Zanubrutinib (previously untreated chronic lymphocytic leukaemia)

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

EXTRACT

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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

The questionnaire on the disease and its treatment was answered by Christa Knebel.

IQWiG thanks the respondent for participating in the written exchange about how she experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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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
17p deletion	deletion in the short arm of chromosome 17
ACT	appropriate comparator therapy
AE	adverse event
CD	cluster of differentiation
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
FCR	fludarabine + cyclophosphamide + rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IGHV	immunoglobulin heavy-chain variable region
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small lymphocytic lymphoma
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
TP53 mutation	mutation of the tumour protein p53
VAS	visual analogue scale

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 zanubrutinib. 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 15 December 2022.

Research question

The aim of the present report is to assess the added benefit of zanubrutinib in comparison with the appropriate comparator therapy (ACT) in adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of zanubrutinib

Therapeutic indication	**ACT**[a]
Adult patients with previously untreated CLL[b]	Ibrutinib or ibrutinib in combination with rituximab or obinutuzumab or FCR[c, d] or **bendamustine in combination with rituximab**[d, e] or chlorambucil in combination with rituximab or obinutuzumab[d, e]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The G-BA assumes for the present therapeutic indication that the patients require treatment (e.g. Binet stage C). Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
c. Only for patients without genetic risk factors and < 65 years of age, for whom therapy with FCR is suitable on the basis of their general condition and comorbidities.
d. According to the G-BA, the following factors are considered genetic risk factors based on the current state of medical knowledge: presence of a 17p deletion/TP53 mutation or an unmutated immunoglobulin heavy-chain variable region.
e. Only for patients without genetic risk factors for whom therapy with FCR is not suitable. According to the G-BA, these are patients ≥ 65 years of age, and patients < 65 years for whom therapy with FCR is not suitable on the basis of their general condition and comorbidity.

17p deletion: deletion in the short arm of chromosome 17; CLL: chronic lymphocytic leukaemia;
FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The company followed the G-BA's specification and chose bendamustine + rituximab as ACT from the options presented. This option is an ACT for patients without genetic risk factors for whom therapy with fludarabine + cyclophosphamide + rituximab (FCR) is unsuitable. According to the G-BA, these include patients ≥ 65 years of age, and patients < 65 years for whom therapy with FCR is not suitable on the basis of their general condition and comorbidity.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The study pool for the benefit assessment consists of the SEQUOIA study. SEQUOIA is an ongoing, open-label, randomized multicentre study comparing zanubrutinib with bendamustine + rituximab. The study included adult patients with previously untreated cluster of differentiation (CD)-20-positive CLL or small lymphocytic lymphoma (SLL) requiring treatment as per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 2 and adequate bone marrow function. In addition, the patients were not allowed to have any clinically relevant cardiovascular disease.

A prerequisite for inclusion in the study was that therapy with FCR was not suitable for the patients. According to the study protocol, this was the case if the patients were ≥ 65 years of age or, if younger, fulfilled at least one of the following criteria:

- Cumulative Illness Rating Scale (CIRS) score > 6
- creatinine clearance < 70 mL/min
- history of severe or frequent infections within the last 2 years

Patients included in the study were assigned to one of 4 cohorts. The active-controlled part of the study comprises cohorts 1 and 1a, which included patients without a deletion in the short arm of chromosome 17 (17p deletion). Cohort 1a consists exclusively of patients from Chinese study centres. The 2 single-arm cohorts 2 and 3 included patients with 17p deletion (cohort 2) or with 17p deletion or a mutation of the tumour protein p53 (TP53 mutation) (cohort 3). From protocol version 5 onwards, patients without 17p deletion were also included in cohort 3. The patients received zanubrutinib (cohort 2) or a combination therapy of zanubrutinib with venetoclax (cohort 3).

For the benefit assessment, the company only used the data from patients in the active-controlled cohort 1 for the comparison of zanubrutinib with bendamustine + rituximab (for further explanation see section below). Cohort 1 of the study included a total of 479 patients,

randomly assigned in a 1:1 ratio either to treatment with zanubrutinib (N = 241) or bendamustine + rituximab (N = 238).

In the intervention arm of cohort 1, treatment with zanubrutinib was administered at 160 mg twice per day and was largely in compliance with the recommendations of the Summary of Product Characteristics (SPC).

In the comparator arm of cohort 1, bendamustine and rituximab were each administered for a maximum of 6 cycles (28 days each). The SPCs contain no specific dosage recommendations for the use of bendamustine in combination therapy with rituximab. However, their use in the SEQUOIA study corresponds to the procedure of the studies conducted on the combination of bendamustine and rituximab in the therapeutic indication. Rituximab treatment was largely in compliance with the SPC.

The primary outcome of the SEQUOIA study is progression-free survival (PFS). Further secondary outcomes are outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects.

Relevance of the 4 cohorts of the SEQUOIA study for the present benefit assessment

The company only used the data from the active-controlled cohort 1 of the SEQUOIA study on the comparison of zanubrutinib with bendamustine + rituximab for the benefit assessment. It did not take into account the results of cohort 1a and cohorts 2 and 3.

Cohort 1a of the SEQUOIA study comprises a total of 80 patients exclusively from Chinese study centres, who were randomized in a 1:1 ratio to the 2 treatment arms of zanubrutinib and bendamustine + rituximab. The company justified the non-consideration of the results of this cohort for the derivation of the added benefit with the lack of transferability of the results to the German health care context. This approach is not appropriate. The patients in cohort 1a represent a relevant subpopulation of the SEQUOIA study for the present benefit assessment. The proportion of 80 patients from cohort 1a in the total number of patients in cohorts 1 and 1a (559 patients) is only 14%. Therefore, cohort 1a is not assumed to have a relevant influence on the result of the benefit assessment. The non-consideration of cohort 1a therefore remains of no consequence for the present benefit assessment.

Cohorts 2 and 3 are not relevant for a comparison of zanubrutinib with the ACT because they do not include a control group, and because, in cohort 3, a combination therapy of zanubrutinib with venetoclax was investigated.

Subpopulation presented by the company

Only the subpopulation of patients without genetic risk factors and ≥ 65 years of age, and patients without genetic risk factors and < 65 years of age for whom therapy with FCR is

unsuitable due to their general condition and comorbidity is relevant for the comparison of zanubrutinib with bendamustine + rituximab. According to the G-BA, a 17p deletion, a TP53 mutation and an unmutated immunoglobulin heavy-chain variable region (IGHV) status are considered genetic risk factors.

In Module 4 A of the dossier, the company presented analyses for the subpopulation of patients from cohort 1 who do not have a TP53 mutation and a mutated IGHV status. This subpopulation comprises 104 patients in the intervention arm and 106 patients in the comparator arm. The company's approach is appropriate.

Data cut-offs

The data cut-off of 7 March 2022 is used for the present benefit assessment. For this data cut-off, the company presented analyses for all patient-relevant outcomes in Module 4 A.

Risk of bias

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

For the results on the outcome of overall survival, the risk of bias is rated as high due to the lack of information on the subsequent therapies used. For the patient-reported outcomes of symptoms, health status and health-related quality of life, the high risk of bias of the results is due to the open-label study design.

For the outcomes in the side effects category, the risk of bias of the results is rated as high due to the large differences in observation period between the intervention arm and the comparator arm as well as the open-label study design. In addition, there are incomplete observations for potentially informative reasons for serious adverse events (SAEs), severe adverse events (AEs) and specific AEs.

Results

Mortality

Overall survival

No statistically significant difference between treatment groups was found. There is no hint of an added benefit of zanubrutinib in comparison with 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, pain, diarrhoea, dyspnoea, insomnia, and constipation

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, pain, diarrhoea, dyspnoea, insomnia, and constipation. In each case, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven for these outcomes.

Nausea and vomiting

No statistically significant difference between treatment groups was found for the outcome of nausea and vomiting. However, an effect modification by the characteristic of sex was found. For men, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven. For women, however, there is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab for the outcome of nausea and vomiting.

Appetite loss

No statistically significant difference between treatment groups was found for the outcome of appetite loss. There is an effect modification by the characteristic of age, however. For patients < 65 years of age, there is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab for the outcome of appetite loss. For patients ≥ 65 years, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status measured with the EQ-5D visual analogue scale (VAS). There is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status, physical functioning, emotional functioning and social functioning

No statistically significant difference between treatment groups was found for the outcomes of health status, physical functioning, emotional functioning and social functioning. In each case, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven for these outcomes.

Role functioning

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for the outcome of role functioning. There is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab.

Cognitive functioning

No statistically significant difference between treatment groups was found for the outcome of cognitive functioning. However, an effect modification by the characteristic of sex was found. For men, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven. For women, however, there is a hint of lesser benefit of zanubrutinib in comparison with bendamustine + rituximab for the outcome of cognitive functioning.

Side effects

With regard to the results on side effects, it should be noted that the large differences in observation periods between the treatment arms mean that the hazard ratio only reflects approximately the first 8 months.

SAEs, severe AEs and discontinuation due to AEs

A statistically significant difference between treatment groups in favour of zanubrutinib was found for each of the outcomes of SAEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs. In each case, there is a hint of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

Haemorrhages (AEs)

A statistically significant difference between treatment groups to the disadvantage of zanubrutinib was shown for the outcome of haemorrhages (AEs). There is a hint of greater harm from zanubrutinib in comparison with bendamustine + rituximab.

Haemorrhages (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of haemorrhages (severe AEs). There is no hint of greater or lesser harm from zanubrutinib in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Cardiac disorders (severe AEs)

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

Infections and infestations (severe AEs)

A statistically significant difference between treatment groups in favour of zanubrutinib was found for the outcome of infections and infestations (severe AEs). There is a hint of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

Infusion related reaction

No suitable data are available for the outcome of infusion related reaction. There is no hint of greater or lesser harm from zanubrutinib in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Further specific AEs

Constipation (AEs), nausea (AEs), fever (AEs), blood and lymphatic system disorders (severe AEs), investigations (severe AEs) and respiratory, thoracic and mediastinal disorders (severe AEs)

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for each of the outcomes of constipation (AEs), nausea (AEs), fever (AEs), blood and lymphatic system disorders (severe AEs), investigations (severe AEs) and respiratory, thoracic and mediastinal disorders (severe AEs). In each case, there is a hint of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

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

On the basis of the results presented, the probability and extent of added benefit of the drug zanubrutinib in comparison with the ACT are assessed as follows:

For the assessment of the added benefit of zanubrutinib in comparison with the ACT, the company presented only data for patients without genetic risk factors for whom therapy with FCR is unsuitable. No data are available for patients without genetic risk factors for whom FCR therapy is suitable, and for patients with genetic risk factors.

Overall, there are both positive and negative effects of zanubrutinib in comparison with bendamustine + rituximab for patients without genetic risk factors for whom therapy with FCR is unsuitable. There are advantages in particular in the outcome category of serious/severe

[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].

side effects with hints of lesser harm with different extents. In the overall rates of both serious and severe AEs, the extent in each case is major. In addition, there are hints of lesser harm in the outcome category of non-serious/non-severe side effects with the extent “considerable”. For the patient-reported outcomes of the outcome categories of morbidity and health-related quality of life, there are hints of added benefit of zanubrutinib in comparison with bendamustine + rituximab for individual symptom and functional scales of the EORTC QLQ-C30 (partly only for subgroups) with considerable and minor extent. On the other hand, there is a hint of lesser benefit with the extent “minor” in the category of health-related quality of life (only for women) and a hint of greater harm with the extent “considerable” in the category of non-serious/non-severe side effects.

Overall, in the present situation, the added benefit is therefore based mainly on advantages in the outcome category of side effects. Due to the large differences in observation periods, the underlying analyses represent only the approximately first 8 months of the study. For outcomes on morbidity and health-related quality of life, which allow a comparison over an observation period that is about 4 times longer, statistically significant differences were only shown in few symptom and functional scales of the EORTC QLQ-C30 (partly only for subgroups). Therefore, it cannot be deduced from this that the advantages of zanubrutinib also exist beyond the first 8 months to a major extent. In this specific data situation, quantification of the added benefit is therefore not possible.

In summary, there is a hint of a non-quantifiable added benefit of zanubrutinib in comparison with bendamustine + rituximab for adult patients with previously untreated CLL who have no genetic risk factors and for whom therapy with FCR is unsuitable.

Due to missing data, an added benefit of zanubrutinib is not proven for patients without genetic risk factors for whom FCR therapy is suitable and for patients with genetic risk factors.

Table 3 shows a summary of probability and extent of the added benefit of zanubrutinib.

Table 3: Zanubrutinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with previously untreated CLL[b]	Ibrutinib or ibrutinib in combination with rituximab or obinutuzumab or FCR[c, d] or **bendamustine in combination with rituximab**[d, e] or chlorambucil in combination with rituximab or obinutuzumab[d, e]	▪ Patients without genetic risk factors for whom therapy with FCR is not suitable: Hint of non-quantifiable added benefit ▪ All other patients in the therapeutic indication: Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The G-BA assumes for the present therapeutic indication that the patients require treatment (e.g. Binet stage C). Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
c. Only for patients without genetic risk factors and < 65 years of age, for whom therapy with FCR is suitable on the basis of their general condition and comorbidities.
d. According to the G-BA, the following factors are considered genetic risk factors based on the current state of medical knowledge: presence of a 17p deletion/TP53 mutation or an unmutated immunoglobulin heavy-chain variable region.
e. Only for patients without genetic risk factors for whom therapy with FCR is not suitable. According to the G-BA, these are patients ≥ 65 years of age, and patients < 65 years for whom therapy with FCR is not suitable on the basis of their general condition and comorbidity.

17p deletion: deletion in the short arm of chromosome 17; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The approach for deriving 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 the present report is to assess the added benefit of zanubrutinib in comparison with the ACT in adult patients with previously untreated CLL.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of zanubrutinib

Therapeutic indication	**ACT**[a]
Adult patients with previously untreated CLL[b]	Ibrutinib or ibrutinib in combination with rituximab or obinutuzumab or FCR[c, d] or **bendamustine in combination with rituximab**[d, e] or chlorambucil in combination with rituximab or obinutuzumab[d, e]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The G-BA assumes for the present therapeutic indication that the patients require treatment (e.g. Binet stage C). Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
c. Only for patients without genetic risk factors and < 65 years of age, for whom therapy with FCR is suitable on the basis of their general condition and comorbidities.
d. According to the G-BA, the following factors are considered genetic risk factors based on the current state of medical knowledge: presence of a 17p deletion/TP53 mutation or an unmutated immunoglobulin heavy-chain variable region.
e. Only for patients without genetic risk factors for whom therapy with FCR is not suitable. According to the G-BA, these are patients ≥ 65 years of age, and patients < 65 years for whom therapy with FCR is not suitable on the basis of their general condition and comorbidity.

17p deletion: deletion in the short arm of chromosome 17; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The company followed the G-BA's specification and chose bendamustine + rituximab as ACT from the options presented. This option is an ACT for patients without genetic risk factors for whom therapy with FCR is unsuitable. According to the G-BA, these include patients ≥ 65 years of age, and patients < 65 years for whom therapy with FCR is not suitable on the basis of their general condition and comorbidity.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on zanubrutinib (status: 19 October 2022)
- bibliographical literature search on zanubrutinib (last search on 20 October 2022)
- search in trial registries/trial results databases for studies on zanubrutinib (last search on 19 October 2022)
- search on the G-BA website for zanubrutinib (last search on 19 October 2022)

To check the completeness of the study pool:

- search in trial registries for studies on zanubrutinib (last search on 21 December 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval 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])
BGB-3111-304 (SEQUOIA[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Study for which the company was sponsor.
b. References 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.

CSR: clinical study report; RCT: randomized controlled trial

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: zanubrutinib vs. 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]
SEQUOIA	RCT (partially randomized)[b], open-label, parallel	Adults with previously untreated CLL or SLL[c] requiring treatment ▪ for whom FCR therapy is unsuitable[d] ▪ ECOG PS ≤ 2 ▪ Life expectancy of ≥ 6 months	Cohort 1: ▪ zanubrutinib (N = 241) ▪ bendamustine + rituximab (N = 238) Cohort 1a[e]: ▪ zanubrutinib (N = 40) ▪ bendamustine + rituximab (N = 40) Non-randomized cohorts[f]: ▪ Cohort 2: ▫ zanubrutinib (N = 111) ▪ Cohort 3: ▫ zanubrutinib + venetoclax (N = ND)[g] Relevant subpopulation of cohort 1[h]: ▪ zanubrutinib (n = 104) ▪ bendamustine + rituximab (n = 106)	▪ Screening: ≤ 35 days ▪ Treatment[i]: until disease progression, unacceptable toxicity, withdrawal of consent, or end of study ▪ Observation[j]: outcome-specific, at most until death, discontinuation of participation in the study, or end of study	153 centres in: Australia, Austria, Belgium, China, Czech Republic, France, Italy, New Zealand, Poland, Russia, Spain, Sweden, Taiwan, United Kingdom, United States 10/2017–ongoing Data cut-offs (interim analyses): ▪ 7 May 2021[k] ▪ 7 September 2021[l] ▪ 7 March 2022[m]	▪ Primary: PFS (ICR) ▪ Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: zanubrutinib vs. 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 consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. The study comprises 4 cohorts: cohort 1 and 1a each with active control group and randomized allocation of patients, cohort 2 and 3 each without control group.
c. Diagnosis of CD20-positive CLL or SLL and need for treatment as per iwCLL criteria [7].
d. Defined as ≥ 65 years of age at the time of consent or 18 to 64 years of age and presence of one or more of the following:
- CIRS score > 6 (a CIRS score at baseline is not required if at least 1 of the following 2 criteria is met)
- creatinine clearance < 70 mL/min
- history of severe or frequent infections within the last 2 years

e. Cohort 1a consists exclusively of patients from Chinese study centres. For the present benefit assessment, no analyses of this cohort are available. This remains without consequence for the assessment (see following text for explanation). Cohort 1a is therefore not shown separately in the following tables.
f. Both cohorts are not relevant for the assessment and are not shown in the following tables.
g. For cohort 3, no information is available on the number of patients included (planned: 110 patients).
h. Includes patients of cohort 1 without genetic risk factors.
i. In the comparator arm (bendamustine + rituximab), treatment was limited to a maximum of 6 cycles.
j. Outcome-specific data are described in Table 8.
k. Predefined interim analysis of PFS after 107 events in cohort 1 (planned after about 86 events in cohort 1).
l. Predefined interim analysis for overall survival at the expected time of the final analysis of PFS (planned after 118 PFS events in cohort 1). The final analysis of PFS was not performed as superiority for the outcome of PFS was already shown in the interim analysis of 7 May 2021.
m. Follow-up analyses for overall survival; conducted due to a requirement by the FDA in support of the approval application.

AE: adverse event; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FCR: fludarabine + cyclophosphamide + rituximab; FDA: Food and Drug Administration; ICR: independent central review; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma

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

Study	Intervention	Comparison[a]
SEQUOIA	Zanubrutinib ▪ 160 mg twice daily, orally[b]	Bendamustine ▪ 90 mg/m² BSA, IV on days 1 and 2 of the cycle, for 6 cycles of 28 days each + rituximab IV, for 6 cycles of 28 days each ▪ cycle 1: on day 0, 375 mg/m² BSA ▪ cycles 2 to 6: on day 1, 500 mg/m² BSA
	Treatment adjustment ▪ Zanubrutinib: treatment interruption in case of toxicity[c]; no more than 2 dose reductions from the second occurrence of severe side effects (grade ≥ 3) according to the SPC [8] ▫ halving the dose in each case ▫ discontinuation of study medication in case of recurrent severe event under minimum dose[d] ▪ Bendamustine: after the first interruption due to cytopenia ≥ grade 3 and/or active infection on day 1 of a cycle, postponement of the next cycle and reduction to 70 mg/m² BSA in further cycles, after the second interruption reduction to 50 mg/m² BSA discontinuation of the study medication after the third occurrence[e] ▪ Rituximab: dose reduction not allowed[e]	
	Prohibited prior and concomitant treatment ▪ previous systemic therapy for CLL/SLL[f] and any cancer therapy for CLL/SLL (cytostatics, biologics, immunotherapy) during study treatment ▪ use of corticosteroids during the study[g] ▪ major surgery within 4 weeks before first administration of study medication ▪ live vaccine within 35 days before the first dose of study medication ▪ ongoing, required treatment with a strong CYP3A inhibitor or inducer[h] **Permitted concomitant treatment** ▪ blood transfusions and growth factors ▪ short-term or intermittent use of corticosteroids[i] ▪ supportive treatment for symptom reduction according to therapy standard and local guidelines	

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

Study	Intervention	Comparison[a]
a. Patients who received treatment in the comparator arm had the option to switch to the zanubrutinib arm after disease progression (confirmed by an ICR). By the data cut-off on 7 March 2022, a total of 9 patients (8.5%) in the comparator arm (N = 106) had switched to the zanubrutinib arm. b. Until disease progression, unacceptable toxicity or end of study. c. Resumption of treatment once toxicity had resolved to grade ≤ 1 or baseline. d. Beyond the requirements of the SPC, treatment with zanubrutinib had to be discontinued in the event of grade ≥ 3 haemorrhages associated with the study medication (unless the cause of the haemorrhage could be fully treated and the risk of re-haemorrhage was considered acceptable). In the case of intracranial haemorrhage, treatment with zanubrutinib had to be discontinued regardless of severity and association with the study medication if the risk of re-haemorrhage was assessed as unacceptable. e. If one treatment component in the comparator arm was interrupted, the other component also had to be interrupted. f. With the exception of a discontinued treatment regimen with a duration of < 2 weeks and > 4 weeks before randomization. g. Systemic corticosteroids had to be completely discontinued at least 5 days before the first dose of study medication. h. If intake of CYP3A inhibitors or inducers was required during study treatment, the dose had to be adjusted in compliance with the SPC. i. For the treatment of diseases not related to CLL/SLL and for the management or prevention of infusion reactions. BSA: body surface area; CLL: chronic lymphocytic leukaemia; CYP: cytochrome P450; ICR: independent central review; IV: intravenous; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; SPC: Summary of Product Characteristics		

The SEQUOIA study is an ongoing, open-label, randomized multicentre study comparing zanubrutinib with bendamustine + rituximab. The study included adult patients with previously untreated CD20-positive CLL or SLL requiring treatment as per iwCLL criteria [7]. The patients had to have an ECOG PS of ≤ 2 and adequate bone marrow function. In addition, the patients were not allowed to have any clinically relevant cardiovascular disease.

A prerequisite for inclusion in the study was that therapy with FCR was not suitable for the patients. According to the study protocol, this was the case if the patients were ≥ 65 years of age or, if younger, fulfilled at least one of the following criteria:

- CIRS score > 6
- creatinine clearance < 70 mL/min
- history of severe or frequent infections within the last 2 years

It is unclear whether severe or frequent infections within the last 2 years before study start is sufficient as a sole criterion to justify non-eligibility for therapy with FCR. The guidelines for the treatment of CLL list physical fitness, age, accompanying diseases (e.g. a CIRS score > 6) and renal insufficiency as criteria. However, there is no uniform scientific consensus on the

criteria for suitability or unsuitability of therapy with FCR in patients with CLL [9,10]. For the present benefit assessment, it is assumed that the criteria applied in the study are sufficient to represent a patient population for whom therapy with FCR is unsuitable.

Patients included in the study were assigned to one of 4 cohorts. The active-controlled part of the study comprises cohorts 1 and 1a, which included patients without 17p deletion. Cohort 1a consists exclusively of patients from Chinese study centres. The 2 single-arm cohorts 2 and 3 included patients with 17p deletion (cohort 2) or with 17p deletion or TP53 mutation (cohort 3). From protocol version 5 onwards, patients without 17p deletion were also included in cohort 3. The patients received zanubrutinib (cohort 2) or a combination therapy of zanubrutinib with venetoclax (cohort 3).

For the benefit assessment, the company only used the data from patients in the active-controlled cohort 1 for the comparison of zanubrutinib with bendamustine + rituximab (for further explanation see section below). Cohort 1 of the study included a total of 479 patients, randomly assigned in a 1:1 ratio either to treatment with zanubrutinib (N = 241) or bendamustine + rituximab (N = 238). Randomization was stratified by age (< 65 years versus ≥ 65 years), disease stage (Binet stage C versus A or B), IGHV mutation status (unmutated vs. mutated) and region (North America versus Europe versus Asia-Pacific).

In the intervention arm of cohort 1, treatment with zanubrutinib was administered at 160 mg twice per day and was largely in compliance with the recommendations of the SPC [8]. The option of a once daily dose of zanubrutinib (320 mg) provided for in the SPC did not exist in the SEQUOIA study. In addition, contrary to the recommendations of the SPC, the study provided for discontinuation of treatment with zanubrutinib in the event of grade ≥ 3 haemorrhages associated with the study medication if the cause of the bleeding could not be fully treated. Treatment with zanubrutinib was planned to be given until disease progression, unacceptable toxicity, withdrawal of consent, or until the end of study.

In the comparator arm of cohort 1, bendamustine and rituximab were each administered for a maximum of 6 cycles (28 days each). The patients received bendamustine intravenously at a dose of 90 mg/m². The SPCs contain no specific dosage recommendations for the use of bendamustine in combination therapy with rituximab. The SPC for rituximab, for example, refers to combination therapy with chemotherapy overall and not explicitly to the combination with bendamustine [11,12]. However, the use in the SEQUOIA study corresponds to the procedure of the studies conducted on the combination of bendamustine and rituximab in the therapeutic indication [13-15]. Treatment with rituximab was largely in compliance with the SPC [12], although it is unclear whether in all treatment cycles the infusion of rituximab preceded the administration of bendamustine. In addition, there is no information on hydration and treatment with uricostatic drugs to prevent tumour lysis syndrome in the study.

Overall, the described uncertainties remain without consequence for the present benefit assessment, however.

The primary outcome of the SEQUOIA study is PFS. Further secondary outcomes are outcomes in the categories of mortality, morbidity, health-related quality of life, and side effects.

Relevance of the 4 cohorts of the SEQUOIA study for the present benefit assessment

The company only used the data from the active-controlled cohort 1 of the SEQUOIA study on the comparison of zanubrutinib with bendamustine + rituximab for the benefit assessment. It did not take into account the results of cohort 1a and cohorts 2 and 3.

Cohort 1a of the SEQUOIA study comprises a total of 80 patients exclusively from Chinese study centres, who were randomized in a 1:1 ratio to the 2 treatment arms of zanubrutinib and bendamustine + rituximab. The company justified the non-consideration of the results of this cohort for the derivation of the added benefit with the lack of transferability of the results to the German health care context. This approach is not appropriate. The patients in cohort 1a represent a relevant subpopulation of the SEQUOIA study for the present benefit assessment. The proportion of 80 patients from cohort 1a in the total number of patients in cohorts 1 and 1a (559 patients) is only 14%. Therefore, cohort 1a is not assumed to have a relevant influence on the result of the benefit assessment. The non-consideration of cohort 1a therefore remains of no consequence for the present benefit assessment.

The company presented the results for cohort 2 as supplementary information in Module 4 A; no results are available for cohort 3. Cohorts 2 and 3 are not relevant for a comparison of zanubrutinib with the ACT because they do not include a control group, and because, in cohort 3, a combination therapy of zanubrutinib with venetoclax was investigated.

Subpopulation presented by the company

Only the subpopulation of patients without genetic risk factors and ≥ 65 years of age, and patients without genetic risk factors and < 65 years of age for whom therapy with FCR is unsuitable due to their general condition and comorbidity is relevant for the comparison of zanubrutinib with bendamustine + rituximab. According to the G-BA, a 17p deletion, a TP53 mutation and an unmutated IGHV status are considered genetic risk factors.

In Module 4 A of the dossier, the company presented analyses for the subpopulation of patients from cohort 1 who do not have a TP53 mutation and a mutated IGHV status. This subpopulation comprises 104 patients in the intervention arm and 106 patients in the comparator arm.

The company's approach is appropriate. Thus, the inclusion criteria for cohort 1 already represent a patient population for whom therapy with FCR was not suitable due to age or

other defined criteria and who did not have a 17p deletion. Besides, according to information in Module 4 A, the company only considered those patients in cohort 1 who did not have a TP53 mutation and had an unmutated IGHV status. Thus, the subpopulation presented by the company overall represents the relevant subpopulation for the comparison of zanubrutinib with bendamustine + rituximab.

Data cut-offs

To date, 3 data cut-offs are available for the SEQUOIA study:

- data cut-off 1: 7 May 2021 (predefined interim analysis of PFS after 107 events in cohort 1)
- data cut-off 2: 7 September 2021 (predefined interim analysis for overall survival at the time originally expected for the final analysis of PFS)
- data cut-off 3: 7 March 2022 (follow-up data for overall survival; data cut-off requested by the Food and Drug Administration)

The data cut-off of 7 March 2022 is used for the present benefit assessment. For this data cut-off, the company presented analyses for all patient-relevant outcomes in Module 4 A.

Planned duration of follow-up observation

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: zanubrutinib vs. bendamustine + rituximab

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SEQUOIA	
Mortality	
Overall survival	▪ Until death or end of study (whichever was first)
Morbidity	
Symptoms (EORTC QLQ-C30), health status (EQ-5D VAS)	▪ Until disease progression
Health-related quality of life (EORTC QLQ-C30)	▪ Until disease progression
Side effects	
All outcomes in the category of side effects	▪ Up to 30 days (zanubrutinib) or up to 90 days (bendamustine + rituximab) after the last dose of study medication or until disease progression (whichever was later[a])[b] ▪ Up to 30 days (zanubrutinib) or up to 90 days (bendamustine + rituximab) after the last dose of study medication or until subsequent CLL therapy (whichever was later[a])[b, c]

a. Contradictory information in the dossier (see text below for explanation).
b. Potentially study drug-related SAEs, AEs that occurred during the planned observation period and subsequently worsened to grade 5, and secondary primary tumours regardless of their relation to the study drug had to be reported beyond the previously defined time periods.
c. Concerns patients who had started a new CLL therapy before disease progression.

AE: adverse event; CLL: chronic lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes of morbidity and health-related quality of life are systematically shortened because they were only recorded until disease progression. Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

According to the information provided by the company in Module 4 A and the study documents, side effects were to be observed up to 30 days (zanubrutinib) or up to 90 days (bendamustine + rituximab) after the last dose of study medication or until disease progression, whichever was later. Patients who started subsequent CLL therapy before disease progression were to be observed until the end of treatment (plus 30 days or 90 days) or until the start of subsequent CLL therapy, whichever was later.

However, based on the information on the course of the study (see Table 10), it can be assumed that the analyses of side effects outcomes presented by the company in Module 4 A

only cover the period until the end of treatment (plus 30 days in the intervention arm and 90 days in the comparator arm). Thus, the median treatment duration in the comparator arm is 4.8 months and the median observation period for the side effects outcomes is 7.8 months (which is approximately the treatment duration plus 90 days). This type of analysis corresponds to the definition of treatment emergent adverse events given in the study protocol. The company did not provide any analyses of outcomes in the category of side effects that cover the period until disease progression or until the start of a new CLL therapy, although the recording over a longer period of time was also predefined according to the information in Module 4 A and the study documents. Module 4 A does not contain an explanation as to why the company did not present analyses that would allow a conclusion to be drawn about a longer period of time than until the end of treatment. Furthermore, it should be noted that analyses over the entire period are necessary also for the side effects outcomes – as described above for the outcomes of morbidity and health-related quality of life – in order to draw reliable conclusions over the entire study period.

Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the patients of the relevant subpopulation in the included study.

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

Study **Characteristic** **Category**	**Zanubrutinib** **N = 104**	**Bendamustine + rituximab** **N = 106**
SEQUOIA		
Age [years], mean (SD)	70 (7)	70 (8)
Age group, n (%)		
< 65 years	18 (17)	18 (17)
≥ 65 to < 74 years	60 (58)	59 (56)
≥ 65 years	26 (25)	29 (27)
Sex [F/M], %	39/61	42/59
Geographical region, n (%)		
Europe	74 (71)	74 (70)
Asia-Pacific region	15 (14)	19 (18)
North America	15 (14)	13 (12)
Family origin, n (%)		
Caucasian	94 (90)	89 (84)
Asian	1 (1)	6 (6)
Black or African American	1 (1)	0 (0)
Unknown	8 (8)	11 (10)

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

Study **Characteristic** **Category**	**Zanubrutinib** **N = 104**	**Bendamustine + rituximab** **N = 106**
ECOG PS, n (%)		
0	52 (50)	50 (47)
1	48 (46)	45 (43)
2	4 (4)	11 (10)
Type of cancer, n (%)		
CLL	93 (89)	95 (90)
SLL	11 (11)	11 (10)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	60.2 (55.0)	43.5 (42.4)
Bulky disease, n (%)		
≥ 5 cm	20 (19)	25 (24)
≥ 10 cm	5 (5)	2 (2)
Binet stage, n (%)		
A	16 (15)	12 (11)
B	50 (48)	59 (56)
C	38 (37)	35 (33)
Cytopenia[a], n (%)		
Yes	49 (47)	50 (47)
No	55 (53)	56 (53)
Beta 2 microglobulin, n (%)		
≤ 3.5 mg/L	47 (45)	49 (46)
> 3.5 mg/L	54 (52)	54 (51)
11q deletion, n (%)		
Yes	11 (11)	13 (12)
No	93 (89)	93 (88)
13q deletion, n (%)		
Yes	69 (66)	66 (62)
No	35 (34)	40 (38)
Trisomy 12, n (%)		
Yes	14 (14)	17 (16)
No	90 (87)	89 (84)
TP53 mutation, n (%)		
Yes	0 (0)	0 (0)
No	102 (98)	99 (93)
Unknown	2 (2)	7 (7)

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

Study Characteristic Category	**Zanubrutinib N = 104**	**Bendamustine + rituximab N = 106**
IGHV status, n (%)		
Mutated	98 (94)	101 (95)
Unmutated	3 (3)	3 (3)
Unknown	3 (3)	2 (2)
Complex karyotype, n (%)		
< 3 abnormalities	51 (49)	45 (43)
≥ 3 abnormalities	7 (7)	5 (5)
Unknown	46 (44)	56 (53)
Treatment discontinuation, n (%)[b]	17 (16)	18 (17)
Study discontinuation, n (%)[c]	10 (10)	21 (20)

a. Haemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L or absolute neutrophil count ≤ 1.5 x 10^9/L
b. The most common reason for treatment discontinuation in the intervention vs. comparator arm was adverse events (11 vs. 14 patients).
c. Common reasons for study discontinuation in the intervention vs. the comparator arm were death (6 vs. 10 patients) and withdrawal of consent (4 vs. 8 patients).

11q deletion: deletion in the long arm of chromosome 11; 13q deletion: deletion in the long arm of chromosome 13; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IGHV: immunoglobulin heavy-chain variable region; M: male; n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SLL: small lymphocytic lymphoma; TP53 mutation: mutation of the tumour protein p53

The patient characteristics of the relevant subpopulation are largely comparable between the 2 treatment arms. The mean age of the patients was 70 years. In both treatment arms, the majority of patients in the relevant subpopulation were men (about 60%). The vast majority (about 93%) of patients had an ECOG PS of 0 or 1. At study inclusion, about 13% of patients had CLL or SLL in Binet stage A, about 52% in Binet stage B, and about 35% in Binet stage C. Despite randomization, there is a clear difference between the treatment arms in the time between initial diagnosis of the disease and randomization (60.2 months in the intervention arm versus 43.5 months in the comparator arm). However, there are no other differences between the treatment arms that indicate differences in disease severity. In particular, the distribution of disease stages is balanced between the 2 treatment arms. Although the company stated that it had considered the IGHV status in the formation of the relevant subpopulation, 3 patients in each of the 2 treatment arms had an unmutated IGHV status.

Information on the course of the study

Table 10 shows patients' median/mean treatment durations and the median/mean observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab

Study **Duration of the study phase** **Outcome category**	**Zanubrutinib** **N = 104**	**Bendamustine + rituximab** **N = 106**
SEQUOIA		
Treatment duration [months]		
Median [Q1; Q3]	36.3 [33.4; 39.8]	4.8 [4.7; 5.2]
Mean (SD)	34.8 (8.5)	7.7 (10.5)
Observation period [months]		
Overall survival[a, b]		
Median [min; max]	36.3 [7.7; 47.0]	35.7 [0; 47.7]
Morbidity, health-related quality of life		
EORTC QLQ-C30		
Median [Q1; Q3]	33.4 [28.3; 38.7]	33.2 [23.1; 34.0]
Mean (SD)	31.5 (8.8)	28.0 (11.9)
EQ-5D VAS		
Median [Q1; Q3]	33.4 [29.2; 38.7]	33.2 [27.7; 34.2]
Mean (SD)	31.6 (8.8)	28.1 (11.9)
Side effects		
Median [Q1; Q3]	36.3 [33.5; 40.0]	7.8 [7.6; 8.1]
Mean (SD)	35.0 (8.2)	7.2 (1.9)

a. Median observation period calculated according to the inverse Kaplan-Meier method.
b. According to the information provided by the company in Module 4 A, in the intervention arm, the maximum treatment duration was 47.5 months and the maximum observation period for the outcome of overall survival was 47.0 months. The company did not provide an explanation for the fact that the treatment duration was 0.5 months longer than the observation period.

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; 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

Within the relevant subpopulation, the patients' median treatment duration was far higher in the intervention arm, at 36.3 months, than in the comparator arm, at 4.8 months. This is due to the fact that in the intervention arm, zanubrutinib was to be administered until disease progression or unacceptable toxicity, whereas in the comparator arm, treatment was for a maximum of 6 cycles.

For the outcomes of the outcome categories of morbidity and health-related quality of life, observation was only planned until disease progression. In the present data situation, the median observation period is nevertheless comparable for the outcome of overall survival as well as for the outcomes of the outcome categories of morbidity and health-related quality of life.

The fixed treatment duration in the comparator arm and linking the observation period for side effects to the treatment duration led to a notably longer observation period for the outcomes in the category of side effects in the intervention arm (median 36.3 months) than in the comparator arm (median 7.8 months). This difference in observation periods is taken into account when deriving the outcome-specific risk bias of the outcomes in the category of side effects (see Section I 4.2).

Information on subsequent therapies

For the entire cohort 1 population, the study documents show that a total of 15 (6.2%) patients in the zanubrutinib arm and 34 (14.3%) patients in the bendamustine + rituximab arm received subsequent anticancer therapy. According to the study documents, B-cell lymphoma-2 inhibitors (venetoclax) were available for second-line therapy, and Bruton tyrosine kinase inhibitors (ibrutinib, acalabrutinib, zanubrutinib) for patients in the comparator arm. These options are also recommended in the guidelines [9,10].

However, the company did not provide any information in Module 4 A regarding subsequent therapies for the subpopulation relevant to the assessment. The proportion of patients with subsequent therapy in the subpopulation is therefore unclear. There is also a lack of concrete information on the therapies used. It is not clear from the information in the study documents what criteria were used to decide on subsequent therapy. According to the recommendations of the S3 guideline on the diagnosis, treatment and follow-up of chronic lymphocytic leukaemia, for example, even in the relapse situation, treatment should only be started if clinical symptoms are present [9].

In addition, it should be noted that patients in the comparator arm of the study were allowed to switch to zanubrutinib treatment after disease progression. Overall, 9 (8.5%) patients in the subpopulation relevant to the assessment had switched from the comparator arm to the zanubrutinib arm by the third data cut-off. Zanubrutinib is approved for the treatment of patients with CLL who have already received one or more pretreatments. However, this approval was at the same time as the approval of zanubrutinib in first-line therapy, which is subject of the present benefit assessment. Thus, it is unclear to what extent the use of zanubrutinib in subsequent therapy is already established. The use of zanubrutinib in subsequent therapy is not described in the S3 guideline [9]. However, the German Society for Haematology and Medical Oncology (DGHO) guideline updated in January 2023 recommends

treatment with Bruton tyrosine kinase inhibitors, including zanubrutinib, in second-line therapy of patients who have not received prior Bruton tyrosine kinase inhibitor treatment [10].

The results of the outcome of overall survival are profoundly influenced by the subsequent antineoplastic therapies used after disease progression or relapse. The use of adequate subsequent therapies is thus of great importance for the assessment of the results on overall survival. For the SEQUOIA study, it is not possible to assess whether the patients of the relevant subpopulation in both treatment arms received guideline-compliant subsequent therapy due to the lack of information on the subsequent therapies used after disease progression or relapse.

The uncertainty regarding the subsequent therapies used as well as the treatment switches from the comparator arm to the zanubrutinib arm are taken into account when assessing the risk of bias for the results of the overall survival outcome (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: zanubrutinib vs. 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			
SEQUOIA	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

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

Limitations resulting from the open-label study design are described in Section I 4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

According to the company, most patients in the relevant subpopulation were included in Europe and North America and were predominantly of Caucasian origin. In addition, from the perspective of the company, the sex distribution in the study was consistent with the estimate

of the Robert Koch Institute and a retrospective analysis of health insurance fund data [16,17]. The company described that the median age of CLL onset was 72 years in men and 75 years in women, and that the median age of the patients in the study thus corresponded to the German health care context. Furthermore, according to the company, the DGHO recommendations were taken into account by considering the iwCLL criteria for diagnosis and need for treatment [10]. The DGHO guideline also recommended combination therapy with bendamustine and rituximab for patients without genetic risk factors for whom a therapy with FCR is not suitable, the company added. According to the company, the study results were thus transferable to the German health care context.

The company did not provide any further information on the transferability of 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 with the EORTC QLQ-C30
  - health status, recorded with the EQ-5D VAS
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - haemorrhages (Standardized Medical Dictionary for Regulatory Activities Query [SMQ], AEs)
  - haemorrhages (SMQ, severe AEs)
  - cardiac disorders (System Organ Class [SOC], severe AEs)
  - infections and infestations (SOC, severe AEs)
  - infusion related reaction
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4 A).

Table 12 shows for which outcomes data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Haemorrhages (SMQ[b], AEs)	Haemorrhages (SMQ[b], severe AEs[a])	Cardiac disorders (SOC, severe AEs[a])	Infections and infestations (SOC, severe AEs[a])	Infusion related reaction	Further specific AEs[a, c]
SEQUOIA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3 events.
b. Without events based on laboratory values.
c. The following events are considered (coded according to MedDRA): constipation (PT, AEs), nausea (PT, AEs), fever (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs), investigations (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
d. The analysis presented by the company is not suitable for the benefit assessment; however, serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; 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

Note on outcomes of the side effects category

SAEs, severe AEs, discontinuation due to AEs, and blood and lymphatic system disorders

The analyses of the outcomes of SAEs, severe AEs, discontinuations due to AEs as well as of the SOC "blood and lymphatic system disorders" include events such as the Preferred Terms (PTs) of anaemia, neutropenia and thrombocytopenia, which can be both side effects and a reflection of the progression of the underlying disease. It cannot be conclusively clarified to what extent the events can be assigned to the outcome category of morbidity or side effects [18]. This remains of no consequence for the present benefit assessment.

Infusion related reaction

In the SEQUOIA study, infusion related reactions were recorded as AEs (PT "infusion related reaction"). In principle, due to the open-label study design (without placebo infusion) and regular intravenous administration only in the comparator arm in contrast to oral administration in the intervention arm, events for the PT "infusion related reaction" could only be recorded in the comparator arm. In addition, it is not clear from the information

provided by the company which events were considered infusion related and were therefore included in the PT “infusion related reaction”. Thus, there are no suitable (comparative) data for the benefit assessment for this outcome; however serious and severe infusion reactions are considered in the overall rates of SAEs and severe AEs (see below). In order to obtain the necessary comparative data for the benefit assessment, it is necessary to consider all symptomatic AEs (whether infusion-related or not; e.g. dyspnoea) within the framework of the AE analysis. For this purpose, the respective symptoms have to be included in the AE analyses via the corresponding PT (e.g. the PT “dyspnoea”) (as was the case in the MAIA study, for example, see [19]). This allows taking these events into account in the benefit assessment even if they occurred in unblinded studies comparing orally and intravenously administered drugs.

It is not clear from the information provided by the company in the dossier whether events that formed the basis of the outcome of infusion related reaction were included in the analyses of AEs at PT or SOC level. It therefore remains unclear whether these events were fully recorded in the PT/SOC analyses presented by the company in Module 4 A. This is not assumed to have a relevant influence on the analyses at SOC and PT level, however. For the superordinate AE outcomes (SAEs, severe AEs), this has also no relevant influence, as it makes no difference whether a patient is included in the analysis with the event “infusion related reaction” or with an underlying event (e.g. dyspnoea). To obtain a complete picture of infusion related reactions, it is in principle desirable to have an aggregated analysis of these specific AEs (e.g. by means of a predefined PT list) including the corresponding PTs for both treatment groups, regardless of a documented relation to an infusion.

I 4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: zanubrutinib vs. 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)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Haemorrhages (SMQ[b], AEs)	Haemorrhages (SMQ[b], severe AEs[a])	Cardiac disorders (SOC, severe AEs[a])	Infections and infestations (SOC, severe AEs[a])	Infusion related reaction	Further specific AEs[a, c]
SEQUOIA	L	H[d]	H[e]	H[e]	H[e]	H[f, g]	H[f, g]	H[e, g]	H[e, f, g]	H[f, g]	H[f, g]	H[f, g]	–[h]	H[e, f, g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Without events based on laboratory values.
c. The following events are considered (coded according to MedDRA): constipation (PT, AEs), nausea (PT, AEs), fever (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs), investigations (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
d. Missing information on subsequent therapies. In addition, after disease progression, patients in the comparator arm were allowed to switch to treatment with zanubrutinib, which affected 8.5% of patients in the comparator arm.
e. Lack of blinding in subjective recording of outcomes or subjective decision to discontinue; for the other specific side effects, this aspect only contributes to a high risk of bias of the results if they are not severe side effects of CTCAE grade ≥ 3.
f. Incomplete observations for potentially informative reasons.
g. Large difference in the median observation period between the intervention arm (36 months) and the comparator arm (8 months).
h. The analysis presented by the company is unsuitable for the benefit assessment (see Section I 4.1).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; 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 outcome-specific risk of bias is rated as high for all patient-relevant outcomes.

For the results on the outcome of overall survival, the risk of bias of the results is rated as high mainly due to the lack of information on the subsequent therapies used. For the patient-reported outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30), the high risk of bias of the results is due to the open-label study design.

For the outcomes in the side effects category, the risk of bias of the results is rated as high due to the large differences in observation period between the intervention arm and the comparator arm. For the outcomes of the category of side effects that cannot be assigned to SAEs or severe AEs, the open-label study design is another potentially biasing factor. In

addition, there are incomplete observations for potentially informative reasons for SAEs, severe AEs and specific AEs.

I 4.3 Results

Table 14 summarizes the results for the comparison of zanubrutinib with bendamustine + rituximab in patients with previously untreated CLL. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

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

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study Outcome category Outcome	Zanubrutinib		Bendamustine + rituximab		Zanubrutinib vs. 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]
SEQUOIA					
Mortality					
Overall survival	104	NA 6 (5.8)	106	NA 10 (9.4)	0.54 [0.20; 1.49]; 0.113
Morbidity					
EORTC QLQ-C30 – symptom scales[b]					
Fatigue	104	19.4 [11.2; 30.8] 58 (55.8)	106	11.1 [5.9; 33.2] 48 (45.3)	0.85 [0.58; 1.25]; 0.415
Nausea and vomiting	104	NA 30 (28.8)	106	NA [38.9; NC] 27 (25.5)	0.83 [0.49; 1.40]; 0.491
Pain	104	11.6 [5.9; 19.7] 64 (61.5)	106	12.2 [8.4; 22.2] 49 (46.2)	1.12 [0.77; 1.63]; 0.541
Appetite loss	104	NA [36.3; NC] 33 (31.7)	106	NA [30.7; NC] 31 (29.2)	0.75 [0.46; 1.23]; 0.253
Diarrhoea	104	39.3 [33.4; NC] 37 (35.6)	106	NA [21.7; NC] 32 (30.2)	0.90 [0.56; 1.44]; 0.655
Dyspnoea	104	NA [25.1; NC] 42 (40.4)	106	NA [33.3; NC] 30 (28.3)	1.13 [0.71; 1.80]; 0.617
Insomnia	104	30.5 [16.9; NC] 49 (47.1)	106	39.3 [21.8; NC] 35 (33.0)	1.06 [0.69; 1.64]; 0.790
Constipation	104	NA [36.0; NC] 35 (33.7)	106	NA [27.7; NC] 29 (27.4)	0.95 [0.58; 1.55]; 0.827
Health status (EQ-5D VAS)[c]	104	NA [38.9; NC] 34 (32.7)	106	NA 22 (20.8)	1.24 [0.72; 2.12]; 0.431
Health-related quality of life					
EORTC QLQ-C30 – functional scales[b]					
Global health status	104	30.8 [14.1; NC] 50 (48.1)	106	33.1 [8.4; NC] 42 (39.6)	0.91 [0.60; 1.37]; 0.640
Physical functioning	104	38.9 [33.3; NC] 38 (36.5)	106	NA [19.6; NC] 32 (30.2)	0.84 [0.52; 1.34]; 0.461
Role functioning	104	33.7 [22.2; NC] 46 (44.2)	106	16.4 [8.3; 28.3] 48 (45.3)	0.61 [0.41; 0.92]; 0.016

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study Outcome category Outcome	Zanubrutinib		Bendamustine + rituximab		Zanubrutinib vs. 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]
Cognitive functioning	104	16.6 [10.3; 20.1] 63 (60.6)	106	14.2 [11.6; 24.9] 46 (43.4)	1.15 [0.79; 1.68]; 0.478
Emotional functioning	104	NA [33.2; NC] 38 (36.5)	106	NA [22.2; NC] 33 (31.1)	0.91 [0.57; 1.45]; 0.693
Social functioning	104	30.8 [17.3; NC] 49 (47.1)	106	14.2 [6.6; 30.6] 48 (45.3)	0.69 [0.46; 1.03]; 0.070
Side effects[d]					
AEs (supplementary information)	104	0.5 [0.5; 1.0] 101 (97.1)	101	0.1 [0.1; 0.2] 93 (92.1)	–
SAEs	104	39.3 [24.8; NC] 50 (48.1)	101	NA 38 (37.6)	0.39 [0.23; 0.68]; < 0.001
Severe AEs[e]	104	25.1 [13.9; NC] 59 (56.7)	101	2.1 [1.2; 3.7] 73 (72.3)	0.27 [0.18; 0.42]; < 0.001
Discontinuation due to AEs	104	NA [44.1; NC] 10 (9.6)	101	NA 14 (13.9)	0.06 [0.01; 0.48]; < 0.001
Haemorrhages (SMQ[f], AEs)	104	21.6 [4.8; NC] 53 (51.0)	101	NA 7 (6.9)	8.43 [3.81; 18.66]; < 0.001
Haemorrhages (SMQ[f], severe AEs[e])	104	NA 4 (3.8)	101	NA 0 (0)	NC[g]; 0.165
Cardiac disorders (SOC, severe AEs[e])	104	NA 8 (7.7)	101	NA 2 (2.0)	1.42 [0.24; 8.53]; 0.697
Infections and infestations (SOC, severe AEs[e])	104	NA 22 (21.2)	101	NA 14 (13.9)	0.31 [0.11; 0.87]; 0.018
Infusion related reaction	Analysis unsuitable[h]				
Constipation (PT, AEs)	104	NA 13 (12.5)	101	NA 24 (23.8)	0.20 [0.08; 0.49]; < 0.001
Nausea (PT, AEs)	104	NA 13 (12.5)	101	NA 34 (33.7)	0.19 [0.09; 0.41]; < 0.001
Fever (PT, AEs)	104	NA 8 (7.7)	101	NA 34 (33.7)	0.09 [0.03; 0.26]; < 0.001
Blood and lymphatic system disorders (SOC, severe AEs[e])	104	NA 17 (16.3)	101	NA [4.8; NC] 41 (40.6)	0.24 [0.13; 0.45]; < 0.001

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study Outcome category Outcome	Zanubrutinib		Bendamustine + rituximab		Zanubrutinib vs. 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]
Investigations (SOC, severe AEs[e])	104	NA 6 (5.8)	101	NA 17 (16.8)	0.21 [0.07; 0.61]; 0.002
Respiratory, thoracic, and mediastinal disorders (SOC, severe AEs[e])	104	NA 2 (1.9)	101	NA 5 (5.0)	0.00 [0.00; NC]; 0.022

a. HR and CI: Cox proportional hazards model; p-value: log-rank test. For the outcome of overall survival: each stratified by age, Binet stage, IGHV status, region; otherwise each unstratified.
b. Time to first deterioration. An EORTC QLQ-C30 increase (symptoms) or decrease (health-related quality of life) by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
c. Time to first deterioration. An EQ-5D VAS decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
d. The fixed treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio only reflects approximately the first 8 months after randomization.
e. Operationalized as CTCAE grade ≥ 3.
f. Without events based on laboratory values.
g. No presentation of effect estimation and CI, as these are not informative.
h. The analysis presented by the company is not suitable for the benefit assessment; however, serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see Section I 4.1).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IGHV: immunoglobulin heavy-chain variable region; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; 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

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

No statistically significant difference between treatment groups was found. There is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales.

Fatigue, pain, diarrhoea, dyspnoea, insomnia, and constipation

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, pain, diarrhoea, dyspnoea, insomnia, and constipation. In each case, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven for these outcomes.

Nausea and vomiting

No statistically significant difference between treatment groups was found for the outcome of nausea and vomiting. However, an effect modification by the characteristic of sex was found. For men, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven. For women, however, there is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab for the outcome of nausea and vomiting (see Section I 4.4).

Appetite loss

No statistically significant difference between treatment groups was found for the outcome of appetite loss. There is an effect modification by the characteristic of age, however. For patients < 65 years of age, there is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab for the outcome of appetite loss. For patients ≥ 65 years, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven (see Section I 4.4).

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status surveyed with the EQ-5D VAS. There is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life was recorded with the EORTC QLQ-C30 functional scales.

Global health status, physical functioning, emotional functioning and social functioning

No statistically significant difference between treatment groups was found for the outcomes of health status, physical functioning, emotional functioning and social functioning. In each

case, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven for these outcomes.

Role functioning

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for the outcome of role functioning. There is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab.

Cognitive functioning

No statistically significant difference between treatment groups was found for the outcome of cognitive functioning. However, an effect modification by the characteristic of sex was found. For men, there is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven. For women, however, there is a hint of lesser benefit of zanubrutinib in comparison with bendamustine + rituximab for the outcome of cognitive functioning (see Section I 4.4).

Side effects

With regard to the results on side effects, it should be noted that the large differences in observation periods between the treatment arms mean that the hazard ratio only reflects approximately the first 8 months.

SAEs, severe AEs and discontinuation due to AEs

A statistically significant difference between treatment groups in favour of zanubrutinib was found for each of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. In each case, there is a hint of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

Haemorrhages (AEs)

A statistically significant difference between treatment groups to the disadvantage of zanubrutinib was shown for the outcome of haemorrhages (AEs). There is a hint of greater harm from zanubrutinib in comparison with bendamustine + rituximab.

Haemorrhages (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of haemorrhages (severe AEs). There is no hint of greater or lesser harm from zanubrutinib in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Cardiac disorders (severe AEs)

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

Infections and infestations (severe AEs)

A statistically significant difference between treatment groups in favour of zanubrutinib was found for the outcome of infections and infestations (severe AEs). There is a hint of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

Infusion related reaction

No suitable data are available for the outcome of infusion related reaction (see Section I 4.1). There is no hint of greater or lesser harm from zanubrutinib in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Further specific AEs

Constipation (AEs), nausea (AEs), fever (AEs), blood and lymphatic system disorders (severe AEs), investigations (severe AEs) and respiratory, thoracic and mediastinal disorders (severe AEs)

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for each of the outcomes of constipation (AEs), nausea (AEs), fever (AEs), blood and lymphatic system disorders (severe AEs), investigations (severe AEs) and respiratory, thoracic and mediastinal disorders (severe AEs). In each case, there is a hint of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (men versus women)
- Binet stage (A or B versus C)

The company submitted subgroup analyses by age, sex and Binet stage for all outcomes listed in the dossier.

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 one subgroup.

Table 15 summarizes the subgroup results for the comparison of zanubrutinib with bendamustine + rituximab in patients with previously untreated CLL. Kaplan-Meier curves on the presented event time analyses can be found in I Appendix B of the full dossier assessment.

Table 15: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study **Outcome**	**Zanubrutinib**		**Bendamustine + rituximab**		**Zanubrutinib vs. bendamustine + rituximab**	
Characteristic **Subgroup**	**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][a]**	**p-value[b]**
SEQUOIA						
Morbidity						
Nausea and vomiting (EORTC QLQ-C30)[c]						
Sex						
Men	63	NA [33.1; NC] 21 (33.3)	62	NA [38.9; NC] 10 (16.1)	1.80 [0.85; 3.84]	0.121
Women	41	NA 9 (22.0)	44	28.1 [6.7; NC] 17 (38.6)	0.33 [0.15; 0.75]	0.005
Total					Interaction:	0.003
Appetite loss (EORTC QLQ-C30)[c]						
Age						
< 65 years	18	NA [19.9; NC] 4 (22.2)	18	11.2 [5.8; NC] 8 (44.4)	0.21 [0.06; 0.75]	0.010
≥ 65 years	86	NA [35.9; NC] 29 (33.7)	88	NA 23 (26.1)	0.94 [0.54; 1.62]	0.819
Total					Interaction	0.034

Table 15: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study Outcome Characteristic Subgroup	Zanubrutinib N	Zanubrutinib Median time to event in months [95% CI] Patients with event n (%)	Bendamustine + rituximab N	Bendamustine + rituximab Median time to event in months [95% CI] Patients with event n (%)	Zanubrutinib vs. bendamustine + rituximab HR [95% CI][a]	 p-value[b]
Health-related quality of life						
Cognitive functioning (EORTC QLQ-C30)[c]						
Sex						
Men	63	19.4 [11.1; 33.1] 35 (55.6)	62	12.1 [6.0; 19.6] 31 (50.0)	0.81 [0.50; 1.32]	0.386
Women	41	11.2 [5.7; 22.3] 28 (68.3)	44	NA [13.9; NC] 15 (34.1)	1.92 [1.02; 3.59]	0.040
Total					Interaction	0.033

a. Unstratified Cox proportional hazards model.
b. Unstratified log-rank test.
c. Time to first deterioration. An EORTC QLQ-C30 increase (symptoms) or decrease (health-related quality of life) by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).

AE: adverse event; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SOC: System Organ Class; VAS: visual analogue scale

Morbidity

Symptoms (EORTC QLQ-C30)

Nausea and vomiting

For the outcome of nausea and vomiting, there was an effect modification by the characteristic of sex. For men, there was no statistically significant difference between the treatment groups. There is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven.

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for women, however. There is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab.

Appetite loss

For the outcome of appetite loss, there was an effect modification by the characteristic of age. For patients < 65 years of age, a statistically significant difference between treatment groups

was shown in favour of zanubrutinib. There is a hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab.

No statistically significant difference between treatment groups was found for patients ≥ 65 years, however. There is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Cognitive functioning

There was an effect modification by the characteristic of sex for the outcome of cognitive functioning. For men, there was no statistically significant difference between the treatment groups. There is no hint of an added benefit of zanubrutinib in comparison with bendamustine + rituximab; an added benefit is therefore not proven.

A statistically significant difference between treatment groups to the disadvantage of zanubrutinib was shown for women, however. There is a hint of lesser benefit of zanubrutinib in comparison with bendamustine + rituximab.

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 *General Methods* of IQWiG [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 the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 16).

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

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

Nausea and vomiting as well as appetite loss (EORTC QLQ-C30)

For the outcomes of nausea and vomiting as well as appetite loss, the available information is insufficient for a classification as serious/severe. The outcomes of nausea and vomiting as well as appetite loss are therefore allocated to the outcome category of non-serious/non-severe symptoms/late complications.

Side effects

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the available severity data are insufficient for a classification as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: zanubrutinib vs. bendamustine + rituximab (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Zanubrutinib vs. bendamustine + rituximab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 0.54 [0.20; 1.49]; p = 0.113	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	19.4 vs. 11.1 HR: 0.85 [0.58; 1.25]; p = 0.415	Lesser/added benefit not proven
Nausea and vomiting Sex Men	NA vs. NA HR: 1.80 [0.85; 3.84]; p = 0.121	Lesser/added benefit not proven
Women	NA vs. 28.1 HR: 0.33 [0.15; 0.75]; p = 0.005 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: “considerable”
Pain	11.6 vs. 12.2 HR: 1.12 [0.77; 1.63]; p = 0.541	Lesser/added benefit not proven
Appetite loss Age < 65 years	NA vs. 11.2 HR: 0.21 [0.06; 0.75]; p = 0.010 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: “considerable”
≥ 65 years	NA vs. NA HR: 0.94 [0.54; 1.62]; p = 0.819	Lesser/added benefit not proven
Diarrhoea	39.3 vs. NA HR: 0.90 [0.56; 1.44]; p = 0.655	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: zanubrutinib vs. bendamustine + rituximab (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Zanubrutinib vs. bendamustine + rituximab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Dyspnoea	NA vs. NA HR: 1.13 [0.71; 1.80]; p = 0.617	Lesser/added benefit not proven
Insomnia	30.5 vs. 39.3 HR: 1.06 [0.69; 1.64]; p = 0.790	Lesser/added benefit not proven
Constipation	NA vs. NA HR: 0.95 [0.58; 1.55]; p = 0.827	Lesser/added benefit not proven
Health status (EQ-5D VAS)		
EQ-5D VAS	NA vs. NA HR: 1.24 [0.72; 2.12]; p = 0.431	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30		
Global health status	30.8 vs. 33.1 HR: 0.91 [0.60; 1.37]; p = 0.640	Lesser/added benefit not proven
Physical functioning	38.9 vs. NA HR: 0.84 [0.52; 1.34]; p = 0.461	Lesser/added benefit not proven
Role functioning	33.7 vs. 16.4 HR: 0.61 [0.41; 0.92]; p = 0.016 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Cognitive functioning Sex Men	19.4 vs. 12.1 HR: 0.81 [0.50; 1.32]; p = 0.386	Lesser/added benefit not proven
Women	11.2 vs. NA HR: 1.92 [1.02; 3.59]; HR: 0.52 [0.28; 0.98][c]; p = 0.040 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: “minor”

Table 16: Extent of added benefit at outcome level: zanubrutinib vs. bendamustine + rituximab (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Zanubrutinib vs. bendamustine + rituximab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Emotional functioning	NA vs. NA HR: 0.91 [0.57; 1.45]; p = 0.693	Lesser/added benefit not proven
Social functioning	30.8 vs. 14.2 HR: 0.69 [0.46; 1.03]; p = 0.070	Lesser/added benefit not proven
Side effects[d]		
SAEs	39.3 vs. NA HR: 0.39 [0.23; 0.68]; p < 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: “major”
Severe AEs	25.1 vs. 2.1 HR: 0.27 [0.18; 0.42]; p < 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: “major”
Discontinuation due to AEs	NA vs. NA HR: 0.06 [0.01; 0.48]; p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm; extent: “considerable”
Haemorrhages (AEs)	21.6 vs. NA HR: 8.43 [3.81; 18.66]; HR: 0.12 [0.05; 0.26][c]; p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: “considerable”
Haemorrhages (severe AEs)	NA vs. NA HR: NC[e]; p = 0.165	Greater/lesser harm not proven
Cardiac disorders (severe AEs)	NA vs. NA HR: 1.42 [0.24; 8.53]; p = 0.697	Greater/lesser harm not proven
Infections and infestations (severe AEs)	NA vs. NA HR: 0.31 [0.11; 0.87]; p = 0.018 Probability: “hint”	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 Lesser harm; extent: “considerable”
Infusion related reaction	Analysis unsuitable[f]	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: zanubrutinib vs. bendamustine + rituximab (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Zanubrutinib vs. bendamustine + rituximab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Constipation (AEs)	NA vs. NA HR: 0.20 [0.08; 0.49]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: "considerable"
Nausea (AEs)	NA vs. NA HR: 0.19 [0.09; 0.41]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: "considerable"
Fever (AEs)	NA vs. NA HR: 0.09 [0.03; 0.26]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: "considerable"
Blood and lymphatic system disorders (severe AEs)	NA vs. NA HR: 0.24 [0.13; 0.45]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: "major"
Investigations (severe AEs)	NA vs. NA HR: 0.21 [0.07; 0.61]; p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: "major"
Respiratory, thoracic and mediastinal disorders (severe AEs)	NA vs. NA HR: 0.00 [0.00; NA]; p = 0.022 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The fixed treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio only reflects approximately the first 8 months after randomization.
e. No presentation of effect estimation and CI, as these are not informative.
f. The analysis presented by the company is not suitable for the benefit assessment; however, serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see Section I 4.1).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of zanubrutinib in comparison with bendamustine + rituximab

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period[a]	
Non-serious/non-severe symptoms/late complications ▪ Nausea and vomiting: ▫ Sex (women): hint of an added benefit – extent: "considerable" ▪ Appetite loss: ▫ Age (< 65 years): hint of an added benefit – extent: "considerable"	–
Health-related quality of life ▪ Role functioning: hint of an added benefit – extent: "minor"	Health-related quality of life ▪ Cognitive functioning: ▫ Sex (women): hint of lesser benefit – extent: "minor"
Serious/severe side effects ▪ SAEs, severe AEs: hint of lesser harm – extent: "major" ▫ Infections and infestations (severe AEs): hint of lesser harm – extent: "considerable" ▫ Blood and lymphatic system disorders (severe AEs), investigations (severe AEs): hint of lesser harm – extent: "major" ▫ Respiratory, thoracic and mediastinal disorders (severe AEs): hint of lesser harm – extent: "non-quantifiable"	–
Non-serious/non-severe side effects ▪ Discontinuation due to AEs, constipation (AEs), nausea (AEs), fever (AEs): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ Haemorrhages (AEs): hint of greater harm – extent: "considerable"
a. The outcomes of the categories of morbidity and health-related quality of life were recorded until disease progression (see Table 8). For the outcomes of side effects, the fixed treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio only reflects approximately the first 8 months after randomization. AE: adverse event; SAE: serious adverse event	

For the assessment of the added benefit of zanubrutinib in comparison with the ACT, the company presented only data for patients without genetic risk factors for whom therapy with

FCR is unsuitable (see Section I 3.2). No data are available for patients without genetic risk factors for whom FCR therapy is suitable, and for patients with genetic risk factors.

Overall, there are both positive and negative effects of zanubrutinib in comparison with bendamustine + rituximab for patients without genetic risk factors for whom therapy with FCR is unsuitable. There are advantages in particular in the outcome category of serious/severe side effects with hints of lesser harm with different extents. In the overall rates of both serious and severe AEs, the extent in each case is major. In addition, there are hints of lesser harm in the outcome category of non-serious/non-severe side effects with the extent “considerable”. For the patient-reported outcomes of the outcome categories of morbidity and health-related quality of life, there are hints of added benefit of zanubrutinib in comparison with bendamustine + rituximab for individual symptom and functional scales of the EORTC QLQ-C30 (partly only for subgroups) with considerable and minor extent. On the other hand, there is a hint of lesser benefit with the extent “minor” in the category of health-related quality of life (only for women) and a hint of greater harm with the extent “considerable” in the category of non-serious/non-severe side effects.

Overall, in the present situation, the added benefit is therefore based mainly on advantages in the outcome category of side effects. Due to the large differences in observation periods, the underlying analyses represent only the approximately first 8 months of the study. For outcomes on morbidity and health-related quality of life, which allow a comparison over an observation period that is about 4 times longer, statistically significant differences were only shown in few symptom and functional scales of the EORTC QLQ-C30 (partly only for subgroups). Therefore, it cannot be deduced from this that the advantages of zanubrutinib also exist beyond the first 8 months to a major extent. In this specific data situation, quantification of the added benefit is therefore not possible. However, it should be noted at this point that according to the study protocol of the SEQUOIA study, data also had to be recorded until disease progression or the start of subsequent CLL therapy for outcomes in the side effects category. However, the company did not present corresponding analyses that cover a notably longer period of time.

In summary, there is a hint of a non-quantifiable added benefit of zanubrutinib in comparison with bendamustine + rituximab for adult patients with previously untreated CLL who have no genetic risk factors and for whom therapy with FCR is unsuitable.

Due to missing data, an added benefit of zanubrutinib is not proven for patients without genetic risk factors for whom FCR therapy is suitable and for patients with genetic risk factors.

Table 18 summarizes the result of the assessment of the added benefit of zanubrutinib in comparison with the ACT.

Table 18: Zanubrutinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with previously untreated CLL[b]	Ibrutinib or ibrutinib in combination with rituximab or obinutuzumab or FCR[c, d] or **bendamustine in combination with rituximab**[d, e] or chlorambucil in combination with rituximab or obinutuzumab[d, e]	▪ Patients without genetic risk factors for whom therapy with FCR is not suitable: Hint of non-quantifiable added benefit ▪ All other patients in the therapeutic indication: Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The G-BA assumes for the present therapeutic indication that the patients require treatment (e.g. Binet stage C). Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
c. Only for patients without genetic risk factors and < 65 years of age, for whom therapy with FCR is suitable on the basis of their general condition and comorbidities.
d. According to the G-BA, the following factors are considered genetic risk factors based on the current state of medical knowledge: presence of a 17p deletion/TP53 mutation or an unmutated immunoglobulin heavy-chain variable region.
e. Only for patients without genetic risk factors for whom therapy with FCR is not suitable. According to the G-BA, these are patients ≥ 65 years of age, and patients < 65 years for whom therapy with FCR is not suitable on the basis of their general condition and comorbidity.

17p deletion: deletion in the short arm of chromosome 17; CLL: chronic lymphocytic leukaemia;
FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The assessment described above deviates from that by the company, which derived a hint of considerable added benefit.

The approach for deriving 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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