from baseline were assessed with parametric and nonparametric methods. (11)
VGPR	Monoclonal IgM protein is detectable • ≥90% reduction in serum IgM level from baseline or normal serum IgM values • Improvement in lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease (11)	VGPR is assessed using an adaptation of the response criteria updated at the IWWM-6. *Data cut-off Aug 2019:* VGPR is assessed by IRC. *Data cut-off Aug 2020:* VGPR is investigator-assessed.	Superiority was to be declared if the 2-sided P-value from the Cochran-Mantel-Haenszel test was <.05 and the estimated difference was positive. (11) Reductions in IgM levels from baseline were assessed with parametric and nonparametric methods. (11)

Outcome measure	Definition	Validity	Clinical relevance
MRR	The proportion of participants achieving a best response of response of CR, VGPR, or partial response (PR) (12) • ≥50% reduction of serum IgM from baseline • Reduction in lymphadenopathy/splenomegaly (if present at baseline) (11)	MRR is assessed using an adaptation of the response criteria updated at the IWWM-6. (1) *Data cut-off Aug 2019:* MRR is assessed by IRC. *Data cut-off Aug 2020:* MRR is investigator-assessed.	Noninferiority is declared if the lower limit of the 95% CI for the estimated difference in MRRs between zanubrutinib and ibrutinib excludes the prespecified margin for non-inferiority, 28%. If the lower limit of the 95% CI excluded 0%, superiority of zanubrutinib in MRR would be declared. (11) Reductions in IgM levels from baseline were assessed with parametric and nonparametric methods. Differences was investigated using the Mantel-Haenszel test. (11)
PFS	Time from randomization to the first documentation of progression or death, whichever occurs first (12) PD: At least one of the following: • Confirmed, ≥25% increase in serum IgM and total on-treatment increase of ≥500 mg/dL from nadirc • New lymph node(s) >1.5 cm, or ≥50% increase from nadir in the sum of the product of diameter	PFS is assessed using an adaptation of the response criteria updated at the IWWM-6. (1) *Data cut-off Aug 2019:* PFS is assessed by IRC. *Data cut-off Aug 2020:* PFS is investigator-assessed.	Clinical relevance investigated using K-M methodology with censoring. Two-sided 95% CIs for median PFS were estimated with the Brookmeyer and Crowley method. 95% CIs estimated using Greenwood's formula. K-M methodology was used to estimate PFS at selected time points, with corresponding 95% CIs estimated using Greenwood's formula. (11) Reductions in IgM levels from baseline were assessed with parametric and nonparametric methods. Differences was investigated using the Mantel-Haenszel test. (11)

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Outcome measure	Definition	Validity	Clinical relevance
	(SPD) of >1 node, or ≥50% increase in longest diameter of a previously identified node • New splenomegaly or ≥ 50% increase from nadir in enlargement • New extranodal disease New or recurrent involvement in bone marrow New symptomatic disease (11)		
DOR	The time from first determination of response (CR, VGPR or PR) until first documentation of progression or death, whichever comes first (12)	DOR is assessed using an adaptation of the response criteria updated at the IWWM-6. (1) *Data cut-off Aug 2019:* DOR is assessed by IRC. *Data cut-off Aug 2020:* DOR is investigator-assessed.	Clinical relevance investigated using K-M methodology with censoring. Two-sided 95% CIs for median PFS were estimated with the Brookmeyer and Crowley method. 95% CIs estimated using Greenwood's formula. Follow-up for DOR was estimated using the reverse K-M method. (11)
Safety assessed by AEs	AE assessments (including AEIs) included incidence, timing and severity of treatment-emergent AEs. (12)	Graded according to the National Cancer Institute Common Toxicity Criteria version 4.03.	Crude incidence rates for all AEs and exposure-adjusted incidence rates for AEIs were summarized using descriptive statistics. The distribution of times to first occurrence of AEIs was summarized using K-M methodology. (11)

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Outcome measure	Definition	Validity	Clinical relevance
	AEIs were identified in accordance with predefined Medical Dictionary for Regulatory Activities, MedDRA, (Version 22.0).		
Resolution of treatment-precipitating symptoms	Absence of the symptoms that triggered initiation of study treatment (per the IWWM treatment guidelines) at any point during study treatment. (12)	Assessed using the IWWM treatment guidelines. (12)	[redacted] (51)
Anti-lymphoma effect	Any reduction in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or hepatosplenomegaly and/or splenomegaly by CT scan, at any time during the course of study treatment. (12)	Assessed by IRC (51)	N/A
OS	Time from randomization to the date of death	N/A	[redacted] (51)
QoL	N/A	QoL was assessed using Cancer European Organization for Research and Treatment of Cancer Quality of	N/A

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Outcome measure	Definition	Validity	Clinical relevance
		Life Questionnaire-Core 30 (EORTC QLQ-C30) and the EuroQol- 5 Dimension (EQ-5D) instrument. (11)	

Results of the ASPEN study.

Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
VGPR/CR *(Data cut-off 2019)* **ITT population**	Zanubrutinib	29/102	28.4 % (20-38)	9	-2.62, 20.66**	0.09 0.13**	RR: 1.48*	RR: 0.89, 2.46*	RR: 0.13*	Cochran-Mantel Haenszel	(11)
	Ibrutinib	19/99	19.2 % (12-28)								
VGPR/CR *(Data cut-off 2019)* **R/R population**	Zanubrutinib	24/83	29 % (20-40)	9	-4.21, 21.78**	0.12 0.18**	RR: 1.46*	RR: 0.84, 2.55*	RR: 0.18*	Cochran-Mantel Haenszel	(11)
	Ibrutinib	16/81	20 % (12-30)								
VGPR/CR *(Data cut-off 2019)* **TN population**	Zanubrutinib	5/19	26% (9-51)	9	-17.79, 34.01**	0.54 0.51**	RR: 1.58*	RR: 0.44, 5.67*	RR: 0.48*	Cochran-Mantel Haenszel	(11)
	Ibrutinib	3/18	17% (4-41)								

Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
VGPR/CR *(Data cut-off 2020)* **ITT population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
VGPR/CR *(Data cut-off 2020)* **R/R population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
VGPR/CR *(Data cut-off 2020)* **TN population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
Major response (PR or better) *(Data cut-off 2019)* **ITT population**	Zanubrutinib	79/102	77.5 % (68-85)	-0.3	-11.22, 11.75**	0.96**	RR: 1.00*	RR: 0.86, 1.16*	RR: 0.96*	Cochran-Mantel Haenszel	(11)
	Ibrutinib	77/99	77.8 % (68-86)								
Major response (PR or better)	Zanubrutinib	65/83	78 % (68-87)	-2		0.75**	RR: 0.98*	RR: 0.83, 1.14*	RR: 0.76*		(11)

Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	Description of methods used for estimation	References
(Data cut-off 2019) R/R population	Ibrutinib	65/81	80 % (70-88)		-10.52, 14.39**					Cochran-Mantel Haenszel	
Major response (PR or better) *(Data cut-off 2019)* TN population	Zanubrutinib	14/19	74 % (49-91)	7	-21.15, 34.08**	0.65**	RR: 1.11*	RR: 0.72, 1.69*	RR: 0.64*	Cochran-Mantel Haenszel	(11)
	Ibrutinib	12/18	67 % (41-87)								
Major response (PR or better) *(Data cut-off 2020)* ITT population	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
Major response (PR or better) *(Data cut-off 2020)* R/R population	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
Major response (PR or better) *(Data cut-off 2020)* TN population	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								

Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Progression free probability 18-mo after first response ***(Data cut-off 2019)*** **ITT population**	Zanubrutinib	27/29	93% (59-99)	29	5.91, 51.75**	0.01**	RR: 1.47	RR: 1.03, 2.11	RR: 0.03	K-M methodology and Greenwood's formula	(11)
	Ibrutinib	12/19	64% (29-85)								
Progression free probability 18-mo after first response ***(Data cut-off 2019)*** **R/R population**	Zanubrutinib	22/24	**90 %** (47-99)	26	0.16, 50.98**	0.05**	RR: 1.47	RR: 0.98, 2.18	RR: 0.06	K-M methodology and Greenwood's formula	(11)
	Ibrutinib	10/16	**64 %** (29-85)								
Progression free probability 18-mo after first response ***(Data cut-off 2019)*** **TN population**	Zanubrutinib	5/5	**100 %** (NE-NE)	N/A	N/A	N/A	N/A	N/A	N/A	K-M methodology and Greenwood's formula	(11)
	Ibrutinib	NE/3	**NE** (NE-NE)								

Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Progression free probability 18, 24, 30-mo after first response *(Data cut-off 2020)* **ITT population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Progression free probability 18, 24, and 30-mo after first response *(Data cut-off 2020)* **R/R population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Progression free probability 18, 24, and 30-mo after first response *(Data cut-off 2020)* **TN population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Ibrutinib	[redacted]	[redacted]							[redacted]	(51)

Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Duration of major response (18-mo event free rate)	Zanubrutinib	67/79	85% (72-93)	-3						K-M methodology and Greenwood's formula	(11)
(Data cut-off 2019)	Ibrutinib	68/77	88% (77-94)		-8.04, 13.96**	0.59**	RR: 0.96*	RR: 0.85, 1.09*	RR: 0.52*		
ITT population											
Duration of major response (18-mo event free rate)	Zanubrutinib	57/65	**87 %** (73-94)	1						K-M methodology and Greenwood's formula	(11)
(Data cut-off 2019)	Ibrutinib	56/65	**86 %** (73-93)		**-11.12, 13.12****	0.89**	RR: 1.02*	RR: 0.89, 1.16*	RR: 0.79*		
R/R population											
Duration of major response (18-mo event free rate)	Zanubrutinib	11/14	**80 %** (39-95)	- 20						K-M methodology and Greenwood's formula	(11)
(Data cut-off 2019)	Ibrutinib	12/12	100 % (NE-NE)		-7.61, 46.11**	0.11**	RR: 0.79*	RR: 0.60, 1.03*	RR: 0.08**		
TN population											
	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)

Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Duration of major response (12-mo event free rate) *(Data cut-off 2020)* **ITT population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (12-mo event free rate) *(Data cut-off 2020)* **R/R population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (12-mo event free rate) *(Data cut-off 2020)* **TN population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)

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Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Duration of major response (18-mo event free rate) ***(Data cut-off 2020)*** **ITT population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (18-mo event free rate) ***(Data cut-off 2020)*** **R/R population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (18-mo event free rate) ***(Data cut-off 2020)*** **TN population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (24-mo event free rate)	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)

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Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
(Data cut-off 2020) **ITT population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (24-mo event free rate)	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
(Data cut-off 2020) **R/R population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (24-mo event free rate)	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
(Data cut-off 2020) **TN population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of major response (30-mo event free rate)	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
(Data cut-off 2020) **ITT population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

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Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Duration of major response (30-mo event free rate) *(Data cut-off 2020)* **R/R population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
Duration of major response (30-mo event free rate) *(Data cut-off 2020)* **TN population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
PFS (12-mo event-free rate) *(Data cut-off 2020)* **ITT population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
PFS (12-mo event-free rate)	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)

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Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
(Data cut-off 2020) **R/R population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
PFS (12-mo event-free rate) ***(Data cut-off 2020)*** **TN population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
PFS (18-mo event-free rate) ***(Data cut-off 2019)*** **ITT population**	Zanubrutinib	87/102	85 % (75-91)	1			HR: 0.846	HR: 0.425, 1.759	HR: 0.6874	K-M methodology and Greenwood's formula	(11)
	Ibrutinib	83/99	84 % (75-90)		-9.96, 11.45**	0.85**	RR: 1.02*	RR: 0.90, 1.15*	RR: 0.78*		
PFS (18-mo event-free rate) ***(Data cut-off 2019)*** **R/R population**	Zanubrutinib	71/83	**86%** (74-93)	4						K-M methodology and Greenwood's formula	(11)
	Ibrutinib	66/81	**82%** (71-89)		-7.36, 15.39**	0.49**	RR: 1.05*	RR: 0.92, 1.20*	RR: 0.48*		

Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
PFS (18-mo event-free rate) ***(Data cut-off 2019)*** **TN population**	Zanubrutinib	15/19	**78%** (52-91)	-16	-8.11, 38.86**	0.17	RR: 0.84*	RR: 0.65, 1.08*	RR: 0.17*	K-M methodology and Greenwood's formula	(11)
	Ibrutinib	17/18	**94%** (63-99)								
PFS (18-mo event-free rate) ***(Data cut-off 2020)*** **ITT population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
PFS (18-mo event-free rate) ***(Data cut-off 2020)*** **R/R population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
PFS (18-mo event-free rate)	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)

Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
(Data cut-off 2020) **TN population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
PFS (24-mo event-free rate) ***(Data cut-off 2020)*** **ITT population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
PFS (24-mo event-free rate) ***(Data cut-off 2020)*** ***R/R* population**	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
PFS (24-mo event-free rate)	Zanubrutinib	[redacted]	[redacted]	[redacted]						[redacted]	(51)

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Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
(Data cut-off 2020) **TN population**	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
PFS (30-mo event-free rate) ***(Data cut-off 2020)*** **ITT population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
PFS (30-mo event-free rate) ***(Data cut-off 2020)*** **R/R population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
PFS (30-mo event-free rate) ***(Data cut-off 2020)*** **TN population**	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								

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Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Anti-lymphoma effect (Patients with positive baseline BM involvement and/or lymphadenopathy and/or splenomegaly by CT scan (IRC) at baseline)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
ITT population											
Anti-lymphoma effect (reduction in bone marrow involvement)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
ITT population											
Anti-lymphoma effect (reduction in size of lymphadenopathy and/or splenomegaly)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
ITT population											

Table A3a Results of ASPEN (BGB-3111-302)

				Estimated absolute difference in effects			Estimated relative difference in effects				
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Anti-lymphoma effect (Patients with positive baseline BM involvement and/or lymphadenopathy and/or splenomegaly by CT scan (IRC) at baseline)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
R/R population											
Anti-lymphoma effect (reduction in bone marrow involvement)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
R/R population											
Anti-lymphoma effect (reduction in size of lymphadenopathy and/or splenomegaly)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								

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Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	Description of methods used for estimation	References
R/R population											
Anti-lymphoma effect (Patients with positive baseline BM involvement and/or lymphadenopathy and/or splenomegaly by CT scan (IRC) at baseline)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
TN population											
Anti-lymphoma effect (reduction in bone marrow involvement)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
TN population											
Anti-lymphoma effect (reduction in size of lymphadenopathy and/or splenomegaly)	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(11,51)
	Ibrutinib	[redacted]	[redacted]								
TN population											

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Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
Patients with resolution of all treatment-precipitating symptoms	Zanubrutinib	[redacted]	[redacted]	[redacted]							
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
ITT population											
Patients with resolution of any treatment-precipitating symptoms	Zanubrutinib	[redacted]	[redacted]	[redacted]							
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
ITT population											
Patients with resolution of all treatment-precipitating symptoms	Zanubrutinib	[redacted]	[redacted]	[redacted]							
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
R/R population											
Patients with resolution of any treatment-precipitating symptoms	Zanubrutinib	[redacted]	[redacted]	[redacted]							
	Ibrutinib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)

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Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
R/R population											
Patients with resolution of all treatment-precipitating symptoms	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
TN population											
Patients with resolution of any treatment-precipitating symptoms	Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	Ibrutinib	[redacted]	[redacted]								
TN population											
OS *(18-mo event-free rate)*	Zanubrutinib	96/102	97%	4	-2.46, 11.07**	0.19**	RR: 0.1.02*	RR: 0.95, 1.10*	RR: 0.54*	K-M methodology and Greenwood's forrmula	(11,51)
(Data cut-off 2019)	Ibrutinib	91/99	93%								
ITT population											
OS *(24-mo event-free rate)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
(Data cut-off 2020)	[redacted]	[redacted]	[redacted]								
ITT population											

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Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	Description of methods used for estimation	References
OS *(30-mo event-free rate)* *(Data cut-off 2020)* ITT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
OS *(24-mo event-free rate)* *(Data cut-off 2020)* R/R population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
OS *(30-mo event-free rate)* *(Data cut-off 2020)* R/R population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
OS *(24-mo event-free rate)* *(Data cut-off 2020)* TN population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(51)
	[redacted]	[redacted]	[redacted]	[redacted]							(51)

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Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**	**Description of methods used for estimation**	**References**
OS *(30-mo event-free rate)* [redacted]											
(Data cut-off 2020)											
TN population											
≥1 AEs	Zanubrutinib	98/101	97.0%	-2	-2.93, 7.48**	0.32**	RR: 0.98*	RR: 0.94, 1.02*	RR: 0.32*	Descriptive statistics used	(11,52)
	Ibrutinib	97/98	99.0%								
AEs grade 3 or higher	Zanubrutinib	59/101	58.4%	-4.9	-8.55, 18.08**	0.48**	RR: 0.92*	RR: 0.74, 1.15*	RR: 0.48*	Descriptive statistics used	(11,52)
	Ibrutinib	62/98	63.3%								
Serious AEs	Zanubrutinib	40/101	39.6%	-1.2	-12.21, 14.57**	0.86**	RR: 0.97*	RR: 0.69, 1.36*	RR: 0.86*	Descriptive statistics used	(11,52)
	Ibrutinib	40/98	40.8%								
AEs leading to death	Zanubrutinib	1/101	1.0%	-3.1	-1.97, 9.11**	0.17**	RR: 0.24*	RR: 0.03, 2.13*	RR: 0.20*	Descriptive statistics used	(52)
	Ibrutinib	4/98	4.1%								
AEs leading to treatment discontinuation	Zanubrutinib	4/101	4%	-5.2	-2.01, 12.95**	0.14**	RR: 0.43*	RR: 0.14, 1.40*	RR: 0.15*	Descriptive statistics used	(11)
	Ibrutinib	9/98	9.2%								
AEs leading to dose reductions	Zanubrutinib	14/101	13.9%	-9.6	-1.28, 20.36**	0.08**	RR: 0.59*	RR: 0.32, 1.08*	RR: 0.09*	Descriptive statistics used	(11)
	Ibrutinib	23/98	23.5%								
AEs leading to dose held	Zanubrutinib	47/101	46.5%	-9.6	-4.22, 22.92**	0.18**	RR: 0.83*	RR: 0.63, 1.09*	RR: 0.18*	Descriptive statistics used	(52)
	Ibrutinib	55/98	56.1%								
≥1 TRAE	Zanubrutinib	80/101	79.2%	-6.5							(52)

Table A3a Results of ASPEN (BGB-3111-302)												
				Estimated absolute difference in effects			Estimated relative difference in effects					
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	Description of methods used for estimation	References
	Ibrutinib	84/98	85.7%		-4.20, 17.02**	0.23**	RR: 0.92*	RR: 0.81, 1.05*	RR: 0.23*	Descriptive statistics used	
≥1 AESI	Zanubrutinib	86/101	85.1%	2.4							
	Ibrutinib	81/98	82.7%		-7.91, 12.76**	0.65**	RR: 1.03*	RR: 0.91, 1.16*	RR: 0.63*	Descriptive statistics used	(52)

Appendix E Safety data for intervention and comparator(s)

Adverse events of special interest

Notably, the AEs of special interest for the disease of WM from the data cut-off in January 2020 have been summarized in Table 1. Particularly to the patient with WM, a significant reduction in the risk of atrial fibrillation/flutter (3.0% vs 18.4%), as well as a lower rates of major bleeding (5.9% vs 10.2%), diarrhea (21.8% vs 32.7%), and hypertension (12.9% vs 20.4%) has been observed and concluded in the zanubrutinib group. Despite higher rates of neutropenia with zanubrutinib, the Grade ≥3 infection rates were similar. (52)
At the data cut-off in January 2020, five additional patients had discontinued ibrutinib treatment due to AEs and no patients from the zanubrutinib arm discontinued treatment due to AEs. (52)

Table 1. AESIs in the ASPEN-study (52).

AE Categories, n (%) (pooled terms)	All Grades		Grade ≥ 3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter†	18 (18.4%)	3 (3.0%)	7 (7.1%)	0 (0)
Diarrhea (preferred term)	32 (32.7%)	22 (21.8%)	2 (2.0%)	3 (3.0%)
Hemorrhage	59 (60.2%)	51 (50.5%)	9 (9.2%)	6 (5.9%)
Major hemorrhage[a]	10 (10.2%)	6 (5.9%)	9 (9.2%)	6 (5.9%)
Hypertension	20 (20.4%)	13 (12.9%)	15 (15.3%)	8 (7.9%)
Neutropenia[b†]	15 (15.3%)	32 (31.7%)	8 (8.2%)	23 (22.8%)
Infection	70 (71.4%)	70 (69.3%)	23 (23.5%)	19 (18.8%)
Second malignancy	12 (12.2%)	13 (12.9%)	1 (1.0%)	3 (3.0%)

[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
[b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
†Descriptive two-sided P-value <0.05.

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Treatment-emergent adverse events

Comparison of incidence and severity of AEs suggest that treatment with zanubrutinib is related to fewer overall TEAE and grade ≥ 3 TEAE. See Table 2. (11)

TEAEs that were reported at >10% higher frequency among ibrutinib recipients were diarrhoea (32% versus 21%), contusion (24% versus 13%), muscle spasms (24% versus 10%), epistaxis (19% versus 13%), peripheral oedema (19% versus 9%), atrial fibrillation (15% versus 2%), and pneumonia (12% versus 2%). Conversely, neutropenia was the only TEAE reported at a > 10% higher frequency among zanubrutinib recipients compared with ibrutinib recipients (29% versus 13%). (11)

Grade 3 or higher TEAEs were reported less frequently in zanubrutinib recipients (58%) compared with ibrutinib recipients (63%). Grade 3 or higher AEs reported at a higher frequency among ibrutinib recipients include pneumonia (7% versus 1%), hypertension (11% versus 6%), and atrial fibrillation (4% versus 0%). Grade 3 or higher AEs reported at a higher frequency among zanubrutinib recipients were neutropenia (20% versus 8%), back pain (4% versus 0%), febrile neutropenia (4% versus 0%), and neutrophil count decreased (4 patients versus 1 patient). (11)

Table 2: TEAEs for the overall ITT population in the ASPEN study (52).

	Zanubrutinib (n = 101)		Ibrutinib (n = 98)	
Event term, n (%)	**All grade**	**Grade ≥ 3**	**All grade**	**Grade ≥ 3**
Nonhematologic AEs				
Diarrhea*	21 (21)	3 (3)	31 (32)	1 (1)
Upper respiratory tract infection	24 (24)	0	28 (29)	1 (1)
Contusion*	13 (13)	0	23 (24)	0
Muscle spasm*	10 (10)	0	23 (24)	1 (1)
Epistaxis	13 (13)	0	19 (19)	0
Peripheral edema*	9 (9)	0	19 (19)	0
Cough	13 (13)	0	17 (17)	0
Rash	13 (13)	0	16 (16)	0
Hypertension	11 (11)	6 (6)	16 (16)	11 (11)

Arthralgia	13 (13)	3 (3)	16 (16)	0
Fatigue	19 (19)	1 (1)	15 (15)	1 (1)
Atrial fibrillation/flutter*	2 (2)	0	15 (15)	4 (4)
Nausea	15 (15)	0	13 (13)	1 (1)
Vomiting	9 (9)	0	13 (13)	1 (1)
Pyrexia	13 (13)	2 (2)	12 (12)	2 (2)
Pneumonia*	2 (2)	1 (1)	12 (12)	7 (7)
Headache	15 (15)	1 (1)	11 (11)	1 (1)
Urinary tract infection	10 (10)	0	10 (10)	2 (2)
Hematuria	7 (7)	0	10 (10)	2 (2)
Dizziness	13 (13)	0	9 (9)	0
Constipation	16 (16)	0	7 (7)	0
Nasopharyngitis	11 (11)	0	7 (7)	0
Extremity pain	11 (11)	1 (1)	7 (7)	0
Back pain	14 (14)	4 (4)	6 (6)	0
Dyspnea	14 (14)	0	6 (6)	0
Hematologic AEs				
Neutropenia*	29 (29)	19 (20)[†]	13 (13)	8 (8)[†]
Febrile neutropenia	4 (4)	4 (4)	0	0
Thrombocytopenia	10 (10)	6 (6)	10 (10)	3 (3)
Anemia	12 (12)	5 (5)	10 (10)	5 (5)

Data are for treatment-emergent AEs in all Cohort 1 patients. Listed events were reported in ≥10% of patients (all grade) or for grade ≥3, in ≥5% in either arm. Events are listed in descending order of frequency by all-grade incidence in the ibrutinib arm.

*The difference in all-grade incidence between arms is ≥10%. P=.05, P=.005, and P=.02 for comparisons of all-grade diarrhea, muscle spasms, and peripheral edema, respectively. P=.0004 and P=.02 for the comparisons of all-grade and grade ≥3 atrial fibrillation, and P=.002 and P=.02 for all-grade and grade ≥3 pneumonia, respectively. All P values (1-sided, testing ibrutinib > zanubrutinib event rates) were calculated using Barnard's exact test without adjustment for multiplicity.

†Includes the *Medical Dictionary for Regulatory Activities*–preferred term "neutrophil count decreased" in 1 and 4 patients in the ibrutinib and zanubrutinib arms, respectively.

Serious advers events

Overall, 41% of ibrutinib and 40% of zanubrutinib patients experienced ≥1 serious AE. The most common of these were associated with infections (pneumonia, neutropenia and febrile neutropenia, influenza, pyrexia, and sepsis). See Table 3. (11,53)

Table 3: Serious AEs reported in >1 patient in either treatmen arm (52,53).

Event term, n (%)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Pneumonia	9 (9)	1 (1)
Sepsis	3 (3)	2 (2)
Pyrexia	3 (3)	2 (2)
Atrial fibrillation/flutter	3 (3)	0 (0)
Cholecystitis	2 (2)	0 (0)
Loss of consciousness	2 (2)	0 (0)
Myocardial infarction	2 (2)	0 (0)
Pericarditis	2 (2)	0 (0)
Urinary tract infection	2 (2)	0 (0)
Influenza	1 (1)	3 (3)
Pleural effusion	1 (1)	2 (2)
Neutropenia	0 (0)	3 (3)
Febrile neutropenia	0 (0)	3 (3)
Anemia	0 (0)	2 (2)
Lower respiratory tract infection	0 (0)	2 (2)
Thrombocytopenia	0 (0)	2 (2)
Basal cell carcinoma	0 (0)	2 (2)

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Appendix F Comparative analysis of efficacy and safety

Not applicable. This submission does not include comparative analyses of efficacy and safety as a head-to-head study exists why this can be omitted according to the DMC's method guideline (47).

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