Acalabrutinib (mantle cell lymphoma, combination with bendamustine and rituximab)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 4 of the dossier assessment *Acalabrutinib (Mantelzell-Lymphom, Kombination mit Bendamustin und Rituximab) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

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Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Michael Schmidt
- Christiane Balg
- Dorothee Ehlert
- Katharina Hirsch
- Kirsten Janke
- Prateek Mishra
- Katrin Nink
- Anne-Kathrin Petri
- Corinna ten Thoren

Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	AEs of special interest
BTKi	Bruton's tyrosine kinase inhibitor
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECI	Events of Clinical Interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
ESMO	European Society for Medical Oncology
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
FDA	US Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention-to-treat
MCL	mantle cell lymphoma
MIPI	MCL International Prognostic Index
NYHA	New York Heart Association
PFS	progression-free survival
PT	Preferred Term
R-CHOP	cyclophosphamide + doxorubicin + vincristine + predniso(lo)ne
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA
SOC	System Organ Class
VRCAP	bortezomib + rituximab + cyclophosphamide, doxorubicin, prednisone

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug acalabrutinib (in combination with bendamustine and rituximab). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 30 June 2025.

Research question

The aim of this report is to assess the added benefit of acalabrutinib in combination with bendamustine and rituximab (hereinafter referred to as 'acalabrutinib + bendamustine + rituximab') compared with individualized treatment as the appropriate comparator therapy (ACT) in adults with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of acalabrutinib + bendamustine + rituximab

Therapeutic indication	**ACT**[a]
Adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant	Individualized treatment[d, e] choosing from ▪ rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, predniso[lo]ne)[f] ▪ VRCAP (bortezomib + rituximab + cyclophosphamide, doxorubicin, prednisone) ▪ BR (bendamustine + rituximab)[g] upon achievement of complete or partial remission following induction therapy with R-CHOP or BR, followed by ▪ maintenance therapy with rituximab[h]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, in this therapeutic indication, it is assumed that patients with mantle cell lymphoma meet the criteria for systemic antineoplastic therapy due to a correspondingly advanced stage of their disease, particularly in terms of a symptomatic course; therefore, a "watchful waiting" strategy, among other options, is not considered. Further, patients are assumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. Furthermore, according to the G-BA, it is assumed that the target population in the therapeutic indication does not include any patients in poor or reduced general health.
d. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
f. Induction therapy with R-CHOP is covered by Part A, Section XXVI of Appendix VI of the AM-RL 'Rituximab for mantle cell lymphoma'.
g. Induction therapy with BR is not approved for this indication. According to the GBA, data from randomized trials comparing BR with R-CHOP in this therapeutic indication are available. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV.
h. According to the G-BA, the current guidelines recommend maintenance therapy with rituximab following induction with R-CHOP and BR. Rituximab is not approved for use following induction therapy with BR. The off-label use of rituximab following treatment with R-CHOP is eligible for prescription in accordance with Annex VI of the AM-RL. The available guidelines refer to a randomized phase II study and a retrospective cohort study for the use of rituximab as maintenance therapy following induction therapy with BR. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of maintenance therapy with BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV. With regard to maintenance therapy with rituximab, the guidelines set out in Appendix VI of the AM-RL must be considered for patients who have previously received R-CHOP therapy. The dosage and treatment regimen should be in line with the generally recognized state of medical knowledge.

AM-NutzenV: Regulation on the Evaluation of the Benefits of Medicinal Products; AM-RL: Medicinal Products Directive; BR: Bendamustine + Rituximab; EU: European Union; G-BA: Joint Federal Committee; HTA: Health Technology Assessment; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone

The G-BA adjusted the ACT according to Table 2 on 27 May 2025, shortly before the company submitted the dossier. The company generally follows the ACT as specified by the G-BA, but refers to a consultation with the G-BA on 8 August 2024 and additionally specifies watchful waiting as maintenance therapy following induction therapy with the combination of bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VRCAP). This deviation has no consequence for the benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit.

Study pool and study design

The ECHO study is an ongoing, double-blind RCT comparing acalabrutinib + bendamustine + rituximab with placebo + bendamustine + rituximab. The study included adult patients with previously untreated mantle cell lymphoma who were 65 years or older at the time of enrolment. Patients had to have a general condition that concurred with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. Patients whose treatment goal was tumour reduction prior to a stem cell transplant were excluded from the study participation. Patients with major cardiovascular disorders, such as uncontrolled or untreated symptomatic arrhythmia, congestive heart failure, myocardial infarction within 6 months prior to the first dose of the study medication, or class 3 or 4 cardiac disorders according to the New York Heart Association (NYHA), were also excluded.

A total of 598 patients were included in the analyses based on the global intention-to-treat (ITT) population (N = 299 each in the intervention and the control arm).

Treatment with acalabrutinib + bendamustine + rituximab was administered in accordance with the Summary of Product Characteristics. In addition to twice-daily oral administration of 100 mg acalabrutinib for up to six four-week cycles, induction therapy with bendamustine + rituximab was administered, followed by maintenance therapy with rituximab every 8 weeks up to Week 120. Treatment with bendamustine + rituximab as part of the induction and maintenance therapy was administered in the comparator arm analogous to the intervention arm. In addition to induction and maintenance therapy, patients in the control arm received a placebo orally twice daily instead of acalabrutinib. Administration of acalabrutinib or placebo will be continued until disease progression, unacceptable toxicity, discontinuation of treatment at the physician's decision, or withdrawal of consent. In the event of disease progression, the study protocol stipulates that patients in the comparator arm may receive monotherapy with acalabrutinib.

Primary outcome of the ECHO study is progression-free survival (PFS). Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Suitability of the comparator therapy used for the assessment

The G-BA identified individualized treatment choosing from rituximab in combination with cyclophosphamide + doxorubicin + vincristine + predniso(lo)ne (R-CHOP), VRCAP and bendamustine + rituximab as the ACT, provided that complete or partial remission is achieved following induction therapy with R-CHOP or bendamustine + rituximab, followed by maintenance therapy with rituximab. In its notes on the ACT, the G-BA further describes that for the implementation of the individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). A rationale had to be provided for the choice and any limitation of treatment options.

In the ECHO study, all patients in the comparator arm received treatment with bendamustine plus rituximab in addition to placebo, followed by maintenance therapy with rituximab upon achieving complete or partial remission. The other treatment options covered by the ACT were not available. The company does not justify the restriction of treatment options in the study to bendamustine plus rituximab upon achievement of complete or partial remission, followed by maintenance therapy with rituximab.

The treatment regimen used in the study is one of the recommendations set out in current guidelines, but it is not the sole standard of care in this therapeutic indication. The guideline of the European Society for Medical Oncology (ESMO) on diagnosis, treatment and follow-up of lymphomas, as well as the guideline of the British Society for Haematology, recommend that, for patients aged ≥ 65 years for who are not eligible for autologous stem cell transplant, first-line treatment should include, in addition to bendamustine plus rituximab, treatment with the other treatment options of the ACT R-CHOP or VRCAP, as specified by the G-BA. According to the G-BA, however, the use of bendamustine plus rituximab is generally preferable to the drugs currently approved in the therapeutic indication for the relevant patient groups or the relevant range of indications. Furthermore, the information provided in the guidelines does not suggest that R-CHOP or VRCAP would be preferable to the use of bendamustine plus rituximab for this indication. Against this background, it is assumed for the present assessment that sufficiently adequate treatment of the patients was ensured despite the lack of choice in the ECHO study.

Overall, the ECHO study was used for the benefit assessment in the present situation despite the uncertainties described. It is assumed that treatment with bendamustine plus rituximab, followed by maintenance therapy with rituximab upon achievement of complete or partial

remission, represents an adequate implementation of an individualized treatment. However, uncertainty remains as to whether other treatment options included in the G-BA's ACT would also have been suitable or even more suitable for some of the patients. This uncertainty is taken into account in the assessment of the certainty of results.

Furthermore, based on the results of the ECHO study, conclusions regarding the added benefit of acalabrutinib in combination with bendamustine + rituximab can only be drawn for patients for whom treatment with bendamustine and rituximab, followed by maintenance therapy with rituximab upon achieving complete or partial remission, is a suitable individualized treatment.

Data cut-offs

In Module 4A, the company used the results of the interim cut-off (15 February 2024) for the benefit assessment. For the outcome overall survival, it presents the results of the data cut-off (12 August 2024) requested by the US Food and Drug Administration (FDA) as supplementary information. For the outcomes of the categories morbidity, health-related quality of life and side effects, Module 4A does therefore not comprise the most recent analyses for all relevant outcomes at the relevant data cut-off of the ECHO study of 12 August 2024 requested by the regulatory authority. However, the data presented by the company can nevertheless be used for the benefit assessment. The data cut-off requested by the FDA was carried out approximately six months after the pre-specified data cut-off. Although the available data show that a relevant proportion of patients were still undergoing treatment at the data cut-off requested by the FDA, the majority of patients had already completed both the approximately 6-month induction therapy and the approximately 2-year maintenance therapy with rituximab by the interim data cut-off of 15 February 2024, and the patients had already been observed for a median period of just under 4 years (based on the outcome overall survival recorded throughout the entire study). The available data also show that, at the data cut-off of 12 August 2024, no relevant number of patients with events were considered in the overall rates for outcomes in the side effects category, for which the observation period is linked to the duration of treatment. Furthermore, the impact of the additional recordings of patient-reported outcomes on the results is also considered to be minor.

In summary, this benefit assessment uses the data cut-off of 12 August 2024 for the outcome overall survival, as requested by the FDA, and the interim data cut-off of 15 February 2024 for the outcomes in the categories morbidity, health-related quality of life and side effects.

Subsequent therapies

The ECHO study involved no restrictions regarding subsequent antineoplastic therapies. However, in the event of disease progression, the study protocol stipulates that patients in

the comparator arm may receive monotherapy with acalabrutinib in case of progressive disease. In contrast, the study protocol does not specify any particular subsequent therapy for patients in the intervention arm.

The proportion of patients undergoing subsequent therapy is very minor compared to the proportion of patients with progressing disease in the intervention arm, whereas in the comparator arm, the proportion of patients receiving subsequent therapy was markedly higher. Assuming that subsequent therapies were essentially administered after disease progression had occurred, around 39% of patients with disease progression in the intervention arm received subsequent therapy, whereas this applied to 75% of patients in the comparator arm.

According to European and British guidelines, treatment with a covalently binding Bruton's tyrosine kinase inhibitor (BTKi) is established for older patients with relapsed disease following immunochemotherapy. Among other things, the guidelines refer to treatment with ibrutinib, which has been available in Germany for quite some time for the treatment of relapsed or refractory mantle cell lymphoma; however, other BTK inhibitors, including acalabrutinib, are also listed in the guidelines. However, monotherapy with acalabrutinib for relapsed or refractory mantle cell lymphoma was approved by the European Medicines Agency in May 2025, at the same time as the therapeutic indication of this assessment (see the parallel dossier assessment on commission A25-90), which is why the therapeutic significance of acalabrutinib in the German health care context remains unclear.

For patients with relapsed or refractory mantle cell lymphoma who have received a covalent BTKi as first-line treatment, the guidelines recommend treatment with pirtobrutinib or re-treatment with a covalently binding BTKi, possibly in combination with venetoclax, in addition to immunochemotherapy. However, in the intervention arm of the ECHO study, these treatment options were used only in isolated cases. In the comparator arm of the study, however, the majority of patients were treated with acalabrutinib monotherapy, in line with the study protocol which allowed for this option in the event of disease progression.

In summary, it should be noted that the study design only specifies a potential subsequent therapy for the comparator arm, but not for the intervention arm. This unequal treatment of the study arms is reflected in the fact that, in an important proportion of patients – particularly in the intervention arm – subsequent therapy was not initiated despite determination of disease progression. In the comparator arm, too, acalabrutinib was used as subsequent therapy instead of ibrutinib, the relevance of which in the German health care context was unclear at the time of this benefit assessment. The described deficiencies in the subsequent therapies used are therefore taken into account in the assessment of the outcome-specific risk of bias for overall survival.

Risk of bias and certainty of conclusions

The risk of bias across outcomes is rated as low for the ECHO study. The risk of bias in the results for the outcome overall survival is rated as high due to uncertainties regarding the use of appropriate subsequent therapies. The risk of bias in the results for each of the other outcomes in the categories morbidity, health-related quality of life and side effects (except for discontinuation due to adverse events [AEs]) is also rated as high, due to incomplete observations for potentially informative reasons caused by the follow-up observation being linked to the treatment. Although the risk of bias is low for the outcome discontinuation due to AEs, the certainty of results for this outcome is limited.

For patients in the ECHO study, it is assumed that treatment with placebo + bendamustine + rituximab in the comparator arm, followed by maintenance therapy with rituximab upon achievement of complete or partial remission, represents an adequate implementation of an individualized treatment. However, uncertainty remains as to whether other treatment options included in the G-BA's ACT would also have been suitable or even more suitable for some of the patients. Based on the ECHO study, at most hints, e.g. of an added benefit, can be derived for all outcomes irrespective of the outcome-specific risk of bias.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome overall survival. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Morbidity

Symptoms

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

No statistically significant difference between the treatment arms was shown for the scales fatigue, nausea and vomiting, dyspnoea, insomnia, appetite loss and constipation of the EORTC QLQ-C30. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

A statistically significant difference between the treatment arms was found the scales pain and diarrhoea of the EORTC QLQ-C30. This difference was no more than marginal, however. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome health status, recorded with the EQ-5D VAS. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning)

No statistically significant difference between the treatment arms was found for any of the scales global health status, physical functioning, role functioning, emotional functioning and cognitive functioning of the EORTC QLQ-C30. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

No statistically significant difference between the treatment arms was found for the social functioning scale of the EORTC QLQ-C30. However, there is an effect modification for the characteristic age. There was a hint of lesser benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab patients ≥ 70 years of age. For patients ≥ 70 years, there is no hint of an added benefit of acalabrutinib + bendamustine + rituximab over bendamustine + rituximab; an added benefit is therefore not proven for this patient group.

Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym)

For the outcome health-related quality of life (recorded using the FACT-Lym), no statistically significant difference between treatment groups was found. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Side effects

Serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

There was no statistically significant difference between the treatment arms for either of the outcomes of SAEs and severe AEs. In each case, this results in no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome

discontinuation due to AEs. There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Specific AEs

Cardiac disorders (System Organ Class [SOC], severe AEs)

There was no statistically significant difference between the treatment arms for the outcome cardiac disorders (SOC, severe AEs). There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Bleeding (Standardized MedDRA Query [SMQ], AEs)

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome bleeding. There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Severe bleeding (SMQ, severe AEs)

There was no statistically significant difference between the treatment arms for the outcome severe bleeding (SMQ, severe AEs). There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Infections and infestations (SOC, severe AEs)

No statistically significant difference between the treatment arms was shown for the outcome infections and infestations (SOC, AEs). There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Vomiting (Preferred Term [PT], AEs)

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome vomiting (PT, AEs). However, there was an effect modification for the characteristic simplified mantle cell lymphoma (MCL) International Prognostic Index (MIPI) score. For patients at low or intermediate risk (0 to 5) in the simplified MIPI score, there is a hint of greater harm from acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab. For patients at high risk (6 to 11) in the simplified MIPI score, there is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for this patient group.

Headache (PT, AEs)

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome headache (PT, AEs). There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Injury, poisoning and procedural complications (SOC, SAEs)

A statistically significant difference in favour of acalabrutinib + bendamustine + rituximab in comparison with placebo + bendamustine + rituximab was shown for the outcome injury, poisoning and procedural complications (SOC, SAEs). However, there is an effect modification by the characteristic of sex. For men, there is a hint of lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab. For women, there is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for this patient group.

Skin and subcutaneous tissue disorders (SOC, severe AEs), decreased leukocyte count (PT, severe AEs)

For each of the outcomes skin and subcutaneous tissue disorders (SOC, severe AEs) and white blood cell count decreased (PT, severe AEs), a statistically significant difference was shown to the disadvantage of acalabrutinib + bendamustine + rituximab compared to placebo + bendamustine + rituximab. In each case, there is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Hepatotoxicity (severe AEs)

For the outcomes hepatotoxicity (operationalized via the SMQs hepatic failure, fibrosis and cirrhosis, and other diseases in connection with liver injury [narrow]; hepatitis, non-infectious [narrow]; liver-related examinations, clinical signs and symptoms [narrow], all severe AEs), there is a statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab. However, there was an effect modification for the characteristic simplified MIPI score. For patients at low or intermediate risk (0 to 5) in the simplified MIPI score, there is a hint of greater harm from acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab. For patients at high risk (6 to 11) in the simplified MIPI score, there is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for this patient group.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug acalabrutinib + bendamustine + rituximab in comparison with the ACT are assessed as follows:

The overall consideration yields a positive effect in one subgroup, which is offset by several negative effects of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab, some of which are observed in the total population and others in individual subgroups. For the total population, there is a hint of greater harm with the extent "considerable", particularly in the outcome discontinuation due to AEs, which is predominantly caused by severe AEs classified as CTCAE grade ≥ 3. Furthermore, in the case of several specific and partly severe AEs, there are hints of greater harm with extents up to "major" (severe AEs: skin and subcutaneous tissue disorders, white blood cell count decreased). In contrast, there is a hint of lesser harm with the extent "major" for the outcome injury, poisoning and procedural complications (SAEs) only for the subgroup of men. The negative effects, which are predominantly of a considerable or major extent, clearly outweigh this positive effect, which only occurs in a subgroup.

In summary, for adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant, and for whom bendamustine plus rituximab is a suitable individualized treatment, there is a hint of lesser benefit from acalabrutinib + bendamustine + rituximab compared with the ACT.

The ECHO study provides no data for an assessment of the added benefit of acalabrutinib + bendamustine + rituximab compared with the ACT for adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant, and for whom bendamustine + rituximab is not a suitable individualized treatment. An added benefit of acalabrutinib + bendamustine + rituximab over the ACT is therefore not proven for adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine + rituximab is not a suitable individualized treatment.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3 shows a summary of the probability and extent of the added benefit of acalabrutinib + bendamustine + rituximab.

Table 3: Acalabrutinib + bendamustine + rituximab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant	Individualized treatment[d, e] choosing from ▪ rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, predniso[lo]ne)[f] ▪ VRCAP (bortezomib + rituximab + cyclophosphamide, doxorubicin, prednisone) ▪ BR (bendamustine + rituximab)[g] upon achievement of complete or partial remission following induction therapy with R-CHOP or BR, followed by ▪ maintenance therapy with rituximab[h]	▪ Patients for whom bendamustine + rituximab is a suitable individualized treatment: hint of a lesser benefit ▪ patients for whom bendamustine + rituximab is not a suitable individualized treatment: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, in this therapeutic indication, it is assumed that patients with mantle cell lymphoma meet the criteria for systemic antineoplastic therapy due to a correspondingly advanced stage of their disease, particularly in terms of a symptomatic course; therefore, a “watchful waiting” strategy, among other options, is not considered. Further, patients are assumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. Furthermore, according to the G-BA, it is assumed that the target population in the therapeutic indication does not include any patients in poor or reduced general health.
d. The term ‘individualized treatment’ is used instead of previously used terms such as ‘patient-specific therapy’ or ‘treatment of physician’s choice’. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
f. Induction therapy with R-CHOP is covered by Part A, Section XXVI of Appendix VI of the AM-RL ‘Rituximab for mantle cell lymphoma’.
g. Induction therapy with BR is not approved for this therapeutic indication. According to the GBA, data from randomized trials comparing BR with R-CHOP in this therapeutic indication are available. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV.

Table 3: Acalabrutinib + bendamustine + rituximab – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
h. According to the G-BA, the current guidelines recommend maintenance therapy with rituximab following induction with R-CHOP and BR. Rituximab is not approved for use following induction therapy with BR. The off-label use of rituximab following treatment with R-CHOP is eligible for prescription in accordance with Annex VI of the AM-RL. The available guidelines refer to a randomized phase II study and a retrospective cohort study for the use of rituximab as maintenance therapy following induction therapy with BR. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of maintenance therapy with BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV. With regard to maintenance therapy with rituximab, the guidelines set out in Appendix VI of the AM-RL must be considered for patients who have previously received R-CHOP therapy. The dosage and treatment regimen should be in line with the generally recognized state of medical knowledge.		

AM-NutzenV: Regulation on the Evaluation of the Benefits of Medicinal Products; AM-RL: Medicinal Products Directive; BR: Bendamustine + Rituximab; EU: European Union; G-BA: Joint Federal Committee; HTA: Health Technology Assessment; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of acalabrutinib in combination with bendamustine and rituximab (hereinafter referred to as 'acalabrutinib + bendamustine + rituximab') compared with individualized treatment as the ACT in adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of acalabrutinib + bendamustine + rituximab: (multipage table)

Therapeutic indication	**ACT**[a]
Adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant	Individualized treatment[d, e] choosing from ▪ rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, predniso[lo]ne)[f] ▪ VRCAP (bortezomib + rituximab + cyclophosphamide, doxorubicin, prednisone) ▪ BR (bendamustine + rituximab)[g] upon achievement of complete or partial remission following induction therapy with R-CHOP or BR, followed by ▪ maintenance therapy with rituximab[h]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, in this therapeutic indication, it is assumed that patients with mantle cell lymphoma meet the criteria for systemic antineoplastic therapy due to a correspondingly advanced stage of their disease, particularly in terms of a symptomatic course; therefore, a "watchful waiting" strategy, among other options, is not considered. Further, patients are assumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. Furthermore, according to the G-BA, it is assumed that the target population in the therapeutic indication does not include any patients in poor or reduced general health.
d. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
f. Induction therapy with R-CHOP is covered by Part A, Section XXVI of Appendix VI of the AM-RL 'Rituximab for mantle cell lymphoma'.
g. Induction therapy with BR is not approved for this indication. According to the GBA, data from randomized trials comparing BR with R-CHOP in this therapeutic indication are available [3,4]. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV.

Table 4: Research questions of the benefit assessment of acalabrutinib + bendamustine + rituximab: (multipage table)

Therapeutic indication	ACT[a]
h. According to the G-BA, the current guidelines [5,6] recommend maintenance therapy with rituximab following induction with R-CHOP and BR. Ritis not approved for use following induction therapy with BR. The off-label use of rituximab following treatment with R-CHOP is eligible for prescription in accordance with Annex VI of the AM-RL. The available guidelines refer to a randomized phase II study and a retrospective cohort study for the use of rituximab as maintenance therapy following induction therapy with BR [7,8]. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of maintenance therapy with BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV. With regard to maintenance therapy with rituximab, the guidelines set out in Appendix VI of the AM-RL must be considered for patients who have previously received R-CHOP therapy. The dosage and treatment regimen should be in line with the generally recognized state of medical knowledge.	

AM-NutzenV: Regulation on the Evaluation of the Benefits of Medicinal Products; AM-RL: Medicinal Products Directive; BR: Bendamustine + Rituximab; EU: European Union; G-BA: Joint Federal Committee; HTA: Health Technology Assessment; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone

The G-BA adjusted the ACT according to Table 4 on 27 May 2025, shortly before the company submitted the dossier. The company generally follows the ACT as specified by the G-BA, but refers to a consultation with the G-BA on 8 August 2024 and additionally specifies watchful waiting as maintenance therapy following induction therapy with the combination of VRCAP. This deviation has no consequence for the benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on acalabrutinib (status: 19 May 2025)
- Bibliographical literature search on acalabrutinib (last search on 20 May 2025)
- Search in trial registries/trial results databases for studies on acalabrutinib (last search on 19 May 2025)
- Search on the G-BA website for acalabrutinib (last search on 20 May 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on acalabrutinib (last search on 10 July 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. bendamustine + rituximab

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
ACE-LY-308 (ECHO[c])	Yes	No[d]	Yes	Yes [9-11]	Yes [12-14]	Yes [15]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
d. The study is sponsored by Acerta Pharma. This is a subsidiary of the company (AstraZeneca).

RCT: randomized controlled trial

The study pool for the present benefit assessment consists of the RCT ECHO. This concurs with the company's study pool.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ECHO	RCT, double-blind, parallel	Adult patients (≥ 65 years) ▪ with pathologically confirmed mantle cell lymphoma[b] without prior systemic treatment[c] ▪ ECOG PS ≤ 2	Acalabrutinib + bendamustine + rituximab (N = 299[d]) placebo + bendamustine + rituximab (N = 299[d])	Screening: up to 30 days treatment: until disease progression[e], unacceptable toxicity, treatment discontinuation according to the physician's decision or withdrawal of consent observation[f]: outcome-specific, at most until death, discontinuation of the study, or end of study	189 study centres in Argentina, Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea, Mexico, New Zealand, Peru, Poland, Romania, Russia, Spain, Taiwan, Ukraine, the United States and Vietnam 05/2017–ongoing Data cut-off: ▪ 15 February 2024[g] ▪ 12 August 2024[h]	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. With proof of a t(11;14)(q13;q32) chromosomal translocation and/or cyclin D1 overexpression in conjunction with other relevant markers (e.g. CD5, CD19, CD20, PAX5).
c. Patients whose treatment goal was tumour reduction prior to a stem cell transplant were excluded from the study participation.
d. In accordance with Protocol Version 4.0 of 6 June 2023, it was prespecified that patients from China who had been randomized ≥ 24 months prior to the data cut-off for the interim analysis were to be included in the global ITT population. Correspondingly, 37 Chinese patients with a follow-up < 24 months at the data cut-off of 15 February 2024 were not considered in the analyses based on the ITT population.
e. In accordance with the study design, patients in the control arm had the option of receiving acalabrutinib monotherapy in the event of disease progression.
f. Outcome-specific information is provided in Table 8.
g. Prespecified interim analysis (originally planned after 152 PFS events; adjusted to 227 events in accordance with Protocol Version 4.0 of 6 June 2023, and adjusted to around 10% more events compared to protocol Version 4.0 [corresponds to approximately 250 events] in accordance with the statistical analysis plan Version 4.0 of 16 January 2024).
h. In accordance with the SAP Version 6.0 of 12 July 2024, and in line with the FDA's comments, two additional data cut-offs on overall survival were added, approximately 6 months and approximately 3 years after the first data cut-off. According to the company, the data cut-off of 12 August 2024 represents the first of these two additional data cut-offs.

AE: adverse events; CD: cluster of differentiation; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FDA: Food and Drug Administration; ITT: intention to treat; N: number of analysed patients; PAX5: paired box 5; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study	Intervention	Comparison
ECHO	Acalabrutinib 100 mg orally, twice daily + immunochemotherapy	Placebo orally twice daily + immunochemotherapy
	Immunochemotherapy ▪ cycles 1–6: Induction therapy bendamustine 90 mg/m² BSA IV on Days 1 & 2 of a 4-week cycle + rituximab 375 mg/m² BSA IV on Day 1 of a 4-week cycle ▪ cycle 8–30: maintenance therapy[a] rituximab 375 mg/m² BSA IV on Day 1 of every second 4-week cycle	
	Treatment adjustments: ▪ acalabrutinib/placebo: ▫ treatment interruption of up to 28 days[b] due to toxicity ▫ dose adjustments[c] are possible for various CTCAE grade 3–4 haematological and non-haematological AEs ▪ bendamustine[d]: treatment interruption for up to 28 days and, where necessary, dose reduction in the event of various CTCAE grade 3 (and in some cases CTCAE grade 4) haematological and non-haematological side effects. If a dose reduction below 70 mg/m² was necessary, treatment with bendamustine was to be discontinued. ▪ rituximab[d]: no dose reductions; treatment interruption permitted for up to 28 days	
	Disallowed pretreatment ▪ systemic anticancer therapy for mantle cell lymphoma ▪ major surgery ≤ 4 weeks before the first administration of the study medication ▪ intravenous anti-infective treatment ≤ 2 weeks prior to the first dose ▪ live vaccines ≤ 4 weeks prior to study start **allowed concomitant treatment** ▪ any treatments necessary for the patient's wellbeing. ▪ short-term high-dose corticosteroids for the treatment of infusion-related or other inflammatory reactions ▪ short-term topical, inhaled or systemic corticosteroids, or low-dose steroids for comorbidities ▪ prophylactic administration of growth factors <u>premedication required before rituximab</u> ▪ paracetamol, antihistamine as per local practice **disallowed concomitant treatment** ▪ any form of anticancer treatment, including chemotherapy, immunotherapy, experimental therapy or radiotherapy ▪ warfarin or other vitamin K antagonists ▪ avoid CYP3A inhibitors/inducers and PPIs wherever possible ▪ immunosuppressive therapy, including long-term administration (≥ 2 weeks) of corticosteroids; and corticosteroids for the treatment of mantle cell lymphoma	

Table 7: Characteristics of the intervention – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study	Intervention	Comparison
a. Maintenance therapy was given to patients who achieved at least a partial response following induction therapy. b. If the side effect persists for a prolonged period (> 28 days), treatment is to be discontinued. c. Treatment interruption and, if necessary, dose reduction in the event of CTCAE grade 3–4 AEs. If the condition improves to a grade ≤ 2, the initial dose is administered following the first occurrence; following the second occurrence, 100 mg is administered once daily. Once the reduced dose has been tolerated for ≥ 4 weeks, it is possible to return to the initial dose. Treatment is discontinued from the third occurrence of non-haematological events, and from the fourth occurrence of haematological events. d. If toxicity occurs as a result of bendamustine or rituximab administration, it should always be both drugs that are discontinued. BSA: body surface area; CTCAE: Common Terminology Criteria for Adverse Events; CYP: cytochrome P; IV: intravenous; PPI: proton pump inhibitor; RCT: randomized controlled trial		

Study design

The ECHO study is an ongoing, double-blind RCT comparing acalabrutinib + bendamustine + rituximab with placebo + bendamustine + rituximab. The study included adult patients with previously untreated mantle cell lymphoma who were 65 years or older at the time of enrolment. Patients had to have a general condition that concurred with an (ECOG PS) of 0 to 2. Patients whose treatment goal was tumour reduction prior to a stem cell transplant were excluded from the study participation. Patients with major cardiovascular disorders, such as uncontrolled or untreated symptomatic arrhythmia, congestive heart failure, myocardial infarction within 6 months prior to the first dose of the study medication, or class 3 or 4 cardiac disorders according to the NYHA, were also excluded.

The ECHO study comprises a global cohort and a cohort of patients from China. Approximately 546 patients were to be recruited worldwide, plus at least 80 additional patients from China. According to the study protocol Version 4.0 dated 6 June 2023, it was prespecified that the global intention to treat (ITT) population would comprise only patients from China who had been randomized at least 24 months prior to the interim data cut-off. In accordance with the study protocol, it was pre-specified for both the interim analysis and the final analysis that the analyses would be conducted for this global ITT population. In addition, an analysis is planned for all patients from China if the percentage of PFS events is the same as in the global cohort.

A total of 635 patients were randomly allocated at a 1:1 ratio to treatment with acalabrutinib + bendamustine + rituximab or placebo + bendamustine + rituximab. Randomization was stratified by geographical region (North America versus Western Europe versus others) and the simplified MIPI score (low risk [0 to 3] versus intermediate risk [4 to 5] versus high risk [6 to 11]). In the analyses based on the global ITT population, 37 of the randomized patients from China with < 24 months of follow-up were not considered in the interim data cut-off of

15 February 2024, in accordance with the study design. A total of 598 patients were included in the analyses based on the global ITT population (N = 299 each in the intervention and the control arm).

Treatment with acalabrutinib + bendamustine + rituximab was in compliance with the Summary of Product Characteristics (SmPC) [16]. In addition to twice-daily oral administration of 100 mg acalabrutinib for up to six four-week cycles, induction therapy with bendamustine + rituximab was administered, followed by maintenance therapy with rituximab every 8 weeks up to Week 120. Treatment with bendamustine + rituximab as part of the induction and maintenance therapy was administered in the comparator arm analogous to the intervention arm. Although in this therapeutic indication, treatment with bendamustine + rituximab is not covered by the marketing authorizations of the two drugs as set out in SmPC [17,18], the dosage and the treatment regimen correspond to those commonly used in clinical trials in this therapeutic indication and in related entities [3,4,7,8]. The duration of maintenance therapy with rituximab, which is two years, is in line with the current recommendations of the ESMO on the diagnosis, treatment and follow-up of lymphomas [19]. In addition to induction and maintenance therapy, patients in the control arm received a placebo orally twice daily instead of acalabrutinib. Administration of acalabrutinib or placebo will be continued until disease progression, unacceptable toxicity, discontinuation of treatment at the physician's decision, or withdrawal of consent. In the event of disease progression, the study protocol stipulates that patients in the comparator arm may receive monotherapy with acalabrutinib.

Primary outcome of the ECHO study is PFS. Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Suitability of autologous stem cell transplant for the patients included

In this therapeutic indication, acalabrutinib is approved exclusively for patients who are not eligible for autologous stem cell transplant. However, the ECHO study did not include any explicit inclusion or exclusion criteria relating to the suitability of stem cell transplant for the patients included. Only patients whose treatment goal was the preparation for an autologous stem cell transplant were excluded from the study participation. Beyond this, only patients aged 65 or over were included.

According to the ESMO guideline and the guideline of the British Society for Haematology on mantle cell lymphoma, autologous stem cell transplant is generally indicated for younger patients who are in good general health [5,19]. It should be noted that this group of patients is typically under 65 years of age (although, at the physician’s discretion, patients may be up to 70 years old). As the ECHO study included only patients aged 65 or over, it can be assumed, in light of the information provided in the guidelines, that stem cell transplant was not an

option for the majority of the study population due to their advanced age. However, the study did not include patients < 65 years pf age for whom autologous stem cell transplant was not an option due to poor general health.

In summary, for the purposes of this assessment, it is assumed that the group of patients included in the ECHO study is a sufficient approximation of the patient population in this therapeutic indication.

Suitability of the comparator therapy used for the assessment

The G-BA identified individualized treatment choosing from rituximab in combination with R-CHOP, VRCAP and bendamustine + rituximab as the ACT, provided that complete or partial remission is achieved following induction therapy with R-CHOP or bendamustine + rituximab, followed by maintenance therapy with rituximab. In its notes on the ACT, the G-BA further describes that for the implementation of the individualized treatment in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision (multicomparator study). A rationale had to be provided for the choice and any limitation of treatment options.

In the ECHO study, all patients in the comparator arm received treatment with bendamustine plus rituximab in addition to placebo, followed by maintenance therapy with rituximab upon achieving complete or partial remission. The other treatment options covered by the ACT were not available. The company does not justify the restriction of treatment options in the study to bendamustine plus rituximab upon achievement of complete or partial remission, followed by maintenance therapy with rituximab.

The treatment regimen used in the study is one of the recommendations set out in current guidelines, but it is not the sole standard of care in this therapeutic indication. For the first-line treatment of patients ≥ 65 years who are not eligible for autologous stem cell transplant, the guidelines recommend the use of the other therapy options of the ACT R-CHOP or VRCAP specified by the G-BA in addition to treatment with bendamustine + rituximab [5,19]. According to the G-BA, however, the use of bendamustine plus rituximab is generally preferable to the drugs currently approved in the therapeutic indication for the relevant patient groups or the relevant range of indications. Furthermore, the information provided in the guidelines does not suggest that R-CHOP or VRCAP would be preferable to the use of bendamustine plus rituximab for this indication. Against this background, it is assumed for the present assessment that sufficiently adequate treatment of the patients was ensured despite the lack of choice in the ECHO study.

Overall, the ECHO study was used for the benefit assessment in the present situation despite the uncertainties described. It is assumed that treatment with bendamustine plus rituximab, followed by maintenance therapy with rituximab upon achievement of complete or partial

remission, represents an adequate implementation of an individualized treatment. However, uncertainty remains as to whether other treatment options included in the G-BA's ACT would also have been suitable or even more suitable for some of the patients. This uncertainty is taken into account when assessing the certainty of conclusions (see Section I 4.2).

Furthermore, based on the results of the ECHO study, conclusions regarding the added benefit of acalabrutinib in combination with bendamustine + rituximab can only be drawn for patients for whom treatment with bendamustine and rituximab, followed by maintenance therapy with rituximab upon achieving complete or partial remission, is a suitable individualized treatment.

Available data cut-offs

A total of 2 data cut-offs have been conducted for the ECHO study to date:

- 15 February 2024: prespecified interim analysis, planned after approximately 250 events in the outcome PFS (see Table 6)
- 12 August 2024: analysis of overall survival and side effects requested by the FDA in accordance with the statistical analysis plan, Version 6.0, dated 12 July 2024

For the ECHO study, protocol Version 4.0 from 6 June 2023 stipulated that only the final analysis (which, according to the company, was to take place 101 months after randomization of the first patient [8 May 2017]) was originally planned after 268 events in the outcome PFS in addition to the interim analysis at the first data cut-off of 15 February 2024. Moreover, in accordance with the SAP Version 6.0 of 12 July 2024, and in line with the FDA’s comments, two additional data cut-offs on overall survival were added, approximately 6 months and approximately 3 years after the first data cut-off. According to company, the data cut-off of 12 August 2024 represents the first of these two additional data cut-off dates requested by the FDA.

In Module 4A, the company used the results of the interim data cut-off (15 February 2024) for the benefit assessment. For the outcome overall survival, it also presents the results for the data cut-off of 12 August 2024, as requested by the FDA. Contrary to the request in the dossier template [20], Module 4A does therefore not comprise the most recent analyses for all relevant outcomes at the relevant data cut-off of the ECHO study of 12 August 2024 requested by the FDA for the outcomes of the categories morbidity, health-related quality of life and side effects. However, the data presented by the company can nevertheless be used for the benefit assessment. This is justified below:

The data cut-off requested by the FDA was carried out approximately six months after the pre-specified data cut-off. Although the available data show that a relevant proportion of patients were still undergoing treatment at the data cut-off requested by the FDA (29% in th

intervention arm vs. 24% in the control arm), the majority of patients had already completed both the approximately 6-month induction therapy and the approximately 2-year maintenance therapy with rituximab by the interim data cut-off of 15 February 2024, and the patients had already been observed for a median period of just under 4 years (based on the outcome overall survival recorded throughout the entire study, see also information on the course of the study in Table 10). The available data also show that, at the data cut-off of 12 August 2024, no relevant number of patients with events were considered in the overall rates for outcomes in the side effects category, for which the observation period is linked to the duration of treatment. Therefore, the data cut-off of 15 February 2024 can be used for the assessment of the outcomes in the side effects category. Furthermore, the impact of the additional recordings of patient-reported outcomes on the results is also considered to be minor. This is because, at the time of the survey for the patient-reported outcomes at the interim data cut-off (which took place 12 months after the last patient had been randomized) only a small proportion of patients remained at risk of a deterioration in patient-reported outcomes (e.g. around one-third for the pain endpoint, see Figure 4 in Appendix B.2), and for these patients, a maximum of two further recordings could have been added individually by the second data cut-off. With regard to patient-reported outcomes, the data cut-off requested by the regulatory authority (12 August 2024) is not expected to yield any essential gain in information compared with the previous data cut-off (15 February 2024). Therefore, the data cut-off of 15 February 2024 can be used for the assessment of the patient-reported outcomes.

In summary, this benefit assessment uses the data cut-off of 12 August 2024 for the outcome overall survival, as requested by the FDA, and the interim data cut-off of 15 February 2024 for the outcomes in the categories morbidity, health-related quality of life and side effects.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab

Study **outcome category** **outcome**	**Planned follow-up observation**
ECHO	
Mortality	
All-cause mortality	Until death, withdrawal of consent or end of study, whichever is first
Morbidity	
Symptoms (EORTC QLQ-C30)	Until the last dose of the study medication[a]
Health status (EQ-5D VAS)	Until the last dose of the study medication[a]
Health-related quality of life	
EORTC QLQ-C30	Until the last dose of the study medication[a]
FACT-Lym	Until the last dose of the study medication[a]
Side effects	
All outcomes in the side effects category	Until 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurs first)[b]

a. The study documents contain discrepant information regarding the planned duration of follow-up for patient-reported outcomes; please refer to the following section for further explanation.
b. Subsequently, investigators should report only SAEs or other precarious AEs that are thought to be related to the study medication. These SAEs and other precarious AEs are not considered in the definition of treatment emergent adverse events for the analyses of the outcomes in the side effects category of the ECHO study.

AE: adverse event; EORTC: European Organization for Research and Treatment of Cancer; FACT-LYM: Functional Assessment of Cancer Therapy - Lymphoma; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In the ECHO study, follow-up over the entire duration of the study is only planned for the outcome overall survival. The observation periods for the outcomes of the categories morbidity, health-related quality of life and side effects, however, were systematically shortened.

The study documents contain discrepant information regarding the planned duration of follow-up for patient-reported outcomes. According to the study protocol, Version 4.0 dated 6 June 2023, patient-reported outcomes should be observed every 12 weeks even after discontinuation of treatment, until the disease progresses or a new antineoplastic therapy is initiated. In contrast, the SAP Version 4.0 dated 16 January 2024 states that the recording of patient-reported outcomes should be terminated upon treatment discontinuation (for example, if the treatment phase was terminated due to disease progression, initiation of an alternative treatment for mantle cell lymphoma, or unacceptable toxicity). Further recordings > 1 day after discontinuation of treatment should not be considered in the analyses. Module 4A of the dossier also states that patient-reported outcomes were only recorded up to the

discontinuation of treatment. Against this background, it is assumed that the analyses presented by the company only cover recordings up to the discontinuation of the study medication, and that no further recordings were carried out within the scope of the study after treatment discontinuation until disease had progressed or a new antineoplastic therapy was initiated.

Regardless of the discrepancies in the follow-up data for patient-reported outcomes, the observation periods for these outcomes of the categories morbidity and health-related quality of life have been systematically shortened, as no data were recorded beyond the point of disease progression or the end of treatment. The observation periods were also systematically shortened for outcomes in the side effects category, as these outcomes were only recorded for the duration of treatment with the study medication plus up to 30 days. However, drawing a reliable conclusion on the total study period or the time until patient death would require for the outcomes of the morbidity, health-related quality of life, and side effects categories to be recorded over the total period of time, as was the case for survival.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study characteristic category	Acalabrutinib + bendamustine + rituximab N = 299	Placebo + bendamustine + rituximab N = 299
ECHO		
Age [years], mean (SD)	72 (5)	72 (5)
Age group		
< 70 years	123 (41.1)	117 (39.1)
≥ 70 years	176 (58.9)	182 (60.9)
Sex [F/M], %	28/72	30/70
Geographical region, n (%)		
North America	82 (27.4)	83 (27.8)
Western Europe	46 (15.4)	46 (15.4)
Other[a]	171 (57.2)	170 (56.9)
ECOG PS, n (%)		
0	156 (52.2)	140 (46.8)
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
3	0 (0)	2 (0.7)
Missing	2 (0.7)	2 (0.7)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study characteristic category	**Acalabrutinib + bendamustine + rituximab N = 299**	**Placebo + bendamustine + rituximab N = 299**
Disease duration: time between first diagnosis and randomization [months], median [min; max]	1.7 [0.0; 116.4]	1.5 [0.1; 142.4]
Ann Arbor stage for lymphomas, n (%)		
I	2 (0.7)	1 (0.3)
II	15 (5.0)	11 (3.7)
III	31 (10.4)	24 (8.0)
IV	251 (83.9)	263 (88.0)
Simplified MIPI score, n (%)		
Low risk (0–3)	99 (33.1)	101 (33.8)
Intermediate risk (4-5)	128 (42.8)	125 (41.8)
High risk (6-11)	72 (24.1)	73 (24.4)
MCL type, n (%)		
Classical	238 (79.6)	243 (81.3)
Blastoid	26 (8.7)	20 (6.7)
Pleomorphic	15 (5.0)	18 (6.0)
Other	0 (0)	5 (1.7)
Unknown	19 (6.4)	11 (3.7)
Not recorded	1 (0.3)	2 (0.7)
Bone marrow involvement, n (%)		
Involvement	211 (70.6)	218 (72.9)
No involvement	82 (27.4)	75 (25.1)
Undetermined	1 (0.3)	2 (0.7)
Missing	5 (1.7)	4 (1.3)
Ki-67, n (%)		
< 30 %	133 (44.5)	126 (42.1)
≥ 30%	139 (46.5)	147 (49.2)
Undetermined	4 (1.3)	4 (1.3)
Missing	23 (7.7)	22 (7.4)
Treatment discontinuation, n (%)[b]	202 (67.6)	220 (73.6)
Study discontinuation, n (%)[c]	142 (47.5)	146 (48.8)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study characteristic category	Acalabrutinib + bendamustine + rituximab N = 299	Placebo + bendamustine + rituximab N = 299
a. The category other includes the following countries: Argentina, Australia, Brazil, China, the Czech Republic, Hungary, Israel, Japan, Korea, Mexico, New Zealand, Peru, Poland, Romania, Russia, Taiwan, Ukraine and Vietnam. b. Common reasons for treatment discontinuation in the intervention arm versus the control arm were (percentages based on randomized patients): adverse event (42.5% vs. 34.4%), objective disease progression (10.4% vs. 20.1%), withdrawal of consent (3.3% vs. 2.0%). In addition, 0.7% vs. 0.7% of randomized patients never started treatment. The data also include patients who died during treatment with the study medication (intervention arm: 4.7% vs. control arm: 6.7%). c. Common reasons for study discontinuation in the intervention arm vs. the control arm were the following (percentages based on randomized patients): death (32.1% vs. 34.4%) and withdrawal of consent (11.7% vs. 10.0%). ECOG PS: Eastern Cooperative Oncology Group – Performance Status; F: female; M: male; max: maximum; MCL: mantle cell lymphoma; min: minimum; MIPI: MCL International Prognostic Index; n: Number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation		

The two treatment arms were balanced in terms of patients' demographic and clinical characteristics. Patients were 72 years of age on average and predominantly male (72% vs. 70%). The proportion of patients from North America or Europe was approximately 43%. The majority of patients had an ECOG PS of 0 or 1; however, most had advanced disease and had Ann Arbor stage IV. The proportion of patients in the different risk categories of the simplified MIPI score was comparable between the two arms. 33.1% vs. 33.8% were classified as being at low risk, 42.8% vs. 41.8% at intermediate risk, and 24.1% vs. 24.4% as high risk.

The most common reasons for treatment discontinuation were AEs (42.5% vs. 34.4%) and objective disease progression (10.4% vs. 20.1%), with a clear difference in the reasons for discontinuation between the study arms in each case. In the intervention arm, more patients discontinued treatment due to AEs, whereas in the comparator arm, more patients discontinued treatment due to objective disease progression.

Course of the study

Table 10 shows the mean/median patient treatment duration and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study **duration of the study phase** **outcome category/outcome**	**Acalabrutinib + bendamustine + rituximab** **N = 299**	**Bendamustine + rituximab** **N = 299**
ECHO (data cut-off of 15 February 2024)		
Treatment duration[a] acalabrutinib/placebo [months]	n = 297	n = 296
Median [Q1; Q3]	28.6 [10.1; 54.3]	24.6 [8.3; 50.4]
Mean (SD)	32.5 (23.5)	29.1 (23.1)
Treatment duration[a] bendamustine [months]	n = 297	n = 296
Median [Q1; Q3]	5.6 [5.5; 5.8]	5.6 [5.5; 5.7]
Mean (SD)	5.3 (1.3)	5.2 (1.2)
Treatment duration[a] rituximab [months]	n = 297	n = 297
Median [Q1; Q3]	27.5 [11.4; 27.6]	23.9 [7.6; 27.6]
Mean (SD)	20.3 (9.5)	18.4 (10.2)
Observation period [months]		
Overall survival[b, c]		
Median [min; max]	46.9 [0.0; 80.4]	45.7 [0.0; 81.3]
Mean (SD)	ND	ND
Morbidity (symptoms, health status), health-related quality of life[d]		
EORTC QLQ-C30		
Median [min; max]	25.3 [0.0; 73.1]	21.3 [0.0; 76.4]
Mean (SD)	ND	ND
EQ-5D VAS		
Median [min; max]	25.3 [0.0; 73.1]	21.3 [0.0; 76.4]
Mean (SD)	ND	ND
FACT-Lym		
Median [min; max]	25.3 [0.0; 73.1]	21.3 [0.0; 76.4]
Mean (SD)	ND	ND
Side effects[a, e]	n = 297	n = 297
Median [min; max]	29.8 [0.2; 80.4]	26.3 [0.1; 77.6]
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study **duration of the study phase** **outcome category/outcome**	**Acalabrutinib + bendamustine + rituximab** **N = 299**	**Bendamustine + rituximab** **N = 299**
a. Data only refer to the safety population. b. The observation period is calculated on the basis of the observed time to event/censoring/end of study of all patients. c. No information is available on the analysed data cut-off of 12 August 2024 as requested by the FDA. d. The observation period is defined as the time from randomization to the earliest date of the last assessment of the questionnaire or the date of the data cut-off. Patients without baseline or post-baseline measurements are grouped together under a duration of one day. e. The observation period is defined as the duration from the date of the first dose of the study medication until the earliest of the following dates: the date of the data cut-off, 30 days after discontinuation of the study medication plus 7 days for clinical laboratory tests, the date of initiation of subsequent anticancer therapy (including the initiation date of acalabrutinib monotherapy), or the date of death. EORTC: European Organisation for Research and Treatment of Cancer; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

The mean and median treatment durations and the median observation periods are largely comparable between the study arms. Although the median treatment durations for acalabrutinib and rituximab in the intervention arm tend to be slightly longer than those for placebo and rituximab in the comparator arm, the median observation periods across the outcome categories are nevertheless comparable between the study arms.

However, regarding the observation period for overall survival, it should be noted that this refers to the first data cut-off for the prespecified interim analysis on 15 February 2024, and not to the second data cut-off of 12 August 2024, which was used for the present assessment. As the observation periods for the other outcomes are each linked to the end of treatment, these are already significantly shortened at the first data cut-off, in contrast to the observation period for overall survival. For these outcomes, conclusions can therefore be drawn only for the period under treatment or up to 30 days after the end of treatment.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥ 0.5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab

Study drug	Patients with at least one subsequent therapy n (%)	
	acalabrutinib + bendamustine + rituximab N = 299	placebo + bendamustine + rituximab N = 299
ECHO		
Total	30 (10.0)	88 (29.4)
Acalabrutinib	1 (0.3)	54 (18.1)
CHOP	2 (0.7)	4 (1.3)
FLU/CY/CAR-T	1 (0.3)	2 (0.7)
Ibrutinib	5 (1.7)	11 (3.7)
Ibrutinib/ixazomib[a]	0 (0)	2 (0.7)
Lenalidomide	1 (0.3)	4 (1.3)
Pirtobrutinib	2 (0.7)	3 (1.0)
R-BAC	0 (0)	2 (0.7)
R-CHOP	1 (0.3)	5 (1.7)
R-CHOP/R-AraC	1 (0.3)	3 (1.0)
R-CHOP/R-DHAOx	0 (0)	2 (0.7)
R-DHAOx	0 (0)	2 (0.7)
R-GEMOx	0 (0)	2 (0.7)
R-lenalidomide	2 (0.7)	2 (0.7)
Radiotherapy	1 (0.3)	2 (0.7)
Rituximab	3 (1.0)	1 (0.3)
Umbralisib/ublituximab[a]	2 (0.7)	1 (0.3)
Venetoclax	1 (0.3)	3 (1.0)
VRCAP	1 (0.3)	3 (1.0)
Zanubrutinib	2 (0.7)	4 (1.3)

a. This was used within the framework of a clinical trial.

AraC: cytarabine; BAC: bendamustine + cytarabine; CAR-T: chimeric antigen receptor T-cells; CHOP: cyclophosphamide + doxorubicin + vincristine + predniso(lo)ne; CY: cyclophosphamide; DHAOX: dexamethasone + high-dose cytarabine + oxaliplatin; FLU: fludarabine; GEMOx: gemcitabine + oxaliplatin; n: number of patients receiving subsequent therapy; N: number of analysed patients; R: rituximab; RCT: randomized controlled trial; VRCAP: bortezomib + rituximab + cyclophosphamide + doxorubicin + prednisone

The ECHO study involved no restrictions regarding subsequent antineoplastic therapies. However, in the event of disease progression, the study protocol stipulates that patients in the comparator arm may receive monotherapy with acalabrutinib in case of progressive disease. In contrast, the study protocol does not specify any particular subsequent therapy for patients in the intervention arm.

In total, the administration of at least one subsequent antineoplastic therapy was documented for 30 versus 88 patients at the time of the interim analysis (15 February 2024). In the intervention arm, the individual drugs were used only in individual patients, and there was no accumulation of particular subsequent therapies. In the comparator arm, however, the majority of patients with at least one subsequent therapy received treatment with acalabrutinib as monotherapy within the framework of the study (51 out of 88). In addition, some patients in the comparator arm received BTKIs outside the study, the majority of whom were treated with ibrutinib (11 patients), but individual patients also received acalabrutinib (3 patients), pirtobrutinib and zanubrutinib. The proportion of patients with subsequent therapy was very small compared to the proportion of patients whose disease had progressed in the intervention arm. In total, disease progression was observed in 57 patients in the intervention arm, and the initiation of a subsequent therapy was documented for 30 patients. Of these 30 patients, 8 had received subsequent therapy prior to disease progression and were therefore censored. It is therefore assumed that the remaining 22 patients received subsequent therapy after their disease had progressed. This would correspond to 39% of patients with disease progression in the intervention arm. The proportion is significantly higher for the comparator arm. In total, disease progression was observed in 99 patients, and the initiation of a subsequent therapy was documented for 88 patients. Of these 88 patients, 14 were censored prior to progression due to a subsequent therapy. Under analogous assumptions, 75% of patients requiring subsequent therapy would have received it.

According to European and British guidelines [5,19], treatment with a covalently binding BTKi is established for older patients with relapsed disease following immunochemotherapy. Among other things, the guidelines refer to treatment with ibrutinib, which has been available in Germany for quite some time for the treatment of relapsed or refractory mantle cell lymphoma; however, other BTK inhibitors, including acalabrutinib, are also listed in the guidelines. However, monotherapy with acalabrutinib for relapsed or refractory mantle cell lymphoma was approved by the European Medicines Agency in May 2025, at the same time as the therapeutic indication of this assessment (see the parallel dossier assessment on commission A25-90 [21]), which is why the therapeutic significance of acalabrutinib in the German health care context remains unclear.

For patients with relapsed or refractory mantle cell lymphoma who have received a covalent BTKi as first-line treatment, the guidelines recommend treatment with pirtobrutinib or re-treatment with another covalently binding BTKi, possibly in combination with venetoclax, in addition to immunochemotherapy [5,19]. However, in the intervention arm of the ECHO study, these treatment options were used only in isolated cases. In the comparator arm of the study, however, the majority of patients were treated with acalabrutinib monotherapy, in line with the study protocol which allowed for this option in the event of disease progression.

In summary, it should be noted that the study design only specifies a potential subsequent therapy for the comparator arm, but not for the intervention arm. This unequal treatment of the study arms is reflected in the fact that, in an important proportion of patients – particularly in the intervention arm – subsequent therapy was not initiated despite determination of disease progression. In the comparator arm, too, acalabrutinib was used as subsequent therapy instead of ibrutinib, the relevance of which in the German health care context was unclear at the time of this benefit assessment. The described deficiencies in the subsequent therapies used are therefore taken into account in the assessment of the outcome-specific risk of bias for overall survival (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ECHO	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the ECHO study.

Transferability of the study results to the German health care context

The company states that the study was conducted worldwide, and that there were no indications of clinically significant differences between population groups and geographical regions within the study. The company further explains that the median age of patients in the ECHO study was slightly higher than the mean age of patients at the time of diagnosis specified in the guidelines of the German Society for Haematology and Medical Oncology (DGHO), meaning that, in the company's view, the study tends to cover an older patient population. However, it must be taken into account that this therapeutic indication comprises patients who are not eligible for autologous stem cell transplant. The company states that, according to the guidelines of the DGHO [22], autologous stem cell transplant is only recommended for patients up to the age of 65 years. The patient population in the study would therefore correspond to the expected population in the therapeutic indication. In the company's view, the sex ratio in the study also reflects the information of the DGHO guideline. Finally, the

company concluded that the results of the ECHO study were transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded using the EORTC QLQ-C30
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the FACT-Lym
- Side effects
  - serious adverse events (SAEs)
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - cardiac disorders (SOC, severe AEs)
  - bleeding (standardized MedDRA Query [SMQ], AEs)
  - severe bleeding (SMQ, severe AEs)
  - infections and infestations (SOC, severe AEs)
  - other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, FACT-Lym)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Cardiac disorders (SOC, severe AEs)[a]	Bleeding (SMQ[c], AEs)	Severe bleeding (SMQ[c], severe AEs[a])	Infections and infestations (SOC, severe AEs)[a]	Further specific AEs[a,d]
ECHO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Discontinuation of at least one drug component.
c. Operationalized via the SMQ bleeding without events that were based on laboratory values.
d. The following events (MedDRA coding) were considered: vomiting (PT, AEs), headache (PT, AEs), injury, poisoning and procedural complications (SOC, SAEs), skin and subcutaneous tissue disorders (SOC, severe AEs), white blood cell count decreased (PT, severe AEs) and hepatotoxicity (operationalized via severe AEs of the SMQs hepatic failure, fibrosis and cirrhosis and other diseases caused by liver damage [narrow]; hepatitis, non-infectious [narrow]; liver-related examinations, clinical signs and symptoms [narrow]).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Analyses of patient-reported outcomes on symptoms, health status and health-related quality of life

In Module 4A, the company presents responder analyses for the time to first deterioration for the outcomes symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30, FACT-Lym) using the following response criteria:

- EORTC QLQ-C30: deterioration by ≥ 10 points each (respective scale range 0 to 100)
- EQ-5D VAS: deterioration by ≥ 15 points (scale range 0 to 100)
- FACT-Lym: deterioration by ≥ 25.2 points (scale range 0 to 168)

The response criteria of the EORTC QLQ-C30, the EQ-5D VAS and the FACT-Lym were not prespecified according to the study design. Since the response criteria used for the analyses

correspond to the criteria described in the General Methods of the Institute [1] for response criteria that reflect a change that is perceptible to patients with sufficient certainty, the responder analyses were used for the benefit assessment.

Side effects

AEs, SAEs, and severe AEs

When considering side effects, the primary factor is how many patients experienced an event. However, when analysing the time until occurrence of the event, effects may also result from an earlier or later occurrence of the event rather than on the basis of the proportions. Time-to-event analyses are of particular relevance in between-group comparisons with different mean observation periods [1]. The company presented time-to-event analyses for all side effects outcomes. In the present situation, however, the median observation periods between the treatment arms are sufficiently similar (see Table 10) to use the relative risk (RR) as an effect measure to derive the added benefit for all outcomes in the side effects category.

Operationalisation of bleeding and severe bleeding

In Module 4A of the dossier, the company provides analyses of various AEs that it has designated as Events of Clinical Interest (ECIs). These are AEs of special interest (AESI) that have been predefined in accordance with the study design, some of which have been recorded from collections of individual PTs, SOCs or SMQs. In doing so, the company provides analyses on all AEs for all ECIs, regardless of severity, as well as analyses on severe AEs classified as CTCAE grade ≥ 3 and on SAEs. In order to assess the outcome bleeding, the SMQ bleeding (without laboratory values) was prespecified as ECI in accordance with the study design. This is used in the present benefit assessment to depict the outcome bleeding. Moreover, in accordance with the study design, severe bleeding was recorded as severe AE (CTCAE grade ≥ 3) of the SMQ bleeding (without laboratory values), whilst also taking into account all SAEs of the SMQ and any bleeding of the central nervous system (CNS), regardless of severity, as recorded using a prespecified PT collection. As this operationalization correspondingly also includes non-severe/non-serious events, it is not suitable for depicting the outcome severe bleeding for the present benefit assessment. For the purposes of this analysis, the outcome severe bleeding is instead defined in as severe AE CTCAE grade ≥ 3 of the bleeding SMQ (without laboratory values). The included events thereby correspond to the severe AEs of CTCAE grade ≥ 3 that occurred in the operationalization of severe bleeding as an event of clinical interest (ECI) in accordance with the study design. It should also be noted that there were no statistically significant differences between the treatment groups, either when considering severe bleeding via the AEs with CTCAE grade ≥ 3 of the SMQ bleeding (without laboratory values) or when including SAEs and CNS bleeding (see Table 16). Whether or not serious bleeding and bleeding of the CNS are additionally taken into account in the operationalization in addition to the severe AEs of CTCAE grade ≥ 3 of the SMQ bleeding (without laboratory values), therefore has no consequences for the present assessment.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab

Study	Study level	Outcomes											
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, FACT-Lym)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Cardiac disorders (SOC, severe AEs)[a]	Bleeding (SMQ[c], AEs)	Severe bleeding (SMQ[c], severe AEs[a])	Infections and infestations (SOC, severe AEs)[a]	Further specific AEs[a,d]
ECHO	L	H[e]	H[f]	H[f]	H[f]	H[f]	H[f]	L[g]	H[f]	H[f]	H[f]	H[f]	H[f]

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Discontinuation of at least one drug component.
c. Operationalized via the SMQ bleeding without events that were based on laboratory values.
d. The following events (MedDRA coding) were considered: vomiting (PT, AEs), headache (PT, AEs), injury, poisoning and procedural complications (SOC, SAEs), skin and subcutaneous tissue disorders (SOC, severe AEs), white blood cell count decreased (PT, severe AEs) and hepatotoxicity (operationalized via severe AEs of the SMQs hepatic failure, fibrosis and cirrhosis and other diseases caused by liver damage [narrow]; hepatitis, non-infectious [narrow]; liver-related examinations, clinical signs and symptoms [narrow]).
e. Due to uncertainties regarding the use of adequate subsequent therapies (see Section I 3.2).
f. Incomplete observations for potentially informative reasons.
g. Despite the low risk of bias, the certainty of results is presumably limited for the outcome discontinuation due to AEs.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias in the results for the outcome overall survival is rated as high due to uncertainties regarding the use of appropriate subsequent therapies (for explanation, see Section I 3.2).

The risk of bias in the results for the symptoms outcomes (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30, FACT-Lym), as well as the outcomes in the side effects category ((except for discontinuation due to AEs), is also rated as

high. For these outcomes, the observations are incomplete for potentially informative reasons due to the follow-up being linked to the treatment duration.

Although the risk of bias is low for the outcome discontinuation due to AEs, the certainty of results for this outcome is limited. Premature treatment discontinuation for reasons other than AEs was a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion 'discontinuation' is no longer applicable to them. It was impossible to estimate how many AEs this affected.

Summary assessment of the certainty of conclusions

For patients in the ECHO study, it is assumed that treatment with placebo + bendamustine + rituximab in the comparator arm, followed by maintenance therapy with rituximab upon achievement of complete or partial remission, represents an adequate implementation of an individualized treatment. However, uncertainty remains as to whether other treatment options included in the G-BA's ACT would also have been suitable or even more suitable for some of the patients (see Section I 3.2 for detailed explanation). It therefore remains unclear whether the results of the study can be transferred to the German health care context without restriction. Based on the ECHO study, at most hints, e.g. of an added benefit, can be derived for all outcomes irrespective of the outcome-specific risk of bias.

I 4.3 Results

Table 15 and Table 16 summarize the results of the comparison of acalabrutinib + bendamustine + rituximab with placebo + bendamustine + rituximab in adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses shown are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity and health-related quality of life) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs placebo + bendamustine + rituximab (multipage table)

Study outcome category outcome	Acalabrutinib + bendamustine + rituximab		Placebo + bendamustine + rituximab		Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
ECHO					
Mortality (cut-off of 12 August 2024)					
Overall survival	299	NA [72.1; NC] 105 (35.1)	299	NA [73.8; NC] 113 (37.8)	0.87 [0.67; 1.14][a]; ND
Morbidity (data cut-off of 15 February 2024)					
Symptoms (EORTC QLQ-C30 – time to first deterioration[b])					
Fatigue	299	3.9 [3.7; 6.5] 190 (63.5)	299	4.1 [3.7; 7.0] 161 (53.8)	1.16 [0.94; 1.44]; 0.166[c]
Nausea and vomiting	299	50.8 [32.2; NC] 110 (36.8)	299	39.4 [25.9; NC] 105 (35.1)	0.95 [0.72; 1.24]; 0.696[a]
Pain	299	13.9 [10.2; 17.6] 157 (52.5)	299	21.4 [17.5; 36.1] 119 (39.8)	1.37 [1.08; 1.74]; 0.011[a]
Dyspnoea	299	28.8 [21.2; 39.6] 122 (40.8)	299	28.6 [21.6; 58.2] 99 (33.1)	1.10 [0.85; 1.44]; 0.475[a]
Insomnia	299	28.7 [17.6; 39.4] 126 (42.1)	299	36.4 [21.2; 69.0] 103 (34.4)	1.20 [0.92; 1.56]; 0.176[a]
Appetite loss	299	24.9 [10.2; 61.3] 129 (43.1)	299	35.9 [18.4; 58.3] 105 (35.1)	1.13 [0.87; 1.46]; 0.355[a]
Constipation	299	35.7 [21.5; NC] 112 (37.5)	299	28.6 [13.8; NC] 108 (36.1)	0.87 [0.67; 1.14]; 0.344[a]
Diarrhoea	299	28.6 [14.3; 50.5] 119 (39.8)	299	47.2 [39.6; NC] 85 (28.4)	1.36 [1.03; 1.80]; 0.030[a]
Health status (EQ-5D VAS, time to first deterioration[d])	299	50.7 [25.0; NC] 111 (37.1)	299	47.2 [35.9; NC] 88 (29.4)	1.18 [0.89; 1.57]; 0.248[a]

Table 15: Results (mortality, morbidity and health-related quality of life) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs placebo + bendamustine + rituximab (multipage table)

Study outcome category outcome	Acalabrutinib + bendamustine + rituximab		Placebo + bendamustine + rituximab		Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Health-related quality of life (data cut-off of 15 February 2024)					
EORTC QLQ-C30 – time to first deterioration[e]					
Global health status	299	13.9 [7.1; 21.3] 146 (48.8)	299	21.2 [13.8; 39.6] 117 (39.1)	1.18 [0.92; 1.51]; 0.197[c]
Physical functioning	299	17.5 [10.2; 25.2] 147 (49.2)	299	13.9 [6.4; 24.6] 138 (46.2)	0.90 [0.71; 1.14]; 0.385[c]
Role functioning	299	13.8 [6.8; 21.3] 161 (53.8)	299	10.1 [6.5; 17.7] 147 (49.2)	0.96 [0.76; 1.20]; 0.701[c]
Emotional functioning	299	58.0 [32.5; NC] 95 (31.8)	299	52.4 [21.3; NC] 96 (32.1)	0.80 [0.60; 1.06]; 0.120[a]
Cognitive functioning	299	14.3 [10.4; 25.0] 146 (48.8)	299	13.9 [10.2; 17.8] 147 (49.2)	0.88 [0.70; 1.10]; 0.273[a]
Social functioning	299	10.2 [6.5; 17.5] 161 (53.8)	299	10.3 [6.5; 25.1] 137 (45.8)	1.09 [0.87; 1.38]; 0.461[c]
FACT-Lym – time to first deterioration[f]					
Total score	299	NA 56 (18.7)	299	69.0 [65.0; NC] 46 (15.4)	1.08 [0.73; 1.60]; 0.713[a]
Physical wellbeing[g]	299	65.3 [39.7; NC] 100 (33.4)	299	46.9 [24.9; NC] 106 (35.5)	0.87 [0.66; 1.14][a]
Social/family wellbeing[g]	299	28.5 [17.7; 39.6] 125 (41.8)	299	28.3 [14.0; 32.5] 112 (37.5)	0.95 [0.74; 1.23][a]
Emotional wellbeing[h]	299	58.3 [47.1; NC] 81 (27.1)	299	NA 67 (22.4)	1.08 [0.78; 1.50][a]
Functional wellbeing[g]	299	24.9 [10.3; 39.6] 133 (44.5)	299	28.6 [17.6; 47.1] 110 (36.8)	1.12 [0.87; 1.45][c]
Lymphoma-specific subscale[i]	299	NA 56 (18.7)	299	NA 52 (17.4)	0.96 [0.66; 1.40][a]

Table 15: Results (mortality, morbidity and health-related quality of life) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs placebo + bendamustine + rituximab (multipage table)

Study **outcome category** **outcome**	**Acalabrutinib + bendamustine + rituximab**		**Placebo + bendamustine + rituximab**		**Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI];** **p-value**

a. Cox proportional hazards model, stratified by MIPI score; profile likelihood confidence intervals; p-value based on two-sided stratified log-rank test.
b. An increase in the EORTC QLQ-C30 score by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. Cox proportional hazards model, stratified by MIPI score and region; profile likelihood confidence intervals; p-value based on two-sided stratified log-rank test.
d. A decrease in the EQ-5D VAS score by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. A decrease in the EORTC QLQ-C30 score by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. A decrease in the EQ-5D FACT-Lym total score by ≥ 25.2 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 168).
g. A decrease by ≥ 4.2 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 28).
h. A decrease by ≥ 3.6 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 24).
i. A decrease by ≥ 9 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 60).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; HR: hazard ratio; MCL: mantle cell lymphoma; MIPI: MCL International Prognostic Index; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

Table 16: Results (side effects) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study outcome category outcome	Acalabrutinib + bendamustine + rituximab		Placebo + bendamustine + rituximab		Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
ECHO					
Side effects (data cut-off of 15 February 2024)					
AEs (supplementary information)	297	296 (99.7)	297	294 (99.0)	–
SAEs	297	205 (69.0)	297	184 (62.0)	1.11 [0.99; 1.25]; 0.074
Severe AEs[b]	297	264 (88.9)	297	262 (88.2)	1.01 [0.95; 1.07]; 0.865
Discontinuation due to AEs[c]	297	150 (50.5)	297	105 (35.4)	1.43 [1.18; 1.73]; < 0.001
Cardiac disorders (SOC, severe AEs)[b]	297	23 (7.7)	297	18 (6.1)	1.28 [0.70; 2.32]; 0.533
Bleeding (SMQ[d], AEs)	297	84 (28.3)	297	51 (17.2)	1.65 [1.21; 2.24]; 0.001
Severe bleeding (SMQ[d], severe AEs[b])[e]	297	6 (2.0)	297	10 (3.4)	0.60 [0.22; 1.63]; 0.327
Infections and infestations (SOC, severe AEs)[b]	297	122 (41.1)	297	101 (34.0)	1.21 [0.98; 1.49]; 0.078
Other specific AEs					
Vomiting (PT, AEs)	297	76 (25.6)	297	41 (13.8)	1.85 [1.31; 2.61]; 0.001
Headache (PT, AEs)	297	90 (30.3)	297	42 (14.1)	2.14 [1.54; 2.98]; 0.001
Injury, poisoning and procedural complications (SOC, SAEs)	297	7 (2.4)	297	18 (6.1)	0.39 [0.16; 0.92]; 0.026
Skin and subcutaneous tissue disorders (SOC, severe AEs)[b])	297	47 (15.8)	297	12 (4.0)	3.92 [2.12; 7.23]; 0.001
White blood cell count decreased (PT, severe AEs)[b]	297	30 (10.1)	297	11 (3.7)	2.73 [1.39; 5.34]; 0.002
Hepatotoxicity (severe AEs)[b, f]	297	20 (6.7)	297	6 (2.0)	3.33 [1.36; 8.18]; 0.005

Table 16: Results (side effects) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab (multipage table)

Study outcome category outcome	Acalabrutinib + bendamustine + rituximab		Placebo + bendamustine + rituximab		Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
a. Institute's calculation; unconditional exact test (CSZ method according to [23]). b. Operationalized as CTCAE grade ≥ 3. c. Discontinuation of at least one drug component. d. Operationalized via the SMQ bleeding without events that were based on laboratory values. e. When severe bleeding was operationalized in accordance with the study design (including SAEs and CNS bleeding in addition to severe AEs classified as CTCAE grade ≥ 3 in the SMQ bleeding), 7 events occurred in the intervention arm and 16 events in the comparator arm. This results in an RR [95% CI] of 0.44 [0.18; 1.05] and a p-value of 0.060 (for a detailed explanation, see Section I 4.1). f. Operationalized via severe AEs of the SMQs hepatic failure, fibrosis and cirrhosis, and other disorders caused by liver damage (narrow); hepatitis, non-infectious (narrow); liver-related examinations, clinical signs and symptoms (narrow). AE: adverse event; CI: confidence interval; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: standardized MedDRA query: SOC: System Organ Class					

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see also Section I 4.2).

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome overall survival. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Morbidity

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

No statistically significant difference between the treatment arms was shown for the scales fatigue, nausea and vomiting, dyspnoea, insomnia, appetite loss and constipation of the EORTC QLQ-C30. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

A statistically significant difference between the treatment arms was found the scales pain and diarrhoea of the EORTC QLQ-C30. This difference was no more than marginal, however (see Section I 5.1). There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome health status, recorded with the EQ-5D VAS. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning)

No statistically significant difference between the treatment arms was found for any of the scales global health status, physical functioning, role functioning, emotional functioning and cognitive functioning of the EORTC QLQ-C30. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

No statistically significant difference between the treatment arms was found for the social functioning scale of the EORTC QLQ-C30. However, there is an effect modification by the characteristic age (see Section I 4.4). There was a hint of lesser benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab patients ≥ 70 years of age. For patients ≥ 70 years, there is no hint of an added benefit of acalabrutinib + bendamustine + rituximab over bendamustine + rituximab; an added benefit is therefore not proven for this patient group.

FACT-Lym

For the outcome health-related quality of life (recorded using the FACT-Lym), no statistically significant difference between treatment groups was found. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment arms for either of the outcomes of SAEs and severe AEs. In each case, this results in no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome discontinuation due to AEs. There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Specific AEs

Cardiac disorders (SOC, severe AEs)

There was no statistically significant difference between the treatment arms for the outcome cardiac disorders (SOC, severe AEs). There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Bleeding (SMQ, AEs)

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome bleeding. There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Severe bleeding (SMQ, severe AEs)

There was no statistically significant difference between the treatment arms for the outcome severe bleeding (SMQ, severe AEs). There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Infections and infestations (SOC, severe AEs)

No statistically significant difference between the treatment arms was shown for the outcome infections and infestations (SOC, AEs). There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Vomiting (PT, AEs)

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome vomiting (PT, AEs). However, there is an effect modification for the characteristic simplified MIPI score (see Section I 4.4). For patients at low or intermediate risk (0 to 5) in the simplified MIPI score, there is a hint of greater harm from acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab. For patients at high risk (6 to 11) in the simplified MIPI score, there is no hint of greater or lesser harm from acalabrutinib + bendamustine +

rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for this patient group.

Headache (PT, AEs)

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for the outcome headache (PT, AEs). There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Injury, poisoning and procedural complications (SOC, SAEs)

A statistically significant difference in favour of acalabrutinib + bendamustine + rituximab in comparison with placebo + bendamustine + rituximab was shown for the outcome injury, poisoning and procedural complications (SOC, SAEs). There was an effect modification for the characteristic of sex, however (see Section I 4.4). For men, there is a hint of lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab. For women, there is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for this patient group.

Skin and subcutaneous tissue disorders (SOC, severe AEs), decreased leukocyte count (PT, severe AEs)

For each of the outcomes skin and subcutaneous tissue disorders (SOC, severe AEs) and white blood cell count decreased (PT, severe AEs), a statistically significant difference was shown to the disadvantage of acalabrutinib + bendamustine + rituximab compared to placebo + bendamustine + rituximab. In each case, there is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

Hepatotoxicity (severe AEs)

For the outcomes hepatotoxicity (operationalized via the SMQs hepatic failure, fibrosis and cirrhosis, and other diseases in connection with liver injury [narrow]; hepatitis, non-infectious [narrow]; liver-related examinations, clinical signs and symptoms [narrow], all severe AEs), there is a statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab. However, there is an effect modification for the characteristic simplified MIPI score (see Section I 4.4). For patients at low or intermediate risk (0 to 5) in the simplified MIPI score, there is a hint of greater harm from acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab. For patients at high risk (6 to 11) in the simplified MIPI score, there is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for this patient group.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (< 70 years versus ≥ 70 years)
- Sex (male versus female)
- Simplified MIPI score (low or intermediate risk [0 to 5] vs. high risk [6 to 11])

Subgroup analyses for age, sex and simplified MIPI score were prespecified for overall survival in accordance with the study design. Results on subgroup analyses based on 2 different, prespecified cut-off values of 70 years and 75 years are available for the characteristic age. The classification into the age categories < 70 years versus ≥ 70 years is considered to be meaningful in the present indication, as an age of 70 years corresponds to the prognostically relevant age limit according to the simplified MIPI [24].

In Module 4A of the dossier, the company submits subgroup analyses for all outcomes presented, except for the outcomes cardiac disorders (SOC, severe AEs) and infections and infestations (SOC, severe AEs). Furthermore, for the outcome overall survival, Module 4A of the dossier contains only subgroup analyses for the prespecified interim data cut-off of 15 February 2024, but not for the data cut-off of 12 August 2024 requested by the FDA. However, for the prespecified interim data cut-off of 15 February 2024, no effect modification is observed for any of the relevant subgroup characteristics. Furthermore, based on the available subgroup results for the interim data cut-off, it can be assumed with a sufficient certainty that there is no relevant difference to the disadvantage of the intervention for individual subgroups at the data cut-off requested by the FDA.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

For the outcome category of side effects, the company considered the time to event, using the hazard ratio (HR) as effect measure. The subgroup analyses conducted by the company for this outcome category were also based on the HR. In contrast to the approach of the company, this assessment used analyses of the number of patients with event with the RR effect measure for the side effect outcomes to derive the added benefit. Analyses based on the RR were therefore also preferable for the subgroup analyses. This benefit assessment therefore examined whether, using the HR, there was a significant effect modification at the

0.2 level. If this was the case, an interaction test was performed using the Q test, based on the RR.

The results are presented in Table 17 and Table 18. Kaplan-Meier curves on the presented time-to-event analyses of the subgroup results can be found in I Appendix B of the full dossier assessment.

Table 17: Subgroups (health-related quality of life) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs placebo + bendamustine + rituximab

Study outcome characteristic subgroup	Acalabrutinib + bendamustine + rituximab		Placebo + bendamustine + rituximab		Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI]	p-value
ECHO (data cut-off of 15 February 2024)						
Health-related quality of life (EORTC QLQ-C30, social functioning - time to first deterioration[a]						
Age						
< 70 years	123	6.5 [3.8; 17.4] 73 (59.3)	117	28.6 [3.8; NC] 47 (40.2)	1.51 [1.05; 2.19]	0.026[b]
≥ 70 years	176	17.5 [6.5; 24.9] 88 (50.0)	182	10.1 [3.9; 17.5] 90 (49.5)	0.90 [0.67; 1.21]	0.498[b]
Total					Interaction:	0.031[b]

a. A decrease in the EORTC QLQ-C30 score by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
b. Cox proportional hazards model, including the covariate subgroup and the interaction term subgroup and treatment; profile likelihood confidence intervals.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; QLQ-C30: Quality of Life Questionnaire-Core 30

Table 18: Subgroups (side effects) – RCT, direct comparison: acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab

Study outcome characteristic subgroup	Acalabrutinib + bendamustine + rituximab N	 patients with event n (%)	Placebo + bendamustine + rituximab N	 patients with event n (%)	Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab RR [95% CI][a]	 p-value
ECHO (data cut-off of 15 February 2024)						
Vomiting (PT, AEs)						
Simplified MIPI score						
Low/intermediate risk (0–5)[b]	225[a]	66 (29.3)[a]	225[a]	29 (12.9)[a]	2.28 [1.53; 3.38]	ND
Low risk (0–3)	*99*	*34 (34.3)*	*101*	*15 (14.9)*	*2.31 [1.35; 3.97]*	*ND*
Intermediate risk (4-5)	*126*	*32 (25.4)*	*124*	*14 (11.3)*	*2.25 [1.26; 4.01]*	*ND*
High risk (6-11)	72	10 (13.9)	72	12 (16.7)	0.83 [0.38; 1.81]	ND
Total					Interaction[c]:	0.023
Injury, poisoning and procedural complications (SOC, SAEs)						
Sex						
Male	212	2 (0.9)	208	15 (7.2)	0.13 [0.03; 0.56]	ND
Female	85	5 (5.9)	89	3 (3.4)	1.75 [0.43; 7.08]	ND
Total					Interaction[c]:	0.012
Hepatotoxicity (severe AEs)[d, e]						
Simplified MIPI score						
Low/intermediate risk (0–5)[b]	225[a]	18 (8.0)[a]	225[a]	3 (1.3)[a]	6.00 [1.79; 20.08]	ND
Low risk (0–3)	*99*	*9 (9.1)*	*101*	*1 (1.0)*	*9.18 [1.19; 71.13]*	*ND*
Intermediate risk (4-5)	*126*	*9 (7.1)*	*124*	*2 (1.6)*	*4.43 [0.98; 20.09]*	*ND*
High risk (6-11)	72	2 (2.8)	72	3 (4.2)	0.67 [0.11; 3.87]	ND
Total					Interaction[c]:	0.044

a. Institute's calculation.
b. Summary of the low-risk and intermediate-risk subgroups
c. Institute's calculation, p-value from Q test for heterogeneity.
d. Operationalized as CTCAE grade ≥ 3.
e. Operationalized via severe AEs of the SMQs: hepatic failure, fibrosis and cirrhosis, and other disorders caused by liver damage (narrow); hepatitis, non-infectious (narrow); liver-related examinations, clinical signs and symptoms (narrow).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; MCL: mantle cell lymphoma; MedDRA: Medical Dictionary for Regulatory Activities; MIPI: MCL International Prognostic Index; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Morbidity

Health-related quality of life (EORTC QLQ-C30)

Social functioning

An effect modification for the characteristic age was found for the social functioning scale of the EORTC QLQ-C30..

A statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown in the age group < 70 years. For this patient group, there is a hint of lesser benefit from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

There was no statistically significant difference between the treatment arms for patients ≥ 70 years of age. There is no hint of an added benefit of acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab for this patient group; an added benefit is therefore not proven.

Side effects

Vomiting (PT, AEs)

There was an effect modification for the simplified MIPI score for the outcome of vomiting (AEs).

For patients at low or intermediate risk (0 to 5) in the simplified MIPI score, there is a statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared to placebo + bendamustine + rituximab. There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

For patients at high risk (6 to 11) in the simplified MIPI-score, there is no difference between the treatment groups. There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Injury, poisoning and procedural complications (SOC, SAEs)

For the outcome injury, poisoning and procedural complications (SOC, SAEs), there is an effect modification for the characteristic sex.

A statistically significant difference in favour of acalabrutinib + bendamustine + rituximab compared with placebo + bendamustine + rituximab was shown for men. There is a hint of lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

For women, there was no difference between the treatment groups. There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Hepatotoxicity (severe AEs)

There was an effect modification for the characteristic simplified MIPI score for the outcome hepatotoxicity (severe AEs).

For patients at low or intermediate risk (0 to 5) in the simplified MIPI score, there is a statistically significant difference to the disadvantage of acalabrutinib + bendamustine + rituximab compared to placebo + bendamustine + rituximab. There is a hint of greater harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab.

For patients at high risk (6 to 11) in the simplified MIPI-score, there is no difference between the treatment groups. There is no hint of greater or lesser harm from acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 19).

Determination of the outcome category for the outcomes "symptoms" and "side effects"

The dossier does not provide any details as to whether the outcomes on symptoms and on side effects were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

EORTC QLQ-C30 (pain and diarrhoea)

For the EORTC QLQ-C30 scales pain and diarrhoea, insufficient information was available to allow a severity category classification of serious/severe. These outcomes were therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Discontinuation due to AEs

For the purposes of this assessment, the outcome discontinuation due to adverse events is operationalized as discontinuation of at least one drug component. The study documents show that the majority of discontinuations of the individual drug components were due to severe AEs of CTCAE grade ≥ 3. For example, at the data cut-off of 15 February 2024, approximately 72% of AEs that led to discontinuation of treatment with acalabrutinib or placebo, approximately 88% of AEs that led to discontinuation of treatment with bendamustine, and 69% of AEs that led to discontinuation of treatment with rituximab had a CTCAE grade ≥ 3. Against this background, it is assumed for the present assessment that predominantly severe AEs of CTCAE grade ≥ 3 led to the discontinuation of at least one drug component. The outcome discontinuation due to AEs was therefore assigned to the outcome category serious/severe side effects.

Table 19: Extent of added benefit at outcome level: acalabrutinib + bendamustine + rituximab vs. bendamustine + rituximab (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality (cut-off of 12 August 2024)		
Overall survival	NA vs. NA HR: 0.87 [0.67; 1.14]; p = ND	Lesser benefit/added benefit not proven
Outcomes with shortened observation period		
Morbidity (data cut-off of 15 February 2024)		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	3.9 vs. 4.1 months HR: 1.16 [0.94; 1.44]; p = 0.166	Lesser benefit/added benefit not proven
Nausea and vomiting	50.8 vs. 39.4 months HR: 0.95 [0.72; 1.24]; p = 0.696	Lesser benefit/added benefit not proven
Pain	13.9 vs. 21.4 months HR: 1.37 [1.08; 1.74] HR: 0.73 [0.57; 0.93][c]; p = 0.011	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Dyspnoea	28.8 vs. 28.6 months HR: 1.10 [0.85; 1.44]; p = 0.475	Lesser benefit/added benefit not proven
Insomnia	28.7 vs. 36.4 months HR: 1.20 [0.92; 1.56]; p = 0.176	Lesser benefit/added benefit not proven
Appetite loss	24.9 vs. 35.9 months HR: 1.13 [0.87; 1.46]; p = 0.355	Lesser benefit/added benefit not proven
Constipation	35.7 vs. 28.6 months HR: 0.87 [0.67; 1.14]; p = 0.344	Lesser benefit/added benefit not proven
Diarrhoea	28.6 vs. 47.2 months HR: 1.36 [1.03; 1.80] HR: 0.74 [0.56; 0.97][c]; p = 0.030	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]

Table 19: Extent of added benefit at outcome level: acalabrutinib + bendamustine + rituximab vs. bendamustine + rituximab (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Health status (EQ-5D VAS - time to first deterioration)	50.7 vs. 47.2 months HR: 1.18 [0.89; 1.57]; p = 0.248	Lesser benefit/added benefit not proven
Health-related quality of life (data cut-off of 15 February 2024)		
EORTC QLQ-C30 – time to first deterioration		
Global health status	13.9 vs. 21.2 months HR: 1.18 [0.92; 1.51]; p = 0.197	Lesser benefit/added benefit not proven
Physical functioning	17.5 vs. 13.9 months HR: 0.90 [0.71; 1.14]; p = 0.385	Lesser benefit/added benefit not proven
Role functioning	13.8 vs. 10.1 months HR: 0.96 [0.76; 1.20]; p = 0.701	Lesser benefit/added benefit not proven
Emotional functioning	58.0 vs. 52.4 months HR: 0.80 [0.60; 1.06]; p = 0.120	Lesser benefit/added benefit not proven
Cognitive functioning	14.3 vs. 13.9 months HR: 0.88 [0.70; 1.10]; p = 0.273	Lesser benefit/added benefit not proven
Social functioning		
Age		
< 70 years	6.5 vs. 28.6 months HR: 1.51 [1.05; 2.19] HR: 0.66 [0.46; 0.95][c]; p = 0.026 probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: “minor”
≥ 70 years	17.5 vs. 10.1 months HR: 0.90 [0.67; 1.21]; p = 0.498	Lesser benefit/added benefit not proven
FACT-Lym – time to first deterioration	NA vs. 69.0 months HR: 1.08 [0.73; 1.60]; p = 0.713	Lesser benefit/added benefit not proven

Table 19: Extent of added benefit at outcome level: acalabrutinib + bendamustine + rituximab vs. bendamustine + rituximab (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects (data cut-off of 15 February 2024)		
SAEs	69.0% vs. 62.0% RR: 1.11 [0.99; 1.25]; p = 0.074	Greater/lesser harm not proven
Severe AEs	88.9% vs. 88.2% RR: 1.01 [0.95; 1.07]; p = 0.865	Greater/lesser harm not proven
Discontinuation due to AEs	50.5 % vs. 35.4 % RR: 1.43 [1.18; 1.73] RR: 0.70 [0.58; 0.85][c] p = 0.001 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Cardiac disorders (severe AEs)	7.7% vs. 6.1% RR: 1.28 [0.70; 2.32]; p = 0.533	Greater/lesser harm not proven
Bleeding (AEs)	28.3 % vs. 17.2 % RR: 1.65 [1.21; 2.24] RR: 0.61 [0.45; 0.83][c] p = 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: minor
Severe bleeding (severe AEs)	2.0% vs. 3.4% RR: 0.60 [0.22; 1.63]; p = 0.327	Greater/lesser harm not proven
Infections and infestations (severe AEs)	41.1% vs. 34.0% RR: 1.21 [0.98; 1.49]; p = 0.078	Greater/lesser harm not proven
Other specific AEs		
Vomiting (AEs) simplified MIPI score low/intermediate risk (0–5)	29.3% vs. 12.9% RR: 2.28 [1.53; 3.38] RR: 0.44 [0.30; 0.65][c]; p = ND probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
High risk (6-11)	13.9% vs. 16.7% RR: 0.83 [0.38; 1.81]; p = ND	Greater/lesser harm not proven

Table 19: Extent of added benefit at outcome level: acalabrutinib + bendamustine + rituximab vs. bendamustine + rituximab (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Headache (AEs)	30.3 % vs. 14.1 % RR: 2.14 [1.54; 2.98] RR: 0.47 [0.34; 0.65][c] p = 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Injury, poisoning and procedural complications (SAEs)		
Sex		
Male	0.9% vs. 7.2% RR: 0.13 [0.03; 0.56]; p = ND probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: major
Female	5.9% vs. 3.4% RR: 1.75 [0.43; 7.08]; p = ND	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders (severe AEs)	15.8 % vs. 4.0 % RR: 3.92 [2.12; 7.23] RR: 0.26 [0.14; 0.47][c] p = 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
White blood cell count decreased (severe AEs)	10.1 % vs. 3.7 % RR: 2.73 [1.39; 5.34] RR: 0.37 [0.19; 0.72][c] p = 0.002 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
Hepatotoxicity (severe AEs)		
simplified MIPI score		
low/intermediate risk (0–5)	8.0% vs. 1.3% RR: 6.00 [1.79; 20.08] RR: 0.17 [0.05; 0.56][c]; p = ND probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
High risk (6-11)	2.8% vs. 4.2% RR: 0.67 [0.11; 3.87]; p = ND	Greater/lesser harm not proven

Table 19: Extent of added benefit at outcome level: acalabrutinib + bendamustine + rituximab vs. bendamustine + rituximab (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Acalabrutinib + bendamustine + rituximab vs. placebo + bendamustine + rituximab** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L). c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. AE: adverse event; CI: confidence interval; CI_U: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma; HR: hazard ratio; MCL: mantle cell lymphoma; MIPI: MCL International Prognostic Index; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 20 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 20: Positive and negative effects from the assessment of acalabrutinib + bendamustine + rituximab in comparison with bendamustine + rituximab

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
–	Health-related quality of life ▪ social functioning: ▫ Age (< 70 years): hint of lesser benefit – extent: “minor”
Serious/severe side effects ▪ injury, poisoning and procedural complications (SAEs) ▫ sex (male): hint of lesser harm – extent “major”	Serious/severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: “considerable” ▪ skin and subcutaneous tissue disorders (severe AEs), white blood cell count decreased (severe AEs): each hint of greater harm – extent: “major” ▪ hepatotoxicity (severe AEs) ▫ simplified MIPI score (low/intermediate risk [0–5]): hint of greater harm – extent: “major”
–	Non-serious/non-severe side effects ▪ bleeding (AEs): hint of greater harm – extent: “minor” ▪ vomiting (AEs) ▫ simplified MIPI score (low/intermediate risk [0–5]): hint of greater harm – extent: “considerable” ▪ headache (AEs): hint of greater harm - extent: “considerable”
AE: adverse event; MCL: mantle cell lymphoma; MIPI: MCL International Prognostic Index; SAE: serious adverse event	

The overall consideration yields a positive effect in one subgroup, which is offset by several negative effects of acalabrutinib + bendamustine + rituximab compared to bendamustine + rituximab, some of which are observed in the total population and others in individual subgroups. For the total population, there is a hint of greater harm with the extent “considerable”, particularly in the outcome discontinuation due to AEs, which is predominantly caused by severe AEs classified as CTCAE grade ≥ 3. Furthermore, in the case of several specific and partly severe AEs, there are hints of greater harm with extents up to “major” (severe AEs: skin and subcutaneous tissue disorders, white blood cell count decreased). In contrast, there is a hint of lesser harm with the extent “major” for the outcome injury, poisoning and procedural complications (SAEs) only for the subgroup of men. The negative effects, which are predominantly of a considerable or major extent, clearly outweigh this positive effect, which only occurs in a subgroup.

In summary, for adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant, and for whom bendamustine plus rituximab is a suitable individualized treatment, there is a hint of lesser benefit from acalabrutinib + bendamustine + rituximab compared with the ACT.

The ECHO study provides no data for an assessment of the added benefit of acalabrutinib + bendamustine + rituximab compared with the ACT for adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant, and for whom bendamustine + rituximab is not a suitable individualized treatment. An added benefit of acalabrutinib + bendamustine + rituximab over the ACT is therefore not proven for adult patients with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine + rituximab is not a suitable individualized treatment.

The result of the assessment of the added benefit of acalabrutinib + bendamustine + rituximab in comparison with the ACT is summarized in Table 21.

Table 21: Acalabrutinib + bendamustine + rituximab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant	Individualized treatment[d, e] choosing from ▪ rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, predniso[lo]ne)[f] ▪ VRCAP (bortezomib + rituximab + cyclophosphamide, doxorubicin, prednisone) ▪ BR (bendamustine + rituximab)[g] upon achievement of complete or partial remission following induction therapy with R-CHOP or BR, followed by ▪ maintenance therapy with rituximab[h]	▪ Patients for whom bendamustine + rituximab is a suitable individualized treatment: hint of a lesser benefit ▪ patients for whom bendamustine + rituximab is not a suitable individualized treatment: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, in this therapeutic indication, it is assumed that patients with mantle cell lymphoma meet the criteria for systemic antineoplastic therapy due to a correspondingly advanced stage of their disease, particularly in terms of a symptomatic course; therefore, a "watchful waiting" strategy, among other options, is not considered. Further, patients are assumed not to be therapeutically indicated for radiotherapy at the time of therapy.
c. Furthermore, according to the G-BA, it is assumed that the target population in the therapeutic indication does not include any patients in poor or reduced general health.
d. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
e. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects study physicians to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
f. Induction therapy with R-CHOP is covered by Part A, Section XXVI of Appendix VI of the AM-RL 'Rituximab for mantle cell lymphoma'.

Table 21: Acalabrutinib + bendamustine + rituximab – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
g. Induction therapy with BR is not approved for this therapeutic indication. According to the GBA, data from randomized trials comparing BR with R-CHOP in this therapeutic indication are available [3,4]. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV. h. According to the G-BA, the current guidelines [5,6] recommend maintenance therapy with rituximab following induction with R-CHOP and BR. Ritis not approved for use following induction therapy with BR. The off-label use of rituximab following treatment with R-CHOP is eligible for prescription in accordance with Annex VI of the AM-RL. The available guidelines refer to a randomized phase II study and a retrospective cohort study for the use of rituximab as maintenance therapy following induction therapy with BR [7,8]. In accordance with the generally recognized state of medical knowledge, it can be determined that, for the relevant patient population or therapeutic indications, the off-label use of maintenance therapy with BR is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV. With regard to maintenance therapy with rituximab, the guidelines set out in Appendix VI of the AM-RL must be considered for patients who have previously received R-CHOP therapy. The dosage and treatment regimen should be in line with the generally recognized state of medical knowledge. AM-NutzenV: Regulation on the Evaluation of the Benefits of Medicinal Products; AM-RL: Medicinal Products Directive; BR: Bendamustine + Rituximab; EU: European Union; G-BA: Joint Federal Committee; HTA: Health Technology Assessment; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone		

The assessment described above deviates from that by the company, which claimed an indication of considerable added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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