IQWiG Reports – Commission No. A20-105

Acalabrutinib (pretreated chronic lymphocytic leukaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Acalabrutinib (vorbehandelte chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 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
BCL-2 protein	B-cell lymphoma 2 protein
BTK	Bruton tyrosine kinase
CLL	chronic lymphocytic leukaemia
DGHO	Deutsche Gesellschaft für Hämatologie und medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TP53 mutation	mutation of the tumour protein p53

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 is 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 comparison with the appropriate comparator therapy (ACT) in adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

In accordance with the G-BA's specification of the ACT, 3 research questions resulted for the assessment. These are presented in Table 2.

Table 2: Research questions of the benefit assessment of acalabrutinib

Research question	Subindication[a]	ACT[b]
1	Adult patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is indicated	Patient-specific therapy[d] choosing from FCR, BR, venetoclax in combination with rituximab and ClbR
2	Adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy[c] is not indicated for other reasons	Ibrutinib or **idelalisib + rituximab** or best supportive care[e, f]
3	Adult patients with CLL after at least 2 prior therapies	Patient-specific therapy[d] choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR, ibrutinib in combination with BR, and best supportive care[f]

a. It is assumed that the patients require treatment and 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**.
c. Or therapy with rituximab in combination with venetoclax.
d. Taking into account the molecular-cytogenetic characteristics of the disease, the general condition and the success and tolerability of the prior therapy. For the implementation of patient-specific therapy, it is expected that a choice of several treatment options is available, allowing a patient-specific therapy decision (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
e. Only for patients with failure of a previous therapy with ibrutinib as monotherapy or idelalisib + rituximab.
f. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy;
BR: rituximab in combination with bendamustine; ClbR: rituximab in combination with chlorambucil;
CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide;
G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The company only investigated the following 2 research questions in its dossier:

- patients without deletion of the short arm of chromosome 17 (17p deletion) and/or without mutation of the tumour protein p53 (TP53 mutation) for whom chemo-immunotherapy is indicated and who have received at least one prior therapy, as well as
- patients with 17p deletion and/or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy.

For research question 1, the company specified a patient-specific chemo-immunotherapy as ACT and thus followed the specification of G-BA. However, the company chose bendamustine + rituximab as the exclusive treatment option.

For research question 2, the company chose idelalisib + rituximab as ACT from the treatment options presented and thus followed the specification of the G-BA for patients with one prior therapy.

The company did not investigate research question 3 separately, but considered the patients together with the subpopulations it had formed for research questions 1 and 2. However, the comparator therapies specified by the company do not correspond to the specification of the G-BA for research question 3.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

The randomized controlled trial (RCT) ASCEND was included in the benefit assessment for the assessment of the added benefit of acalabrutinib. This is a 2-arm, randomized, open-label, multicentre study comparing acalabrutinib with bendamustine + rituximab or idelalisib + rituximab, depending on the investigator's choice. The study included adult patients with relapsed or refractory CLL requiring treatment who had received at least one prior therapy. Patients pretreated with a B-cell lymphoma 2 protein (BCL-2 protein) inhibitor, a Bruton tyrosine kinase (BTK) inhibitor, or a phosphatidylinositol 3-kinase (PI3K) inhibitor were excluded from the study.

A total of 310 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms.

Before randomization, the investigators assessed for all patients whether they should receive either bendamustine + rituximab or idelalisib + rituximab in the comparator arm.

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

The subpopulations formed by the company are unsuitable to answer the research questions of the benefit assessment

The company used subpopulations of the ASCEND study in order to answer the research questions of the benefit assessment. However, the subpopulations formed by the company are not suitable for answering the 3 questions of the benefit assessment for the reasons described below.

For the derivation of the added benefit, the company formed subpopulations from the total number of patients included in accordance with its 2 research questions. In this approach, it assigned patients with at least one prior therapy who, at the discretion of the investigators, were to receive bendamustine + rituximab if randomized to the comparator arm (35 patients in the acalabrutinib arm, 36 in the comparator arm; referred to as "suitable for chemo-immunotherapy" in the company's dossier) to research question 1. The company's

subpopulation for research question 2 consisted of patients with at least one prior therapy who, at the discretion of the investigators, were to receive idelalisib + rituximab if randomized to the comparator arm (120 patients in the acalabrutinib arm, 119 in the comparator arm; referred to as "unsuitable for chemo-immunotherapy" in the company's dossier).

Allocation of patients with ≥ 2 prior therapies does not correspond to the present research questions

In addition to patients with one prior therapy, the 2 subpopulations considered by the company also included patients with ≥ 2 prior therapies. In accordance with the G-BA's specification of the ACT, the latter would have to be assigned to research question 3. However, the company did not investigate this research question.

For the present assessment, the analyses presented in the dossier are not suitable for assessing the added benefit of acalabrutinib in comparison with the ACT already due to the division of the patient populations without separate consideration of patients with ≥ 2 prior therapies.

Operationalization of the suitability for chemo-immunotherapy not comprehensible

Irrespective of the number of prior therapies, the assignment of patients with one prior therapy to the 2 subpopulations is also not comprehensible. For example, there is no information in the company's dossier on the criteria used by the investigators to assign patients to treatment with bendamustine + rituximab or idelalisib + rituximab in the ASCEND study. In addition, with the exception of the mutation status, the information in the company's dossier does not allow checking whether or to what extent the assignment of patients to the subpopulations was based on common criteria and, therefore, whether or not chemo-immunotherapy was suitable for these patients. However, already based on the information on cytogenetics and mutation status at baseline presented by the company in the dossier, it is doubtful that the allocation was at least made according to these criteria.

Overall, the operationalization of the subpopulations relevant here is not appropriate, as each of these subpopulations partly include patients who, according to the number of prior therapies received, their mutation status or their cytogenetics, would have to be assigned to another one of a total of 3 instead of 2 research questions.

No implementation of a patient-specific therapy in the ASCEND study

For research questions 1 and 3, the data presented by the company are not suitable for the assessment of the added benefit of acalabrutinib in comparison with the respective ACT, even beyond the reasons stated. The reason for this is that, in deviation from the ACT specified by the G-BA, the decision for the therapy option in the comparator arm was not made on an individual patient basis, but that all patients in the subpopulation operationalized by the company in research question 1 received chemo-immunotherapy with bendamustine + rituximab. Patients with ≥ 2 prior therapies, who would have to be assigned to research question 3, were treated with bendamustine + rituximab or idelalisib + rituximab. The company

did not explain why other therapy options specified by the G-BA were not considered for the patients.

Overall, the company thus did not present any relevant data in its dossier to assess the added benefit of acalabrutinib in adult patients with CLL who have received at least one prior therapy in comparison with the ACTs. This resulted in no hint of an added benefit of acalabrutinib in comparison with the ACT for all 3 research questions; 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 comparison with the ACT are assessed as follows:

The data presented by the company for the assessment of the added benefit of acalabrutinib in adult patients with CLL who have received at least one prior therapy are not suitable for deriving an added benefit of acalabrutinib in comparison with the ACTs. An added benefit of acalabrutinib is therefore not proven for all 3 research questions.

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

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

Table 3: Acalabrutinib – probability and extent of added benefit

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
1	Adult patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is indicated	Patient-specific therapy[d] choosing from FCR, BR, venetoclax in combination with rituximab and ClbR	Added benefit not proven
2	Adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy[c] is not indicated for other reasons	Ibrutinib or **idelalisib + rituximab** or best supportive care[e, f]	Added benefit not proven
3	Adult patients with CLL after at least 2 prior therapies	Patient-specific therapy[d] choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR, ibrutinib in combination with BR, and best supportive care[f]	Added benefit not proven

a. It is assumed that the patients require treatment and 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**.
c. Or therapy with rituximab in combination with venetoclax.
d. Taking into account the molecular-cytogenetic characteristics of the disease, the general condition and the success and tolerability of the prior therapy. For the implementation of patient-specific therapy, it is expected that a choice of several treatment options is available, allowing a patient-specific therapy decision (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
e. Only for patients with failure of a previous therapy with ibrutinib as monotherapy or idelalisib + rituximab.
f. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy;
BR: rituximab in combination with bendamustine; ClbR: rituximab in combination with chlorambucil;
CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide;
G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

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 comparison with the ACT in adult patients with CLL who have received at least one prior therapy.

In accordance with the G-BA's specification of the ACT, 3 research questions resulted for the assessment. These are presented in Table 4.

Table 4: Research questions of the benefit assessment of acalabrutinib

Research question	Subindication[a]	ACT[b]
1	Adult patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is indicated	Patient-specific therapy[d] choosing from FCR, BR, venetoclax in combination with rituximab and ClbR
2	Adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is not indicated for other reasons	Ibrutinib or **idelalisib + rituximab** or best supportive care[e, f]
3	Adult patients with CLL after at least 2 prior therapies	Patient-specific therapy[d] choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR, ibrutinib in combination with BR, and best supportive care[f]

a. It is assumed that the patients require treatment and 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**.
c. Or therapy with rituximab in combination with venetoclax.
d. Taking into account the molecular-cytogenetic characteristics of the disease, the general condition and the success and tolerability of the prior therapy. For the implementation of patient-specific therapy, it is expected that a choice of several treatment options is available, allowing a patient-specific therapy decision (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
e. Only for patients with failure of a previous therapy with ibrutinib as monotherapy or idelalisib + rituximab.
f. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy;
BR: rituximab in combination with bendamustine; ClbR: rituximab in combination with chlorambucil;
CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide;
G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53; vs.: versus

The company described that the G-BA had adjusted the ACT on 11 November 2020 as a result of a reassessment of the generally accepted state of medical knowledge. In accordance with the specification of the ACT, this resulted in 3 research questions instead of the 2 research questions discussed in the consultation. The company stated that the adjustment of the ACT by the G-BA

could not be taken into account in the dossier due to its short-term nature. It therefore only investigated the following 2 research questions in its dossier:

- patients without 17p deletion and/or TP53 mutation for whom chemo-immunotherapy is indicated and who have received at least one prior therapy, as well as
- patients with 17p deletion and/or TP53 mutation or patients for whom chemo-immunotherapy is not indicated for other reasons and who have received at least one prior therapy.

For research question 1, the company specified a patient-specific chemo-immunotherapy as ACT and thus followed the specification of G-BA. However, the company chose bendamustine + rituximab as the exclusive treatment option. The company did not justify this restriction to only one treatment option (see also Section 2.3.1).

For research question 2, the company chose idelalisib + rituximab as ACT from the treatment options presented and thus followed the specification of the G-BA for patients with one prior therapy.

The company did not investigate research question 3 separately, but considered the patients together with the subpopulations it had formed for research questions 1 and 2. However, the comparator therapies specified by the company do not correspond to the specification of the G-BA for research question 3.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on acalabrutinib (status: 4 November 2020)
- bibliographical literature search on acalabrutinib (last search on 4 November 2020)
- search in trial registries/trial results databases for studies on acalabrutinib (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 (last search on 2 December 2020)

The check did not identify any additionally relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: acalabrutinib vs. treatment of investigator's choice

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])
ASCEND	Yes	No	Yes	No[c]	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. 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; RCT: randomized controlled trial; vs.: versus

The company used the RCT ASCEND for the assessment of the added benefit of acalabrutinib (for the characterization of the study, see Table 10 in Appendix A of the full dossier assessment). This is a 2-arm, randomized, open-label, multicentre study comparing acalabrutinib with bendamustine + rituximab or idelalisib + rituximab, depending on the investigator's choice. It included adult patients with relapsed or refractory CLL requiring treatment according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (2008) [6] who had received at least one prior therapy. Patients pretreated with a BCL-2 protein inhibitor, a BTK inhibitor, or a PI3K inhibitor were excluded from the study.

A total of 310 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms. Randomization was stratified by 17p deletion status (yes versus no), Eastern Cooperative Oncology Group Performance Status ([ECOG PS]; ≤ 1 versus 2) and number of prior therapies (1–3 versus ≥ 4).

The company used subpopulations of the ASCEND study in order to answer the research questions of the benefit assessment. The following section describes the operationalization and relevance of these subpopulations.

Before randomization, the investigators assessed for all patients whether they should receive either bendamustine + rituximab or idelalisib + rituximab in the comparator arm. Patients in the intervention arm of the study received acalabrutinib in compliance with the Summary of Product Characteristics (SPC) [7].

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

The subpopulations formed by the company are unsuitable to answer the research questions of the benefit assessment

For the derivation of the added benefit, the company formed subpopulations from the total number of patients included in accordance with its 2 research questions. In this approach, it assigned patients with at least one prior therapy who, at the discretion of the investigators, were to receive bendamustine + rituximab if randomized to the comparator arm (35 patients in the acalabrutinib arm, 36 in the comparator arm; referred to as "suitable for chemo-immunotherapy" in the company's dossier) to research question 1. The company's subpopulation for research question 2 consisted of patients with at least one prior therapy who, at the discretion of the investigators, were to receive idelalisib + rituximab if randomized to the comparator arm (120 patients in the acalabrutinib arm, 119 in the comparator arm; referred to as "unsuitable for chemo-immunotherapy" in the company's dossier).

The data on the ASCEND study presented in the dossier are not suitable for assessing the added benefit of acalabrutinib in comparison with the respective ACT for any of the 3 research questions. This is justified below.

Allocation of patients with ≥ 2 prior therapies does not correspond to the present research questions

In addition to patients with one prior therapy, the 2 subpopulations considered by the company also included patients with ≥ 2 prior therapies. In accordance with the G-BA's specification of the ACT, the latter would have to be assigned to research question 3. However, the company did not investigate this research question.

The publication of the ASCEND study shows that about half of the patients in the overall population had received ≥ 2 prior therapies [5]. However, it is not clear from the data provided by the company how these patients are distributed between the 2 research questions of the company.

For the present assessment, the analyses presented in the dossier are therefore not suitable for assessing the added benefit of acalabrutinib in comparison with the ACT already due to the division of the patient populations without separate consideration of patients with ≥ 2 prior therapies. For this purpose, separate data corresponding to the 3 research question would have to be available.

Operationalization of the suitability for chemo-immunotherapy not comprehensible

Irrespective of the number of prior therapies, the assignment of patients with one prior therapy to the 2 subpopulations is also not comprehensible. The company assigned the patients to its 2 subpopulations (suitable for chemo-immunotherapy or unsuitable for chemo-immunotherapy) in accordance with the therapy with either bendamustine + rituximab or idelalisib + rituximab chosen for them by the investigators. However, there is no information in the company's dossier on the criteria used by the investigators to assign patients to treatment with bendamustine + rituximab or idelalisib + rituximab.

Based on the research questions, criteria in the second-line setting are number of prior therapies, cytogenetics (17p deletion) and mutation status (TP53 mutation), as well as suitability for chemo-immunotherapy. In addition to the criteria mentioned, the type of prior therapy, type and duration of response to prior therapy, side effects, contraindications, as well as comorbidities are further common characteristics that play a role in the choice of therapy [8-10]. Information on these characteristics for the subpopulations – with the exception of mutation status – is not available at all or is incomplete in the company's dossier. Thus, the information in the company's dossier does not allow checking whether or to what extent the assignment of patients to the subpopulations was based on common criteria and, therefore, whether or not chemo-immunotherapy was suitable for these patients.

However, already based on the information on cytogenetics and mutation status at baseline presented by the company in the dossier, it is doubtful that the allocation was at least made according to these criteria. For example, about 15% of the patients in the subpopulation 1 formed by the company had a 17p deletion or TP53 mutation. These are patients who would in principle have to be assigned to research question 2, although the therapy in the comparator arm (bendamustine + rituximab) does not correspond to the ACT of research questions 2. Furthermore, for example, more than 20% of the patients had a complex karyotype. According to guidelines, chemo-immunotherapy is no longer an option for these patients [8-10]. On the other hand, only 32% of the patients assigned to research question 2 had a 17p deletion or TP53 mutation and 33% had a complex karyotype. Whether chemo-immunotherapy was therefore not an option for all patients cannot be inferred from the information in the dossier. The company did not justify these deviations. For the present assessment, the assignment of patients with 1 prior therapy to the 2 subpopulations is therefore questioned.

In order to assess the added benefit of acalabrutinib in comparison with the ACT for the respective target population, it would be necessary to explain and justify the criteria used by the investigators to assign the patients to a therapy with bendamustine + rituximab or idelalisib + rituximab and by the company to ultimately assign the patients to subpopulation 1 or 2.

In summary, the operationalization of the subpopulations relevant here is not appropriate, as each of these subpopulations partly include patients who, according to the number of prior therapies received, their mutation status or their cytogenetics, would have to be assigned to another one of a total of 3 instead of 2 research questions. For this reason, the data presented are not suitable for assessing the added benefit of acalabrutinib in comparison with the ACT.

No implementation of a patient-specific therapy in the ASCEND study

For research questions 1 and 3, the data presented by the company are not suitable for the assessment of the added benefit of acalabrutinib in comparison with the respective ACT, even beyond the reasons stated. The reason for this is that, in deviation from the ACT specified by the G-BA, the decision for the therapy option in the comparator arm was not made on an individual patient basis, but that all patients in the subpopulation operationalized by the

company in research question 1 received chemo-immunotherapy with bendamustine + rituximab. Patients with ≥ 2 prior therapies, who would have to be assigned to research question 3, were treated with bendamustine + rituximab or idelalisib + rituximab. The company did not explain why other therapy options specified by the G-BA were not considered for the patients.

In the second-line setting, chemo-immunotherapy is listed as a treatment option in the CLL guidelines only in the case of late relapse [8-10]. In the case of good response and a remission duration of at least 2 to 3 years, the German Society for Haematology and Medical Oncology (DGHO) considers repeated chemo-immunotherapy only as a secondary therapy option [8]. For patients with refractory CLL, who were also included in the ASCEND study, treatment with chemo-immunotherapy is not a regular treatment option according to the guidelines [8-10]. At most, reasons for the repeated use of chemo-immunotherapy could therefore lie in the response to first-line therapy and the duration of remission. This cannot be inferred from the company's dossier, however.

For patients with ≥ 2 prior therapies, both therapies used in the ASCEND study in the comparator arm (bendamustine + rituximab and idelalisib + rituximab) are options for patient-specific therapy. However, it is necessary also for these patients that the company explains why the respective therapy corresponds to a patient-specific implementation of the ACT, taking into account the molecular-cytogenetic characteristics of the disease, the general condition, as well as the success and tolerability of the prior therapy.

Based on the information in the company's dossier, it cannot be verified whether bendamustine + rituximab and – only for research question 3 – idelalisib + rituximab are appropriate and patient-specific therapy options for all patients in research questions 1 and 3. In addition, the company did not discuss to what extent other therapy options that are available in principle were not considered for these patients.

Overall, the data presented by the company do not allow a comparison of acalabrutinib with the ACTs specified by the G-BA for each of the 3 research questions.

2.4 Results on added benefit

Overall, the company did not present any relevant data in its dossier to assess the added benefit of acalabrutinib in adult patients with CLL who have received at least one prior therapy in comparison with the ACTs. This resulted in no hint of an added benefit of acalabrutinib in comparison with the ACT for all 3 research questions; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The data presented by the company for the assessment of the added benefit of acalabrutinib in adult patients with CLL who have received at least one prior therapy are not suitable for deriving an added benefit of acalabrutinib in comparison with the ACTs. An added benefit of acalabrutinib is therefore not proven for all 3 research questions.

This deviates from the assessment of the company, which derived a hint of considerable added benefit on the basis of 2 subpopulations of the ASCEND study formed by the company.

The result of the assessment of the added benefit of acalabrutinib in comparison with the ACT is summarized in Table 6.

Table 6: Acalabrutinib – probability and extent of added benefit

Research question	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is indicated	Patient-specific therapy[d] choosing from FCR, BR, venetoclax in combination with rituximab and ClbR	Added benefit not proven
2	Adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is not indicated for other reasons	Ibrutinib or **idelalisib + rituximab** or best supportive care[e, f]	Added benefit not proven
3	Adult patients with CLL after at least 2 prior therapies	Patient-specific therapy[d] choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR, ibrutinib in combination with BR, and best supportive care[f]	Added benefit not proven

a. It is assumed that the patients require treatment and 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**.
c. Or therapy with rituximab in combination with venetoclax.
d. Taking into account the molecular-cytogenetic characteristics of the disease, the general condition and the success and tolerability of the prior therapy. For the implementation of patient-specific therapy, it is expected that a choice of several treatment options is available, allowing a patient-specific therapy decision (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
e. Only for patients with failure of a previous therapy with ibrutinib as monotherapy or idelalisib + rituximab.
f. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy;
BR: rituximab in combination with bendamustine; ClbR: rituximab in combination with chlorambucil;
CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide;
G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53; vs.: versus

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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