Zanubrutinib (chronic lymphocytic leukaemia, relapsed/refractory)

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

EXTRACT

Project: A22-132 Version: 1.0 Status: 10 March 2023

[1] Translation of Sections I 1 to I 8 of the dossier assessment *Zanubrutinib (chronische lymphatische Leukämie, rezidiviert / refraktär) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Zanubrutinib (chronic lymphocytic leukaemia, relapsed/refractory) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

15 December 2022

Internal Project No.

A22-132

Address of publisher

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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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Keywords

Zanubrutinib, Leukemia – Lymphocytic – Chronic – B-Cell, Benefit Assessment, NCT03734016

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BCL2	B-cell lymphoma 2
BTK	Bruton's tyrosine kinase
CLL	chronic lymphatic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und. Medizinische Onkologie (German Society for Hematology and Medical Oncology)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D	European Quality of Life 5 Dimensions
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
ORR	objective response rate (overall response rate)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SLL	small lymphocytic lymphoma
SPC	Summary of Product Characteristics
TP53	tumour protein 5
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 ACT in patients with recurrent/refractory chronic lymphatic leukaemia (CLL).

Depending on the patients' prior treatment, the G-BA distinguished between different treatment scenarios and specified an ACT for each of them. This results in the research questions presented in Table 2.

Table 2: Research question of the benefit assessment of zanubrutinib

Research question	**Therapeutic indication**	**ACT[a]**
Patients with recurrent/refractory CLL[b]		
1	Without prior therapy with a BTK inhibitor and/or BCL2 inhibitor[c]	▪ **Ibrutinib** or ▪ venetoclax + rituximab or ▪ chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors)[d]
2	After prior therapy with at least 1 BTK inhibitor	▪ Venetoclax + rituximab
3	After prior therapy with at least 1 BCL2 inhibitor	▪ Ibrutinib
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL-2 inhibitor	Individualized treatment selected from ▫ idelalisib in combination with rituximab ▫ bendamustine in combination with rituximab ▫ chlorambucil in combination with rituximab and ▫ best supportive care[e] ▪ taking into account comorbidities, general health, genetic risk factors[d] as well as the success of and tolerance to prior therapy

a. Presented is the respective 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. In the present therapeutic indication, the G-BA presumes patients to be indicated for treatment (e.g. Binet stage C). Moreover, allogeneic stem cell transplantation is presumably not indicated at the time of treatment.
c. In contrast to the other research questions, this one comprises patients who have received neither a BTK inhibitor nor a BCL2 inhibitor. Below, research question 1 will be referred to as “patients with recurrent/refractory CLL who have received neither a BTK inhibitor nor a BCL2 inhibitor”.
d. According to current state of medical knowledge, the following are deemed genetic risk factors: presence of 17p deletion / TP53 mutation as well as unmutated IGHV.
e. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; BCL2: B-cell lymphoma 2; BR: bendamustine in combination with rituximab; BTK: Bruton’s tyrosine kinase; ClbR: chlorambucil in combination with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of tumour protein p53

The company followed the G-BA's specification and chose ibrutinib as ACT from the options presented. This option represents an ACT for patients whose pretreatment includes neither a Bruton’s tyrosine kinase (BTK) inhibitor nor a B-cell lymphoma 2 (BCL2) inhibitor (research question 1) as well as for those pretreated with at least 1 BCL2 inhibitor (research question 3).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trial (RCTs) are used for the derivation of added benefit.

Research question 1: Patients with recurrent/refractory CLL who have received neither a BTK inhibitor nor a BCL2 inhibitor

Study pool and study design

The ALPINE study was included in the benefit assessment.

The ALPINE study is an ongoing, open-label RCT comparing zanubrutinib versus ibrutinib. The study enrolled adult patients indicated for treatment of recurrent and/or refractory CLL or small lymphocytic lymphoma (SLL) who had been pretreated with at least 1 systemic therapy. Prior treatment with a BTK inhibitor was disallowed. Indication for treatment was determined based on International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. A total of 652 patients were randomly allocated, with 327 patients to the zanubrutinib arm and 325 patients to the ibrutinib arm.

Zanubrutinib treatment in the intervention arm and ibrutinib treatment in the comparator arm were administered as per Summary of Product Characteristics (SPC) continuously until disease progression, the occurrence of unacceptable toxicity, treatment discontinuation, or termination of participation as decided by the patient or physician.

The primary outcome of the study was the overall response rate (ORR). Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and adverse events (AEs).

The benefit assessment uses the analyses of the final data cut-off, 8 August 2022, which were presented by the company.

Relevance of the ALPINE study for the benefit assessment

All patients enrolled in the study had received prior treatment, but no BTK inhibitor. The majority of patients (approximately 82%) had received 1 to 2 prior therapies. Most prior therapies (approximately 78%) were chemoimmunotherapies. A small proportion (2%) of patients had received prior BCL2 inhibitor treatment.

The majority of study participants exhibited genetic risk factors. Genetic risk factors were defined as deletion in the short arm of chromosome 17 (17p deletion), mutation of tumour protein p53 (TP53 mutation) as well as unmutated IGHV. According to the CLL treatment guideline issued by the German Society for Hematology and Medical Oncology (DGHO), a complex karyotype is also deemed a genetic risk factor. In the ALPINE study, about 23% of

patients had a 17p deletion and/or TP53 mutation; about 73% had an unmutated IGHV status, and about 19% exhibited a complex karyotype.

According to the current S3 guideline for CLL treatment and the European Society for Medical Oncology (ESMO) guideline, first-line chemoimmunotherapy is to be administered only to patients without genetic risk factors or to fit patients without 17p deletion and/or TP53 mutation. The updated DGHO guideline no longer recommends chemoimmunotherapy in first-line therapy, irrespective of the presence of genetic risk factors.

In view of the high proportion of patients with prior chemoimmunotherapy and the high prevalence of genetic risk factors in the study population, prior treatment in the ALPINE study presumably inadequately reflects the German healthcare context.

This did not lead to the exclusion of the study from the benefit assessment. However, the aspects described were taken into account in the assessment of the certainty of conclusions of results.

Risk of bias and certainty of conclusions

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

There is a low risk of bias for the results of the outcome of overall survival. For the results on the outcomes from the morbidity, health-related quality of life, and side effects categories, the risk of bias was rated as high. With the outcomes which cannot be aligned with serious AEs (SAEs) or severe AEs (CTCAE grade ≥ 3), the open-label study design leads to high risk of bias. Observations are incomplete for the results on SAEs, severe AEs, and non-serious or non-severe specific AEs; this is due to the duration of follow-up observation being linked to the treatment duration as well as a potential relationship between the outcome and the reason for treatment discontinuation. The reasons for discontinuation are potentially of informative value, and some of them differ between study arms.

Summary assessment of the certainty of conclusions

The risk of bias is rated as high for all outcomes except overall survival. Furthermore, the high proportion of patients with prior chemoimmunotherapy does not adequately reflect the current health care context in Germany. This reduces the reliability of results.

Based on the results of the ALPINE study, only hints, e.g. of added benefit, can therefore be derived in the present situation.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. However, there is an effect modification by the characteristic of age. This results in a hint of added benefit of zanubrutinib compared to ibrutinib for patients < 65 years. For patients ≥ 65 years, there is no hint of added benefit of zanubrutinib compared to ibrutinib; thus, there is no proof of added benefit.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30])

Fatigue, nausea and vomiting, pain, appetite loss, dyspnoea, insomnia, and constipation

No statistically significant difference between treatment groups was shown for any of the following outcomes: fatigue, nausea and vomiting, pain, appetite loss, dyspnoea, insomnia, and constipation. In each case, there is no hint of added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Diarrhoea

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for the outcome of diarrhoea. However, for this non-serious/non-severe outcome, the extent of the effect was no more than marginal. This results in no hint of an added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Health status (determined using the European Quality of Life 5 Dimensions [EQ-5D] visual analogue scale [VAS])

There is no statistically significant difference between treatment groups for the outcome of health status, recorded with the EQ-5D VAS. This results in no hint of an added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

General health status, physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning

No statistically significant difference between treatment arms was shown for any of the outcomes of general health status, physical functioning, role functioning, emotional functioning, or social functioning. In each case, there is no hint of added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, there is a statistically significant difference in favour of zanubrutinib in comparison with ibrutinib. For each of these outcomes, this results in a hint of lesser harm from zanubrutinib in comparison with ibrutinib.

Severe AEs

There is no statistically significant difference between treatment groups for the outcome of severe AEs. This results in no hint of lesser or greater harm from zanubrutinib in comparison with ibrutinib; lesser or greater harm is therefore not proven.

Cardiac disorders (severe AEs)

A statistically significant difference in favour of zanubrutinib compared with ibrutinib was shown for the outcome of cardiac disorders (severe AEs). This results in a hint of lesser harm from zanubrutinib in comparison with ibrutinib.

Muscle spasms (AEs)

A statistically significant difference in favour of zanubrutinib compared with ibrutinib was shown for the outcome of muscle spasms (AEs). However, there is an effect modification by the characteristic of sex. For men, this results in a hint of lesser harm from zanubrutinib in comparison with ibrutinib. For women, this results in no hint of lesser or greater harm from zanubrutinib in comparison with ibrutinib; lesser or greater harm is therefore not proven.

Infections and infestations (severe AEs) and bleeding (AEs)

No statistically significant difference between treatment groups was shown for either of the outcomes infections and infestations (severe AEs) or bleeding (AEs). This results in no hint of lesser or greater harm from zanubrutinib in comparison with ibrutinib for any of them; lesser or greater harm is therefore not proven.

Research question 2: patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the appropriate comparator therapy (ACT) for patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor. This results in no hint of an added benefit of zanubrutinib in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: patients with recurrent/refractory CLL after prior therapy with at least 1 BCL2 inhibitor

The company has not submitted any suitable data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL after prior therapy with at least 1 BCL2 inhibitor. This results in no hint of an added benefit of zanubrutinib in comparison with the ACT; an added benefit is therefore not proven for this research question.

Research question 4: patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the ACT in patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor. This results in no hint of an added benefit of zanubrutinib in comparison with the ACT; an added benefit is therefore not proven.

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 is assessed as follows:

Research question 1: Patients with recurrent/refractory CLL who have previously received neither a BTK inhibitor nor a BCL2 inhibitor

Overall, only favourable effects were found for zanubrutinib in comparison with ibrutinib. In the outcome category of mortality, a hint of added benefit of major extent was found for patients < 65 years of age.

In the outcome category of side effects, SAEs, severe AEs, and discontinuation due to AEs are each associated with hints of lesser harm of minor extent for the total population.

In summary, for patients < 65 years of age with recurrent/refractory CLL who have previously received neither a BTK inhibitor nor a BCL2 inhibitor, this results in a hint of major added benefit of zanubrutinib versus ibrutinib. For patients ≥ 65 years of age with

[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].

recurrent/refractory CLL who have previously received neither a BTK inhibitor nor a BCL2 inhibitor, this results in a hint of minor added benefit of zanubrutinib versus ibrutinib.

Research question 2: patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor. An added benefit of zanubrutinib in comparison with the ACT is therefore not proven.

Research question 3: patients with recurrent/refractory CLL after prior therapy with at least 1 BCL2 inhibitor

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL after prior therapy with at least 1 BTK2 inhibitor. An added benefit of zanubrutinib in comparison with the ACT is therefore not proven.

Research question 4: patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor and a BCL2 inhibitor. An added benefit of zanubrutinib in comparison with the ACT is therefore not proven.

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

Table 3: Zanubrutinib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
	Patients with recurrent/refractory CLL[b]		
1	Without prior therapy with a BTK inhibitor and/or BCL2 inhibitor[c]	▪ **Ibrutinib** or ▪ venetoclax + rituximab or ▪ chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors)[d]	Patients ▪ < 65 years: hint of major added benefit ▪ ≥ 65 years: hint of minor added benefit
2	After prior therapy with at least 1 BTK inhibitor	▪ Venetoclax + rituximab	Added benefit not proven
3	After prior therapy with at least 1 BCL2 inhibitor	▪ Ibrutinib	Added benefit not proven
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor	Individualized treatment selected from ▫ idelalisib in combination with rituximab ▫ bendamustine in combination with rituximab ▫ chlorambucil in combination with rituximab and ▫ best supportive care[e] ▪ taking into account comorbidities, general health, genetic risk factors[d] as well as the success of and tolerance to prior therapy	Added benefit not proven

a. Presented is the respective 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. In the present therapeutic indication, the G-BA presumes patients to be indicated for 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. In contrast to the other research questions, this one comprises patients who have received neither a BTK inhibitor nor a BCL2 inhibitor. Below, research question 1 will be referred to as “patients with recurrent/refractory CLL who have received neither a BTK inhibitor nor a BCL2 inhibitor”.
d. According to current medical knowledge, the following are deemed genetic risk factors: presence of 17p deletion / TP53 mutation as well as unmutated IGHV.
e. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

Table 3: Zanubrutinib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; BCL2: B-cell lymphoma 2; BR: bendamustine in combination with rituximab; BTK: Bruton's tyrosine kinase; ClbR: chlorambucil in combination with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of tumour protein p53			

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

I 2 Research questions

The aim of the present report is to assess the added benefit of zanubrutinib in comparison with the ACT in patients with recurrent/refractory CLL.

Depending on the patients' prior treatment, the G-BA distinguished between different treatment scenarios and specified an ACT for each of them. This results in the research questions presented in Table 4.

Table 4: Research question of the benefit assessment of zanubrutinib

Research question	Therapeutic indication	ACT[a]
Patients with recurrent/refractory CLL[b]		
1	Without prior therapy with a BTK inhibitor and/or BCL2 inhibitor[c]	▪ **Ibrutinib** or ▪ venetoclax + rituximab or ▪ chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors)[d]
2	After prior therapy with at least 1 BTK inhibitor	▪ Venetoclax + rituximab
3	After prior therapy with at least 1 BCL2 inhibitor	▪ Ibrutinib
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor	Individualized treatment selected from ▫ idelalisib in combination with rituximab ▫ bendamustine in combination with rituximab ▫ chlorambucil in combination with rituximab and ▫ best supportive care[e] taking into account comorbidities, general health, genetic risk factors[d] as well as the success of and tolerance to prior therapy

a. Presented is the respective 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. In the present therapeutic indication, the G-BA presumes patients to be indicated for 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. In contrast to the other research questions, this one comprises patients who have received neither a BTK inhibitor nor a BCL2 inhibitor. Below, research question 1 will be referred to as "patients with recurrent/refractory CLL who have received neither a BTK inhibitor nor a BCL2 inhibitor".
d. According to current medical knowledge, the following are deemed genetic risk factors: presence of 17p deletion / TP53 mutation as well as unmutated IGHV.
e. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

17p deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; BCL2: B-cell lymphoma 2; BR: bendamustine in combination with rituximab; BTK: Bruton's tyrosine kinase; ClbR: chlorambucil in combination with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of tumour protein p53

The company followed the G-BA's specification and chose ibrutinib as ACT from the options presented. This option represents an ACT for patients whose prior treatment included neither a BTK inhibitor nor a BCL2 inhibitor (research question 1) or who have been pretreated with at least 1 BCL2 inhibitor (research question 3).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided 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 Research question 1: Patients with recurrent/refractory CLL who have previously received neither a BTK inhibitor nor a BCL2 inhibitor

I 3.1 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: 20 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 studies.

I 3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: zanubrutinib versus ibrutinib

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 and other sources[c] (yes/no [citation])
BGB-3111-305 (ALPINE[d])	Yes	Yes	No	Yes [3-5]	Yes [6,7]	Yes [8-10]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.1.2 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 versus ibrutinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ALPINE	RCT, open-label, parallel-group	Adults with recurrent and/or refractory[b] CLL or SLL[c] indicated for treatment ▪ ≥ 1 prior therapy[d] ▪ without prior therapy with a BTK inhibitor ▪ ECOG PS ≤ 2 ▪ life expectancy of ≥ 6 months	Zanubrutinib (N = 327) Ibrutinib (N = 325)	Screening: ≤ 35 days Treatment: until disease progression, unacceptable toxicity, treatment discontinuation or termination of study participation decided by patient or physician Observation: outcome-specific[e], at most until death, revocation of consent, lost to follow-up, or end of study	117 study centres in: Australia, Belgium, China, Czech Republic, France, Germany, Great Britain, Italy, Netherlands, New Zealand, Poland, Spain, Sweden, Turkey, United States 11/2018–ongoing Data cut-offs: ▪ 1st data cut-off: 31 December 2020[f] ▪ 2nd data cut-off: 1 December 2021[g] ▪ 3rd data cut-off (final analysis): 8 August 2022[h]	Primary: ORR Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: zanubrutinib versus ibrutinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment. b. Refractory disease is defined as either no objective response or progression of disease within 6 months after the most recent CLL/SLL treatment. Recurrent disease is defined as reappearance of disease more than 6 months after the last CLL/SLL treatment and subsequent progression. c. Indication for treatment established according to the criteria of the international CLL working group, iwCLL [11]. d. Defined as the completion of at least 2 treatment cycles with a standard regimen in accordance with the valid NCCN or ESMO guidelines or with an investigational product in the context of a clinical trial. e. Outcome-specific information is described in Table 8. f. Planned to take place 12 months after randomization of 415 patients. g. Planned to take place 12 months after randomization of 600 patients. h. Planned to take place after 205 PFS events. AE: adverse event; BTK: Bruton's tyrosine kinase; CLL: chronic lymphatic leukaemia; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; ESMO: European Society for Medical Oncology; iwCLL: International Workshop on CLL; N: number of randomized patients; NCCN: National Comprehensive Cancer Network; ORR: objective response rate; PFS: progression-free survival; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma					

Table 7: Characteristics of the interventions – RCT, direct comparison: zanubrutinib versus ibrutinib

Study	Intervention	Comparison
ALPINE	Zanubrutinib 160 mg twice daily, orally	Ibrutinib 420 mg once daily, orally
	Treatment adjustments ▪ In case of toxicity, treatment interruption[a]; maximum of 2 dose reductions from the 2nd occurrence of severe side effects (grade ≥ 3) ▫ for zanubrutinib, dose cut in half each time ▫ for ibrutinib, dose reduction by 140 mg each time ▪ Discontinuation of study medication in case of recurrent severe event on minimal dosage[b]	
	Allowed prior treatment[c] ▪ Prior systemic therapy for CLL/SLL is to be completed before the first dose of the study medication ▫ chemotherapy or radiotherapy (> 21 days) ▫ stem cell transplantation (> 90 days) ▫ monoclonal antibodies (> 28 days) ▫ major surgery (> 4 weeks) ▫ vaccination with a live vaccine (> 35 days) **Disallowed prior treatment** ▪ BTK inhibitors **Allowed concomitant treatment** ▪ Blood product transfusions and growth factors ▪ Standard of care concomitant symptomatic therapy or prophylaxis of opportunistic infections and tumour lysis syndrome ▪ Short-term or intermittent corticosteroid administration[d] **Disallowed concomitant treatment** ▪ Other CLL/SLL treatment ▪ Ongoing, medically necessary treatment with strong CYP3A inhibitors/inducers[e], warfarin, or other vitamin K antagonists prior to and during the study	

a. Resumption of treatment as soon as toxicity has subsided to grade ≤ 1 or baseline value.
b. In case of bleeding grade ≥ 3 which was related to the study medication, treatment with zanubrutinib is to be discontinued (unless the cause of bleeding has been fully treated and the risk of another bleeding event is deemed acceptable by the medical monitor and investigator). In case of intracranial bleeding, zanubrutinib treatment was to be discontinued regardless of severity and association with study medication if the risk of another bleeding event was deemed unacceptable.
c. Prior therapy is defined as the completion of ≥ 2 treatment cycles with a standard regimen in accordance with the valid NCCN or ESMO guidelines or with an investigational product in the context of a clinical trial.
d. For the treatment of diseases unrelated to CLL/SLL; ongoing systemic treatment with corticosteroids had to be completely discontinued ≥ 5 days prior to the first dose of study medication.
e. If use of CYP3A inhibitors or inducers was required during study treatment, dose adjustment was to be implemented according to the SPC.

BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; CYP3A: cytochrome P450 3A; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma

The ALPINE study is an ongoing, open-label RCT comparing zanubrutinib versus ibrutinib.

The study enrolled adult patients requiring treatment of recurrent and/or refractory CLL or SLL who had been pretreated with at least 1 systemic therapy. Prior treatment with a BTK inhibitor was disallowed. Indication for treatment was determined based on iwCLL criteria [11]. Patients had to have an ECOG-PS of 0 to 2 as a measure of general health as well as a life expectancy of > 6 months.

Patients were randomized 1:1 into the 2 study arms stratified by age (< 65 years versus ≥ 65 years), geographic region (China versus non-China), refractory status (yes versus no), and deletion in the short arm of chromosome 17 (17p deletion) / tumour protein p53 (TP53) mutation status (yes versus no). A total of 652 patients were randomly allocated, with 327 patients to the zanubrutinib arm and 325 patients to the ibrutinib arm.

Treatment with zanubrutinib in the intervention arm and ibrutinib in the comparator arm was administered according to the respective SPCs [12,13].

Zanubrutinib or ibrutinib treatment was continuously administered until disease progression, the occurrence of unacceptable toxicity, discontinuation of therapy, or termination of study participation decided by the patient or physician.

The primary outcome of the study was ORR. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and AEs.

Data cutoffs

A total of 3 predefined data cutoffs are available for the ALPINE study:

- 1st data cut-off (31 December 2020): 12 months after randomization of about 415 patients
- 2nd data cut-off (1 December 2021): 12 months after randomization of about 600 patients
- 3rd data cutoff (8 August 2022): event-driven analysis after the occurrence of 205 progression-free survival events (final data cutoff)

The analyses presented by the company for the final data cutoff dated 8 August 2022 are used for the benefit assessment.

Relevance of the ALPINE study for the benefit assessment

All patients enrolled in the study had received prior treatment, but no BTK inhibitor. The majority of patients (approximately 58%) had received 1 prior therapy. Most of the prior therapies were chemoimmunotherapies (approximately 78%) (see Table 9). For the purposes

of the benefit assessment, this prior treatment presumably does not reflect the current context of care in Germany. This is explained below:

The majority of study participants exhibited genetic risk factors. Analysed genetic risk factors were 17p deletion, TP53 mutation, and unmutated IGHV. Furthermore, according to the DGHO guideline for the treatment of CLL, a complex karyotype is likewise deemed a genetic risk factor [14].

In the ALPINE study, about 23% of patients had a 17p deletion and/or TP53 mutation, about 73% had an unmutated IGHV status, and about 19% exhibited a complex karyotype.

According to current guidelines for the treatment of CLL, genetic risk factors are to be taken into account when choosing an appropriate therapy [14,15].

According to the 2018 S3 guideline on CLL treatment, patients with 17p deletion and/or TP53 mutation are to be offered the BTK inhibitor ibrutinib as first-line therapy [15]. Patients who are not eligible for ibrutinib may alternatively be offered therapy with idealisib in combination with rituximab or ofatumumab or venetoclax. Chemoimmunotherapy, on the other hand, is to be administered only to patients without genetic risk factors [15].

In the 2020 ESMO guideline, first-line chemoimmunotherapy is recommended only for fit patients without 17p deletion and/or TP53 mutation [16].

In the updated 2023 DGHO guideline, chemoimmunotherapy is no longer recommended in first-line therapy irrespective of genetic risk factors [14].

Approximately 42% of patients in the ALPINE trial had received more than 1 prior therapy at baseline and thus had already been treated with relapse therapy at least once.

The 2018 S3 guideline recommends chemoimmunotherapy for relapse therapy. Patients with 17p deletion and/or TP53 mutation who have late relapse indicated for treatment are to be offered ibrutinib or idelalisib-based combination therapy (with rituximab or ofatumumab) or venetoclax [15]. According to the 2020 ESMO guideline, treatment with venetoclax plus rituximab or a BTK inhibitor is to be offered in case of relapse. Chemoimmunotherapy is to be resorted to only in patients without 17p deletion and/or TP53 mutation or only in the absence of therapeutic options [16]. The current DGHO guideline does not recommend chemoimmunotherapy, even in case of relapse [14].

The above clearly demonstrates that first-line chemoimmunotherapy is, at best, an option for patients without genetic risk factors. Even in patients with relapse, chemoimmunotherapy is recommended only with reservations. In view of the high proportion of patients with prior chemoimmunotherapy and the high prevalence of genetic risk factors in the study population,

prior treatment in the ALPINE study presumably inadequately reflects the German healthcare context.

This did not lead to the exclusion of the study from the benefit assessment. However, the uncertainties described above were taken into account in the assessment of the certainty of conclusions of the results (see Section I 3.2.2).

Treatment duration and 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 versus ibrutinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ALPINE	
Mortality	
Overall survival	Until death, revocation of consent, lost to follow-up, or end of study
Morbidity	
Symptoms/health status (EORTC QLQ-C30, EQ-5D VAS)	Until disease progression
Health-related quality of life (EORTC QLQ-C30)	Until disease progression
Side effects	
All outcomes in the side effects category	Until 30 days after the last dose of the study medication or until initiation of a new cancer treatment, whichever occurs first
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality of Life 5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes of morbidity, health-related quality of life, and side effects were systematically shortened because they were recorded only until disease progression or for the period of treatment with the study medication (plus 30 days). 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.

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: zanubrutinib versus ibrutinib (multipage table)

Study **Characteristic** **Category**	**Zanubrutinib** **N = 327**	**Ibrutinib** **N = 325**
ALPINE		
Age [years], mean (SD)	67 (10)	67 (9)
Age group, n (%)		
< 65 years	126 (39)	125 (38)
≥ 65 to < 75 years	127 (39)	131 (40)
≥ 75 years	74 (23)	69 (21)
Sex [f/m], %	35/65	29/71
ECOG-PS, n (%)		
0	129 (39)	122 (38)
1	191 (58)	190 (58)
2	7 (2)	13 (4)
Disease duration: time between first diagnosis and randomization [months], mean (SD)	90 (55)	94 (60)
Geographical region, n (%)		
Asia	49 (15)	45 (14)
Australia	28 (9)	30 (9)
Europe	198 (61)	191 (59)
North America	52 (16)	59 (18)
Ancestry, n (%)		
Asian	47 (14)	44 (14)
White	261 (80)	265 (82)
Other[a]	10 (3)	4 (1)
Unknown[b]	9 (3)	12 (4)
Cancer type, n (%)		
CLL	314 (96)	309 (95)
SLL	13 (4)	16 (5)
Bulky disease, n (%)		
Target lesion < 5 cm	182 (56)	176 (54)
Target lesion ≥ 5 cm and < 10 cm[c]	115 (35)	120 (37)
Target lesion ≥ 10 cm	30 (9)	29 (9)
CLL disease stage at baseline, n (%)		
Binet A	33 (10)	34 (10)
Binet B	148 (45)	154 (47)
Binet C	133 (41)	120 (37)
Unknown	0 (0)	1 (< 1)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: zanubrutinib versus ibrutinib (multipage table)

Study **Characteristic** **Category**	**Zanubrutinib** **N = 327**	**Ibrutinib** **N = 325**
SLL disease stage at baseline, n (%)		
Ann Arbor stage I	1 (< 1)	1 (< 1)
Ann Arbor stage III	6 (2)	7 (2)
Ann Arbor stage IV	6 (2)	8 (2)
Cytopenia[d], n (%)		
Yes	172 (53)	170 (52)
No	155 (47)	155 (48)
Beta 2 microglobulin, n (%)		
≤ 3.5 mg/L	104 (32)	92 (28)
> 3.5 mg/L	177 (54)	183 (56)
Unknown	46 (14)	50 (15)
Chromosome anomaly/mutation, n (%)		
17p deletion	45 (14)	50 (15)
TP53 mutation	50 (15)	45 (14)
17p deletion and/or TP53 mutation	75 (23)	75 (23)
11q deletion	91 (28)	88 (27)
13q deletion	197 (60)	200 (62)
Trisomy 12	60 (18)	44 (14)
IGHV mutation status, n (%)		
Mutated	79 (24)	70 (22)
Unmutated	239 (73)	239 (74)
Unknown	9 (3)	16 (5)
Complex karyotype[e], n (%)	56 (17)	70 (22)
Number of prior therapies, n (%)		
1	192 (59)	186 (57)
2	86 (26)	71 (22)
3	25 (8)	38 (12)
≥ 4[c]	24 (7)	30 (9)
Prior therapies, n (%)		
Anti-CD20 antibodies	274 (84)	269 (83)
Alkylating agents (other than bendamustine)	274 (84)	258 (79)
Purine analogue	178 (54)	169 (52)
Bendamustine	84 (26)	94 (29)
PI3K/SYK inhibitor	11 (3)	19 (6)
BCL2 inhibitor	7 (2)	8 (2)
IMiD	6 (2)	1 (< 1)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: zanubrutinib versus ibrutinib (multipage table)

Study **Characteristic** **Category**	**Zanubrutinib** **N = 327**	**Ibrutinib** **N = 325**
Alemtuzumab	2 (1)	1 (< 1)
Chemoimmunotherapy	260 (80)	247 (76)
Treatment discontinuation, n (%)[f]	86 (26)	134 (41)
Study discontinuation, n (%)[g]	67 (20)	85 (26)

a. Institute's calculation; aggregation of data for Black or African American, Hawaiian Native or Other Pacific Islander, and multiple.
b. Institute's calculation; aggregation of data for not reported and unknown.
c. Institute's calculation.
d. Cytopenia is defined as follows: haemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L, or absolute neutrophil count ≤ 1.5 x 10^9/L.
e. Complex karyotype is defined as 3 or more genetic abnormalities.
f. Common reasons for treatment discontinuation in the zanubrutinib arm versus the ibrutinib arm were adverse events (16% vs. 23%), disease progression (7% vs. 13%), and withdrawal of consent (2% vs. 4%).
g. Common reasons for study discontinuation in the zanubrutinib arm vs. ibrutinib arm were death (15% vs. 18%) and withdrawal of consent (4% vs. 5%).

11q deletion: deletion of the long arm of chromosome 11; 13q deletion: deletion in the long arm of chromosome 13; 17p deletion: deletion of the short arm of chromosome 17; BCL2: B-cell lymphoma 2; CLL: chronic lymphocytic leukaemia; ECOG-PS: Eastern Cooperative Oncology Performance Status; F: female; IGHV: immunoglobulin heavy chain variable region; IMiD: immunomodulatory imide drugs; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; SLL: small lymphocytic leukaemia; TP53 mutation: mutation of tumour protein p53

The patient characteristics were largely balanced between the study arms. The mean age of the patients was about 67 years, and female patients made up about 1/3 of participants. About 4% of enrolled patients were diagnosed with SLL. The vast majority (approximately 97%) of patients had an ECOG-PS of 0 or 1. See above for a further assessment of patient characteristics.

A small proportion (2%) of patients had received prior BCL2 inhibitor treatment. Hence, they do not correspond to the patient population analysed in research question 1 (patients who had received neither a BTK inhibitor nor a BLC2 inhibitor). Patients who had received no prior BTK inhibitor but at least 1 BCL2 inhibitor are analysed in research question 3 (see Section I 5).

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: zanubrutinib versus ibrutinib

Study **Duration of the study phase** **Outcome category**	**Zanubrutinib** **N = 327**	**Ibrutinib** **N = 325**
ALPINE		
Treatment duration[a] [months]		
Median [Q1; Q3]	28.4 [21.9; 34.5]	24.3 [15.0; 33.7]
Mean (SD)	26.9 (9.8)	23.5 (11.3)
Observation period [months]		
Overall survival[b]		
Median [95% CI]	32.9 [32.5; 33.2]	32.7 [32.2; 33.2]
Symptoms, health-related quality of life (EORTC QLQ-C30)		
Median [Q1; Q3]	27.7 [19.5; 33.3]	22.6 [15.8; 33.2]
Mean (SD)	25.6 (9.9)	22.9 (10.8)
Health status (EQ-5D VAS)		
Median [Q1; Q3]	27.7 [19.5; 33.3]	22.5 [15.8; 33.2]
Mean (SD)	25.6 (9.9)	22.9 (10.8)
Side effects		
Median [Q1; Q3]	28.5 [22.1; 34.5]	24.4 [15.9; 33.8]
Mean (SD)	26.9 (9.9)	23.8 (11.1)

a. Information is based on the safety population, which comprises all patients who had received any dose of the study medications (324 vs. 324 patients).
b. Median follow-up observation duration is calculated based on the inverse Kaplan Meier method.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life 5 Dimensions; N: number of randomized patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The treatment duration was comparable between the treatment arms. The shortened observation period for the outcomes of symptoms, health-related quality of life (HrQoL), health status, and side effects is particularly evident in the ibrutinib arm because these outcomes were surveyed only until disease progression or only for the period of treatment with the study medication (plus 30 days) (also see Table 8).

Information on subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: zanubrutinib versus ibrutinib (ALPINE)

Study Drug	Patients with subsequent therapy n (%)	
	Zanubrutinib N = 327	Ibrutinib N = 325
ALPINE		
Total	24 (7.3)	45 (13.8)
Cyclophosphamide	5 (1.5)	6 (1.8)
Ibrutinib	3 (0.9)	7 (2.2)
Acalabrutinib	2 (0.6)	6 (1.8)
Doxorubicin	5 (1.5)	3 (0.9)
BTK inhibitors	3 (0.9)	3 (0.9)
Dexamethasone	1 (0.3)	4 (1.2)
Bendamustine	1 (0.3)	1 (0.3)
Bendamustine hydrochloride	1 (0.3)	1 (0.3)
Chlorambucil	1 (0.3)	1 (0.3)
Venetoclax	8 (2.4)	22 (6.8)
Rituximab	10 (3.1)	14 (4.3)
Vincristine	5 (1.5)	3 (0.9)
Obinutuzumab	2 (0.6)	2 (0.6)
Prednisone	2 (0.6)	2 (0.6)
Methylprednisolone sodium succinate	0 (0.0)	3 (0.9)
Vincristine sulphate	0 (0.0)	2 (0.6)

a. Subsequent therapies which were administered in ≥ 2 patients.

BTK: Bruton's tyrosine kinase ; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Patients in both study arms were allowed to receive subsequent therapies without restrictions. Overall, 86 patients (25%) in the zanubrutinib arm and 134 patients (41%) in the ibrutinib arm discontinued treatment with the study medication. Among these, 24 patients (7.3%) in the intervention arm and 45 patients (13.8%) in the comparator arm had received a subsequent therapy by the 3rd data cutoff. The recommendations of the S3 guideline specify that even in the relapse scenario, therapy should be started only in case of clinical symptoms [15]; it is therefore plausible for only some of the patients to have received subsequent therapy. Among the subsequent therapies, venetoclax and rituximab were the most commonly administered drugs. About half of patients with subsequent therapy in the comparator arm versus about one-third in the intervention arm received venetoclax. Further, BTK inhibitors as well as different chemotherapies were used again. For relapse, the current guidelines recommend a combination of venetoclax + rituximab in addition to BTK inhibitors, each depending on prior therapy [14,16].

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: zanubrutinib versus ibrutinib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
ALPINE	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

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

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company reports that most ALPINE participants were from Europe or North America and of White ancestry and that the sex distribution corresponds to that of CLL patients in Germany. In addition, the company deems the treatment recommendations of the DGHO guideline, which applies in Germany, to be adequately implemented.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, measured with the symptom scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30)
  - health status, recorded using the EQ-5D VAS

- Health-related quality of life
  - surveyed with the EORTC QLQ-HCC18 functioning scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - infections and infestations (system organ class [SOC], AEs)
  - cardiac disorders (SOC, severe AEs)
  - bleeding (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ], AEs)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from the company's, which used further outcomes in the dossier (Module 4).

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

Table 13: Matrix of outcomes – RCT, direct comparison: zanubrutinib versus ibrutinib

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**	**Infections and infestations (SOC, severe AEs[a])**	**Cardiac disorders (SOC, severe AEs[a])**	**Haemorrhage (SMQ[b], AEs)**	**Further specific AEs[c]**
ALPINE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Not including events based on laboratory values.
c. The following event is taken into account (MedDRA coding): muscle spasms (PT, AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life 5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

SAEs, severe AEs and discontinuation due to AEs

The analyses of the outcomes of SAEs, severe AEs, and discontinuation due to AEs include events such as the PTs of anaemia, neutropoenia, and thrombocytopoenia, which may represent either side effects or reflect progression of the underlying illness. It is impossible to definitively determine to what extent the events which occurred are to be allocated to the outcome category of morbidity or side effects [17]. This has no consequence for the present benefit assessment.

Notes on the analyses of the side effects outcomes

The company presented time-to-event analyses for all side effects outcomes. Time-to-event analyses are of particular relevance in between-group comparisons with different mean observation periods [1]. In the current scenario, the mean observation durations are sufficiently comparable between the study arms (see Table 10).

In the assessment of side effects, the number of patients in whom an even occurred is primarily relevant. In addition, when analysing the time until occurrence of the event, effects may also result solely from an earlier or later occurrence of the event rather than on the basis of the proportions. For this reason, the analyses of relative risk are used in the present assessment for deriving added benefit.

I 3.2.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: zanubrutinib versus ibrutinib

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	Infections and infestations (SOC, severe AEs[a])	Cardiac disorders (SOC, severe AEs[a])	Haemorrhage (SMQ[b], AEs)	Further specific AEs[c]
ALPINE	L	L	H[d]	H[d]	H[d]	H[e, f]	H[e, f]	H[f, g]	H[e]	H[e]	H[d, e]	H[d, e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Not including events based on laboratory values.
c. The following event is taken into account (MedDRA coding): muscle spasms (PT, AEs).
d. Lack of blinding in subjective recording of outcomes.
e. Incomplete observations for potentially informative reasons.
f. Events included which may be either side effects or reflect progression of the underlying illness.
g. Lack of blinding in subjective decision for discontinuation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life 5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

There was a low risk of bias for the results of the outcome of overall survival. For the results on the outcomes from the morbidity, health-related quality of life, and side effects categories, the risk of bias was rated as high. With the outcomes which cannot be allocated to SAEs or severe AEs, the open-label study design leads to a high risk of bias. Observations are incomplete for the results on SAEs, severe AEs, and non-serious or non-severe specific AEs; this is due to the duration of follow-up observation being linked to the treatment duration as well as a potential relationship between the outcome and the reason for treatment discontinuation. In this context, the reasons for discontinuation are potentially informative and also in part differ between study arms (e.g. discontinuations due to progression: 7.3% versus 12.9%).

Summary assessment of the certainty of conclusions

The open-label RCT ALPINE is available for the assessment. The risk of bias is rated as high for all outcomes except overall survival. As described in Section I 3.1.2, the high proportion of patients with prior chemoimmunotherapy does not adequately reflect the current health care

context in Germany. This reduces the reliability of results. Thus, based on the results of the ALPINE study, only hints, e.g. of added benefit, can be derived in the present situation.

I 3.2.3 Results

Table 15 and Table 16 summarize the results on the comparison of zanubrutinib versus ibrutinib in patients with recurrent/refractory CLL.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix B of the full dossier assessment, and the Kaplan-Meier curves on the included outcomes are presented in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: zanubrutinib versus ibrutinib (multipage table)

Study Outcome category Outcome	Zanubrutinib N	Zanubrutinib Median time to event in months [95% CI][a] Patients with event n (%)	Ibrutinib N	Ibrutinib Median time to event in months [95% CI][a] Patients with event n (%)	Zanubrutinib vs. Ibrutinib HR [95% CI]; p-value[b]
ALPINE					
Mortality					
Overall survival	327	NR 48 (14.7)	325	NR 60 (18.5)	0.76 [0.51; 1.11]; 0.153
Morbidity					
Symptoms (EORTC QLQ-C30)[c]					
Fatigue	327	28.0 [22.6; NC] 141 (43.1)	325	30.4 [16.6; NC] 136 (41.8)	0.91 [0.72; 1.16]; 0.463
Nausea and vomiting	327	NR [36.0; NC] 78 (23.9)	325	NR 75 (23.1)	0.87 [0.64; 1.20]; 0.404
Pain	327	22.1 [16.6; 28.8] 161 (49.2)	325	14.1 [11.2; 19.6] 160 (49.2)	0.85 [0.69; 1.06]; 0.158
Appetite loss	327	NR 84 (25.7)	325	NR 78 (24.0)	0.90 [0.66; 1.23]; 0.515
Diarrhoea	327	NR 73 (22.3)	325	NR [36.1; NC] 89 (27.4)	0.68 [0.50; 0.93]; 0.015
Dyspnoea	327	39.4 [NC; NC] 96 (29.4)	325	43.7 [34.8; NC] 91 (28.0)	0.96 [0.72; 1.28]; 0.779
Insomnia	327	NR [30.5; NC] 117 (35.8)	325	NR [25.3; NC] 111 (34.2)	0.90 [0.70; 1.17]; 0.450
Constipation	327	NR [36.0; NC] 101 (30.9)	325	36.3 [36.1; NC] 81 (24.9)	1.16 [0.87; 1.55]; 0.322
Health status (EQ-5D VAS)[d]	327	NR 85 (26.0)	325	NR [35.9; NC] 91 (28.0)	0.80 [0.59; 1.07]; 0.128
Health-related quality of life					
EORTC QLQ-C30[c]					
General health status	327	39.4 [33.2; NC] 119 (36.4)	325	NR [24.9; NC] 116 (35.7)	0.89 [0.69; 1.15]; 0.366
Physical functioning	327	NR [33.1; NC] 118 (36.1)	325	NR [31.4; NC] 105 (32.3)	0.96 [0.74; 1.25]; 0.768
Role functioning	327	30.2 [19.9; NC] 148 (45.3)	325	30.5 [19.4; NC] 130 (40.0)	1.01 [0.80; 1.28]; 0.920
Cognitive functioning	327	22.1 [14.3; 25.0] 166 (50.8)	325	24.9 [16.7; NC] 138 (42.5)	1.09 [0.87; 1.36]; 0.470

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: zanubrutinib versus ibrutinib (multipage table)

Study Outcome category Outcome	Zanubrutinib N	Zanubrutinib Median time to event in months [95% CI][a] Patients with event n (%)	Ibrutinib N	Ibrutinib Median time to event in months [95% CI][a] Patients with event n (%)	Zanubrutinib vs. Ibrutinib HR [95% CI]; p-value[b]
Emotional functioning	327	NR [36.0; NC] 107 (32.7)	325	NR 91 (28.0)	1.02 [0.77; 1.35]; 0.873
Social functioning	327	27.7 [22.1; NC] 142 (43.4)	325	43.7 [30.6; NC] 107 (32.9)	1.23 [0.96; 1.59]; 0.102

a. Median time-to-event [95%] from Kaplan-Meier estimate.
b. HR and CI: Cox proportional hazards model; p-value: log-rank test. For overall survival: each stratified by age, region, refractory status, 17p deletion / TP53 mutation; for morbidity and health-related quality of life: each unstratified.
c. Time to first deterioration. A score decrease by ≥ 10 points (for the functioning scales) or an increase by ≥ 10 points (for the symptoms scales) from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
d. Time to first deterioration. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).

17p deletion: deletion in the short arm of chromosome 17; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; TP53 mutation: mutation of the p53 tumour protein; VAS: visual analogue scale

Table 16: Results (side effects) – RCT, direct comparison: zanubrutinib versus ibrutinib

Study Outcome category Outcome	Zanubrutinib		Ibrutinib		Zanubrutinib vs. Ibrutinib
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ALPINE					
Side effects[b]					
AEs (supplementary information)	324	318 (98.1)	324	321 (99.1)	–
SAEs	324	136 (42.0)	324	162 (50.0)	0.84 [0.71; 0.99]; 0.043
Severe AEs[c]	324	218 (67.3)	324	228 (70.4)	0.96 [0.86; 1.06]; 0.530
Discontinuation due to AEs	324	50 (15.4)	324	72 (22.2)	0.69 [0.50; 0.96]; 0.028
Infections and infestations (SOC, severe AEs[c])	324	86 (26.5)	324	91 (28.1)	0.95 [0.74; 1.22]; 0.753
Cardiac disorders (SOC, severe AEs[c])	324	17 (5.2)	324	31 (9.6)	0.55 [0.31; 0.97]; 0.038
Bleeding (SMQ[d], AEs)	324	137 (42.3)	324	134 (41.4)	1.02 [0.85; 1.23]; 0.875
Muscle spasms (PT, AEs)	324	10 (3.1)	324	41 (12.7)	0.24 [0.12; 0.48]; < 0.001

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [18]).
b. Information is based on the safety population, which comprises all patients who had received any dose of the study medications (324 vs. 324 patients).
c. Operationalized as CTCAE grade ≥ 3.
d. Excluding events based on laboratory values.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: standardized MedDRA query: SOC: System Organ Class

Based on the information available on the risk of bias and the patients' prior treatment, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 3.2.2).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. However, there is an effect modification by the characteristic of age (see Table 17). This results in a hint of added benefit of zanubrutinib compared to ibrutinib for patients < 65 years. For patients ≥ 65 years, there is no hint of added benefit of zanubrutinib compared to ibrutinib; thus there is no proof of added benefit.

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue, nausea and vomiting, pain, appetite loss, dyspnoea, insomnia, and constipation

No statistically significant difference between treatment groups was shown for any of the following outcomes: fatigue, nausea and vomiting, pain, appetite loss, dyspnoea, insomnia, and constipation. In each case, there is no hint of added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Diarrhoea

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for the outcome of diarrhoea. The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however (see Section I 3.3.1). This results in no hint of an added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There is no statistically significant difference between treatment groups for the outcome of health status, recorded with the EQ-5D VAS. This results in no hint of an added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

General health status, physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning

No statistically significant difference between treatment arms was shown for any of the outcomes of general health status, physical functioning, role functioning, emotional functioning, or social functioning. In each case, there is no hint of added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, there is a statistically significant difference in favour of zanubrutinib in comparison with ibrutinib. For each of these outcomes, this results in a hint of lesser harm from zanubrutinib in comparison with ibrutinib.

Severe AEs

There is no statistically significant difference between treatment groups for the outcome of severe AEs. This results in no hint of lesser or greater harm from zanubrutinib in comparison with ibrutinib; lesser or greater harm is therefore not proven.

Cardiac disorders (severe AEs)

A statistically significant difference in favour of zanubrutinib compared with ibrutinib was shown for the outcome of cardiac disorders (severe AEs). This results in a hint of lesser harm from zanubrutinib in comparison with ibrutinib.

Muscle spasms (AEs)

A statistically significant difference in favour of zanubrutinib compared with ibrutinib was shown for the outcome of muscle spasms (AEs). However, there is an effect modification by the characteristic of sex (see Table 17). For men, this results in a hint of lesser harm from zanubrutinib in comparison with ibrutinib. For women, this results in no hint of lesser or greater harm from zanubrutinib in comparison with ibrutinib; lesser or greater harm is therefore not proven.

Infections and infestations (severe AEs) and bleeding (AEs)

No statistically significant difference between treatment groups was shown for either of the outcomes infections and infestations (severe AEs) or bleeding (AEs). This results in no hint of lesser or greater harm from zanubrutinib in comparison with ibrutinib for any of them; lesser or greater harm is therefore not proven.

I 3.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- disease stage at baseline (Binet stage A/B and Ann Arbor stage I to II bulky versus Binet stage C and Ann Arbor stage III/IV)

The subgroup characteristics selected in the present benefit assessment had been defined a priori, but only for the primary outcome of ORR.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

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

Table 17 summarizes the subgroup results comparing zanubrutinib versus ibrutinib in patients with recurrent/refractory CLL.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the outcomes included are presented in I Appendix C of the full dossier assessment.

Table 17: Subgroups (overall survival, side effects) – RCT, direct comparison: zanubrutinib versus ibrutinib

Study Outcome Characteristic Subgroup	Zanubrutinib N	Zanubrutinib Median time to event in months [95% CI] Patients with event n (%)	Ibrutinib N	Ibrutinib Median time to event in months [95% CI] Patients with event n (%)	Zanubrutinib vs. ibrutinib HR [95% CI][a]	Zanubrutinib vs. ibrutinib p-value[b]
ALPINE						
Mortality						
Overall survival						
Age						
< 65years	126	NR 7 (5.6)	125	NR 19 (15.2)	0.35 [0.15; 0.82]	0.012
≥ 65 years	201	NR 41 (20.4)	200	NR 41 (20.5)	0.96 [0.62; 1.48]	0.851
Total					Interaction:	0.039[c]
Side effects						
Muscle spasms (PT, AE)						
Sex						
Male	212	– 3 (1.4)	231	– 30 (13.0)	RR[d]: 0.11 [0.03; 0.35]	< 0.001
Female	112	– 7 (6.3)	93	– 11 (11.8)	RR[d]: 0.53 [0.21; 1.31]	0.190
Total					Interaction:	0.037[e]

a. Unstratified Cox proportional hazards model.
b. Unstratified log-rank test.
c. Interaction test from Cox proportional hazards regression model, stratified by subgroup and interaction term between treatment and subgroup.
d. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [18]).
e. Institute's calculation, p-value from Q test for heterogeneity.

AE: adverse event; CI: confidence interval; CSZ: convex, symmetry, z-score; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; PT: preferred term; RCT: randomized controlled trial; RR: relative risk

Mortality

Overall survival

There is an effect modification by the characteristic of age for the outcome of overall survival. For patients < 65 years of age, a statistically significant difference was shown in favour of zanubrutinib versus ibrutinib. This results in a hint of added benefit of zanubrutinib in comparison with ibrutinib. There was no statistically significant difference between the treatment groups for patients ≥ 65 years. This results in no hint of an added benefit of zanubrutinib in comparison with ibrutinib; an added benefit is therefore not proven.

Side effects

Muscle spasms (AEs)

There was an effect modification by the characteristic of sex for the outcome of muscle spasms (AEs). A statistically significant difference in favour of zanubrutinib compared with ibrutinib was shown for men. For men, this results in a hint of lesser harm from zanubrutinib in comparison with ibrutinib.

For women, in contrast, no statistically significant difference between treatment groups was found. This results in no hint of greater or lesser harm of zanubrutinib in comparison with ibrutinib; greater or lesser harm is therefore not proven for women.

I 3.3 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 3.3.1 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 3.2 (see Table 18).

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

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification of these outcomes is justified as follows.

Symptoms

Diarrhoea (EORTC QLQ-C30)

For the outcome of diarrhoea, the severity data are insufficient to allow classifying them as serious/severe. The outcome of diarrhoea was therefore assigned to the outcome category non-serious/non-severe symptoms.

Side effects

Discontinuation due to AEs

For the ALPINE study, information is available on the severities of the AEs due to which treatment was discontinued. The outcome of discontinuation due to AEs is allocated to the outcome category of serious/severe side effects because, in over 80% of AEs leading to treatment discontinuation, an event was of CTCAE grade ≥ 3.

Table 18: Extent of added benefit at outcome level: zanubrutinib versus ibrutinib (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Zanubrutinib vs. ibrutinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Outcomes with observation throughout the study		
Mortality		
Overall survival		
Age		
< 65 years	Median: NR vs. NR HR: 0.35 [0.15; 0.82] p = 0.012 Probability: hint	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: major
≥ 65 years	Median: NR vs. NR HR: 0.96 [0.62; 1.48] p = 0.851	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	Median: 28.0 vs. 30.4 HR: 0.91 [0.72; 1.16] p = 0.463	Lesser/added benefit not proven
Nausea and vomiting	Median: NR vs. NR HR: 0.87 [0.64; 1.20] p = 0.404	Lesser/added benefit not proven
Pain	Median: 22.1 vs. 14.1 HR: 0.85 [0.69; 1.06] p = 0.158	Lesser/added benefit not proven
Appetite loss	Median: NR vs. NR HR: 0.90 [0.66; 1.23] p = 0.515	Lesser/added benefit not proven
Diarrhoea	Median: NR vs. NR HR: 0.68 [0.50; 0.93] p = 0.015 Probability: hint	Outcome category: non-serious/non-severe symptoms $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[c]
Dyspnoea	Median: 39.4 vs. 43.7 HR: 0.96 [0.72; 1.28] p = 0.779	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: zanubrutinib versus ibrutinib (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Zanubrutinib vs. ibrutinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Insomnia	Median: NR vs. NR HR: 0.90 [0.70; 1.17] p = 0.450	Lesser/added benefit not proven
Constipation	Median: NR vs. 36.3 HR: 1.16 [0.87; 1.55] p = 0.322	Lesser/added benefit not proven
Health status (EQ-5D VAS)	Median: NR vs. NR HR: 0.80 [0.59; 1.07] p = 0.128	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30		
General health status	Median: 39.4 vs. NR HR: 0.89 [0.69; 1.15] p = 0.366	Lesser/added benefit not proven
Physical functioning	Median: NR vs. NR HR: 0.96 [0.74; 1.25] p = 0.768	Lesser/added benefit not proven
Role functioning	Median: 30.2 vs. 30.5 HR: 1.01 [0.80; 1.28] p = 0.920	Lesser/added benefit not proven
Cognitive functioning	Median: 22.1 vs. 24.9 HR: 1.09 [0.87; 1.36] p = 0.470	Lesser/added benefit not proven
Emotional functioning	Median: NR vs. NR HR: 1.02 [0.77; 1.35] p = 0.873	Lesser/added benefit not proven
Social functioning	Median: 27.7 vs. 43.7 HR: 1.23 [0.96; 1.59] p = 0.102	Lesser/added benefit not proven
Side effects		
SAEs	Proportion of events: 42.0 vs. 50.0 RR: 0.84 [0.71; 0.99] p = 0.043 Probability: hint	Outcome category: severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor

Table 18: Extent of added benefit at outcome level: zanubrutinib versus ibrutinib (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Zanubrutinib vs. ibrutinib** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Severe AEs	Proportion of events: 67.3 vs. 70.4 RR: 0.96 [0.86; 1.06] p = 0.530	Greater/lesser harm not proven
Discontinuation due to AEs	Proportion of events: 15.4 vs. 22.2 RR: 0.69 [0.50; 0.96] p = 0.028 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Infections and infestations (severe AEs)	Proportion of events: 26.5 vs. 28.1 RR: 0.95 [0.74; 1.22] p = 0.753	Greater/lesser harm not proven
Cardiac disorders (severe AE)	Proportion of events: 5.2 vs. 9.6 RR: 0.55 [0.31; 0.97] p = 0.038 Probability: hint	Outcome category: severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Bleeding (AEs)	Proportion of events: 42.3 vs. 41.4 RR: 1.02 [0.85; 1.23] p = 0.875	Greater/lesser harm not proven
Muscle spasms (AEs)		
Sex		
Male	Proportion of events: 1.4 vs. 13.0 RR: 0.11 [0.03; 0.35] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Female	Proportion of events: 6.3 vs. 11.8 RR: 0.53 [0.21; 1.31] p = 0.190	Greater/lesser harm not proven

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. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

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

I 3.3.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Favourable and unfavourable effects from the assessment of zanubrutinib versus ibrutinib

Favourable effects	**Unfavourable effects**
Outcomes with observation throughout the study	
Mortality ▪ Overall survival: ▫ age < 65 years: hint of added benefit – extent: major	–
Outcomes with shortened observation period	
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: minor ▪ Discontinuation due to AEs: hint of lesser harm – extent minor ▪ Cardiac disorders (severe AEs): hint of lesser harm – extent: minor	–
Non-serious/non-severe side effects ▪ Muscle spasms (AEs): ▫ men: hint of lesser harm – extent: considerable	–
AE: adverse event; SAE: serious adverse event	

Overall, only favourable effects were found for zanubrutinib in comparison with ibrutinib. In the outcome category of mortality, a hint of added benefit of major extent was found for patients < 65 years of age,

In the outcome category of side effects, SAEs, severe AEs, and discontinuation due to AEs are each associated with hints of lesser harm of minor extent for the total population.

In summary, for patients < 65 years of age with recurrent/refractory CLL who have previously received neither a BTK inhibitor nor a BCL2 inhibitor, this results in a hint of major added benefit of zanubrutinib versus ibrutinib. For patients ≥ 65 years of age with recurrent/refractory CLL who have previously received neither a BTK inhibitor nor a BCL2 inhibitor, this results in a hint of minor added benefit of zanubrutinib versus ibrutinib.

I 4 Research question 2: patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor

I 4.1 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: 20 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

No relevant study was identified from the check.

I 4.2 Results on added benefit

The company did not submit any data for assessing the added benefit of zanubrutinib in comparison with the ACT for adult patients with recurrent/refractory CLL following prior therapy with at least 1 BTK inhibitor. This results in no hint of an added benefit of zanubrutinib in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 4.3 Probability and extent of added benefit

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor. An added benefit of zanubrutinib in comparison with the ACT is therefore not proven.

I 5 Research question 3: patients with recurrent/refractory CLL after prior therapy with at least 1 BCL2 inhibitor

I 5.1 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: 20 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

No relevant study was identified from the check. The company submitted the ALPINE study. The ALPINE study is described in detail in Section I 3. The study enrolled few patients with recurrent/refractory CLL after prior therapy with at least 1 BCL-2 inhibitor (zanubrutinib arm: N = 7; ibrutinib arm: N = 8). The company did not present any separate analyses for this small subpopulation. The ALPINE study is not relevant for the benefit assessment in patients with recurrent/refractory CLL following prior therapy with at least 1 BCL-2 inhibitor.

I 5.2 Results on added benefit

The company has not submitted any suitable data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL following prior therapy with at least 1 BCL2 inhibitor. This results in no hint of an added benefit of zanubrutinib in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 5.3 Probability and extent of added benefit

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL after prior therapy with at least 1 BTK2 inhibitor. An added benefit of zanubrutinib in comparison with the ACT is therefore not proven.

I 6 Research question 4: patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor

I 6.1 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: 20 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

No relevant study was identified from the check.

I 6.2 Results on added benefit

The company has not submitted any data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL following prior therapy with at least 1 BTK inhibitor and a BCL2 inhibitor. This results in no hint of an added benefit of zanubrutinib in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 6.3 Probability and extent of added benefit

The company has not presented any data for assessing the added benefit of zanubrutinib in comparison with the ACT in adult patients with recurrent/refractory CLL after prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor. An added benefit of zanubrutinib in comparison with the ACT is therefore not proven.

I 7 Probability and extent of added benefit – summary

Table 20 summarizes the result of the assessment of added benefit for zanubrutinib in comparison with the ACT.

Table 20: Zanubrutinib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
	Patients with recurrent/refractory CLL[b]		
1	Without prior therapy with a BTK inhibitor and/or BCL2 inhibitor[c]	▪ **Ibrutinib** or ▪ Venetoclax + rituximab or ▪ Chemoimmunotherapy with FCR or BR or ClbR (each only in patients with a long relapse-free interval and without genetic risk factors)[d]	Patients ▪ < 65 years: hint of major added benefit ▪ ≥ 65 years: hint of minor added benefit
2	After prior therapy with at least 1 BTK inhibitor	▪ Venetoclax + rituximab	Added benefit not proven
3	After prior therapy with at least 1 BCL2 inhibitor	▪ Ibrutinib	Added benefit not proven
4	After prior therapy with at least 1 BTK inhibitor and 1 BCL2 inhibitor	Individualized treatment selected from ▫ Idelalisib in combination with rituximab ▫ Bendamustine in combination with rituximab ▫ Chlorambucil in combination with rituximab and ▫ Best supportive care[e] ▪ taking into account comorbidities, general health, genetic risk factors[d] as well as the success of and tolerance to prior therapy	Added benefit not proven

Table 20: Zanubrutinib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective 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. In the present therapeutic indication, the G-BA presumes patients to be indicated for 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. In contrast to the other research questions, this one comprises patients who have received neither a BTK inhibitor nor a BCL2 inhibitor. Below, research question 1 will be referred to as “patients with recurrent/refractory CLL who have received neither a BTK inhibitor nor a BCL2 inhibitor”. d. According to current medical knowledge, the following are deemed genetic risk factors: presence of 17p deletion / TP53 mutation as well as unmutated IGHV. e. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. 17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; BCL2: B-cell lymphoma 2; BR: bendamustine in combination with rituximab; BTK: Bruton’s tyrosine kinase; ClbR: chlorambucil in combination with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of tumour protein p53			

The assessment described above deviates from the company’s assessment, which derived a hint of considerable added benefit for (a) patients with recurrent/refractory CLL who have received neither a BTK inhibitor nor a BCL2 inhibitor and (b) for patients with recurrent/refractory CLL after prior therapy with at least 1 BCL2 inhibitor.

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

I 8 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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. BeiGene. A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (ALPINE); Clinical Study Report (data cutoff date: 08 August 2022) [unpublished]. 2022.

4. BeiGene. A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (ALPINE); Clinical Study Report (data cut-off date: 01 December 2021) [unpublished]. 2022.

5. BeiGene. A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (ALPINE); Clinical Study Report (data cutoff date: 31 December 2020) [unpublished]. 2021.

6. A Study of Zanubrutinib (BGB-3111) Versus Ibrutinib in Participants With Relapsed/Refractory Chronic Lymphocytic Leukemia (ALPINE) [online]. 2022 [Accessed: 09.02.2023]. URL: https://clinicaltrials.gov/ct2/show/NCT03734016.

7. A Phase 3, Randomized Study of Zanubrutinib (BGB-3111) Compared with Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. EudraCT Number: 2018-001366-42 [online]. 2022 [Accessed: 09.02.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=bgb-3111-305.

8. Hillmen P, Eichhorst B, Brown JR et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. J Clin Oncol 2023; 41(5): 1035-1045. https://dx.doi.org/10.1200/JCO.22.00510.

9. Hillmen P, Brown JR, Eichhorst BF et al. ALPINE: zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Future Oncol 2020; 16(10): 517-523. https://dx.doi.org/10.2217/fon-2019-0844.

10. Brown JR, Eichhorst B, Hillmen P et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 2023; 388(4): 319-332. https://dx.doi.org/10.1056/NEJMoa2211582.

11. Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008; 111(12): 5446-5456. https://dx.doi.org/10.1182/blood-2007-06-093906.

12. Janssen-Cilag International. IMBRUVICA 140 mg/-280 mg/-420 mg/-560 mg [online]. 2022 [Accessed: 09.02.2023]. URL: https://www.fachinfo.de/suche/fi/022468.

13. BeiGene Ireland. BRUKINSA 80 mg Hartkapseln [online]. 2022 [Accessed: 09.02.2023]. URL: https://www.fachinfo.de/suche/fi/023639.

14. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Chronische Lymphatische Leukämie (CLL) [online]. 2023 [Accessed: 14.02.2023]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html.

15. Leitlinienprogramm Onkologie. S3-Leitlinie zur Diagnostik, Therapie und Nachsorge für Patienten mit einer chronischen lymphatischen Leukämie (CLL) [online]. 2018 [Accessed: 09.02.2023]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/CLL/LL_CLL_Langversion_1.0.pdf .

16. Eichhorst B, Robak T, Montserrat E et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021; 32(1): 23-33. https://dx.doi.org/10.1016/j.annonc.2020.09.019.

17. Hallek M, Cheson BD, Catovsky D et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018; 131(25): 2745-2760. https://dx.doi.org/10.1182/blood-2017-09-806398.

18. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

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