Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2684

zanubrutinib hard capsules (Brukinsa®)

BeiGene UK Ltd.

08 November 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission under the orphan medicine process

zanubrutinib (Brukinsa®) is accepted for use within NHSScotland.

Indication Under Review: as monotherapy for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.

In a single-arm, open-label, phase II study, zanubrutinib monotherapy resulted in an overall response rate of 68% in patients with MZL who had received at least one prior anti-CD20-based therapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Zanubrutinib is a covalently binding irreversible inhibitor of Bruton's tyrosine kinase (BTK). BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. These pathways are involved in the pathogenesis of several B-cell lymphomas.[1, 2]

The recommended dose of zanubrutinib is either 320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily. Treatment should be continued until disease progression or unacceptable toxicity. Dose adjustments are required when co-administered with CYP3A4 inhibitors or inducers (including antimicrobial agents that are recommended for the treatment of pathogens commonly associated with MZL [for example clarithromycin and ciprofloxacin]); refer to the Summary of Product Characteristics for more details.[1]

Zanubrutinib is licensed as monotherapy for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy. Anti-CD20 therapies refer to immunotherapies that specifically targets the cluster of differentiation 20 (CD20) protein.[3] At present, the only anti-CD20 therapy that is recommended in guidelines for MZL is rituximab; whilst obinutuzumab is specifically not recommended in current guidelines for MZL.[4]

Zanubrutinib monotherapy has been accepted for use by SMC for other B-cell cancers including Waldenström's macroglobulinaemia (WM) (SMC2528), and chronic lymphocytic leukaemia (CLL) (SMC2600).

1.2. Disease background

Marginal zone lymphoma (MZL) is an indolent type of non-Hodgkin lymphoma (NHL) that originates from B-lymphocytes which are normally present at the edge of areas of lymph node tissues. It accounts for up to 15% of all cases of NHL and the incidence increases with age, with the median age of diagnosis ranging between 60 and 75 years depending on subtype.[5-7] The estimated UK incidence of MZL is 2.62 per 100,000 people.[4, 5]

There are three distinct subtypes of MZL: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), also known as MALT lymphoma, accounting for approximately 60% to 70% of cases; splenic marginal zone lymphoma (SMZL), approximately 20% of cases; and nodal marginal zone lymphoma (NMZL), approximately 10% of cases. EMZL can occur at any site, with the stomach being the most common. Some sites have an association with chronic stimulation from an underlying pathogen, for example *Helicobacter pylori* has a strong aetiopathogenic link in gastric EMZL. The hepatitis C virus is associated with splenic MZL, and guidelines recommend that patients with hepatitis C associated SMZL should receive up-front anti-viral therapy.[4, 8]

Indolent lymphomas like MZL are typically slow-growing, with early progression within 24 months of initial systemic therapy being unusual, though associated with inferior survival.[4] However, MZL is incurable and the 5-year (>90%) and 10-year (75% to 80%) survival rates for gastric EMZL highlight the good prognosis for these patients.[4] Survival rates at 3 to 6 years of >86% for SMZL and >83% for NMZL have also been reported.[4, 9]

1.3. Treatment pathway and relevant comparators

There are no other medicines specifically licensed for the treatment of MZL and few clinical studies have been performed in this patient population. Initial treatment varies depending on MZL subtype, disease stage, and whether it is symptomatic; it may also include antimicrobials. MZL treatment is associated with long periods of remission however relapse is common, particularly when patients present with advanced disease.

Guidelines recommend initial treatment with off-label rituximab (an anti-CD20 monoclonal antibody) alone or in combination with chemotherapy.[2, 4, 8] This was confirmed by clinical experts consulted by SMC who outlined potential regimens for the treatment of MZL include: rituximab monotherapy (usually used first-line); rituximab plus cyclophosphamide, vincristine, and prednisolone (R-CVP); rituximab plus bendamustine (BR); rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP); and rituximab plus chlorambucil (used as second-line for frailer patients). These treatment options are included in the BSH guidelines.[4] The submitting company considered these rituximab-based therapies to be relevant comparators; however, the company have conducted comparisons with a 'basket' of treatment options that includes other treatments as well as these.

Relapsed MZL can normally be retreated with the same modality as at diagnosis, provided the first remission was at least 24 months in duration.[2, 4, 8] Other available treatments include: consolidation autologous stem cell transplant (ASCT) for chemosensitive relapsed MZL in selected fit patients; splenectomy for patients with relapsed SMZL when rituximab monotherapy is ineffective or contraindicated; radiotherapy for localised, symptomatic relapsed disease; and targeted therapies within a clinical trial should be offered to those with multiply relapsed disease who are unsuitable for standard therapy.[4]

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The evidence to support the use of zanubrutinib for this indication comes from the MAGNOLIA and AU-003 studies. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	MAGNOLIA study.[2, 10]	AU-003 study.[2, 11]
Study Design	International, open-label, single-arm phase II study.	International, open-label, multiple-dose, multi-cohort phase I/II study. The relevant disease-specific cohort enrolled 20 patients with MZL in the single-arm, part 2 (dose expansion) of the study.
Eligible Patients	• Aged ≥ 18 years with an ECOG PS of 0 to 2. • Histologically confirmed MZL[a] including splenic (SMZL), nodal (NMZL) and extranodal (EMZL) subtypes. • MZL that requires systemic therapy according to the investigator's assessment.[b] • Received at least one prior line of therapy, including at least one anti-CD20-directed regimen.[c] • Documented failure to achieve at least a PR or had progressive disease after the most recent systemic treatment. • Life expectancy of ≥ 6 months. • No prior treatment with a BTK inhibitor.	

Treatments	All patients received zanubrutinib 160 mg twice daily orally until disease progression, unacceptable toxicity, death, withdrawal of consent or study termination.	MZL patients received either zanubrutinib 320 mg once daily or 160 mg twice daily orally. Patients who received 320 mg once daily had the option to switch to 160 mg twice daily. Treatment continued until disease progression or unacceptable toxicity.
Primary outcome	ORR by IRC, defined as the proportion of patients achieving a best overall response of CR or PR as determined by IRC in accordance with the Lugano classification.	
Secondary outcomes	These included but were not limited to: ORR (investigator-assessed), PFS (IRC- and investigator-assessed) and OS.	
Statistical analysis	Both studies were single-arm and exploratory, therefore the results reported for all outcomes are descriptive only.	

[a]WHO-defined MZL (AU-003)[11], or measurable disease (≥1 nodal lesion of >1.5 cm in the longest diameter and/or ≥1 extranodal lesion of >1.0 cm) by computed tomography (CT) or magnetic resonance imaging (MAGNOLIA).[12]
[b]According to a pre-specified list of symptoms.
[c]Either as monotherapy or chemoimmunotherapy.

Abbreviations: BTK = Bruton's tyrosine kinase; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EMZL = extranodal marginal zone lymphoma; IRC = independent review committee; MZL = marginal zone lymphoma, NMZL = nodal marginal zone lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SMZL = splenic marginal zone lymphoma.

Results for MAGNOLIA have been published after a primary analysis (data cut-off January 2021) and a final analysis (data cut-off May 2022) with a consistent overall response rate (ORR) at both. Detailed results from the final analysis are presented in table 2.2 along with results from AU-003. OS and PFS (IRC- and investigator-assessed) results from the final analysis of MAGNOLIA (May 2022 data cut-off) were used to inform the economic model. Whilst in AU-003, outcomes from the March 2021 data cut-off (OS and investigator-assessed PFS) and October 2020 data cut-off (IRC-assessed PFS) informed the economic model.

Table 2.2 Primary and selected secondary outcomes from the MAGNOLIA study, and the AU-003 study (MZL patients only, n=20).[2, 11, 12]

	MAGNOLIA study	**AU-003 study**
	Zanubrutinib 160 mg twice daily (n=66)[a]	**Zanubrutinib 160 mg twice daily (n=17) and 320 mg once daily (n=3)**
Data cut-off (unless otherwise specified)	May 2022[12, 13]	October 2020[11]
Median follow-up	28.0 months	35.2 months
Primary outcome: Overall Response Rate as per IRC assessment		
Overall response rate, % (n)	68% (45)	80% (16)
CR, % (n)	26% (17)	20% (4)
PR, % (n)	42% (28)	60% (12)
Secondary outcome: PFS as per IRC assessment		
Median PFS follow-up	27.4 months	33.8 months
PFS events, n (%)	*	5 (25%)
Median PFS (95% CI), months	NR (27.6 to NR)	NR (20.3 to NR)
KM estimated PFS at 24 months	71%	72%
Secondary outcome: PFS as per investigator-assessment		
Median PFS follow-up	27.4 months	39.2 months (March 2021 data cut-off)
PFS events, n (%)	*	7 (35%)
Median PFS (95% CI)	*	*

KM estimated PFS at 24 months	58%	*
Secondary outcome: overall survival		
Median OS follow-up	28.7 months	39.2 months
Deaths, n (%)	12 (18%)	* (March 2021 data cut-off)
Median overall survival (95% CI), months	NR (NR to NR)	*
KM estimated overall survival at 24 months	86%	*

[a] Two patients were excluded from the efficacy analysis set because central review determined their diagnosis as diffuse large B-cell lymphoma.

Abbreviations: CI = confidence interval; CR = complete response; KM = Kaplan-Meier; NR = not reached; PFS = progression-free survival; PR = partial response.

*Other data were also assessed but remain confidential.**

In MAGNOLIA (n=66) and AU-003 (n=20) respectively: 38% and 45% had EMZL; 38% and 25% had NMZL; 18% and 30% had SMZL; and 5.9% and 0 had an unknown subtype.[2] At the May 2022 (MAGNOLIA) and October 2020 (AU-003) data cut-offs, high overall response rates (ORR) were consistently observed in both studies for the: EMZL (64% and 89%), NMZL (76% and 100%) and SMZL (67% and 50%) subtypes; the ORR was 50% for the unknown subtype in MAGNOLIA.[2, 11, 12]

2.2. Health-related quality of life (HRQoL) outcomes

HRQoL was assessed in MAGNOLIA using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L). Zanubrutinib resulted in slight improvements from baseline in HRQoL, as early as cycle 3, and maintained to cycle 30.[12] EQ-5D-5L data was only recorded whilst patients were progression-free in MAGNOLIA and this data was mapped to EQ-5D-3L to inform the economics. No HRQoL data were collected in AU-003.

2.3. Supportive studies

Patients from the MAGNOLIA and AU-003 studies (as well as patients with B-cell cancers from other zanubrutinib studies, including from comparator arms) were eligible to enrol in the open-label, multicentre, long-term extension study BGB-3111-LTE1 (NCT04170283).[14] This study is still ongoing with an integrated interim safety report not expected until 2025.[2]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct comparative evidence, the submitting company presented an unanchored matching adjusted indirect comparison (MAIC) of zanubrutinib (using pooled data from the MAGNOLIA and AU-003 studies) against a mixture of comparators from real-world data from the Haematological Malignancy Research Network (HMRN) registry, as detailed in table 2.3. The primary efficacy outcomes assessed included PFS and OS; these results informed the economic analyses. The HMRN registry gathered data on treatment patterns from 2,085 patients diagnosed with MZL in the UK between 2005 and 2020. The submitting company extracted data to form a subgroup of 90 patients who had received prior anti-CD20-based therapy and using exclusion criteria to improve comparability with the MAGNOLIA and AU-003 studies (excluding those: with an ECOG PS ≥3; enrolled in the registry prior to 2014 to align with the start date of the MAGNOLIA study; who received irrelevant treatments after receipt of prior anti-CD20-based therapy).[15]

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored MAIC matched for: two lines of prior therapy; ≥3 line of prior therapy; refractory to last systemic therapy; POD24; mean age; median time since diagnosis.
Population	Adult patients with relapsed or refractory MZL who have received at least one prior anti-CD20 based therapy.
Comparators	Patients included in the HMRN registry (includes patients treated with BR, rituximab monotherapy, cyclophosphamide-rituximab with or without steroids, R-CVP, chlorambucil monotherapy, R-CHOP, FCR, other rituximab[a] and other non-rituximab).
Studies included	MAGNOLIA[12] and AU-003[11] studies for zanubrutinib; and HMRN[15] for the HMRN comparator basket.
Outcomes	PFS and OS.
Results	The results suggest that zanubrutinib has superior efficacy against the HMRN registry comparator basket of treatments for PFS and OS supported by multiple sensitivity analyses.

[a]rituximab plus chlorambucil was under this heading.

Abbreviations: BR = bendamustine-rituximab; HMRN= haematological malignancy research network; FCR= fludarabine, cyclophosphamide and rituximab; R-CHOP= rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; MAIC = matching adjusted indirect comparison; MZL = marginal zone lymphoma; PFS = progression-free survival; OS = overall survival; POD24 = relapse or progression within 24 months of initiating systemic therapy; R-CVP= rituximab plus cyclophosphamide, vincristine and prednisone.

*Other data were also assessed but remain confidential.**

The submitting company also presented an exploratory matching adjusted indirect comparison (MAIC) analysis utilising data from the double-blind, phase III CHRONOS-3 study.[16, 17] The analysis pooled the zanubrutinib patients from MAGNOLIA and AU-003 (n=88) to compare against the subgroup of MZL patients in the rituximab monotherapy treatment arm in the CHRONOS-3 study (n=29). After matching, the results demonstrated benefit in PFS but numerical improvement for OS where the confidence intervals crossed one.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

The European regulator concluded that the safety observations observed in patients with relapsed and/or refractory MZL were consistent with the safety profile for zanubrutinib that has been observed in patients with other B-cell malignancies (such as CLL, WM, and follicular lymphoma).[2]

Pooled safety data from the MAGNOLIA (May 2022 data cut-off; median treatment duration of 24.2 months)[12] and AU-003 (October 2020 data cut-offs; median treatment duration of 32.1 months)[11] studies were used to inform the economic analyses. In the pooled safety population (n=88), any treatment-emergent adverse event (AE) was reported by 100% of patients. Very small proportions of patients had an AE leading to: a dose reduction (2.3%), treatment discontinuation (6.8%), or death (5.7%); none of these were treatment-related. 40% of patients had an AE leading to treatment interruption.[11, 12] Overall, the European regulator concluded that zanubrutinib is reasonably well tolerated in patients with MZL.[2]

Grade ≥3 AEs occurred in 50% of the pooled MZL safety population (n=88). Grade ≥3 AEs that occurred in ≥2% of patients were included in the economic model and were: neutropenia (10%), anaemia (5.7%), pneumonia (4.5%), COVID-19 pneumonia (4.5%), pyrexia (4.5%), diarrhoea, thrombocytopenia (3.4%), neutrophil count decreased, hypertension (3.4%), and syncope (3.4%).[11, 12]

Grade ≥3 AEs of special interest included: second primary malignancies (4.5%), major haemorrhage (2.3%), and opportunistic infections (2.3%); the SPC provides some recommendations for monitoring for haemorrhages, infections, cytopenias, and second primary malignancies.[11, 12]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Zanubrutinib is the first medicine to be licensed in the UK for MZL.[1]
- Zanubrutinib monotherapy demonstrated high ORRs in both studies, with a good proportion achieving a complete response. High ORRs were also consistently seen in all three subtypes of MZL which support the main findings, though it is noted that these subgroups were very small.[2, 12]
- The ORRs of 68% and 80% for zanubrutinib monotherapy that was observed in the MAGNOLIA and AU-003 studies respectively appear to compare favourably to other targeted therapies recommended by the BSH guidelines for patients with relapsed and remitting MZL, such as ibrutinib (48%),[18] and lenalidomide plus rituximab (65%).[19] However, these therapies are not currently licensed for in the UK for MZL.[4]
- Relevant to the indication under review, all patients in both studies had at least one prior line of therapy. Additionally, the vast majority of patients in the MAGNOLIA (99%) and AU-003 (95%) studies had prior rituximab-based chemotherapy.[2]
- Clinical experts consulted by SMC indicated that the likely preferred place of therapy would be second-line, with some saying second-line and beyond. Only 28% (19/68) and 20% (16/20) of patients in the MAGNOLIA and AU-003 studies respectively[2] had 3 or more prior lines of therapy; this enhances the external validity of these studies to Scottish clinical practice.

4.2. Key uncertainties

- MAGNOLIA and AU-003 are both open-label, single-arm studies which recruited a small number of patients, (pooled population, n=88); meaning the data is limited in quality and quantity.[2, 12]
- Both studies have limited follow-up (approximately 3 years each) in the context of a condition which has a relatively good prognosis over 10 years (see section 1.2). At the final analysis of MAGNOLIA (data cut-off May 2022), median PFS and OS had not been reached and the data were considered immature (only 18% of OS events). Given there is no clear correlation of ORR

to PFS and OS in relapsed and refractory MZL patients[2], this means the long-term survival benefit of zanubrutinib is uncertain.

- There is no standard of care for second- and subsequent lines of treatment of MZL, and determining the main comparator(s) is challenging. Guidelines and clinical experts consulted by SMC have confirmed that rituximab-based therapies (mainly rituximab monotherapy, BR, R-CVP, R-CHOP, and R-chlorambucil) are predominantly used in practice for this indication. However, their relative proportions are difficult to determine.
- There is no direct comparative evidence, and the indirect evidence compares with a basket of treatments which may differ in treatment choice and proportion used in Scottish clinical practice. The submitting company highlighted that the small patient numbers in the HMRN comparator basket (n=90) meant that comparisons against individual treatment regimens could not be carried out and thus prohibited the completion of a robust ITC.
- There were several limitations with the MAIC that make the company's conclusions highly uncertain including:
    - The primary outcomes of the MAGNOLIA and AU-003 studies were not PFS and OS, and the median PFS and OS were not reached in either of these studies.
    - Comparisons of study results with real-world data are prone to bias where patients could respond better to treatment in a regulated study setting than clinical practice.
    - Despite the matching of several characteristics, some were unable to be matched and had large differences in the HMRN (n=90) and pooled studies (n=88) respectively, such as those aged ≥ 65 years (65% versus 80%).[2, 15]
    - Feedback from a statistician contacted by SMC highlighted several issues with the MAIC, including the pooling of AU-003 data with MAGNOLIA which relies on the assumption that baseline characteristics are comparable. Whilst, eligibility criteria appeared comparable across the studies, many of these characteristics were unbalanced and some were not adjusted for.[2] There were also concerns of potentially relevant evidence being excluded.

4.3. Clinical expert input

Clinical experts consulted by SMC advised that zanubrutinib is a therapeutic advancement and would fill an unmet need for these patients.

4.4. Service implications

Clinical experts consulted by SMC advised that they did not expect zanubrutinib to have a significant negative service impact. They also highlighted that since this is an oral treatment then it may offer advantages to the service since other regimens are mainly parenteral.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **zanubrutinib (Brukinsa®),** as an **orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Marginal zone lymphoma (MZL) is a rare slow-growing lymphoma meaning it can take many years for a patient to develop any symptoms. However, the condition can affect people differently; some patients may be entirely asymptomatic, whilst others can have significant symptoms (for example fatigue). The diagnosis of MZL can have a significant impact on the quality of life of patients.
- The evidence base for treating MZL is limited, and for some subtypes, is based on the extrapolation of evidence from other conditions such as follicular lymphoma. At present, MZL is usually treated with off-label rituximab alone or in combination with chemotherapy; treatment choice depends patient fitness, MZL subtype, the disease stage, whether a patient is symptomatic, and their prior therapies.
- MZL remains incurable, though median survival does exceed 10 years, and treatment is associated with long periods of remission. However, relapse is common, particularly when patients present with advanced disease; the potential for relapse can have a significant psychological burden on patients and their families/carers. Additionally, MZL typically affects older people, meaning patients may not be fit for non-targeted chemotherapy options due to their toxicity profile. There is a clear unmet need for patients who have relapsed after initial standard treatment approaches for MZL.
- Current evidence suggests that zanubrutinib may achieve disease response and delay disease progression for patients in MZL; this in turn could mean reduced symptoms (such as fatigue and weight loss) and improved survival. However, there are limitations with this evidence.
- Zanubrutinib is an oral treatment which offers a number of benefits for patients such as being able to be administered at home outwith the hospital setting and fewer hospital attendances for drug administration. This should improve patient's psycho-emotional wellbeing.
- Overall, zanubrutinib appears to be well tolerated though there is no direct data to allow comparisons with other treatments. Long-term use of zanubrutinib may also worsen side effects such as hypertension. Having another treatment option available would ease some of the psychological burden for patients and their families/carers.
- Zanubrutinib would be used as per the licensed indication. However, the exact place in therapy (that is second-line or third-line use) for zanubrutinib may vary depending on the MZL subtype and the joint decision made between the individual patient and clinician.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 8.25% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the patient group participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as presented in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime horizon of 27 years (100 – baseline age of 73 years).
Population	Adults with relapsed and refractory MZL who have had at least one prior anti-CD20-based therapy.
Comparators	HMRN registry basket, comprising of rituximab with or without chemotherapy and chemotherapy alone (n=90).
Model description	A partitioned survival model was used. The model health states were progression-free (PF), progressed disease (PD) and death. The model had four-week (28 day) cycle length with a half-cycle correction applied over a lifetime time horizon. The patients entered the model in the progression-free health state and moved either to the progressed health state, death or they discontinued treatment. Those who progressed were assumed to receive subsequent treatments.
Clinical data	The economic evaluation was based on individual survival analyses. PFS and OS for zanubrutinib were derived from pooling two single-arm trials, MAGNOLIA[12] and AU-003[11] (referred to as MAGNOLIA-003). HMRN registry[15] data were used in the MAIC for indirect treatment comparison with zanubrutinib. Pooled MAGNOLIA-003 data were adjusted via a MAIC to match to the HMRN registry basket (n=90). Three alternative adjusted MAIC datasets, namely, MAGNOLIA, weighted to HMRN (n=90); MAGNOLIA-003, weighted to HMRN; and MAGNOLIA-003, weighted to CHRONOS-3[16, 17], were provided by the submitting company.
Extrapolation	To determine the time spent in each health state and the accrued costs and QALYs, survival functions were fitted to the pooled patient-level survival data from MAGNOLIA-003 to estimate long-term extrapolations of PFS, OS, and time-to-treatment discontinuation (TTD). The process of selecting the most appropriate parametric model was assessed using a selection process algorithm by NICE DSU TSD-14. In the base case, the log-logistic curve was used to extrapolate OS, PFS for both treatment arms and TTD for zanubrutinib. Alternative curves were explored in the scenario analysis.
Quality of life	PF utility value was derived from MAGNOLIA EQ-5D-5L data and mapped to EQ-5D-3L. This value was higher than age-gender matched general population utility (0.772).[22] Therefore, it was capped to general population utility to ensure patients could not have a better quality of life compared to the general population. PD health state utility (0.618) was derived from CADTH pCODR submission for bendamustine for NHL.[23] The utilities in base case are non-treatment specific. Other assumptions were explored in scenario analysis.
Costs and resource use	The acquisition costs, administration costs, adverse event (AE) costs, subsequent treatment costs, health state resource use costs and terminal care costs were included. The health state resource use costs were assumed to be equal between the study arms.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

Abbreviations: BR = bendamustine-rituximab; CADTH = Canadian Drug and Heath Technology Agency; HMRN = Haematological Malignancy Research Network; MAIC = matching adjusted indirect comparison; MZL = marginal zone lymphoma; NHL = Non-Hodgkin's Lymphoma; pCODR = Pan-Canadian Oncology Drug Review; PFS = progression-free survival; OS = overall survival; R-CVP= rituximab plus cyclophosphamide, vincristine and prednisone.

*Other data were also assessed but remain confidential.**

6.2. Results

Base case results are presented in Table 6.2. Over a lifetime time horizon, treatment with zanubrutinib in patients with relapsed and refractory MZL was associated with an incremental cost-effectiveness ratio (ICER) of £17,797 per quality-adjusted life-year (QALY), compared to the HMRN registry basket. The incremental costs were driven by acquisition costs of zanubrutinib and incremental QALYs were driven by PF health state utilities.

Table 6.2 Base Case Results (PAS price)

	ICER(£/QALY)
Zanubrutinib vs HMRN registry basket	17,797

Abbreviations: HMRN = Haematological Malignancy Research Network; ICER = incremental cost-effectiveness ratio; QALYs =quality-adjusted life years

6.3. Sensitivity analyses

The sensitivity analysis included probabilistic, deterministic one-way and scenario analysis.

In the submitting company's deterministic sensitivity analysis, the parameter with the greatest impact on the ICER was PFS health state utility score. Varying utility for PFS health state between 95% confidence intervals (i.e. 0.72 to 0.81) had the highest variation on ICER (£16,876 to £18,895 per QALY gained). Various scenarios were explored, and these are presented in Table 6.3. The scenarios that had the highest impact on ICER were naïve (unweighted) estimates of comparative efficacy, MAIC adjusted dataset with MAGNOLIA (weighted to HMRN n=90 dataset) and most conservative scenario for PFS extrapolation.

*Other data were also assessed but remain confidential.**

Table 6.3 Summary of Scenario Analysis (PAS price)

No.	Parameter	Base case	Scenario	ICER (£/QALY)
			Base case results	17,797
1	Time horizon	27 years	20 years	17,858
2A	MAIC adjusted dataset	MAGNOLIA-003, weighted to HMRN N=90	MAGNOLIA, weighted to HMRN N=90	19,689
2B			MAGNOLIA-003, weighted to HMRN	17,861
2C			MAGNOLIA-003, weighted to CHRONOS-3	15,566
3	Comparative efficacy of the MAGNOLIA-003 and HMRN dataset (n=90)	Weighted estimated	Population characteristics not weighted (representing naïve analysis)	22,186
4	Disease-specific background mortality adjustment	SMR=1	SMR = 1.41 (NICE TA649)	19,193
5	PFS distribution	Zanubrutinib: Log-logistic	Most conservative analysis: Zanubrutinib: Exponential	20,209

No.	Parameter	Base case	Scenario	ICER (£/QALY)
		HMRN: Log-logistic	HMRN registry basket: Log-normal	
6	OS distribution	Zanubrutinib: Log-logistic HMRN: Log-logistic	Most conservative analysis: Zanubrutinib: Weibull HMRN registry basket: log-normal	18,090
7	TTD distribution: Zanubrutinib:	Log-logistic	Exponential	12,642
8	Treatment waning	None	At 5 years	18,547
9A	Utilities	Non-treatment specific (PF: 0.77; PD: 0.618)	Treatment specific utilities from WhiMSICAL[24]	15,595
9B			NICE TA627 EAG (PF: 0.805; PD: 0.620)	17,800
9C			MAGNOLIA PF utility not capped by age-sex matched general population	16,353

Abbreviations: AE = Adverse event; EAG = External assessment group; HMRN = Haematological Malignancy Research Network; MZL = Marginal zone lymphoma; NICE = National Institute for Health and Care Excellence; OS = Overall survival; PFS = Progression-free survival; QALY = Quality-adjusted life-year; SMR = Standardised mortality ratio; TTD = Time-to-treatment discontinuation; PF = progression-free; PD = progressed disease.

6.4. Key strengths

- The model structure was appropriate and consistent with the approach used in the assessment of other oncology treatments.
- The submitting company conducted a systematic literature review for relevant health state utility value studies, which enhanced its face validity.
- A comprehensive selection of variables was explored in sensitivity analysis.

6.5. Key uncertainties

- The HMRN registry treatment basket in the base case may not accurately represent the treatment choices and proportions of treatments used in Scottish clinical practice for this indication; based on clinical experts contacted by SMC it appears that rituximab-based therapies are predominantly used here. Chemotherapy alone may not be an appropriate comparator. However, scenario 2B, with MAGNOLIA-003 versus HMRN treatment basket with chemotherapy alone excluded had a minor impact on the ICER.
- There were methodological issues associated with the indirect treatment comparison, specifically related to missing prognostic factors for matching, poor overlap between the combined studies and HMRN registry and small effective sample size after matching. The scenarios 2A-C explored alternative MAIC adjusted datasets (MAGNOLIA, weighted to HMRN N=90 dataset; MAGNOLIA-003, weighted to HMRN dataset; and MAGNOLIA-003, weighted to CHRONOS-3) which resulted in ICERs between £17,861 to £19,689 per QALY gained. To understand the impact of weighting MAIC estimates of comparative efficacy, naïve estimates

were explored which increased the ICER to £22,186 per QALY gained (scenario 3).

- There is uncertainty in the survival estimates. First, the median OS and PFS were not reached in both studies, suggesting that the clinical evidence may be immature. Second, the heterogeneity between MAGNOLIA and AU-003 increases uncertainty when combining their patient-level data. Third, compared to empirical evidence, all extrapolated survival curves for HMRN basket may underestimate actual survival for current standard of care in NHSScotland. The most conservative survival scenarios, 5 and 6, increased ICER to £20,209 and £18,090, respectively. Although the choice of survival curve did not have a major impact on ICER, the extrapolated efficacy estimates for HMRN registry basket lack face validity. As a result, improvement in survival rate of the comparator could potentially increase the ICER, making zanubrutinib comparatively less cost-effective.
- The study derived utility for the PF health state was higher than general population utility meaning PF utility was capped to general population utility. A further decrease in the PF utility could potentially lead to a rise in the ICER, making zanubrutinib comparatively less cost-effective. However, the ICER remained stable in other explored scenarios with literature-based utility values (Scenarios 9A, B) and in one-way sensitivity analyses where the utility values were varied.

7. Conclusion

The Committee considered the benefits of zanubrutinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as zanubrutinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted zanubrutinib for use in NHSScotland.

8. Guidelines and Protocols

The British Society for Haematology (BSH) published "Guidelines for the diagnosis and management of marginal zone lymphomas. A British Society of Haematology Guideline." in November 2023.[4]

The European Society for Medical Oncology (ESMO) published "Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in April 2020.[8]

9. Additional Information

9.1. Product availability date

January 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Zanubrutinib 80 mg hard capsules	**320 mg (four 80 mg capsules) once daily or 160 mg (two 80 mg capsules) twice daily. Treatment should be continued until disease progression or unacceptable toxicity**	**59,801**

Costs from BNF online on 27 June 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 16 July 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.