Gemeinsamer Bundesausschuss

# Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Acalabrutinib (Chronic lymphocytic leukaemia, after at least 1 previous treatment)

of 5 August 2021

**Contents**

## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient acalabrutinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 December 2020. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 November 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 March 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of acalabrutinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements

submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of acalabrutinib.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

## 2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

### 2.1.1 Approved therapeutic indication of acalabrutinib (Calquence) in accordance with the product information

Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior treatment.

**Therapeutic indication of the resolution (resolution of 05.08.2021):**

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior treatment.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

(a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

**Appropriate comparator therapy:**

- a patient-individual therapy under selection of
  - rituximab in combination with fludarabine and cyclophosphamide (FCR),
  - rituximab in combination with bendamustine (BR),
  - venetoclax in combination with rituximab and
  - rituximab in combination with chlorambucil (ClbR);

  taking into account the molecular-cytogenetic characteristics of the disease, the general condition as well as the success and tolerability of the previous therapy

1 General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

(b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons

**Appropriate comparator therapy:**

- Ibrutinib

*or*

- idelalisib in combination with rituximab

*or*

- best supportive care (only for patients who have failed prior therapy with ibrutinib or idelalisib in combination with rituximab)

(c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies

**Appropriate comparator therapy:**

- a patient-individual therapy under selection of
  - ibrutinib,
  - idelalisib in combination with rituximab,
  - venetoclax in combination with rituximab,
  - rituximab in combination with fludarabine and cyclophosphamide (FCR),
  - rituximab in combination with bendamustine (BR),
  - rituximab in combination with chlorambucil (ClbR),
  - ibrutinib in combination with BR and
  - best supportive care;

  taking into account the molecular-cytogenetic characteristics of the disease, the general condition as well as the success and tolerability of the previous therapy

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.

4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. Approved for this therapeutic indication are, in addition to acalabrutinib, the active ingredients bendamustine, chlorambucil, cyclophosphamide, fludarabine, ibrutinib (as a single agent or in combination with bendamustine and rituximab), idelalisib (in combination with rituximab), venetoclax (as a single agent or in combination with rituximab), rituximab (in combination with chemotherapy), prednisolone and prednisone. Chronic lymphocytic leukaemia is assigned to non-Hodgkin lymphoma. Accordingly, the drugs cytarabine, doxorubicin, etoposide, mitoxantrone, trofosfamide, vinblastine and vincristine are also approved. Some of the marketing authorisations are tied to specific combination preparations.

on 2. In the present therapeutic indication, allogeneic stem cell transplantation represents a non-medicinal treatment option. However, the G-BA expects for the present therapy situation that allogeneic stem cell transplantation is not indicated at the time of therapy, or eligible only in individual cases for a few patients and is therefore not included among the standard therapies in the therapeutic indication.

on 3. For the present therapeutic indication, resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- ibrutinib: resolutions of 21 July 2016 and 16 March 2017
- Idelalisib: resolutions of 15 September 2016 and 16 March 2017
- Venetoclax: resolutions of 16 May 2019

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

For the present therapeutic indication, it is presumed that the patients are in need of treatment (for example, stage C Binet).

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

On the basis of the available evidence, the G-BA considers it appropriate to divide patients with chronic lymphocytic leukaemia who have received at least one prior therapy into three relevant patient populations.

(a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

Patients without 17p deletion and/or TP53 mutation and eligible for chemoimmunotherapy may also benefit from the combination of a chemotherapeutic agent with rituximab in the second line of therapy. In guidelines, treatment with the BTK inhibitor ibrutinib, the BCL2 inhibitor venetoclax and the PI3Kdelta inhibitor idelalisib is recommended in addition to a

combination therapy consisting of a chemotherapeutic agent and rituximab. A treatment decision should be made taking into account the molecular-cytogenetic characteristics, the general condition as well as the success and tolerability of the previous therapy.

Under these conditions, for chemoimmunotherapy, rituximab in combination with fludarabine and cyclophosphamide (FCR), rituximab in combination with bendamustine (BR) and rituximab in combination with chlorambucil (ClbR) are possible treatment options included in the appropriate comparator therapy. Re-therapy with the active agents of the previous therapy is also possible in patients with late relapse.

An indication of a minor additional benefit was identified for venetoclax in combination with rituximab compared with the appropriate comparator therapy for patients without a 17p-deletion and/or TP53 mutation, for whom bendamustine in combination with rituximab is the appropriate patient-individual therapy (resolution of 16 May 2019).

An additional benefit of idelalisib in combination with rituximab and ibrutinib as a single agent is not proven for patients for whom chemotherapy is indicated in the approved therapeutic indication (resolutions of 21 July 2016 and 15 September 2016). Furthermore, no additional benefit was identified for ibrutinib in combination with BR compared with the appropriate comparator therapy for patients with prior therapy (resolution of 16 March 2017). Furthermore, no additional benefit was attested for idelalisib in combination with ofatumumab for the treatment of patients for whom chemotherapy is indicated (resolution of 16 March 2017). Ofatumumab is currently no marketing authorisation in Germany. The marketing authorisation was withdrawn at the request of the authorisation holder[2]. Ibrutinib (as a single agent and in combination in BR) and idelalisib in combination with rituximab and ofatumumab are currently not appropriate comparator therapies for the patient population.

Overall, the available evidence does not allow us to derive a standard therapy for patients after prior therapy who do not have a 17p deletion or TP53 mutation and for whom chemoimmunotherapy is indicated. The choice of treatment should be based on patient-individual factors, such as the molecular-cytogenetic characteristics of the disease, the general condition of the patient, and the success and tolerability of previous therapies.

Thus, a patient-individual therapy was determined as the appropriate comparator therapy for the present patient population, taking into account the molecular-cytogenetic characteristics of the disease, the general condition of the patient, and the success and tolerability of previous therapies. According to the statements, the therapy options FCR, BR, ClbR and venetoclax in combination with rituximab are considered suitable comparators in the context of a patient-individual therapy.

(b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons

Patients with a 17p deletion or TP53 mutation respond significantly worse to chemoimmunotherapy, and response is usually short-lived. Therefore, for patients with 17p deletion or TP53 mutation, chemoimmunotherapy is not considered a regularly appropriate therapeutic option and, therefore, not determined as an appropriate comparator therapy. Guidelines recommend treatment with the BTK inhibitor ibrutinib, the BCL2 inhibitor venetoclax, and the PI3Kdelta inhibitor idelalisib in the therapy situation.

2 https://www.ema.europa.eu/en/documents/public-statement/public-statement-arzerra-withdrawal-marketing-authorisation-european-union_en.pdf

For ibrutinib as a single agent (resolution of 21 July 2016) as well as for idelalisib in combination with rituximab (resolution of 15 September 2016), a hint for a non-quantifiable additional benefit is identified for patients not indicated for chemo-immunotherapy compared with best supportive care.

In a resolution dated 16 March 2017, no additional benefit was attested for idelalisib in combination with ofatumumab for the treatment of patients for whom chemotherapy is not indicated. Ofatumumab is currently no marketing authorisation in Germany. The marketing authorisation was withdrawn at the request of the authorisation holder[2]. Furthermore, no additional benefit was identified for venetoclax as monotherapy or in combination with rituximab compared with the appropriate comparator therapy for patients in the sub-population (resolution of 16 May 2019). In combination with ofatumumab and venetoclax, Idelalisib is currently not an appropriate comparator therapy for the present patient population.

After the failure of ibrutinib or idelalisib + rituximab in the primary treatment of CLL, there is no high-quality evidence for the benefit of changing therapy to the other B-cell receptor inhibitor. Nevertheless, especially considering the medical treatment situation of patients with a 17p deletion or TP53 mutation, subsequent therapy with ibrutinib or idelalisib + rituximab, depending on which active ingredient was used in the previous therapy, is considered a possible therapy alternative to best supportive care.

Best supportive care" (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

Ibrutinib, idelalisib + rituximab, and BSC (only for patients who have failed prior therapy with ibrutinib or idelalisib in combination with rituximab) are equally appropriate comparator therapies.

(c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies

The therapy of patients with chronic lymphocytic leukaemia who have already received at least two previous therapies is characterized by patient-individual treatment decisions. In guidelines, treatment with the BTK inhibitor ibrutinib, the BCL2 inhibitor venetoclax and the PI3Kdelta inhibitor idelalisib is recommended in addition to a combination therapy consisting of a chemotherapeutic agent and rituximab.

According to the recommendations from guidelines, the approved therapy options are rituximab in combination with fludarabine and cyclophosphamide (FCR), rituximab in combination with bendamustine (BR) and rituximab in combination with chlorambucil (ClbR) are used in the context of chemoimmunotherapy. Re-therapy with the active agents of the previous therapy is also possible in patients with late relapse.

An additional benefit for venetoclax as monotherapy has not been demonstrated for this sub-population in the approved therapeutic indication (resolution of 16 May 2019). Overall, venetoclax as monotherapy is not an appropriate comparator therapy for the sub-population.

For ibrutinib in combination with BR, a hint of considerable additional benefit compared with the appropriate comparator therapy was identified for patients with at least two prior therapies for whom BR represents the patient-individual optimised therapy (resolution of 16 March 2017).

For the agents ibrutinib as a single agent, venetoclax in combination with rituximab, and idelalisib in combination with rituximab and combination with ofatumumab, refer to the comments above under patient populations a) and b).

Due to the primarily palliative therapy situation in patients after more than two prior systemic therapies, the implementation of best supportive care in the context of a patient-individual treatment decision may also represent a treatment alternative. Best Supportive Care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

Overall, the available evidence does not allow the derivation of standard therapy for patients after at least two prior therapies. The choice of treatment should be based on patient-individual factors, such as the molecular-cytogenetic characteristics of the disease, the general condition of the patient, and the success and tolerability of previous therapies.

Thus, a patient-individual therapy was determined as the appropriate comparator therapy for the present patient population, taking into account the molecular-cytogenetic characteristics of the disease, the general condition of the patient, and the success and tolerability of previous therapies. According to the explanations, the therapy options ibrutinib, ibrutinib in combination with BR, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR and BSC are considered suitable comparators in the context of patient-individual therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

### 2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of acalabrutinib is assessed as follows:

a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

*a1) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom bendamustine in combination with rituximab is the appropriate patient-individual therapy*

An additional benefit is not proven.

Justification:

*Description of the ASCEND study*

The present benefit assessment of acalabrutinib is based on results from the pivotal, randomised, open-label, phase III ASCEND study comparing acalabrutinib with bendamustine + rituximab or idelalisib + rituximab, depending on the principal investigator. This is an ongoing (start of the study: February 2017), international, multicentre study conducted in 25 countries and 102 study sites.

Adult patients with relapsed or refractory CLL requiring treatment according to International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) criteria (2008) who received at least one prior treatment were included. Patients who were pretreated with a B-cell lymphoma 2 protein (BCL-2 protein) inhibitor, Bruton tyrosine kinase (BTK) inhibitor or phosphatidylinositol 3-kinase (PI3K) inhibitor were excluded from the study. The patients must have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 - 2.

A total of 310 patients were enrolled in the study, who were randomised in a 1:1 ratio to the two treatment arms. Prior to randomization, all patients were individually assessed as to whether they should receive either bendamustine + rituximab or idelalisib + rituximab in the

comparator arm. Randomization was stratified by 17p deletion status (yes vs no), ECOG-PS (≤ 1 vs 2), and the number of pretreatments (1-3 vs ≥ 4).

In the intervention arm, acalabrutinib was continued until disease progression or unacceptable toxicity. Patients treated with bendamustine + rituximab in the comparator arm received bendamustine as well as rituximab for six cycles of 28 days each. Patients treated with idelalisib + rituximab in the comparator arm received idelalisib until disease progression or unacceptable toxicity in combination with up to eight cycles of rituximab. After confirmed disease progression, patients could cross over from the comparator arm to the acalabrutinib arm and be treated until disease progression or unacceptable toxicity.

The primary endpoint of the study is progression-free survival (PFS). Furthermore, the overall survival, endpoints for morbidity, health-related quality of life and adverse events, amongst others, are surveyed.

For the ASCEND study, evaluations are available for two data cut-offs: The first data cut-off from 15 January 2019 is an *a priori* planned evaluation according to 79 PFS events. The second data cut-off, dated 1 August 2019, is a request from EMA as part of a safety update. The final analysis is planned after 119 PFS events. For the endpoint categories morbidity and health-related quality of life, evaluations are only available for the first data cut-off, for the endpoint categories mortality and side effects only for the second data cut-off.

*Sub-populations of the ASCEND study submitted by the pharmaceutical company*

For the benefit assessment, the pharmaceutical company presents in its dossier evaluations of two sub-populations of the ASCEND study: a) patients with at least one prior treatment who, at the discretion of the principal investigators, should receive bendamustine + rituximab at randomisation into the comparator arm and b) patients with at least one prior treatment who, at the discretion of the principal investigators, should receive idelalisib + rituximab at randomisation into the comparator arm. Accordingly, the evaluations presented in the dossier do not correspond to the patient populations according to the defined appropriate comparator therapy of the G-BA.

The pharmaceutical company describes in his dossier that the notification of the G-BA on the re-determination of the appropriate comparator therapy occurred shortly before the relevant date for the submission of the dossier. Due to the short-term nature of the study, corresponding adjustments with regard to the patient populations could not be taken into account in the dossier. Within the framework of the written statement procedure, the pharmaceutical company presents evaluations on sub-populations of the ASCEND study for the patient populations a), b) and c). The G-BA commissioned the IQWIG to carry out the assessment of the sub-populations. These will be used for the present assessment.

Sub-population submitted by the pharmaceutical company for the assessment of the patient population a)

For the proof of additional benefit in patient population a), the pharmaceutical company used the results of the ASCEND study described above. For this purpose, the pharmaceutical company submitted results from a sub-population of those patients with prior therapy who, at the principal investigator's discretion, should receive bendamustine + rituximab at randomisation into the comparator arm. In the intervention arm, 17 patients remain for the evaluation and in the comparator arm, 19 patients. Almost all patients in the sub-population formed by the pharmaceutical company did not have a 17p deletion or TP53 mutation at the start of the study.

*Implementation of the appropriate comparator therapy:*

Relapse therapy depends on several individual factors. These are the success and tolerability of the pre-treatment, the general condition of the patient and the molecular-cytogenetic characteristics of the disease. There is neither sufficient plausible information in the dossier of the pharmaceutical company nor in the documents of its written statement based on which criteria patients were assigned to therapy with bendamustine + rituximab in the ASCEND study and why bendamustine + rituximab is the appropriate patient-individual therapy for the patients compared to the other therapy options considered.

The patients included in the study have already received chemoimmunotherapy in the previous therapy. According to guideline recommendations, renewed chemoimmunotherapy is only considered in patients with late relapse. Reasons for a renewed treatment with chemoimmunotherapy reside, therefore, especially in the remission duration. The pharmaceutical company does not provide any information on this.

In the ASCEND study, the investigator had a choice of treatment options consisting of chemoimmunotherapy (bendamustine + rituximab) and non-chemoimmunotherapy (idelalisib + rituximab). It can be assumed that the choice between these two therapy options was made according to medical expertise and therefore represents the individually suitable therapy option for the patient with regard to the suitability of chemoimmunotherapy.

According to the guidelines, molecular cytogenetic characteristics should be taken into account in the treatment decision. The decision-making criteria in this respect are currently in a state of flux. In addition to a 17p deletion and TP53 mutation, immunoglobulin heavy chain variable region (IGHV) mutational status and complex karyotype are increasingly playing a role. According to the clinical experts' comments in the written statement procedure, chemoimmunotherapy is not indicated in patients with an unmutated IGHV and a complex karyotype in relapse. However, the majority of patients in the sub-population had unmutated IGHV at the start of the study (59% of patients in the intervention arm, 84% of patients in the comparator arm). In addition, 29% of patients in the intervention arm and no patient in the comparator arm had a complex karyotype. The sub-population considered by the pharmaceutical company comprises predominantly patients for whom, according to the statements of the clinical experts in the written statement procedure, a therapy with bendamustine in combination with rituximab is no longer recommended. This is not further justified by the pharmaceutical company.

However, the G-BA assumes overall that chemoimmunotherapy with bendamustine in combination with rituximab is an adequate therapy option for the majority of patients in the sub-population formed by the pharmaceutical company. Nevertheless, the other therapy options of the appropriate comparator therapy are not shown. Consequently, the results of the ASCEND study cannot be used to derive an additional benefit in the entire sub-population a). The division of the population into patients for whom bendamustine in combination with rituximab represents the appropriate patient-individual therapy (a1) and patients for whom a therapy other than bendamustine in combination with rituximab represents the appropriate patient-individual therapy (a2) is therefore appropriate.

Extent and probability of the additional benefit

Mortality

*Overall survival*

In the ASCEND study, the endpoint overall survival is defined as the time from randomisation to death from any cause.

There are no signs of statistically significant differences between both treatment groups.

Morbidity

*Progression-free survival*

Progression-free survival (PFS) is the primary endpoint in the ASCEND study and was assessed by an independent review committee (IRC) according to iwCLL criteria. The PFS is operationalised as the time from randomisation to disease progression or death from any cause.

There are no signs of statistically significant differences between both treatment groups.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The morbidity component "Disease progression" is assessed according to iwCLL criteria and thus predominantly by means of laboratory parametric, imaging and haematological procedures.

Considering the aspects mentioned above, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

*Fatigue (FACIT-Fatigue)*

In the ASCEND study, FACIT fatigue was assessed until disease progression.

The pharmaceutical company presented responder analyses operationalised as the time to first improvement or deterioration by ≥ 15% of scale range compared to baseline (Global Fatigue Score: ≥ 7.8 points [scale range: 0-52]), which cover all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses operationalised as the time to first deterioration by ≥ 15% of scale range compared with baseline are considered. There are no statistically significant differences between the treatment groups.

The evaluations of the pharmaceutical company regarding the subscales Fatigue Symptomatology Score and Fatigue Impact Score presented in the written statement procedure are not used due to a lack of information on the evaluation of subscales of the FACIT-Fatigue.

*Disease-related symptomatology*

In the ASCEND study, disease-related symptomatology (fatigue, fever, night sweats, weight loss) were recorded during the course of the study.

The pharmaceutical company submits evaluations for the endpoint "disease-related symptoms". These included the following symptoms in the ASCEND study: unintentional weight loss of ≥ 10% within the past 6 months, significant fatigue (e.g., Eastern Cooperative Oncology Group Performance Status [ECOG-PS] ≥ 2, inability to work or perform usual activities), fever > 38 °C for more than 2 weeks without evidence of infection and night sweats for more than 1 month without evidence of infection.

The pharmaceutical company submits evaluations operationalised as the time to the first absence of any disease-related symptoms of patients who had at least one disease-related symptom at the start of the study. Thus, only 9 patients in the acalabrutinib arm (53% of patients) and 9 patients in the bendamustine + rituximab comparator arm (47% of patients) were included in the analyses. Therefore, a statement for all patients of the relevant sub-population is not possible, and the presented evaluations are not used.

*Symptomatology (EORTC QLQ-C30)*

In the ASCEND study, the symptomatology was assessed using the EORTC QLQ-C30 symptom scales until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline. There are no statistically significant differences between the treatment groups.

*Health status (EQ-5D VAS)*

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline. There are no signs of statistically significant differences between the treatment groups.

<u>Quality of life</u>

*EORTC QLQ-C30 (functional scales)*

Health-related quality of life will be assessed in the ASCEND study using the EORTC QLQ-C30 functional scales until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline. There are no statistically significant differences between the treatment groups.

Side effects

Endpoints in the category side effects were collected up to 30 days after the end of treatment.

*Adverse events (AE) in total*

Nearly all study participants experienced an adverse event. These are only presented in a supplementary manner.

*Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuations due to AEs (≥ 1 component)*

With regard to SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs (≥ 1 component), there was no statistically significant difference between the treatment groups.

*Specific AEs*

In detail, the analysis of the specific adverse events for the endpoints "diarrhoea" (PT, AE) and "neutropenia" (PT, severe AE [CTCAE grade ≥ 3]), there was a statistically significant difference in the benefit of acalabrutinib compared to bendamustine + rituximab.

For the endpoint "headache" (PT, AEs), there is a statistically significant difference to the disadvantage of acalabrutinib compared to bendamustine + rituximab.

For the endpoints "infections and infestations" (SOC, severe AE [CTCAE grade ≥ 3]) and "bleeding", there was no statistically significant difference between the treatment groups.

No usable data are available for the endpoint "cardiac disorders" (SOC, AE).

Overall, neither an advantage nor a disadvantage is identified for the endpoint category side effects.

Overall assessment

For the assessment of the additional benefit of acalabrutinib for the treatment of adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy, results are available for the endpoint categories mortality, morbidity, health-related quality of life and side effects.

The basis of the evaluation is the ASCEND study, which compares acalabrutinib with bendamustine + rituximab or idelalisib + rituximab, depending on the principal investigator's choice. The results of a sub-population of patients after prior therapy for whom chemoimmunotherapy is indicated are relevant for the evaluation. Data comparing acalabrutinib versus bendamustine in combination with rituximab are available for this sub-population.

For overall survival, there is no statistically significant difference between the treatment groups.

There were no statistically significant differences between the treatment groups for the endpoints of the morbidity category, assessed by the FACIT-Fatigue, EORTC-QLQ-C30 and the EQ-5D visual analogue scale.

There were also no statistically significant differences between the treatment groups for the endpoints of the health-related quality of life category, assessed by the EORTC-QLQ-C30.

In the category side effects, there were no statistically significant differences between treatment arms for the endpoints serious adverse events, severe adverse events (CTCAE grade ≥ 3), and therapy discontinuations due to adverse events. In detail, the specific adverse events for the endpoints "diarrhoea" (PT, AE) and "neutropenia" (PT, severe AE [CTCAE grade ≥ 3]) present a statistically significant difference to the benefit of acalabrutinib. For the endpoint "Headache" (PT, AE), there is a statistically significant difference to the disadvantage of acalabrutinib. Overall, neither an advantage nor a disadvantage can be determined for the side effects.

Overall, it is concluded that an additional benefit is not proven for acalabrutinib for the treatment of adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy.

*a2) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom other than bendamustine in combination with rituximab is the appropriate patient-individual therapy*

An additional benefit is not proven.

Justification

For the sub-population patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom other than bendamustine in combination with rituximab is the appropriate patient-individual therapy, no statements can be made to the additional benefit considering the ASCEND study. Since only results with a comparison to bendamustine in combination with rituximab were presented for the benefit assessment, no usable data are available overall.

An additional benefit of acalabrutinib is therefore not proven for sub-population a2).

(b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons

There is a hint for a considerable additional benefit for acalabrutinib for the treatment of adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons.

Justification

For the proof of additional benefit patient population b), the pharmaceutical company used the results of the ASCEND study described above. For this purpose, the pharmaceutical company submitted results from a sub-population of those patients with prior therapy who, at the principal investigator's discretion, should receive idelalisib + rituximab at randomisation into the comparator arm.

In the intervention arm, 65 patients remain for the evaluation and in the comparator arm, 48 patients. The mean age of the patients was 66 years. 27% of patients had a 17p deletion or TP53 mutation at the start of the study. Furthermore, an unmutated immunoglobulin heavy chain variable (IGHV) region was present in the majority of patients (82% of patients in the intervention arm, 75% of patients in the comparator arm). In addition, 27% of patients had a complex karyotype.

Approximately 30% of patients in the comparator arm switched to the intervention arm after disease progression.

In addition to a 17p deletion and TP53 mutation, IGHV mutational status and complex karyotype are increasingly playing a role. According to the clinical experts' comments in the written statement procedure, chemoimmunotherapy is not indicated anymore in patients with an unmutated IGHV and a complex karyotype in relapse.

For some of the patients in the sub-population, no information is available as to why chemoimmunotherapy was not indicated.

The patients included in the ASCEND study have already received chemoimmunotherapy as first-line therapy. However, according to the current guideline recommendations, renewed chemoimmunotherapy is only considered in patients with late relapse. However, the pharmaceutical company does not provide information on the duration of remission for the sub-population, so that it remains unclear whether, according to the current guideline recommendations, a renewal of chemoimmunotherapy was indicated for some of the patients.

Overall, however, in the view of the G-BA, it can be assumed that for the majority of the included patients of the sub-population, no renewed chemoimmunotherapy was an option, so that the evaluations submitted by the pharmaceutical company are used for the present evaluation of patient population b).

Extent and probability of the additional benefit

Mortality

*Overall survival*

In the ASCEND study, the endpoint overall survival is defined as time from randomisation to death from any cause.

There are no signs of statistically significant differences between both treatment groups.

Morbidity

*Progression-free survival*

Progression-free survival (PFS) is the primary endpoint in the ASCEND study and was assessed by an independent review committee (IRC) according to iwCLL criteria. The PFS is operationalised as the time from randomisation to disease progression or death from any cause.

The acalabrutinib arm showed statistically significantly longer progression-free survival than the comparator arm idelalisib + rituximab.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The morbidity component "Disease progression" is assessed according to iwCLL criteria and thus predominantly by means of laboratory parametric, imaging and haematological procedures.

Considering the aspects mentioned above, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

*Fatigue (FACIT-Fatigue)*

In the ASCEND study, FACIT fatigue was assessed until disease progression.

The pharmaceutical company presented responder analyses operationalised as the time to first improvement or deterioration by ≥ 15% of scale range compared to baseline (Global Fatigue Score: ≥ 7.8 points [scale range: 0-52]), which cover all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses operationalised as the time to first deterioration by ≥ 15% of scale range compared with baseline are considered. There are no statistically significant differences between the treatment groups.

The evaluations of the pharmaceutical company regarding the subscales Fatigue Symptomatology Score and Fatigue Impact Score presented in the written statement procedure are not used due to a lack of information on the evaluation of subscales of the FACIT-Fatigue.

*Disease-related symptomatology*

In the ASCEND study, disease-related symptomatology (fatigue, fever, night sweats, weight loss) were recorded during the course of the study.

The pharmaceutical company submits evaluations for the endpoint "disease-related symptoms". These included the following symptoms in the ASCEND study: unintentional weight loss of ≥ 10% within the past 6 months, significant fatigue (e.g., Eastern Cooperative Oncology Group Performance Status [ECOG-PS] ≥ 2, inability to work or perform usual activities), fever > 38 °C for more than 2 weeks without evidence of infection and night sweats for more than 1 month without evidence of infection.

The pharmaceutical company submits evaluations operationalised as the time to the first absence of any disease-related symptoms of patients who had at least one disease-related symptom at the start of the study. Thus, only 35 patients in the acalabrutinib arm (54% of patients) and 31 patients in the comparator arm idelalisib + rituximab (65% of patients) were included in the analyses. Therefore, a statement for all patients of the relevant sub-population is not possible, and the presented evaluations are not used.

*Symptomatology (EORTC QLQ-C30)*

The ASCEND study assessed the symptomatology using the EORTC QLQ-C30 symptom scales until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline. There are no statistically significant differences between the treatment groups.

*Health status (EQ-5D VAS)*

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline. There are no signs of statistically significant differences between the treatment groups.

Quality of life

*EORTC QLQ-C30 (functional scales)*

The ASCEND study will assess health-related quality of life using the EORTC QLQ-C30 functional scales until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline. There are no statistically significant differences between the treatment groups.

Side effects

Endpoints in the category side effects were collected up to 30 days after the end of treatment.

*Adverse events (AE) in total*

Nearly all study participants experienced an adverse event. These are only presented in a supplementary manner.

*Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuations due to AEs (≥ 1 component)*

With regard to SAE, severe AEs (CTCAE grade ≥ 3), and therapy discontinuations due to AEs (≥ 1 component), there is a statistically significant difference in each case for the benefit of acalabrutinib compared with idelalisib + rituximab.

*Specific AEs*

In detail, the analysis of the specific adverse events for the endpoints "Infections and infestations" (SOC, severe AE [CTCAE grade ≥ 3]), "General disorders and administration site conditions" (SOC, severe AE [CTCAE grade ≥ 3]), "Respiratory, thoracic, and mediastinal

disorders" (SOC, severe AE [CTCAE grade ≥ 3]), "Skin and subcutaneous tissue disorders" (SOC, severe AE [CTCAE grade ≥ 3]), "Kidney failure" (PT, severe AE [CTCAE grade ≥ 3]), "Blood and lymphatic system disorders" (SOC, severe AE [CTCAE grade ≥ 3]), "Gastrointestinal disorders" (SOC, severe AE [CTCAE-grade ≥ 3]), "Hepatobiliary disorders" (SOC, severe AE [CTCAE grade ≥ 3]), "Metabolism and nutrition disorders" (SOC, severe AE [CTCAE grade ≥ 3]), "Investigations" (SOC, severe AE [CTCAE grade ≥ 3])" present each a statistically significant difference to the benefit of acalabrutinib compared with idelalisib + rituximab.

For the endpoint "Headache" (PT, AEs), there is a statistically significant difference to the disadvantage of acalabrutinib compared to idelalisib + rituximab.

For the endpoints "Cardiac disorders" (SOC, AE) and "Bleeding" (severe AE [CTCAE grade ≥ 3]), there was no statistically significant difference between the treatment groups.

Overall side effects endpoints show advantages for acalabrutinib compared to idelalisib + rituximab for serious adverse events, severe adverse events (CTCAE grade ≥ 3), therapy discontinuations due to adverse events (≥ 1 component) and in detail predominantly for specific adverse events. Overall, the differences are significant and represent a meaningful improvement in therapeutic benefit compared to idelalisib + rituximab.

Overall assessment

For the assessment of the additional benefit of acalabrutinib for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) after one prior therapy that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons, results are available for the endpoint categories mortality, morbidity, health-related quality of life and side effects.

The basis of the evaluation is the ASCEND study, which compares acalabrutinib with bendamustine + rituximab or idelalisib + rituximab, depending on the principal investigator's choice. The results of a sub-population of patients after one prior therapy for whom chemoimmunotherapy is not indicated are relevant for the evaluation. Data comparing acalabrutinib versus idelalisib in combination with rituximab are available for this sub-population.

For overall survival, there is no statistically significant difference between the treatment groups.

There was no statistically significant difference between the treatment groups for the endpoints of the morbidity category, measured by the FACIT-Fatigue, EORTC-QLQ-C30 and the EQ-5D visual analogue scale.

There was also no statistically significant difference between treatment groups in health-related quality of life data collected using the EORTC-QLQ-C30.

In the side effects category, benefits with acalabrutinib are seen for serious adverse events, severe adverse events (CTCAE grade ≥ 3), and therapy discontinuations due to adverse events. In detail, the analysis of specific adverse events also shows advantages for the treatment with acalabrutinib predominantly. Due to the large magnitude of the available positive effects, there is a clear overall advantage for acalabrutinib compared to idelalisib + rituximab in the endpoint category side effects.

In the overall analysis of the results for the patient-relevant endpoints, there is thus an advantage for acalabrutinib in the side effects category. The differences in this regard are significant and represent a meaningful improvement in therapeutic benefit compared to idelalisib + rituximab. The overall assessment takes into account that these significant differences in the extent of side effects do not correspond to a change in the patients' quality

of life, insofar as the data collected on quality of life do not show a statistically significant difference.

As a result, a considerable additional benefit is identified for acalabrutinib for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) after one prior therapy that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons.

Reliability of data (probability of additional benefit)

The present evaluation is based on the results of the open-label, randomised ASCEND study.

The risk of bias at the study level is rated as low.

Uncertainty of the sub-population of the ASCEND study formed by the pharmaceutical company exists since it remains unclear whether chemoimmunotherapy would have been an option for some of the patients so that the reliability of data for the evaluation of the present patient population is limited.

Due to the open study design, all endpoints have a high risk of bias, except for the endpoints overall survival and the endpoints on severe AEs (CTCAE grade ≥ 3).

Furthermore, the available data on the duration of observation of the patient-reported endpoints of the endpoint category morbidity and health-related quality of life is not plausible if the time to disease progression differs considerably between the study arms so that the results of these endpoints are limited in their reliability.

According to the statements of the clinical experts in the written statement procedure, idelalisib + rituximab has an overall decreasing significance in clinical practice in the present therapeutic indication due to the side effect profile. The significance of the available results on endpoints for side effects, which are the main reasons for the additional benefit, is therefore limited for health care practice, especially with regard to the extent of the existing differences.

Furthermore, the endpoint therapy discontinuation due to AEs has a high risk of bias due to possible competing events (discontinuation due to AEs after discontinuation for reasons other than AEs, e.g. because of progression). However, against the background of the clear difference here, the reliability of data for this endpoint is considered sufficient.

Therefore, the reliability of data for the additional benefit determined is classified in the category “hint”.

(c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies

*c1) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies for whom idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy*

Hint for a minor additional benefit

Justification

For the proof of additional benefit in the patient population c), the pharmaceutical company used the results of the ASCEND study described above. For this purpose, the pharmaceutical company presented results from a sub-population comprising patients with at least two prior therapies. In the intervention arm, 73 patients remain for the evaluation and in the comparator arm, 88 patients.

The majority of patients in the sub-population did not have a 17p deletion (approximately 81% patients) or TP53 mutation (70% of patients) at the start of the study. Furthermore, an unmutated immunoglobulin heavy chain variable (IGHV) region was present in the majority of patients (79% of patients). 38% of the patients showed a complex karyotype.

*Implementation of the appropriate comparator therapy:*

Relapse therapy after at least two prior therapies depends on several individual factors. These are the success and tolerability of the pre-treatment, the patient's general condition, and the molecular-cytogenetic characteristics of the disease. There is neither sufficient plausible information in the dossier of the pharmaceutical company nor in the documents of its written statement on the basis of which criteria patients were assigned to therapy with bendamustine + rituximab or idelalisib + rituximab in the ASCEND study and why bendamustine + rituximab or idelalisib + rituximab is the most suitable therapy for the patients compared to the other therapy options considered.

Patients included in the study have already received chemoimmunotherapy in both prior therapies. According to current guideline recommendations, renewed chemoimmunotherapy is only considered in patients with a double late relapse. Reasons for a renewed treatment with chemoimmunotherapy reside, therefore, especially in the remission duration. The pharmaceutical company does not provide any information on this.

In the ASCEND study, the investigator had a choice of treatment options consisting of chemoimmunotherapy (bendamustine + rituximab) and non-chemoimmunotherapy (idelalisib + rituximab). It can be assumed that the choice between these two therapy options was made according to medical expertise and therefore represents the individually suitable therapy option for the patient with regard to the suitability of chemoimmunotherapy.

According to the guidelines, the molecular-cytogenetic characteristics, among others, should be taken into account for the treatment decision. The decision-making criteria in this respect are currently in a state of flux. According to guideline recommendations, chemoimmunotherapy is not considered a regularly appropriate therapeutic option for patients with a 17p deletion or TP53 mutation. In addition to a 17p deletion and TP53 mutation, IGHV mutational status and complex karyotype increasingly play a role. According to the clinical experts' comments in the written statement procedure, chemoimmunotherapy is not indicated in patients with an unmutated IGHV and a complex karyotype in relapse. Uncertainties remain as to whether the sub-population essentially includes patients for whom therapy with bendamustine + rituximab is recommended according to current scientific knowledge. The pharmaceutical company does not further explain this.

However, the G-BA assumes overall that the therapies with bendamustine in combination with rituximab as well as idelalisib in combination with rituximab represent adequate therapy options for the majority of patients in the sub-population formed by the pharmaceutical company. Nevertheless, the other therapy options of the appropriate comparator therapy are not shown. Consequently, the results of the ASCEND study cannot be used to derive an additional benefit in the entire sub-population c). The division of the population into patients for whom bendamustine in combination with rituximab or idelalisib in combination with rituximab is the appropriate patient-individual therapy (c1) and patients for whom a therapy other than rituximab in combination with bendamustine or idelalisib in combination with rituximab is the appropriate patient-individual therapy (c2) is therefore appropriate.

Extent and probability of the additional benefit

Mortality

*Overall survival*

In the ASCEND study, the endpoint overall survival is defined as the time from randomisation to death from any cause.

There are no signs of statistically significant differences between both treatment groups.

Morbidity

*Progression-free survival*

Progression-free survival (PFS) is the primary endpoint in the ASCEND study and was assessed by an independent review committee (IRC) according to iwCLL criteria. The PFS is operationalised as the time from randomisation to disease progression or death from any cause.

The acalabrutinib arm showed statistically significantly longer progression-free survival than the comparator arm.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" is already assessed via the endpoint "overall survival" as an independent endpoint. The morbidity component "Disease progression" is assessed according to iwCLL criteria and thus predominantly by means of laboratory parametric, imaging and haematological procedures.

Considering the aspects mentioned above, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

*Fatigue (FACIT-Fatigue)*

In the ASCEND study, FACIT fatigue was assessed until disease progression.

The pharmaceutical company presented responder analyses operationalised as the time to first improvement or deterioration by ≥ 15% of scale range compared to baseline (Global Fatigue Score: ≥ 7.8 points [scale range: 0-52]), which cover all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses operationalised as the time to first deterioration by ≥ 15% of scale range compared with baseline are considered. There are no statistically significant differences between the treatment groups.

The evaluations of the pharmaceutical company regarding the subscales Fatigue Symptomatology Score and Fatigue Impact Score presented in the written statement procedure are not used due to a lack of information on the evaluation of subscales of the FACIT-Fatigue.

*Disease-related symptomatology*

In the ASCEND study, disease-related symptomatology (fatigue, fever, night sweats, weight loss) were recorded during the course of the study.

The pharmaceutical company submits evaluations for the endpoint "disease-related symptoms". These included the following symptoms in the ASCEND study: unintentional weight loss of ≥ 10% within the past 6 months, significant fatigue (e.g., Eastern Cooperative Oncology Group Performance Status [ECOG-PS] ≥ 2, inability to work or perform usual

activities), fever > 38 °C for more than 2 weeks without evidence of infection and night sweats for more than 1 month without evidence of infection.

The pharmaceutical company submits evaluations operationalised as the time to the first absence of any disease-related symptoms of patients who had at least one disease-related symptom at the start of the study. Thus, only 47 patients in the acalabrutinib arm (64% of patients) and 57 patients in the comparator arm (65% of patients) were included in the evaluations. Therefore, a statement for all patients of the relevant sub-population is not possible, and the presented evaluations are not used.

*Symptomatology (EORTC QLQ-C30)*

The ASCEND study assessed the symptomatology using the EORTC QLQ-C30 symptom scales until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline.

For the symptom scales fatigue, pain and insomnia, there was a statistically significant difference to the disadvantage of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab. For the symptom scale nausea and vomiting, there is a statistically significant advantage of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab.

*Health status (EQ-5D VAS)*

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline. There are no signs of statistically significant differences between the treatment groups.

Overall, the symptom scales fatigue, pain, and insomnia show statistically significant disadvantages of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab. In contrast, for the symptom scale nausea and vomiting, there is a statistically significant advantage of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab.

Quality of life

*EORTC QLQ-C30 (functional scales)*

The ASCEND study will assess health-related quality of life using the EORTC QLQ-C30 functional scales until disease progression.

The pharmaceutical company submitted responder analysis operationalised as the time to first improvement or deterioration by ≥ 15 points (scale range: 0-100), covering all survey time points regardless of return rates. As part of the evaluation, patients were censored at the time of the last survey before two or more missed visits if symptoms had progressed thereafter. According to the pharmaceutical company, this censoring affects a maximum of two patients in the respective treatment arm in the ASCEND study. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the present assessment, responder analyses are considered operationalised as the time to first deterioration by ≥ 15 points compared with baseline.

For the physical functioning scale, there is a statistically significant difference to the disadvantage of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab.

Side effects

Endpoints in the category side effects were collected up to 30 days after the end of treatment.

*Adverse events (AE) in total*

Nearly all study participants experienced an adverse event. These are only presented in a supplementary manner.

*Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuations due to AEs (≥ 1 component)*

With regard to SAEs, severe AEs (CTCAE grade ≥ 3), and therapy discontinuations due to AEs (≥ 1 component), there is a statistically significant difference in the benefit of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab in each case.

*Specific AEs*

In detail, at the examination of specific adverse events for the endpoints "infections and infestations" (SOC, severe AE [CTCAE grade ≥ 3]), "blood and lymphatic system disorders" (SOC, severe AE [CTCAE grade ≥ 3]), "gastrointestinal disorders" (SOC, severe AE [CTCAE-grade ≥ 3]), "investigations" (SOC, severe AE [CTCAE grade ≥ 3])" each showed a statistically significant difference in the benefit of acalabrutinib compared with bendamustine + rituximab or Idelalisib + rituximab.

For the endpoint "headache" (PT, AE), there is a statistically significant difference to the disadvantage of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab.

For the endpoints "Cardiac disorders" (SOC, AE) and "Bleeding" (severe AE [CTCAE grade ≥ 3]), there was no statistically significant difference between the treatment groups.

Overall side effects endpoints show advantages for acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab for serious adverse events, severe adverse events (CTCAE grade ≥ 3), therapy discontinuations due to adverse events (≥ 1 component) and in detail for specific adverse events. Overall, the differences are significant and represent a significant improvement in therapeutic benefit compared to bendamustine + rituximab or idelalisib + rituximab.

Overall assessment

For the assessment of the additional benefit of acalabrutinib for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) after at least two prior therapies, results are available for the endpoint categories mortality, morbidity, health-related quality of life and side effects.

The basis of the evaluation is the ASCEND study, which compares acalabrutinib with bendamustine + rituximab or idelalisib + rituximab, depending on the principal investigator's choice. The results of a sub-population of patients after at least two prior therapies are relevant for the evaluation.

However, there were no statistically significant differences between the treatment groups for the overall survival.

For the endpoints of the morbidity category, evaluations are available for symptomatology using the FACIT-Fatigue and EORTC-QLQ-C30 measurement instruments and for health status using the EQ-5D visual analogue scale. Overall, the symptom scales fatigue, pain, and insomnia show statistically significant disadvantages of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab. In contrast, for the symptom scale nausea and vomiting, there is a statistically significant advantage of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab.

For the endpoints of the health-related quality of life category, assessed using the EORTC-QLQ-C30 measurement instrument, a statistically significant disadvantage of acalabrutinib compared to bendamustine + rituximab or idelalisib + rituximab was shown for the physical functioning scales.

In the side effects category, benefits with acalabrutinib are seen for serious adverse events, severe adverse events (CTCAE grade ≥ 3), and therapy discontinuations due to adverse events. In detail, the analysis of specific adverse events also shows advantages for the treatment with acalabrutinib. Due to the large magnitude of the available positive effects, there is a clear overall advantage for acalabrutinib in the endpoint category of side effects.

In the overall analysis of the results for the patient-relevant endpoints, moderate disadvantages for acalabrutinib can be determined for the category morbidity and health-related quality of life. In contrast, benefits in the side effects category are significant and represent a meaningful improvement in therapeutic benefit compared to bendamustine + rituximab or idelalisib + rituximab. The overall assessment takes into account that these clear advantages in terms of side effects do not correspond to a positive change in the quality of life of the patients and that there is even a disadvantage in one domain of quality of life (physical functioning).

As a result, the G-BA concluded that acalabrutinib for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) after at least two prior therapies is of minor additional benefit.

Reliability of data (probability of additional benefit)

The present evaluation is based on the results of the open-label, randomised ASCEND study.

The risk of bias at the study level is rated as low.

Uncertainty about the sub-population of the ASCEND study formed by the pharmaceutical company exists since it remains partly unclear based on which criteria a therapy with bendamustine + rituximab or idelalisib + rituximab represents an adequate therapy option for a part of the patients.

Due to the open study design, all endpoints have a high risk of bias, except for the endpoints overall survival and the endpoints on severe AEs (CTCAE grade ≥ 3).

Furthermore, the available data on the duration of observation of the patient-reported endpoints of the endpoint category morbidity and health-related quality of life is not plausible if the time to disease progression differs considerably between the study arms so that the results regarding the advantages and disadvantages of these endpoints are limited in their reliability of data.

According to the statements of the clinical experts in the written statement procedure, idelalisib + rituximab has an overall decreasing significance in clinical practice in the present therapeutic indication due to the side effect profile. The significance of the available results on endpoints for side effects, which are the main reasons for the additional benefit, is therefore limited for health care practice, especially with regard to the extent of the existing differences.

Furthermore, the endpoint therapy discontinuation due to AEs has a high risk of bias due to possible competing events (discontinuation due to AEs after discontinuation for reasons other than AEs, e.g. because of progression). However, against the background of the clear difference here, the reliability of data for this endpoint is considered to be sufficient.

Therefore, the reliability of data for the additional benefit determined is classified in the category “hint”.

c2) *Adult patients with chronic lymphocytic leukaemia after at least two prior therapies for whom therapy other than idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy*

An additional benefit is not proven.

Justification

For the sub-population of patients with chronic lymphocytic leukaemia after at least two prior therapies, for whom a therapy other than idelalisib in combination with rituximab or rituximab in combination with bendamustine is the most suitable patient-individual therapy, no statements on the additional benefit can be made taking into account the ASCEND study. As only results comparing to idelalisib in combination with rituximab and rituximab in combination with bendamustine were presented for the benefit assessment, no usable data are available overall.

An additional benefit of acalabrutinib is therefore not proven for sub-population c2).

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Calquence with active ingredient acalabrutinib. The therapeutic indication assessed here is as follows: Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior treatment.

In the therapeutic indication to be considered, three patient populations were differentiated:

a) Adult patients with CLL after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy

b) Adult patients with CLL after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons

c) Adult patients with chronic CLL after at least two prior therapies

Patient population a)

The appropriate comparator therapy was determined as follows by the G-BA:

- a patient-individual therapy under the selection of
  - rituximab in combination with fludarabine and cyclophosphamide (FCR),
  - rituximab in combination with bendamustine (BR),
  - venetoclax in combination with rituximab and
  - rituximab in combination with chlorambucil (ClbR);

  taking into account the molecular-cytogenetic characteristics of the disease, the general condition as well as the success and tolerability of the previous therapy

*a1) Adult patients with CLL after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom bendamustine in combination with rituximab is the appropriate patient-individual therapy*

For patients after one prior therapy who do not have a 17p deletion or TP53 mutation and for whom chemoimmunotherapy is indicated and for whom bendamustine in combination with rituximab is the appropriate patient-individual therapy, data from a sub-population (patients after one prior therapy for whom chemoimmunotherapy is indicated) of the ASCEND study (acalabrutinib vs bendamustine + rituximab) submitted by the pharmaceutical company are used.

For overall survival, the endpoints of the category morbidity, health-related quality of life and side effects, no advantage or disadvantage can be determined overall.

Therefore, an additional benefit is not proven.

*a2) Adult patients with CLL after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom other than bendamustine in combination with rituximab is the appropriate patient-individual therapy*

No usable data are available for patients after one prior therapy with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy and for whom other than bendamustine in combination with rituximab is the appropriate patient-individual therapy. The additional benefit is therefore not proven for this sub-population.

Patient population b)

The appropriate comparator therapy was determined as follows by the G-BA:

- Ibrutinib

*or*

- Idelalisib in combination with rituximab

*or*

- Best supportive care (only for patients who have failed prior therapy with ibrutinib or idelalisib in combination with rituximab)

The pharmaceutical company submits data from a relevant sub-population (patients after one prior therapy for whom chemoimmunotherapy is not indicated) of the ASCEND study (acalabrutinib vs idelalisib + rituximab).

There was no statistically significant difference between the two treatment groups with regard to overall survival or the endpoint categories morbidity and health-related quality of life.

In the side effects category, there is an overall advantage for acalabrutinib, representing a significant improvement in therapeutic benefit compared to idelalisib + rituximab.

Uncertainties remain about the relevant sub-population regarding the suitability of chemoimmunotherapy.

In the overall view, a hint of considerable additional benefit is identified.

Patient population c)

The appropriate comparator therapy was determined as follows by the G-BA:

- a patient-individual therapy under selection of
  - ibrutinib,
  - idelalisib in combination with rituximab,
  - venetoclax in combination with rituximab,
  - rituximab in combination with fludarabine and cyclophosphamide (FCR),
  - rituximab in combination with bendamustine (BR),
  - rituximab in combination with chlorambucil (ClbR),
  - ibrutinib in combination with BR and
  - best supportive care;

  taking into account the molecular-cytogenetic characteristics of the disease, the general condition as well as the success and tolerability of the previous therapy

*c1) Adult patients with CLL after at least two prior therapies, for whom idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy*

For patients after at least two prior therapies, for whom idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy, the data provided by the pharmaceutical company of a sub-population (patients after at least two prior therapies) of the ASCEND study will be used (acalabrutinib vs bendamustine + rituximab or idelalisib + rituximab, depending on the principal investigator's choice).

In the overall analysis of the results on the patient-relevant endpoints, there was no statistically significant difference between the treatment arms with regard to overall survival.

For the categories morbidity and health-related quality of life, a moderate disadvantage for acalabrutinib can be determined in each case.

In contrast, benefits in the side effects category are significant and represent a meaningful improvement in therapeutic benefit compared to bendamustine + rituximab or idelalisib + rituximab.

Uncertainties remain about the relevant sub-population, as it remains partly unclear on the basis of which criteria a therapy with bendamustine + rituximab or idelalisib + rituximab represents an adequate therapy option for part of the patients.

In the overall view, a hint of minor additional benefit is identified.

*c2) Adult patients with CLL leukaemia after at least two prior therapies for whom therapy other than idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy*

No usable data are available for patients after at least two prior therapies for whom therapy other than idelalisib in combination with rituximab or rituximab in combination with bendamustine is the appropriate patient-individual therapy. The additional benefit is therefore not proven for this sub-population.

### 2.1.5 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The evaluations of the patient numbers presented by the pharmaceutical company in the dossier do not correspond to the patient populations according to the defined appropriate comparator therapy of the G-BA. Within the framework of the written statement procedure, the pharmaceutical company submits corresponding evaluations according to the patient populations a), b), and c) on which the resolution is based.

The baseline of patients who have received at least one pre-treatment used by the pharmaceutical company was originally based on data available in the benefit assessment of idelalisib (resolution of 19 March 2015). As already described in the resolution, these are subject to uncertainties. However, these patient numbers are in line with the resolution on venetoclax in combination with rituximab (resolution of 16 May 2019).

For the numbers per sub-population, the pharmaceutical company uses a database analysis (Oncology Dynamics study, IQVIA), which, however, has uncertainties. In the proportion calculation, the pharmaceutical company takes into account patients who had pre-treatment but could not be assigned to patient populations a) and b) due to lack of information. The pharmaceutical company assumes that these are distributed between patient populations a) and b) as are the remaining patients with pre-treatment. Furthermore, it remains unclear whether all pre-treatment patients were included, as those who received medical tumour therapy as part of a clinical study at the time of documentation were excluded. For the allocation of patient population b), there are also uncertainties because, in addition to patients with 17p deletion / TP53 mutation or patients with a shorter time to relapse than 24 months after previous therapy, the evaluation also took into account patients for whom chemoimmunotherapy is unsuitable for other reasons. However, there is no information on which other specific reasons were decisive for the allocation.

Overall, patient numbers are subject to uncertainty. However, there are no reliable data from previous procedures on patient populations.

### 2.1.6 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Calquence (active ingredient: acalabrutinib) at the following publicly accessible link (last access: 05 February 2021):

https://www.ema.europa.eu/en/documents/product-information/calquence-epar-product-information_de.pdf

Initiation and monitoring of treatment with acalabrutinib should be performed only by specialists in internal medicine and haematology and oncology experienced in the therapy of patients with chronic lymphocytic leukaemia.

## 2.2 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2021).

The annual treatment costs shown refer to the first year of treatment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment duration:

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Days of treatment/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Acalabrutinib | continuously, twice daily | 365 | 1 | 365 |
| Appropriate comparator therapy | | | | |
| a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy | | | | |
| Fludarabin + cyclophosphamide + rituximab (FCR)[3] | | | | |
| Fludarabine | Day 1, 2 and 3 of 28 day cycle | 6 cycles | 3 | 18 |
| Cyclophosphamide | Day 1, 2 and 3 of 28 day cycle | 6 cycles | 3 | 18 |
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Bendamustine + rituximab (BR)[4] | | | | |
| Bendamustine | Day 1 and 2 of 28 day cycle | 6 cycles | 2 | 12 |

3 The basis for the calculation is the total consumption for a complete treatment over 6 cycles.
4 Fischer K et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukaemia: a multicentre phase II trial of the German Chronic Lymphocytic Leukaemia Study Group. J Clin Oncol. 2011 Sep 10; 29(26):3559-66

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Days of treatment/ patient/ year |
|---|---|---|---|---|
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Chlorambucil + rituximab (ClbR)[5] | | | | |
| Chlorambucil | Day 1 and 15 of 28 day cycle | 6 cycles | 2 | 12 |
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Venetoclax + rituximab | | | | |
| Venetoclax | continuously, Once daily | 365 | 1 | 365 |
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons. | | | | |
| Ibrutinib | | | | |
| Ibrutinib | continuously, Once daily | 365 | 1 | 365 |
| Idelalisib + rituximab[6] | | | | |
| Idelalisib | continuously, twice daily | 365 | 1 | 365 |
| Rituximab | once on week 1, 2, 4, 6, 8, 12, 16 and 20 | 8 cycles | 1 | 8 |
| Best supportive care | | | | |
| Best supportive care | Patient-individual | | | |
| c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies | | | | |
| Fludarabine + cyclophosphamide + rituximab (FCR) | | | | |
| Fludarabine | Day 1, 2 and 3 of 28 day cycle | 6 cycles | 3 | 18 |
| Cyclophosphamide | Day 1, 2 and 3 of 28 day cycle | 6 cycles | 3 | 18 |

5 Goede, V., et al., Obinutuzumab + chlorambucil in patients with CLL and coexisting conditions.N Engl J Med, 2014. 370(12): p. 1101-10

6 Dosing of idelalisib in combination with rituximab according to the regimen shown in the product information in the 312-0116 study.

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Days of treatment/ patient/ year |
|---|---|---|---|---|
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Bendamustine + rituximab (BR) | | | | |
| Bendamustine | Day 1 and 2 of 28 day cycle | 6 cycles | 2 | 12 |
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Chlorambucil + rituximab (ClbR) | | | | |
| Chlorambucil | Day 1 and 15 of 28 day cycle | 6 cycles | 2 | 12 |
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Venetoclax + rituximab | | | | |
| Venetoclax | continuously, Once daily | 365 | 1 | 365 |
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Ibrutinib | | | | |
| Ibrutinib | continuously, Once daily | 365 | 1 | 365 |
| Ibrutinib + BR | | | | |
| Ibrutinib | continuously, Once daily | 365 | 1 | 365 |
| Bendamustine | Day 2 and 3 of cycle 1 or on day 1 and 2 (subsequent cycles) of a 28-day cycle | 6 cycles | 2 | 12 |
| Rituximab | Day 1 of 28 day cycle | 6 cycles | 1 | 6 |
| Idelalisib + rituximab | | | | |
| Idelalisib | continuously, twice daily | 365 | 1 | 365 |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Days of treatment/ patient/ year |
|---|---|---|---|---|
| Rituximab | once on week 1, 2, 4, 6, 8, 12, 16 and 20 | 8 cycles | 1 | 8 |
| Best supportive care | | | | |
| Best supportive care | Patient-individual | | | |

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

| Designation of the therapy | Dosage/ application | Dosage/ patient/ days of treatment | Consumption according to potency/day of treatment | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Acalabrutinib | 100 mg | 200 mg | 2 x 100 mg | 365 | 730 x 100 mg |
| Appropriate comparator therapy | | | | | |
| a) Adult patients with chronic lymphocytic leukaemia after one prior therapy, with absence of 17p deletion or TP53 mutation and that are eligible for chemoimmunotherapy | | | | | |
| Fludarabine + cyclophosphamide + rituximab (FCR) | | | | | |
| Fludarabine | 25 mg/m² | 47.5 mg | 1 x 50 mg | 18 | 18 x 50 mg |
| Cyclophosphamide | 250 mg/m² | 475 mg | 1 x 500 mg | 18 | 18 x 500 mg |
| Rituximab | Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m² | Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg 11 x 500 mg |
| Bendamustine + rituximab (BR) | | | | | |
| Bendamustine | 70 mg/m² | 133 mg | 6 x 25 mg | 12 | 72 x 25 mg |
| Rituximab | Cycle 1: 375 mg/m² | Cycle 1: 712.5 mg | Cycle 1: 3 x 100 mg | 6 | 3 x 100 mg 11 x 500 mg |

| Designation of the therapy | Dosage/ application | Dosage/ patient/ days of treatment | Consumption according to potency/day of treatment | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| | Cycle 2 - 6: 500 mg/m$^2$ | Cycle 2 - 6: 950 mg | 1 x 500 mg<br>Cycle 2 - 6: 2 x 500 mg | | |
| Chlorambucil + rituximab (ClbR) | | | | | |
| Chlorambucil | 0.5mg/kg | 38.5 mg | 19 x 2 mg | 12 | 228 x 2 mg |
| Rituximab | Cycle 1: 375 mg/m$^2$<br>Cycle 2 - 6: 500 mg/m$^2$ | Cycle 1: 712.5 mg<br>Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg<br>1 x 500 mg<br>Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg<br>11 x 500 mg |
| Venetoclax + rituximab | | | | | |
| Venetoclax | Week 1: 20 mg<br>Week 2: 50 mg<br>Week 3: 100 mg<br>Week 4: 200 mg<br>Week 5ff: 400 mg | Week 1: 20 mg<br>Week 2: 50 mg<br>Week 3: 100 mg<br>Week 4: 200 mg<br>Week 5ff: 400 mg | Week 1: 2 x 10 mg<br>Week 2: 1 x 50 mg<br>Week 3: 1 x 100 mg<br>Week 4: 2 x 100 mg<br>Week 5ff: 4 x 100 mg | 365 | 14 x 10 mg +<br>7 x 50 mg +<br>1,369 x 100 mg |
| Rituximab | Cycle 1: 375 mg/m$^2$<br>Cycle 2 - 6: 500 mg/m$^2$ | Cycle 1: 712.5 mg<br>Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg<br>1 x 500 mg<br>Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg +<br>11 x 500 mg |
| b) Adult patients with chronic lymphocytic leukaemia after one prior therapy, that have 17p deletion or TP53 mutation or that are not eligible for chemoimmunotherapy due to other reasons. | | | | | |
| Ibrutinib | | | | | |
| Ibrutinib | 420 mg | 420 mg | 1 x 420 mg | 365 | 365 x 420 mg |
| Idelalisib + rituximab | | | | | |
| Idelalisib | 150 mg | 300 mg | 2 x 150 mg | 365 | 730 x 150 mg |
| Rituximab | Cycle 1: 375 mg/m$^2$<br>Cycle 2 - 8: 500 mg/m$^2$ | Cycle 1: 712.5 mg cycle | Cycle 1: 3 x 100 mg<br>1 x 500 mg<br>Cycle 2 - 8: 2 x 500 mg | 8 | 3 x 100 mg +<br>15 x 500 mg |

| Designation of the therapy | Dosage/ application | Dosage/ patient/ days of treatment | Consumption according to potency/day of treatment | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Best supportive care | | | | | |
| Best supportive care | Patient-individual | | | | |
| c) Adult patients with chronic lymphocytic leukaemia after at least two prior therapies | | | | | |
| Fludarabine + cyclophosphamide + rituximab (FCR) | | | | | |
| Fludarabine | 25 mg/m² | 47.5 mg | 1 x 50 mg | 18 | 18 x 50 mg |
| Cyclophosphamide | 250 mg/m² | 475 mg | 1 x 500 mg | 18 | 18 x 500 mg |
| Rituximab | Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m² | Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg 11 x 500 mg |
| Bendamustine + rituximab (BR) | | | | | |
| Bendamustine | 70 mg/m² | 133 mg | 6 x 25 mg | 12 | 72 x 25 mg |
| Rituximab | Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m² | Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg 11 x 500 mg |
| Chlorambucil + rituximab (ClbR) | | | | | |
| Chlorambucil | 0.5mg/kg | 38.5 mg | 19 x 2 mg | 12 | 228 x 2 mg |
| Rituximab | Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m² | Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg 11 x 500 mg |
| Venetoclax + rituximab | | | | | |
| Venetoclax | Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg | Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg | Week 1: 2 x 10 mg Week 2: 1 x 50 mg Week 3: 1 x 100 mg Week 4: 2 x100 mg | 365 | 14 x 10 mg + 7 x 50 mg + 1,369 x 100 mg |

| Designation of the therapy | Dosage/ application | Dosage/ patient/ days of treatment | Consumption according to potency/day of treatment | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| | Week 5ff: 400 mg | Week 5ff: 400 mg | Week 5ff: 4 x100 mg | | |
| Rituximab | Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m² | Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg + 11 x 500 mg |
| Ibrutinib | | | | | |
| Ibrutinib | 420 mg | 420 mg | 1 x 420 mg | 365 | 365 x 420 mg |
| Ibrutinib + BR | | | | | |
| Ibrutinib | 420 mg | 420 mg | 1 x 420 mg | 365 | 365 x 420 mg |
| Bendamustine | 70 mg/m² | 133 mg | 6 x 25 mg | 12 | 72 x 25 mg |
| Rituximab | Cycle 1: 375 mg/m² Cycle 2 - 6: 500 mg/m² | Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg | Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 6: 2 x 500 mg | 6 | 3 x 100 mg 11 x 500 mg |
| Idelalisib + rituximab | | | | | |
| Idelalisib | 150 mg | 300 mg | 2 x 150 mg | 365 | 730 x 150 mg |
| Rituximab | Cycle 1: 375 mg/m² Cycle 2 - 8: 500 mg/m² | Cycle 1: 712.5 mg cycle | Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2 - 8: 2 x 500 mg | 8 | 3 x 100 mg + 15 x 500 mg |
| Best supportive care | | | | | |
| Best supportive care | Patient-individual | | | | |

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both based on the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. I To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of

the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

**Costs of the medicinal products:**

| Designation of the therapy | Packaging size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Acalabrutinib | 60 HC | € 8,791.76 | € 1.77 | € 498.82 | € 8,291.17 |
| Appropriate comparator therapy | | | | | |
| Bendamustine 25 mg | 5 PIC | € 402.03 | € 1.77 | € 49.49 | € 350.77 |
| Bendamustine 25 mg | 1 PIC | € 96.47 | € 1.77 | € 10.81 | € 83.89 |
| Best supportive care | Patient-individual | | | | |
| Chlorambucil 2 mg | 50 FCT | € 36.31 | € 1.77 | € 1.40 | € 33.14 |
| Cyclophosphamide 500 mg | 6 PIE | € 81.98 | € 1.77 | € 8.98 | € 71.23 |
| Fludarabine 50 mg | 5 DSS | € 546.58 | € 1.77 | € 25.41 | € 519.40 |
| Fludarabine 50 mg | 1 CIS | € 118.26 | € 1.77 | € 5.09 | € 111.40 |
| Ibrutinib 420 mg | 28 FCT | € 5,772,62 | € 1.77 | € 0.00 | € 5,770.85 |
| Idelalisib 150 mg | 60 FCT | € 4,534,80 | € 1.77 | € 255.71 | € 4,277.32 |
| Rituximab 100 mg | 2 CIS | € 716.94 | € 1.77 | € 39.08 | € 676.09 |
| Rituximab 500 mg | 1 CIS | € 1,777.06 | € 1.77 | € 98.21 | € 1,677.08 |
| Venetoclax 10 mg | 14 FCT | € 86.72 | € 1.77 | € 0.00 | € 84.95 |
| Venetoclax 50 mg | 7 FCT | € 200.22 | € 1.77 | € 0.00 | € 198.45 |
| Venetoclax 100 mg | 112 FCT | € 5,926.03 | € 1.77 | € 0.00 | € 5,924.26 |
| Abbreviations: FCT = film-coated tablets; HC = Hard capsules; CIS = concentrate for the preparation of an infusion solution; PIE = powder for concentrate for solution for infusion, PIC = powder for the preparation of an infusion solution concentrate; DSS = dry substance without solvent | | | | | |

LAUER-TAXE® last revised: 15 July 2021

<u>Costs for additionally required SHI services:</u>

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations

(e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

| Designation of the therapy | Type of service | Costs/ pack or service | Days of treatment/ year | Annual costs/ patient |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Acalabrutinib | *HBV test*<br>Hepatitis B surface antigen status (GOP number 32781) | € 5.50 | 1 | € 5.50 |
| | Hepatitis B antibody status (GOP number 32614) | € 5.90 | 1 | € 5.90 |
| Appropriate comparator therapy | | | | |
| Ibrutinib | *HBV test*<br>Hepatitis B surface antigen status (GOP number 32781) | € 5.50 | 1 | € 5.50 |
| | Hepatitis B antibody status (GOP number 32614) | € 5.90 | 1 | € 5.90 |
| Rituximab | *HBV test*<br>Hepatitis B surface antigen status (GOP number 32781) | € 5.50 | 1 | € 5.50 |
| | Hepatitis B antibody status (GOP number 32614) | € 5.90 | 1 | € 5.90 |
| | *Premedication*<br>Antihistamines e.g. dimetindene i.v. 4 mg<br>Antipyretics e.g. paracetamol 2 x 500 mg | € 14.93[7]<br>€ 1.36[7,8] | 6<br>6 | € 44.79<br>€ 1.36 |
| | *Premedication in combination with idelalisib* | € 14.93[7] | 8 | € 59.72 |

7 On the basis of a fixed reimbursement rate

8 Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Section 12, paragraph 7, of the AM-RL (information as accompanying medication in the product information of the prescription medicinal product) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured subject in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003: FB Paracetamol tablets 20 pieces = 1.50 € (pharmacy discount according to Section 130 paragraph 1 and 2, 5% from FB; manufacturer discount = 0.06 €)

| | | | | |
|---|---|---|---|---|
| | Antihistamines e.g. dimetindene i.v. 4 mg<br>Antipyretics e.g. paracetamol 2 x 500 mg | € 1.36[7, 8] | 8 | € 1.36 |

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (contract on price formation for substances and preparation of substances) from 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and only approximates the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

## 3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

## 4. Process sequence

At its session on 7 February 2017, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 10 November 2020.

On 30 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of acalabrutinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 November 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient acalabrutinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2021. The deadline for submitting written statements was 6 April 2021.

The oral hearing was held on 26 April 2021.

Due to extensive additional evaluation of data submitted by the pharmaceutical company during the written statement procedure, a postponement of resolution from 3 June 2021 to 5 August 2021 has become unavoidable, which, however, does not affect the parties' rights to the proceedings. By letters dated 27 April 2021 and 22 June 2021, the IQWiG was commissioned with a supplementary assessment. The addenda prepared by the IQWiG was submitted to the G-BA on 9 June 2021 and 9 July 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the sessions of the subcommittee on 22 June 2021, and 27 July 2021, and the proposed resolution was approved in the subcommittee's session on 27 July 2021.

At its session on 05 August 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 7 February 2017 | Determination of the appropriate comparator therapy |
| Subcommittee Medicinal products | 10 November 2020 | New implementation of the appropriate comparator therapy |
| Working group Section 35a | 13 April 2021 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 27 April 2021 | Conduct of the oral hearing,<br>Commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 1 June 2021<br>15 June 2021 | Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure |
| Subcommittee Medicinal products | 22 June 2021 | Consultation of the draft resolution,<br>Commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 14 July 2021<br>21 July 2021 | Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure |
| Subcommittee Medicinal products | 27 July 2021 | Concluding consultation of the draft resolution |

| | | |
|---|---|---|
| Plenum | 5 August 2021 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 5 August 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken