IQWiG Reports – Commission No. A20-104

Acalabrutinib (previously untreated chronic lymphocytic leukaemia; combination with obinutuzumab) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Acalabrutinib (nicht vorbehandelte chronische lymphatische Leukämie; Kombination mit Obinutuzumab) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 March 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
17p deletion	deletion of the short arm of chromosome 17
ACT	appropriate comparator therapy
AE	adverse event
CD	cluster of differentiation
CI	confidence interval
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FCR	fludarabine + cyclophosphamide + rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IGHV	immunoglobulin heavy-chain variable region
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
TP53 mutation	mutation of the tumour protein p53
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug acalabrutinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 November 2020.

Research question

The aim of the present report is the assessment of the added benefit of acalabrutinib in combination with obinutuzumab (hereinafter referred to as "acalabrutinib + obinutuzumab") in comparison with the appropriate comparator therapy (ACT) in patients with previously untreated chronic lymphocytic leukaemia (CLL).

For the present benefit assessment, the research questions presented in Table 2 resulted from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of acalabrutinib + obinutuzumab

Research question	Subindication[a]	ACT[b]
1	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is an option	FCR
2	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option	▪ Bendamustine in combination with rituximab or ▪ **chlorambucil in combination** with rituximab or **obinutuzumab**
3	Adult patients with previously untreated CLL with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

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

In the present assessment, the following terms are used for the patient populations of the 3 research questions:

- Research question 1: patients for whom treatment with fludarabine + cyclophosphamide + rituximab (FCR) is an option
- Research question 2: patients for whom treatment with FCR is not an option
- Research question 3: patients with deletion of the short arm of chromosome 17 (17p deletion) or mutation of the tumour protein p53 (TP53 mutation) or for whom chemo-immunotherapy is not indicated for other reasons

The company followed the specification of the ACT for the 3 research questions.

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

Results for research question 1: patients for whom treatment with FCR is an option

Results

In its dossier, the company did not present any data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT for patients for whom treatment with FCR is an option. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

Results for research question 2: patients for whom treatment with FCR is not an option

Study pool and study characteristics

The study pool for the benefit assessment of acalabrutinib + obinutuzumab in comparison with the ACT consists of the RCT ELEVATE-TN.

The ELEVATE-TN study is an ongoing, randomized, 3-arm, open-label phase 3 study comparing acalabrutinib or acalabrutinib + obinutuzumab with chlorambucil + obinutuzumab. The study included adult patients with previously untreated cluster of differentiation (CD)20+ CLL requiring treatment according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (2008). Patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2 and be ≥ 65 years of age or, if younger, meet at least one of the following criteria:

- presence of a renal function disorder (creatinine clearance 30 to 69 mL/min, estimated using the Cockcroft-Gault equation)
- presence of comorbidities (Cumulative Illness Rating Scale-Geriatric [CIRS-G] > 6)

A total of 179 patients each were randomized to the intervention arms acalabrutinib or acalabrutinib + obinutuzumab, and 177 patients to the comparator arm chlorambucil + obinutuzumab. Randomization was stratified by presence of 17p deletion (yes versus no), ECOG PS (0−1 versus 2) and geographical region (North America, Western Europe versus

others). The treatment arms acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab are relevant for the present benefit assessment.

The ELEVATE-TN study included patients irrespective of whether or not FCR therapy was an option for them. The company presented analyses for the relevant subpopulation of those patients for whom FCR therapy was unsuitable. These were 99 patients in the acalabrutinib + obinutuzumab arm and 95 patients in the chlorambucil + obinutuzumab arm.

Acalabrutinib was initially administered as monotherapy for one cycle, followed by 6 cycles in combination with obinutuzumab. Thereafter, acalabrutinib monotherapy could be continued until disease progression or occurrence of unacceptable toxicity. Chlorambucil and obinutuzumab were also each administered for a maximum of 6 cycles (28 days each), provided no disease progression or unacceptable toxicities occurred. If one component of the combination therapy was discontinued, the other component could be continued. The treatments were carried out in compliance with the recommendations of the Summaries of Product Characteristics (SPCs).

The primary outcome of the ELEVATE-TN study was progression-free survival (PFS). Secondary outcomes were overall survival and outcomes of the outcome categories of morbidity, health-related quality of life and side effects.

For the ELEVATE-TN study, 2 data cut-offs were available in the company's dossier:

- First data cut-off from 8 February 2019 (planned interim analysis on achieving a total of 111 PFS events in the study arms acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab or 24 months after randomization of the last patient).
- Second data cut-off from 1 August 2019 (not prespecified).

The company presented analyses only for the first data cut-off for the outcome categories of mortality, morbidity and health-related quality of life, and only for the second data cut-off for the outcome category of side effects. The data cut-offs considered by the company were used for the present benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for the ELEVATE-TN study.

There was a low risk of bias for the results of the outcome "overall survival". Overall, no data or no usable data were available for the outcome categories of morbidity and health-related quality of life. For this reason, the risk of bias for the outcomes of these outcome categories was not assessed. The risk of bias for the results of the outcomes of the outcome category of side effects was rated as high in each case.

Results

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Morbidity

Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue])

There were no usable data for the outcome "fatigue" recorded with the FACIT-Fatigue. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Disease-related symptoms

There were no analyses for the outcome "disease-related symptoms". This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

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

There were no usable data for the outcome "symptoms" recorded with the EORTC QLQ-C30 symptom scales. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

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

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (functional scales)

There were no usable data for the outcome "health-related quality of life" recorded with the EORTC QLQ-C30 functional scales. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Side effects

With regard to the results on side effects, it should be noted that the large differences in observation periods between the treatment arms mean that the hazard ratio (HR) only reflects approximately the first 7 months.

Serious adverse events (SAEs)

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of lesser or greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; lesser or greater harm is therefore not proven.

Severe adverse events [AEs] (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

Discontinuation due to AEs (≥ 1 component)

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "discontinuation due to AEs (≥ 1 component)". This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

Infections and infestations, cardiac disorders

No statistically significant difference between the treatment groups was shown for each of the outcomes "infections and infestations" and "cardiac disorders". This resulted in no hint of lesser or greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; in each case, lesser or greater harm is therefore not proven.

Haemorrhages

No HR using Cox regression could be calculated for the observed data on the outcome "haemorrhages" (severe AEs). Only 2 events occurred in the intervention arm. There was no statistically significant difference between the treatment groups. This resulted in no hint of lesser or greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; lesser or greater harm is therefore not proven.

Infusion related reaction

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "infusion related reaction". This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

Headache

A statistically significant difference to the disadvantage of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "headache". This

resulted in a hint of greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

Further specific AEs in favour of acalabrutinib + obinutuzumab

Nausea; blood and lymphatic system disorders; febrile neutropenia; metabolism and nutrition disorders; tumour lysis syndrome

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "nausea" (AE) and for each of the outcomes "blood and lymphatic system disorders" including "febrile neutropenia", and "metabolism and nutrition disorders" including "tumour lysis syndrome" (all severe AEs). This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for each of the outcomes "nausea", "blood and lymphatic system disorders", "febrile neutropenia" and "metabolism and nutrition disorders". The consideration of the Kaplan-Meier curves of the outcome "tumour lysis syndrome" showed an immediate decrease in the comparator group curve and an almost event-free, constant course of the intervention group curve. Linked with the size of the observed effect and the associated 95% CI, there was an indication of lesser harm from acalabrutinib in comparison with chlorambucil + obinutuzumab for tumour lysis syndrome.

Results for research question 3: patients with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Results

In its dossier, the company presented no data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT for patients with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab 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]

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

[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].

Research question 1: patients for whom treatment with FCR is an option

Since the company presented no data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT in patients for whom treatment with FCR is an option, an added benefit is not proven.

Research question 2: patients for whom treatment with FCR is not an option

In the overall consideration of the data, there are mainly positive effects of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. These effects were shown exclusively in the outcome category of side effects in serious/severe and in non-serious/non-severe side effects. Due to the high risk of bias, there is a hint of lesser harm with the extent "major" for the superordinate outcome of severe AEs (CTCAE grade ≥ 3). Among the severe AEs, there are several AEs at System Organ Class (SOC) and Preferred Term (PT) level in favour of acalabrutinib + obinutuzumab with considerable or major extent.

For the non-serious/non-severe side effects, there are hints of lesser harm of minor or considerable extent from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. In contrast, there is a disadvantage of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab in the outcome "headache".

There are no usable data for the outcome categories of morbidity and health-related quality of life.

In the present situation, the added benefit is thus based exclusively on differences in the category of side effects. A balancing of the effects under consideration of the outcome categories of morbidity and health-related quality of life is not possible, however, because data were not usable or not available. It is therefore not possible to assess whether and to what extent the advantages in side effects are also reflected in the morbidity and health-related quality of life of the patients. Due to the size of the observed effects in the side effects, however, it cannot be assumed that these can be completely questioned by the missing data in the outcome categories of morbidity and health-related quality of life. However, the extent of the added benefit cannot be assessed due to the lack of usable analyses on morbidity and health-related quality of life.

In summary, there is therefore a hint of a non-quantifiable added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option.

Research question 3: patients with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

Since the company presented no data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT in patients with 17p deletion or TP53 mutation or

for whom chemo-immunotherapy is not indicated for other reasons, an added benefit is not proven.

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

Table 3: Acalabrutinib + obinutuzumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is an option	FCR	Added benefit not proven
2	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option	▪ Bendamustine in combination with rituximab or ▪ **chlorambucil in combination** with rituximab or **obinutuzumab**	Hint of non-quantifiable added benefit
3	Adult patients with previously untreated CLL with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	Added benefit not proven

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

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

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of acalabrutinib in combination with obinutuzumab (hereinafter referred to as "acalabrutinib + obinutuzumab") in comparison with the ACT in patients with previously untreated CLL.

For the present benefit assessment, the research questions presented in Table 4 resulted from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of acalabrutinib + obinutuzumab

Research question	Subindication[a]	ACT[b]
1	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is an option	FCR
2	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option	▪ Bendamustine in combination with rituximab or ▪ **chlorambucil in combination** with rituximab or **obinutuzumab**
3	Adult patients with previously untreated CLL with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

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

In the present assessment, the following terms are used for the patient populations of the 3 research questions:

- Research question 1: patients for whom treatment with FCR is an option
- Research question 2: patients for whom treatment with FCR is not an option
- Research question 3: patients with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

The company followed the specification of the ACT for the 3 research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

2.3 Research question 1: patients for whom treatment with FCR is an option

2.3.1 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 acalabrutinib + obinutuzumab (status: 4 November 2020)
- bibliographical literature search on acalabrutinib + obinutuzumab (last search on 4 November 2020)
- search in trial registries/trial results databases for studies on acalabrutinib + obinutuzumab (last search on 4 November 2020)
- search on the G-BA website for acalabrutinib (last search on 4 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on acalabrutinib + obinutuzumab (last search on 2 December 2020)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of acalabrutinib + obinutuzumab versus the ACT.

2.3.2 Results on added benefit

In its dossier, the company did not present any data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT for patients for whom treatment with FCR is an option. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT in patients for whom treatment with FCR is an option, an added benefit is not proven.

In its dossier, the company did not make an assessment of the added benefit for this research question.

2.4 Research question 2: patients for whom treatment with FCR is not an option

2.4.1 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 acalabrutinib + obinutuzumab (status: 4 November 2020)
- bibliographical literature search on acalabrutinib + obinutuzumab (last search on 4 November 2020)
- search in trial registries/trial results databases for studies on acalabrutinib + obinutuzumab (last search on 4 November 2020)
- search on the G-BA website for acalabrutinib + obinutuzumab (last search on 4 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on acalabrutinib + obinutuzumab (last search on 2 December 2020)

The check did not identify any additional relevant studies.

2.4.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
ACE-CL-007 (ELEVATE-TN[c])	Yes	No[d]	Yes[d]	No[e]	Yes [3,4]	Yes [5]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. The study was sponsored by Acerta Pharma.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; FCR: fludarabine + cyclophosphamide + rituximab; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of acalabrutinib + obinutuzumab in comparison with the ACT consists of the RCT ELEVATE-TN and corresponds to the study pool of the company.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ELEVATE-TN	RCT, open-label, parallel	Adult patients with previously untreated CD20+ CLL requiring treatment[b] ▪ Age ▫ ≥ 65 years, or ▫ > 18 and < 65 years and meeting ≥ 1 of the following criteria: - creatinine clearance 30–69 mL/min[c] - CIRS-G > 6 ▪ ECOG PS 0–2	Intervention arm 1: acalabrutinib (N = 179)[d] Intervention arm 2: acalabrutinib + obinutuzumab (N = 179) Comparator arm: chlorambucil + obinutuzumab (N = 177) Relevant subpopulation thereof[e]: Intervention arm 2: acalabrutinib + obinutuzumab (n = 99) Comparator arm: chlorambucil + obinutuzumab (n = 95)	Screening: ≤ 28 days Treatment: ▪ 6 or 7 cycles[f] (28 days each) or until progression or unacceptable toxicity ▪ following the 6 or 7 cycles[f]: continued treatment until progression or unacceptable toxicity ▫ Intervention arms: acalabrutinib monotherapy ▫ Comparator arm: possible switch to acalabrutinib monotherapy[g] only after progression Observation[h]: outcome-specific, at most until end of study	142 centres in Australia, Belgium, Brazil, Canada, Chile, Columbia, France, Germany, Hungary, Israel, Italy, Lithuania, New Zealand, Poland, Spain, Sweden, United Kingdom, USA 9/2015–ongoing First data cut-off: 8 February 2019 (interim analysis) Second data cut-off: 1 August 2019[i]	Primary: progression-free survival Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Diagnosis and treatment requirement according to the iwCLL criteria (2008) [6].
c. Using the Cockcroft-Gault equation.
d. The arm is not relevant for the present assessment and is no longer presented in the following tables.
e. Patients for whom treatment with FCR is not an option.
f. In intervention arm 2, acalabrutinib was administered as monotherapy for 1 cycle before the start of the combination therapy; this was followed by the 6 cycles of combination therapy.
g. After confirmation of disease progression by the IRC and at the discretion of the investigator; administration then possible until disease progression or unacceptable toxicity.
h. Outcome-specific information is provided in Table 8.
i. According to information provided by the company, these are data that were prepared for the EMA as part of a safety update.

AE: adverse event; CD: cluster of differentiation; CIRS-G: Cumulative Illness Rating Scale-Geriatric; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; FCR: fludarabine + cyclophosphamide + rituximab; IRC: independent review committee; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study	Intervention	Comparison
ELEVATE-TN	Acalabrutinib 200 mg (2 x daily 100 mg), oral[a] + obinutuzumab, 1000 mg IV, for 6 cycles[b] ▪ cycle 2[c]: 100 mg on day 1, 900 mg on day 2, 1000 mg each on day 8 and day 15 ▪ cycles 3–7[c]: 1000 mg on day 1	Chlorambucil 0.5 mg/kg BW, orally on day 1 and day 15, for 6 cycles[b] + obinutuzumab, 1000 mg IV, for 6 cycles[b] ▪ cycle 1: 100 mg on day 1, 900 mg on day 2, 1000 mg each on day 8 and day 15 ▪ cycles 2–6: 1000 mg on day 1
	Treatment discontinuations ▪ treatment interruptions ≤ 28 days due to toxicity[d] allowed ▪ after multiple interruptions[e]: discontinuation of the respective study medication, the other study medication could be continued.	
	Dose adjustments after treatment interruptions	
	▪ acalabrutinib: after the first and second interruption, continuation of the therapy at the same dosage possible; after the third interruption, dose reduction to 100 mg/day[f] ▪ obinutuzumab: dose reduction not allowed	▪ chlorambucil: after the first interruption due to grade 3 or 4 cytopenia, continuation of the therapy at 75% of the original dose, after the second interruption, continuation of the therapy at 50% of the original dose[g] ▪ obinutuzumab: dose reduction not allowed
	Prior and concomitant treatment ▪ steroids as premedication for the administration of the study medication **Prohibited prior/concomitant treatment** ▪ any previous systemic CLL therapy (except local radiotherapy) ▪ systemic corticosteroids with a daily dose > 20 mg/day ≤ 1 week before the start of the study medication as well as steroids for leukaemia treatment or to lower the leukocyte count (except inhaled steroids for asthma treatment and topical steroids) ▪ warfarin or an equivalent vitamin K antagonist ≤ 7 days before start of study medication ▪ proton pump inhibitors ▪ strong CYP3A inhibitors and inducers ▪ vaccination with a live vaccine ≤ 4 weeks before start of study medication	

a. Acalabrutinib was administered until disease progression or unacceptable toxicity.
b. A treatment cycle comprises 28 days.
c. In the intervention arm, acalabrutinib was administered as monotherapy for 1 cycle before the start of the combination therapy.
d. Additional treatment interruption of acalabrutinib for other important clinical events had to be discussed with the medical monitor.
e. Acalabrutinib: after the fourth interruption, chlorambucil: after the third interruption or in case of treatment interruption > 28 days; obinutuzumab: no data.
f. If the reduced dosage was well tolerated for ≥ 4 weeks, a re-escalation to 200 mg/day was allowed at the discretion of the investigator.
g. Dose adjustments according to the respective guidelines of the local SPCs were also permitted to the investigators.

BW: body weight; CLL: chronic lymphocytic leukaemia; CYP3A: cytochrome P450 3A; FCR: fludarabine + cyclophosphamide + rituximab; IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The ELEVATE-TN study is an ongoing, randomized, 3-arm, open-label phase 3 study comparing acalabrutinib or acalabrutinib + obinutuzumab with chlorambucil + obinutuzumab. The study included adult patients with previously untreated CD20+ CLL requiring treatment according to iwCLL criteria (2008) [6]. Patients were required to have an ECOG PS of 0 to 2 and be ≥ 65 years of age or, if younger, meet at least one of the following criteria:

- presence of a renal function disorder (creatinine clearance 30 to 69 mL/min, estimated using the Cockcroft-Gault equation)
- presence of comorbidities (CIRS-G > 6)

A total of 179 patients each were randomized to the intervention arms acalabrutinib or acalabrutinib + obinutuzumab, and 177 patients to the comparator arm chlorambucil + obinutuzumab. Randomization was stratified by presence of 17p deletion (yes versus no), ECOG PS (0−1 versus 2) and geographical region (North America, Western Europe versus others). The treatment arms acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab as well as only a subpopulation of the ELEVATE-TN study are relevant for the present benefit assessment (for further details on the subpopulation, see below). The intervention arm in which acalabrutinib was administered as monotherapy was considered in the dossier assessment of acalabrutinib (A20-103 [7]).

In the relevant intervention arm, acalabrutinib was administered orally at a dose of 100 mg twice daily (total daily dose of 200 mg) until disease progression or unacceptable intolerance occurred, and obinutuzumab was administered intravenously at a dose of 1000 mg each for 6 cycles (28 days each).

Acalabrutinib was initially administered as monotherapy for one cycle, which was followed in cycle 2 by 6 cycles in combination with obinutuzumab. The use of acalabrutinib and obinutuzumab was in compliance with the recommendations in the SPCs; however, the combination treatment of both drugs is described exclusively in the SPC for acalabrutinib [8,9].

In the comparator arm, chlorambucil and obinutuzumab were each administered for a maximum of 6 cycles (28 days each), provided no disease progression or unacceptable toxicities occurred. The dosage of chlorambucil was dependent on body weight (0.5 mg/kg), obinutuzumab was administered at intravenous doses of 1000 mg each. According to the SPC, chlorambucil is approved as monotherapy for the treatment of CLL; its use as part of a combination therapy with obinutuzumab is not described [10]. However, the combination therapy of chlorambucil + obinutuzumab, including the dosing of chlorambucil, is included in the SPC of obinutuzumab [9]. Treatment with chlorambucil and obinutuzumab in the ELEVATE-TN study was in accordance with the recommendations of the SPCs [9,10].

The primary outcome of the ELEVATE-TN study was PFS. Secondary outcomes were overall survival and outcomes of the outcome categories of morbidity, health-related quality of life and side effects.

Treatment duration and follow-up observation

Treatment with acalabrutinib + obinutuzumab or with chlorambucil + obinutuzumab was for 6 cycles or until disease progression or the occurrence of unacceptable toxicity. If one component of the combination therapies was discontinued, the other component could be continued. After the maximum 6 cycles in the intervention arm, treatment with acalabrutinib as monotherapy was continued until disease progression or unacceptable toxicity occurred. After disease progression, patients in the comparator arm could receive monotherapy with acalabrutinib as subsequent therapy. This is an approved use because acalabrutinib as monotherapy can also be administered to patients with CLL who have received at least one pretreatment.

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ELEVATE-TN	
Mortality	
Overall survival	Until death, lost to follow-up or end of study
Morbidity	
Symptoms (FACIT-Fatigue, EORTC QLQ-C30), health status (EQ-5D VAS)	Until disease progression
Disease-related symptoms[a]	ND
Health-related quality of life (EORTC QLQ-C30)	Until disease progression
Side effects	
All outcomes in the category of side effects	Until 30 days after the last dose of the study medication

a. Weight loss, fever, night sweat, fatigue.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; FCR: fludarabine + cyclophosphamide + rituximab; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes of the outcome categories of morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded until disease progression or for the period of treatment with the study medication (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the

patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Data cut-offs and analyses

For the ELEVATE-TN study, 2 data cut-offs were available in the company's dossier:

- First data cut-off from 8 February 2019 (planned interim analysis on achieving a total of 111 PFS events in the study arms acalabrutinib + obinutuzumab and chlorambucil + obinutuzumab or 24 months after randomization of the last patient). As the efficacy criterion was achieved with the interim analysis, this data cut-off is the final data cut-off.
- Second data cut-off from 1 August 2019 (not prespecified). The company stated in the dossier that a safety update had been submitted to the European Medicines Agency (EMA) on this date.

The company presented analyses only for the first data cut-off for the outcome categories of mortality, morbidity and health-related quality of life, and only for the second data cut-off for the outcome category of side effects. The data cut-offs considered by the company were used for the present benefit assessment.

It is not clear from the information in the European assessment report that the data cut-off of 1 August 2019 for the assessment-relevant study ELEVATE-TN was requested by the EMA [11]. Nevertheless, the presentation of only the later data cut-off in the dossier of the company has no consequence for the analysis of side effects in the present assessment procedure. In the comparator arm, there was a fixed treatment duration of 6 months and a follow-up observation of 30 days. The last patient was enrolled on 8 February 2017. Thus, treatment and follow-up observation in the comparator arm was already completed by the first data cut-off (8 February 2019). Thus, only the events of the first 7 months since the start of the study were included in the effect estimations, as data from the comparator arm are only available for this period. It can therefore not be assumed that the effect estimations for the side effects differ between the 2 data cut-offs.

Subpopulation relevant for research question 2

The ELEVATE-TN study included patients irrespective of whether or not FCR therapy was an option for them. However, only those patients for whom chemo-immunotherapy is an option, but treatment with FCR is not, are relevant for the present research question 2.

In its dossier, the company presented analyses of a subpopulation for whom, from its point of view, treatment with FCR was not an option.

Approach of the company to form the relevant subpopulation

To form the subpopulation relevant for research question 2 from the total population of the ELEVATE-TN study, the company used various criteria (age, renal function, thrombocytopenia, anaemia, general condition, comorbidities, 17p deletion and/or TP53

mutation), which can cause unsuitability for FCR therapy. The company stated that patients with 17p deletion and/or TP53 mutation are neither suitable for treatment with FCR nor for another chemo-immunotherapy and were therefore excluded from the subpopulation of patients for whom treatment with FCR is not an option. When forming the subpopulation, the company considered the other criteria as follows:

- Sufficient criterion
  - presence of renal function disorder (creatinine clearance < 70 mL/min)
- Combined criteria (if ≥ 2 criteria are met, FCR therapy is no longer an option)
  - age ≥ 65 years
  - general condition: ECOG PS ≥ 2
  - comorbidities: CIRS-G > 6
  - anaemia and/or reduced platelet count

Taking into account the aforementioned criteria, the company therefore considered 194 (54.5%) of the 356 patients in the relevant study arms (acalabrutinib + obinutuzumab arm: N = 99; chlorambucil + obinutuzumab arm: N = 95) for the present research question.

Assessment of the approach of the company to form the relevant subpopulation

There is no consistent scientific consensus regarding the criteria for the suitability or unsuitability of therapy with FCR in patients with CLL. In its approach, the company considered criteria that are mentioned, for instance, in guidelines in connection with the decision on a suitable treatment [12-14].

The company itself justified the choice of its criteria on the basis of a previous benefit assessment procedure in the same therapeutic indication [15,16]. The criteria used by the company are considered sufficient for an adequate representation of the subpopulation relevant for research question 2.

The subpopulation formed by the company was included in the present benefit assessment as sufficient approximation to the subpopulation relevant for research question 2.

Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 2.

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study **Characteristic** **Category**	**Acalabrutinib + obinutuzumab** **N[a] = 99**	**Chlorambucil + obinutuzumab** **N[a] = 95**
ELEVATE-TN		
Age [years], mean (SD)	72 (8)	73 (7)
Sex [F/M], %	32/68	41/59
Region, n (%)		
North America	32 (32)	33 (35)
South America	4 (4)	2 (2)
Western Europe	31 (31)	29 (31)
Central/Eastern Europe	26 (26)	23 (24)
Australia/New Zealand	6 (6)	8 (8)
Family origin, n (%)		
White	88 (89)	88 (93)
Other[b]	11 (11)[c]	7 (7)[c]
ECOG PS, n (%)		
0–1	94 (95)	87 (92)
2	5 (5)	8 (8)
Disease duration: time between first diagnosis and randomization [months], median [min; max]	26.8 [0.4; 196.6]	35.4 [0.6; 207.7]
Creatinine clearance [mL/min], median [min; max]	64.5 [28.0; 151.0]	61.0 [30.0; 205.0]
Bulky disease[d], n (%)		
< 5 cm	74 (75)	64 (67)
≥ 5 cm	23 (23)	29 (31)
No measurable lymph nodes	2 (2)	2 (2)
Rai stage, n (%)		
0/I/II	37 (37)[c]	40 (42)[c]
III/IV	62 (63)[c]	55 (58)[c]
Beta 2 microglobulin, n (%)		
> 3.5 mg/L	79 (80)	79 (83)
≤ 3.5 mg/L	19 (19)	15 (16)
Missing	1 (1)	1 (1)
Cytopenia[e], n (%)	72 (73)	53 (56)
Disease-related symptoms[f], n (%)	47 (48)	45 (47)
Chromosome anomaly, n (%)		
17p deletion	0 (0)	0 (0)
11q deletion	18 (18)	15 (16)
TP53 mutation	0 (0)	0 (0)

Table 9: Characteristics of the relevant subpopulation – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study Characteristic Category	Acalabrutinib + obinutuzumab N[a] = 99	Chlorambucil + obinutuzumab N[a] = 95
IGHV status, n (%)		
Mutated	40 (40)	39 (41)
Unmutated	58 (59)	56 (59)
Missing	1 (1)	0 (0)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Composed of Native Americans or Alaskans, Black/African American or Asian family origin, or not reported.
c. Institute's calculation.
d. Only target lesions with a diameter of > 1.5 cm were evaluated. The assessment was made by the investigator.
e. Either neutrophil count ≤ 1,5 x 10^9/L or haemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L)
f. Summary of the following symptoms: weight loss, fever, night sweats, fatigue; the company does not specify the criteria for these symptoms.

11q deletion: deletion of the long arm of chromosome 11; 17p deletion: deletion of the short arm of chromosome 17; ECOG PS: Eastern Cooperative Oncology Performance Status; F: female; FCR: fludarabine + cyclophosphamide + rituximab; IGHV: immunoglobulin heavy-chain variable region; M: male; max.: maximum; min.: minimum; n: number of patients in the category; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TP53 mutation: mutation of the tumour protein p53; vs.: versus

Patient characteristics were sufficiently similar between the treatment groups. The mean ages of the patients were 72 and 73 years, and most study participants were male. Almost all patients were of white family origin and had an ECOG PS of 0 or 1. The median duration of disease at study inclusion was 27 months in the intervention arm and 35 months in the control arm. More than half of the patients had a prognostically unfavourable unmutated immunoglobulin heavy-chain variable region (IGHV) and advanced stage of the disease (Rai stage III or IV). There was no information on treatment or study discontinuation.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study **Duration of the study phase** **Outcome category**	**Acalabrutinib + obinutuzumab** **N = 99**	**Chlorambucil + obinutuzumab** **N = 95**
ELEVATE-TN		
Treatment duration [months]		
Median [Q1; Q3]	ND[a]	ND[a]
Mean (SD)	ND	ND
Observation period [months][b]		
Overall survival		
Median [min; max]	29.11 [ND]	29.11 [ND]
Mean (SD)	ND	ND
Morbidity		
Fatigue (FACIT-Fatigue), symptoms (EORTC QLQ-C30), health status (EQ-5D VAS)		
Median [min; max]	16.72 [ND]	11.27 [ND]
Mean (SD)	ND	ND
Disease-related symptoms[c]	ND[d]	ND[d]
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	16.72 [ND]	11.27 [ND]
Mean (SD)	ND	ND
Side effects		
Median [min; max]	34.1 [ND]	6.1 [ND]
Mean (SD)	ND	ND

a. The company's dossier contains no data for the relevant subpopulation; data (median [min; max]) for the total population: acalabrutinib + obinutuzumab arm (N = 179): 27.7 [25.0; 32.8] for acalabrutinib and 5.5 [5.5; 5.6] for obinutuzumab; chlorambucil + obinutuzumab arm (N = 177): 5.5 [5.5; 5.7] for chlorambucil and 5.6 [5.5; 5.9] for obinutuzumab.
b. For overall survival and the outcomes of the outcome categories of morbidity and health-related quality of life, the data are based on the data cut-off of 8 February 2019, for side effects on the data cut-off of 1 August 2019.
c. Weight loss, fever, night sweat, fatigue.
d. Outcome was recorded in the ELEVATE-TN study. No data for the relevant subpopulation are available in the company's dossier.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; FCR: fludarabine + cyclophosphamide + rituximab; max.: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

The company's dossier did not provide any data on treatment duration in the relevant study population. Based on the data on the total population of the ELEVATE-TN study, it can be seen

that the treatment in the intervention arm was about 5 times longer overall than in the comparator arm. This is due to the fact that in the intervention arm, after completion of the combination therapy with obinutuzumab as monotherapy acalabrutinib was to be administered until disease progression or unacceptable intolerances, whereas in the comparator arm, chlorambucil + obinutuzumab could be administered for a maximum of 6 cycles.

The median observation period for the outcome "overall survival" is comparable between the 2 study arms, whereas it is approximately 5 months longer in the intervention arm for the outcomes of the outcome categories of morbidity and health-related quality of life. These differences are due to the fact that these outcomes were recorded until disease progression, which occurred earlier in the comparator arm. Observation of side effects was about 6 times longer in the intervention arm than in the comparator arm. This is due to the fact that the follow-up observation for side effects was only planned up to 30 days after the last dose of the study medication and there were large differences in the treatment durations between the study arms.

Information on subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study Drug	Patients with subsequent therapy n (%)	
	Acalabrutinib + obinutuzumab N = 99	Chlorambucil + obinutuzumab N = 95
ELEVATE-TN		
Total	2 (2.0)	25 (26.3)
Acalabrutinib	0 (0)	19 (20.0)
Bendamustine	0 (0)	1 (1.1)
Anti-CD20 monoclonal antibodies	2 (2.0)	3 (3.2)
Ibrutinib	0 (0)	4 (4.2)
Investigational preparations	2 (2.0)	0 (0)
Steroids	0 (0)	1 (1.1)
PI3K inhibitor	1 (1.0)	0 (0)

CD: cluster of differentiation; FCR: fludarabine + cyclophosphamide + rituximab; n: number of patients with subsequent therapy; N: number of analysed patients; PI3K: phosphoinositide 3-kinase; RCT: randomized controlled trial; vs.: versus

Subsequent therapy was allowed for patients in both study arms after disease progression. Patients from the comparator arm with confirmed disease progression could receive acalabrutinib as monotherapy at the discretion of the investigator. In the relevant subpopulation, a total of 2 patients in the relevant intervention arm and 25 patients in the comparator arm received subsequent therapy until the first data cut-off (8 February 2019). The most common

subsequent therapy administered was acalabrutinib. This is an approved use because acalabrutinib as monotherapy can also be administered to patients with CLL who have received at least one pretreatment.

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ELEVATE-TN	Yes	Yes	No	No	Yes	Yes	Low
FCR: fludarabine + cyclophosphamide + rituximab; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the ELEVATE-TN study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that the median age of the patients in the ELEVATE-TN study and the sex distribution correspond to the values for patients with CLL in Germany [13,17]. In addition, the patients in the relevant subpopulation were mostly from Europe and North America. The company described that there were no indications of clinically significant differences between population groups and geographical regions within the study. According to the company, the study results were thus basically transferable to the German health care context.

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

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality

- overall survival

- Morbidity
  - fatigue (FACIT-Fatigue)
  - disease-related symptoms
  - symptoms measured with the EORTC QLQ-C30 symptom scales
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - infections and infestations (SOC, AEs)
  - cardiac disorders (SOC, AEs)
  - haemorrhages (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ], severe AEs)
  - infusion related reaction (PT, AEs)
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study	Outcomes													
	Overall survival	Fatigue (FACIT-Fatigue)	Disease-related symptoms	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, AEs)	Cardiac disorders (SOC, AEs)	Haemorrhages (SMQ, severe AEs[a])	Infusion related reaction (PT, AEs)	Further specific AEs[b]
ELEVATE-TN	Yes	No[c]	No[d]	No[c]	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): nausea (PT, AEs), headache (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), febrile neutropenia (PT, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3]), and tumour lysis syndrome (PT, severe AEs [CTCAE grade ≥ 3]).
c. No usable data available; for reasons, see Section 2.4.2.1.
d. No data available.

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

Analyses of the company on the patient-reported outcomes of fatigue (FACIT-Fatigue), symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30) cannot be used

In its dossier, the company presented both analyses of mean changes and responder analyses for the following outcomes: fatigue recorded with the FACIT-Fatigue, symptoms and health-related quality of life recorded with the EORTC QLQ-C30, and health status recorded with the EQ-5D VAS. None of these analyses is considered usable. This is justified as follows:

MMRM analyses on the instruments FACIT-Fatigue, EQ-5D VAS, EORTC QLQ-C30

For the analyses of mean changes, the company considered only time points with a response rate ≥ 70% in both study arms and a change from baseline for at least 10% of the patients in both study arms. In principle, the benefit assessment requires analyses that take into account all data recorded. In the present case, it cannot be estimated how analyses with all recorded data would differ from the results presented. In addition, it is not clear from the information provided by the company which criteria it used for the definition of the change and which time points

were not considered in the analysis due to the condition "change from baseline for at least 10% of the patients in both study arms".

Overall, the analyses of the mean change were assessed as not usable and were not used in the present benefit assessment.

Responder analyses on the instruments FACIT-Fatigue, EQ-5D VAS, EORTC QLQ-C30

As was the case in the analyses of mean changes, the company included only time points with a response rate of at least 70% in the responder analyses. This led to a non-consideration of a period of about one year, for which, however, data were available. In principle, the benefit assessment requires analyses that take into account all data recorded.

According to the company, in addition, patients were censored at the time point of the last recording before 2 or more missed visits if symptoms had progressed thereafter. If the progression of symptoms means that a deterioration by more than the respective response threshold had occurred, events would not have been counted, but patients with event would have been censored instead. This is not appropriate and no information is available on how many cases this approach affected.

Overall, the responder analyses were therefore assessed as not usable.

Irrespective of this, the response thresholds used by the company are not suitable.

As explained in the *General Methods* of the Institute [1,18], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). The response criteria chosen by the company (FACIT-Fatigue: time to improvement or deterioration by ≥ 3 points; EQ-5D VAS: time to improvement or deterioration by ≥ 7 points or by ≥ 10 points) do not meet these requirements. For the suitability of the response criterion of ≥ 10 points for the EORTC QLQ-C30 used by the company, see dossier assessment A20-97 [19].

Disease-related symptoms

Disease-related symptoms (fatigue, fever, night sweat, weight loss) were recorded during the course of the ELEVATE-TN study [5,11,20]. However, the company's dossier contained neither information on the operationalization nor analyses for this patient-relevant outcome.

2.4.2.2 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: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study		Outcomes													
	Study level	Overall survival	Fatigue (FACIT-Fatigue)	Disease-related symptoms	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, AEs)	Cardiac disorders (SOC, AEs)	Haemorrhages (SMQ, severe AEs[a])	Infusion related reaction (PT, AEs)	Further specific AEs[b]
ELEVATE-TN	L	L	–[c]	–[d]	–[c]	–[c]	–[c]	H[e]	H[e]	H[e, f]	H[e, f]	H[e, f]	H[e]	H[e, f]	H[e, f]

a. Operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): nausea (PT, AEs), headache (PT, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), febrile neutropenia (PT, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3]), and tumour lysis syndrome (PT, severe AEs [CTCAE grade ≥ 3]).
c. No usable data available; for reasons, see Section 2.4.2.1.
d. No data available.
e. When interpreting the results on side effects (second data cut-off on 1 August 2019, 30 months after inclusion of the last patient), it should be noted that the fixed treatment duration and the associated discontinuation of observation in the control arm mean that the hazard ratio only reflects approximately the first 7 months after randomization.
f. Unblinded study design. For the other specific side effects, this aspect only contributes to a high risk of bias if these are not severe side effects of CTCAE grade ≥ 3.

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

There was a low risk of bias for the results of the outcome "overall survival". The progression-related switch of 20% of the patients in the subpopulation from the comparator arm to monotherapy with acalabrutinib had no influence on the risk of bias. This use of acalabrutinib is also in compliance with the approval. This deviates from the assessment of the company, which assumed a high risk of bias for the results for this outcome due to the proportion of patients who switched treatment.

Overall, no data or no usable data were available for the outcome categories of morbidity and health-related quality of life (see Section 2.4.2.1). For this reason, the risk of bias for the outcomes of these outcome categories was not assessed. This deviates from the assessment of the company, which used the outcomes "fatigue" and "health status" as well as "symptoms"

and “health-related quality of life” recorded with the EORTC QLQ-C30 for the assessment and assumed a high risk of bias for each of these. The company did not consider the outcome “disease-related symptoms”; an assessment of the risk of bias by the company was not available.

The risk of bias for the results of the outcomes of the outcome category of side effects was rated as high in each case. In each case, this was due to the fixed treatment duration and the associated discontinuation of observation after 7 months in the comparator arm. For the outcomes that cannot be assigned to SAEs or severe AEs, the open-label study design is another aspect of bias. This concurs with the company’s assessment.

2.4.2.3 Results

Table 15 summarizes the results of the comparison of acalabrutinib + obinutuzumab with chlorambucil + obinutuzumab in patients with previously untreated CLL for whom treatment with FCR is not an option. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

Kaplan-Meier curves on the event time analyses are presented in Appendix A of the full dossier assessment. The results on the common AEs, SAEs and severe AEs, as well as on all AEs that led to treatment discontinuation are presented in Appendix B of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study **Outcome category** **Outcome**	**Acalabrutinib + obinutuzumab**		**Chlorambucil + obinutuzumab**		**Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
ELEVATE-TN					
Mortality					
Overall survival	99	NA 5 (5.1)	95	NA 10 (10.5)	0.46 [0.14; 1.31]; 0.151
Morbidity					
Fatigue (FACIT-Fatigue)	No usable data available[b]				
Disease-related symptoms	ND[c]				
EORTC QLQ-C30 – symptom scales	No usable data available[b]				
Health status (EQ-5D VAS)	No usable data available[b]				
Health-related quality of life					
EORTC QLQ-C30 – functional scales	No usable data available[b]				
Side effects					
AEs (supplementary information)	99	0.2 [0.1; 0.3] 96 (97.0)	91	0.0 [NC; NC] 90 (98.9)	–
SAEs	99	25.7 [14.8; NC] 53 (53.5)	91	NA 21 (23.1)	1.06 [0.60; 1.89]; 0.848
Severe AEs[d]	99	2.9 [1.8; 5.6] 77 (77.8)	91	0.5 [0.3; 1.1] 74 (81.3)	0.49 [0.34; 0.69]; < 0.001
Discontinuation due to AEs (≥ 1 component)	99	NA 16 (16.2)	91	NA 21 (23.1)	0.39 [0.18; 0.81]; 0.011
Infections and infestations (SOC, AEs)	99	8.2 [4.6; 13.0] 72 (72.7)	91	NA 44 (48.4)	0.92 [0.61; 1.39]; 0.695
Cardiac disorders (SOC, AEs)	99	NA 21 (21.2)	91	NA 6 (6.6)	1.33 [0.48; 3.98]; 0.584
Cardiac disorders (SOC, severe AEs[d])	*99*	*NA* *9 (9.1)*	*91*	*NA* *1 (1.1)*	*2.68 [0.34; 54.07];* *0.375*
Haemorrhages (SMQ[e], severe AEs[d])	99	NA 2 (2.0)	91	NA 0 (0)	NC; 0.346
Infusion related reaction (PT, AEs)	99	NA 15 (15.2)	91	NA 37 (40.7)	0.28 [0.15; 0.50]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study Outcome category Outcome	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Nausea (PT, AEs)	99	NA 18 (18.2)	91	NA 32 (35.2)	0.33 [0.17; 0.61]; < 0.001
Headache (PT, AEs)	99	NA 36 (36.4)	91	NA 14 (15.4)	2.66 [1.46; 5.11]; 0.002
Blood and lymphatic system disorders (SOC, severe AEs[d])	99	NA 47 (47.5)	91	2.9 [1.1; 5.7] 54 (59.3)	0.49 [0.32; 0.74]; < 0.001
Febrile neutropenia (PT, severe AEs[d])	99	NA 3 (3.0)	91	NA 6 (6.6)	0.15 [0.01; 0.85]; 0.038
Metabolism and nutrition disorders (SOC, severe AEs[d])	99	NA 10 (10.1)	91	NA 20 (22.0)	0.26 [0.10; 0.60]; 0.002
Tumour lysis syndrome (PT, severe AEs[d])	99	NA 1 (1.0)	91	NA 11 (12.1)	0.08 [0.00; 0.40]; 0.002

a. HR (incl. 95% CI) calculated using an unstratified Cox proportional hazards model. The p-value was calculated using an unstratified log-rank test.
b. Non-consideration of entire documentation time points; ambiguities regarding definition and effects of a censoring mechanism (see also Section 2.4.2.1)
c. Outcome was recorded in the ELEVATE-TN study. There are no analyses for the relevant subpopulation.
d. Operationalized as CTCAE grade ≥ 3.
e. The company does not specify in Module 4 B which events it has taken into account for the outcome "haemorrhage". According to the information from the European assessment report [11], it is assumed that this is the SMQ "haemorrhage".

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; FCR: fludarabine + cyclophosphamide + rituximab; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome "overall survival".

Despite the high risk of bias, indications, e.g. of lesser harm, can partly be determined for the outcomes of the outcome category of side effects because the certainty of results was partly not reduced due to the large number of early events and the clear difference between the treatment arms. Further information can be found in the description of the results below.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Fatigue (FACIT-Fatigue)

There were no usable data for the outcome "fatigue" recorded with the FACIT-Fatigue (see Section 2.4.2.1). This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

This corresponds in part to the assessment of the company, which did not determine any statistically significant and clinically relevant differences for this outcome based on its analyses. Overall, however, it derived a hint of an added benefit for all outcomes of the outcome category of morbidity considered jointly by the company.

Disease-related symptoms

There were no analyses for the outcome "disease-related symptoms" (see Section 2.4.2.1). This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

The company did not use this outcome in its assessment.

Symptoms (EORTC QLQ-C30)

There were no usable data for the outcome "symptoms" recorded with the EORTC QLQ-C30 symptom scales (see Section 2.4.2.1). This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

This differs from the assessment of the company, which, based on its analyses, saw a statistically significant difference between the treatment arms for the individual symptom diarrhoea and for financial difficulties. Overall, it derived a hint of an added benefit for all outcomes of the outcome category of morbidity considered jointly by the company.

Health status (EQ-5D VAS)

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.4.2.1). This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

This corresponds in part to the assessment of the company, which also did not determine any statistically significant and clinically relevant differences for this outcome based on its analyses. Overall, however, it derived a hint of an added benefit for all outcomes of the outcome category of morbidity considered jointly by the company.

Health-related quality of life

EORTC QLQ-C30 (functional scales)

There were no usable data for the outcome "health-related quality of life" recorded with the EORTC QLQ-C30 functional scales (see Section 2.4.2.1). This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

This concurs with the assessment of the company, which used the analyses, however.

Side effects

With regard to the results on side effects, it should be noted that the large differences in observation periods between the treatment arms mean that the HR only reflects approximately the first 7 months.

The company derived a hint of an added benefit for all superordinate side effect outcomes based on the results for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". It drew no conclusion on individual outcomes. For this reason, the following superordinate side effect outcomes (SAEs, severe AEs [CTCAE grade ≥ 3], discontinuation due to AEs [≥ 1 component]) are not described in terms of the extent to which the conclusion on the added benefit deviates from the assessment of the company.

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of lesser or greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; lesser or greater harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

Discontinuation due to AEs (≥ 1 component)

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "discontinuation due to AEs (≥ 1 component)". This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

Infections and infestations

No statistically significant difference between the treatment groups was shown for the outcome "infections and infestations". This resulted in no hint of lesser or greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; lesser or greater harm is therefore not proven.

This concurs with the company's assessment.

Cardiac disorders

No statistically significant difference between the treatment groups was shown for the outcome "cardiac disorders". This resulted in no hint of lesser or greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; lesser or greater harm is therefore not proven.

This concurs with the company's assessment.

Haemorrhages

No HR using Cox regression could be calculated for the observed data on the outcome "haemorrhages" (severe AEs), as no events occurred in the comparator arm. Only 2 events occurred in the intervention arm. There was no statistically significant difference between the treatment groups. This resulted in no hint of lesser or greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; lesser or greater harm is therefore not proven.

This concurs with the company's assessment.

Infusion related reaction

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "infusion related reaction". This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

The company did not use this outcome separately for the derivation of the added benefit.

Headache

A statistically significant difference to the disadvantage of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "headache". This

resulted in a hint of greater harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

The company did not use this outcome separately for the derivation of the added benefit.

Further specific AEs in favour of acalabrutinib + obinutuzumab

Nausea; blood and lymphatic system disorders; febrile neutropenia; metabolism and nutrition disorders; tumour lysis syndrome

A statistically significant difference in favour of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the outcome "nausea" (AE) and for each of the outcomes "blood and lymphatic system disorders" including "febrile neutropenia", and "metabolism and nutrition disorders" including "tumour lysis syndrome" (all severe AEs). This resulted in a hint of lesser harm from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for each of the outcomes "nausea", "blood and lymphatic system disorders", "febrile neutropenia" and "metabolism and nutrition disorders". The consideration of the Kaplan-Meier curves of the outcome "tumour lysis syndrome" showed an immediate decrease in the comparator group curve and an almost event-free, constant course of the intervention group curve. Linked with the size of the observed effect and the associated 95% CI, there was an indication of lesser harm from acalabrutinib in comparison with chlorambucil + obinutuzumab for tumour lysis syndrome.

Of these additional specific AEs, the company only considered the outcome "tumour lysis syndrome" separately as an AE of special clinical interest. For the AEs of special clinical interest, the company derived overall a hint of an added benefit.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (< 75 years versus ≥ 75 years)
- sex (male versus female)
- Rai stage at baseline (0/I/II versus III/IV)

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

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

In accordance with the methods described, no effect modification by age, sex or disease severity at study inclusion was identified for the outcomes for which usable analyses were available.

2.4.3 Probability and extent of added benefit

Probability and extent of the 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.

2.4.3.1 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 2.4.2 (see Table 16).

Determination of the outcome category for side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The outcome “discontinuation due to AEs” was assigned to the outcome category of non-serious/non-severe side effects because no information was available on the severity of the AEs that led to discontinuation of at least one treatment component.

Table 16: Extent of added benefit at outcome level: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Outcome category **Outcome**	**Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: NA vs. NA HR: 0.46 [0.14; 1.31]; p = 0.151	Lesser benefit/added benefit not proven
Morbidity		
Fatigue (FACIT-Fatigue)	No usable data available	Lesser benefit/added benefit not proven
Disease-related symptoms	No data available	Lesser benefit/added benefit not proven
EORTC QLQ-C30 – symptom scales	No usable data available	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data available	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – functional scales	No usable data available	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 25.7 vs. NA HR: 1.06 [0.60; 1.89]; p = 0.848	Greater/lesser harm not proven
Severe AEs[c]	Median: 2.9 vs. 0.5 HR: 0.49 [0.34; 0.69]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: “major”
Discontinuation due to AEs (≥ 1 component)	Median: NA vs. NA HR: 0.39 [0.18; 0.81]; p = 0.011 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.90 lesser harm, extent: “minor”
Infections and infestations (SOC, AEs)	Median: 8.2 vs. NA HR: 0.92 [0.61; 1.39]; p = 0.695	Greater/lesser harm not proven
Cardiac disorders (SOC, AEs)	Median: NA vs. NA HR: 1.33 [0.48; 3.98]; p = 0.584	Greater/lesser harm not proven
Haemorrhages (SMQ, severe AEs[c])	Median: NA vs. NA 2 (2.0) vs. 0 (0) patients HR: NC; p = 0.346	Greater/lesser harm not proven
Infusion related reaction (PT, AEs)	Median: NA vs. NA HR: 0.28 [0.15; 0.50]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”

Table 16: Extent of added benefit at outcome level: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Outcome category **Outcome**	**Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Nausea (PT, AEs)	Median: NA vs. NA HR: 0.33 [0.17; 0.61]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Headache (PT, AEs)	Median: NA vs. NA HR: 2.66 [1.46; 5.11]; p = 0.002 HR: 0.38 [0.20; 0.68][d]; probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Blood and lymphatic system disorders (SOC, severe AEs[c])	Median: NA vs. 2.9 HR: 0.49 [0.32; 0.74]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Febrile neutropenia (PT, severe AEs[c])	Median: NA vs. NA HR: 0.15 [0.01; 0.85]; p = 0.038 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Metabolism and nutrition disorders (SOC, severe AEs[c])	Median: NA vs. NA HR: 0.26 [0.10; 0.60]; p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Tumour lysis syndrome (PT, severe AEs[c])	Median: NA vs. NA HR: 0.08 [0.00; 0.40]; p = 0.002 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Operationalized as CTCAE grade ≥ 3.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; FCR: fludarabine + cyclophosphamide + rituximab; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Positive effects	Negative effects
Serious/severe side effects[a] ▪ Severe AEs: hint of lesser harm – extent: "major" including ▫ blood and lymphatic system disorders: hint of lesser harm – extent: "major" including - febrile neutropenia: hint of lesser harm – extent: "considerable" ▫ metabolism and nutrition disorders: hint of lesser harm – extent: "major" including - tumour lysis syndrome: indication of lesser harm – extent: "major"	–
Non-serious/non-severe side effects[a] ▪ discontinuation due to AEs: hint of lesser harm – extent "minor" ▪ infusion related reaction: hint of lesser harm – extent "considerable" ▪ nausea: hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects[a] ▪ headache: hint of greater harm – extent: "considerable"
There are no usable data for the outcome categories of morbidity and health-related quality of life.	
a. When interpreting the results on side effects, it should be noted that the great differences in observation periods between the treatment arms mean that the hazard ratio only reflects approximately the first 7 months. AE: adverse event; FCR: fludarabine + cyclophosphamide + rituximab	

In the overall consideration of the data, there are mainly positive effects of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. These effects were shown exclusively in the outcome category of side effects in serious/severe and in non-serious/non-severe side effects. Due to the high risk of bias, there is a hint of lesser harm with the extent "major" for the superordinate outcome of severe AEs (CTCAE grade ≥ 3). Among the severe AEs, there are several AEs at SOC and PT level in favour of acalabrutinib + obinutuzumab with considerable or major extent.

For the non-serious/non-severe side effects, there are hints of lesser harm of minor or considerable extent from acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. In contrast, there is a disadvantage of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab in the outcome "headache".

There are no usable data for the outcome categories of morbidity and health-related quality of life.

In the present situation, the added benefit is thus based exclusively on differences in the category of side effects. A balancing of the effects under consideration of the outcome categories of morbidity and health-related quality of life is not possible, however, because data were not usable or not available. It is therefore not possible to assess whether and to what extent the advantages in side effects are also reflected in the morbidity and health-related quality of life of the patients. Due to the size of the observed effects in the side effects, however, it cannot be assumed that these can be completely questioned by the missing data in the outcome categories of morbidity and health-related quality of life. However, the extent of the added benefit cannot be assessed due to the lack of usable analyses on morbidity and health-related quality of life.

In summary, there is therefore a hint of a non-quantifiable added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option.

This deviates from the assessment of the company, which derived a hint of a considerable added benefit for acalabrutinib + obinutuzumab.

2.5 Research question 3: patients with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons

2.5.1 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 acalabrutinib + obinutuzumab (status: 4 November 2020)
- bibliographical literature search on acalabrutinib + obinutuzumab (last search on 4 November 2020)
- search in trial registries/trial results databases for studies on acalabrutinib + obinutuzumab (last search on 4 November 2020)
- search on the G-BA website for acalabrutinib + obinutuzumab (last search on 4 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on acalabrutinib + obinutuzumab (last search on 2 December 2020)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of acalabrutinib + obinutuzumab versus the ACT.

2.5.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT for patients with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons. This resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT in patients with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons, an added benefit is not proven.

In its dossier, the company did not make an assessment of the added benefit for this research question.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of acalabrutinib + obinutuzumab in comparison with the ACT is summarized in Table 18.

Table 18: Acalabrutinib + obinutuzumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is an option	FCR	Added benefit not proven
2	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option	▪ Bendamustine in combination with rituximab or ▪ **chlorambucil in combination** with rituximab or **obinutuzumab**	Hint of non-quantifiable added benefit
3	Adult patients with previously untreated CLL with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	Added benefit not proven

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

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

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

References for English extract

Please see full dossier assessment for full reference list.

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

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