05 November 2020
EMA/OD/0000021547
EMADOC-1700519818-522503
Committee for Orphan Medicinal Products

# Orphan designation withdrawal assessment report

Calquence (Acalabrutinib)
Treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma
EU/3/16/1624

Sponsor: AstraZeneca AB

**Note**

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Table of contents

# 1. Product and administrative information

| **Product** | |
|---|---|
| Designated active substance(s) | Acalabrutinib |
| Other name(s) | - |
| International Non-Proprietary Name | - |
| Tradename | Calquence |
| Orphan condition | Treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma |
| Sponsor's details: | AstraZeneca AB<br>151 85<br>Södertälje<br>Sweden |
| **Orphan medicinal product designation procedural history** | |
| Sponsor/applicant | AstraZeneca AB |
| COMP opinion date | 18 February 2016 |
| EC decision date | 21 March 2016 |
| EC registration number | EU/3/16/1624 |
| **Marketing authorisation procedural history** | |
| Rapporteur / Co-rapporteur | Filip Josephson / Blanca Garcia-Ochoa |
| Applicant | AstraZeneca AB |
| Application submission date | 14 October 2019 |
| Procedure start date | 31 October 2019 |
| Procedure number | EMA/H/C/005299 |
| Invented name | Calquence |
| Proposed therapeutic indication | Treatment of adult patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)<br>Further information on Calquence can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Calquence |
| CHMP opinion date | 23 July 2020 |
| **COMP review of orphan medicinal product designation procedural history** | |
| COMP rapporteur(s) | Karri Penttila / Frauke Naumann-Winter |
| Sponsor's report submission | 12 November 2019 |
| COMP discussion and adoption of list of questions | 14-16 July 2020 |
| Oral explanation | 08 September 2020 |
| Sponsor's removal request | 10 September 2020 |

# 2. Grounds for the COMP opinion

**Orphan medicinal product designation**

The COMP opinion that was the basis for the initial orphan medicinal product in 18 February 2016 designation was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing acalabrutinib was considered justified based on preliminary clinical data showing improved survival;
- the condition is life-threatening and chronically debilitating due to the development of cytopaenias (anaemia, neutropaenia, thrombocytopaenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections;
- the condition was estimated to be affecting approximately 4.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing acalabrutinib will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate an improved survival. The Committee considered that this constitutes a clinically relevant advantage.

# 3. Review of criteria for orphan designation at the time of marketing authorisation

## Article 3(1)(a) of Regulation (EC) No 141/2000

***Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made***

**Condition**

CLL/SLL is a lymphoproliferative malignancy characterized by progressive accumulation of morphologically mature but functionally incompetent lymphocytes in the blood, bone marrow, and lymphoid tissues that affects mainly elderly individuals with the median age at presentation of 65 to 70 years. They are both characterized by the presence of small B-lymphocytes that typically express CD5 and CD23 cell surface antigens (Jaffe et al, 2001). Whereas CLL is associated with a leukaemic phase, SLL is characterized by a nodal or solid phase. Based on their similar morphological and immunophenotypic features, the World Health Organization (WHO) classification scheme for haematopoietic malignancies considers CLL and SLL to be different manifestations of the same disease and combines these entities into one disease category (CLL/SLL) (Jaffe et al,2001). The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Moreover, the number of B lymphocytes in the peripheral blood should not exceed 5x109/L (Hallek, 2008).

The COMP continues to designate the condition.

The approved therapeutic indication "*Calquence monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). Calquence monotherapy is indicated for treatment of adult patients with chronic lymphocytic leukaemia (CLL) /small lymphocytic lymphoma (SLL) who have received at least one prior therapy.*" falls within the scope of the designated orphan condition "Treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma"

**Intention to diagnose, prevent or treat**

The medical plausibility has been confirmed by a positive benefit/risk assessment of the CHMP.

**Chronically debilitating and/or life-threatening nature**

The clinical course is highly variable. Some patients survive for decades, whereas others develop aggressive disease and die within several years of diagnosis. Additional markers are available to predict the prognosis of patients with CLL, in particular at early stages. Patients with a detectable del(17p) or a mutation of TP53 (~5% at diagnosis and up to 10% at treatment initiation) have the poorest prognosis, with a median OS of 2–5 years. With the new treatment options available, the overall survival (OS) of patients with advanced disease stages has improved. The median survival from diagnosis generally varies between 6.5 years to well beyond 10 years (ESMO, 2015).

The disease is frequently presented in the elderly, with a median age of 72 years at diagnosis. The condition is life-threatening and chronically debilitating due to development of cytopenias (anaemia, neutropenia, thrombocytopenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections.

**Number of people affected or at risk**

The sponsor has provided a mix of publications which were published over a range of years spanning from 1990 to 2016. Data is reported from the UK Cancer registry covering prevalence up to 2010 and Nordcan data up to 2016. It is a mix of prevalence data over a wide range of dates which could lead to an under-estimate of the prevalence as the number of patients with the condition can evolve over time. There is no information provided from ECIS.

The sponsor has focused on available data on prevalence and has not provided data on the incidence and overall survival and the alternative methodology of using incidence times duration, which could offer an additional perspective on the current situation in Europe. A table of previous orphan designations has been submitted, however, it is the responsibility of each sponsor to establish the prevalence at the given time. The COMP does not normally accept Orphanet figures as it is not a primary source of data.

It has been noted that the epidemiological landscape for CLL/SLL has been changing since 2000. An interesting article can be found in Haematologica (Baliakas P et al, Letter to the Editor, Haematologica 2018; 103:e158) regarding the change in survival of CLL patients with the introduction of new treatments. The article states: "*A milestone in the management of CLL was the introduction of combined chemoimmunotherapy, in particular the fludarabine-cyclophosphamide-rituximab (FCR) regimen. FCR is the gold standard first-line treatment for medically fit CLL patients except those carrying aberrations of the TP53 gene (TP53abs: i.e. deletion of chromosome 17p, del(17p) and/or TP53 mutations) who should be managed using signaling inhibitors. Additional options, consisting of different combinations of chemotherapeutic agents, anti-CD20 antibodies, signalling inhibitors and the BCL2 inhibitor venetoclax hold promise for further improvement of patients' care.*" The authors provide

a table of the change in survival from 1980 to 2014 which clearly shows the impact of the new therapies introduced.

Table 1. Main clinicobiological features of cases treated before and after 2006.

| | Treated 1980-2005 n=2093 | Treated 2006-2014 n=1411 | P |
|---|---|---|---|
| Male | 1443/2093, 69% | 968/1411, 69% | 0.83 |
| Median age at treatment[a](years, range) | 63 (22-92) | 64.4 (33-92) | 0.001 |
| M-CLL | 768/2093, 37% | 518/1411, 37% | 0.99 |
| del(13q)* | 323/570, 57% | 205/383, 54% | 0.33 |
| Trisomy 12* | 133/706, 19% | 106/495, 21% | 0.27 |
| del(11q)* | 199/937, 21% | 140/676, 21% | 0.79 |
| del(17p)* | 111/1059, 10% | 106/798, 13% | 0.063 |
| Subset #2[b] | 105/2093, 5% | 61/1411, 4% | 0.34 |
| Subset #1[c] | 68/2093, 3.2% | 42/1411, 3% | 0.65 |
| Median overall survival | 9.5 years | 17.5 years | <0.0001 |

[a]Despite the fact that the two groups have a similar median age, the identified 1.4-year difference emerged as statistically significant due to the variation within groups as well as the large number of cases included in each group. *According to the Döhner hierarchical model, [b]Assignment to stereotyped subset #2, [c]Assignment to stereotyped subset #1.

The sponsor's calculation does not consider the recent substantial increase in the overall survival from 2006 to 2014 as is reported in 2018. Given that CLL is a relapsing disease, the appropriate epidemiological index to report the number of affected individuals for the purpose of orphan designation is complete prevalence, regardless of how long ago the diagnosis has been made.

The COMP considered that the sponsor should be invited to recalculate the prevalence estimate with more current information than that provided in the submission.

## Article 3(1)(b) of Regulation (EC) No 141/2000

***Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.***

### Existing methods

The sponsor lists several products that have been authorised for use in the treatment of patients with CLL/SLL. The products cited are: rituximab, bendamustine, chlorambucil, venetoclax, ibrutinib and idelalisib. The sponsor cites the 2012 ESMO Guidelines for CLL but has not taken note of the more updated 2015 ESMO Guideline (Annals of Oncology 26 (Supplement 5): v78–v84, 2015). The revised treatment algorithm from the ESMO 2015 Guidelines is presented below.

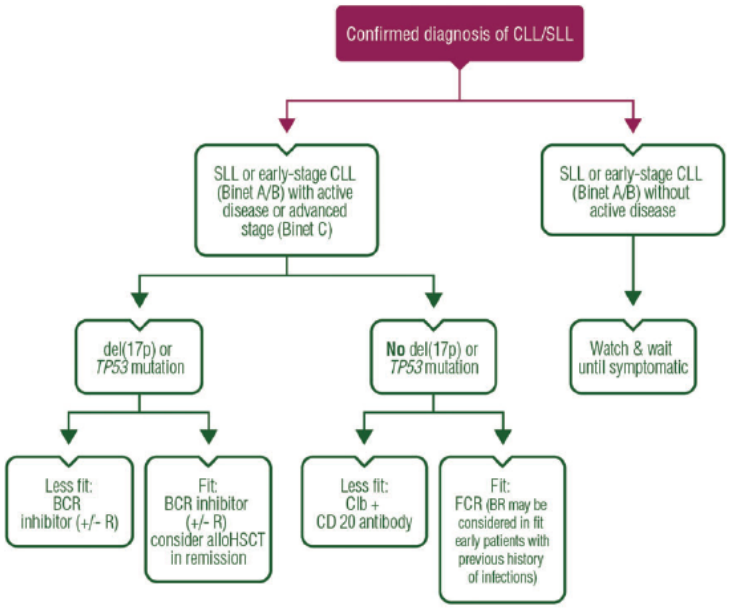


**Figure 1.** Front-line treatment. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; BCR, B-cell receptor; R, rituximab; alloHSCT, allogeneic haematopoietic stem cell transplantation; FCR, fludarabine, cyclophosphamide and rituximab; BR, bendamustine plus rituximab; Clb, chlorambucil.

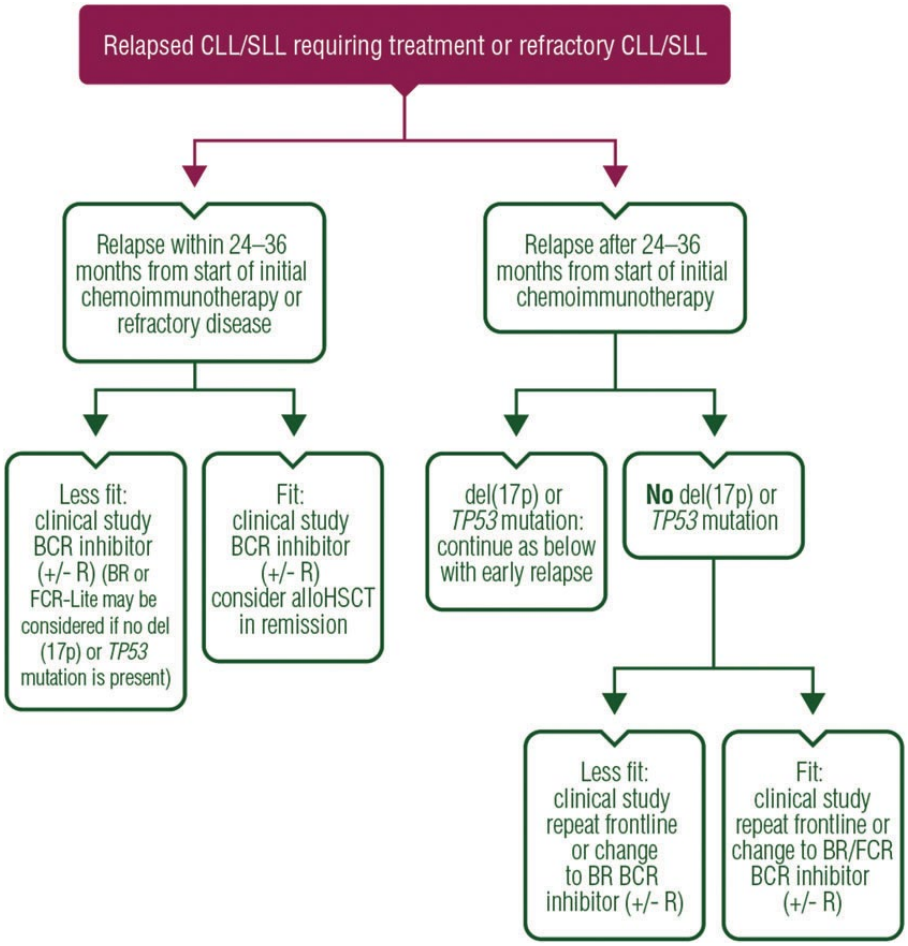


*Figure 2 Relapse treatment. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; BCR, B-cell receptor; R, rituximab; BR, bendamustine plus rituximab; FCR, fludarabine, cyclophosphamide and rituximab; alloHSCT, allogeneic haematopoietic stem cell transplantation.*

On 27 June 2017 ESMO published an update involving recommendations for treatment of advanced disease stage – front line treatment. The text states: *Patients with TP53 deletion/mutation have a poor prognosis even after FCR therapy. Therefore, it is recommended that with TP53 deletion/mutation are treated with ibrutinib in front-line. Because of severe infectious complications, PI3K inhibitor idelalisib combined with rituximab is only recommended for frontline therapy in patients not suitable for Btk inhibitors, if anti-infective prophylaxis is taken and measures to prevent infection are followed. Patients unsuitable for BCR inhibitor therapy may otherwise be treated with BCL2 inhibitor venetoclax. Recommendation: Patients with del(17p) or TP53 mutation who are unsuitable for BCR inhibitor therapy may be treated with the BCL2 inhibitor venetoclax.*

**Significant benefit**

The sponsor's product is acalabrutinib has the same mode of action as ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor. The sponsor's proposed indication currently at CHMP is:

*"Calquence monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). Calquence monotherapy is indicated for treatment of adult patients with chronic lymphocytic leukaemia (CLL) /small lymphocytic lymphoma (SLL) who have received at least one prior therapy."*

The authorized indication for ibrutinib in CLL/SLL is:

- *IMBRUVICA as a single agent or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).*
- *IMBRUVICA as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy*.

The sponsor obtained orphan designation in 2019 shortly before their submission for marketing authorization and as such they did not have the possibility to discuss the requirements for significant benefit with COMP during a protocol assistance. The sponsor came for Scientific Advice twice (2016 and 2018).

The sponsor argues significant benefit based on:

**Direct comparison**

A direct comparison is available against Obinutuzumab in combination with Chlorambucil for previously untreated patients, and against idelalisib+rituximab or bendamustine+rituximab (investigator's best choice) for previously treated patients. With a median-follow up of 28 months and an event rate of 52% in the control arm IRC-assessed PFS for Acala+Obin *vs* clb+obi, the primary outcome, showed a HR of 0.10 [95% CI: 0.06, 0.17]; p<0.0001, in favour of the Acala+Obin arm. The sensitivity analyses are supportive of this outcome. The median estimated PFS for the experimental arm was not reached; the median estimated PFS for the control arm was 22.6 months (95%CI: 20.2, 27.6). In terms of HR for PFS, the subgroup analyses consistently favour the experimental arm.

The Significant benefit is based on improved efficacy can be accepted over obinutuzumab, idelalisib and bendamustine in combination with rituximab.

Significant benefit over the newer agents venetoclax and ibrutinib must be demonstrated based on cross-trial comparisons or formally matched-adjusted indirect comparison (MAIC). Prior treatment with

either ibrutinib or venetoclax was an exclusion criterion for the pivotal trial for previously treated CLL, but external data provide some evidence for acalabrutinib post venetoclax or ibrutinib.

**Indirect comparisons**

The sponsor submits a number of crude or matched indirect comparisons (MAICs) to either treatment options **for previously untreated** or **previously treated** patients to different regimens, but not to FCR. Practically all trials are different with respect to inclusion criteria so that crude comparisons are of limited value and the effective sample size of acalabrutinib studies are sometimes very much reduced for the MAICs (e.g. exclusion of 2/3 of the patient population for the comparison of the monotherapies with ibrutinib/acalabrutinib).

The sponsor presents safety/tolerability data both based on crude comparison and before and after matching and highlights reduced rates of any grade AEs or reduced specific grade 3/4 AEs or SAE.

The sponsor also provides indirect comparison of the two monotherapy treatments in **previously untreated patients** and the three trials which compared Obi+Clb to ibrutinib or acalabrutinib or venetoclax in combination with obinuzumab.

In the following table, efficacy is compared between the **obinutuzumab-combinations**. The comparison of demographics from these studies suggests general comparability between the acalabrutinib+obinutuzumab (AG) arm and the venetoclax+obinutuzumab (VG) arm. However, the demographics of the ibrutinib+obinutuzumab (IG) arm appears to present less favourable demographics compared with the AG arm. This may be a result of inclusion criteria that limited the study to subjects who were unfit for fludarabine.

**Table 17. Efficacy Outcome Comparison for Ibrutinib, Venetoclax, and Acalabrutinib Arms When Combined with Obinutuzumab in Phase 3 Studies of Previously Untreated CLL**

| | Ibrutinib + Obinutuzumab (iLLUMINATE)[a,b] | Acalabrutinib+ Obinutuzumab (ACE-CL-007) | Venetoclax+ Obinutuzumab (CLL-14)[c,d] |
|---|---|---|---|
| **ORR (+PRL)** | 88% (IRC) | **93.9% (IRC)** | 85% (INV) |
| **CR/CRi Rate** | 19% | 13.4% | **50%** |
| **MRD Negativity** *Peripheral Blood* | 30% | NA | 76%[e] 58%[f] |
| **MRD Negativity** *Bone Marrow* | 20% | NA | 57% |
| **PFS HR,** | 0.23 | **0.10 (0.06-0.17)** | 0.33 |
| **G+CLB mPFS** | 19mo | 22.6mo | NR |
| **OS HR** | 0.92 (0.479-1.722) | 0.47 (0.21-1.06) | 1.24 (0.64- 2.40) |
| **PFS at 24 months** | 80% | **92.7% (87.4-95.8)** | 88% |

CR=complete response; CRi=complete response with incomplete blood count recovery; HR=hazard ratio; IRC=Independent Review Committee; mPFS=median progression-free survival; NR=not reported; PFS=progression-free survival; ORR=overall response rate; OS=overall survival.
Note: Green text indicates acalabrutinib is favored; red text indicates comparator is favored.

Safety appears overall more favourable (also with respect to rate differences) for AG

**Table 18. Safety Outcomes Comparison for Ibrutinib, Venetoclax, and Acalabrutinib Arms When Combined with Obinutuzumab in Phase 3 Studies of Previously Untreated CLL**

| | Ibrutinib + Obinutuzumab (iLLUMINATE)[a,b] | | | Acalabrutinib + Obinutuzumab (ACE-CL-007) | | | Venetoclax + Obinutuzumab (CLL-14)[c,d] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Gr1/2 | Gr3+ | Any Grade | Gr 1/2 | G3+ | Any Grade | Gr 1/2 | G3+ |
| Neutropenia | 43% | 7% | 37% | 31.5% | 1.7% | 29.8% | 60% | 4% | 56% |
| Febrile Neutropenia | 6% | 1% | 5% | 1.7% | 0% | 1.7% | 6% | 1% | 5%** |
| Thrombocytopenia | 35% | 17% | 19% | 12.9% | 4.5% | 8.4% | 24%** | 10%** | 14%** |
| Anemia | 17% | 13% | 4% | 11.8% | 6.2% | 5.6% | 17% | 9% | 8% |
| Rash | 36% | 33% | 3% | 11.8% | 11.2% | 0.6% | - | - | NR |
| Bruising (Contusion) | 32% | 29% | 3% | 23.6% | 23.6% | 0% | - | - | NR |
| Diarrhea | 34% | 31% | 3% | 38.8% | 34.3% | 4.5% | 28% | 24% | 4% |
| Constipation | 16% | 16% | 0% | 14% | 14% | 0% | 13% | 13% | 0% |
| Nausea | 12% | 12% | 0% | 20.2% | 20.2% | 0% | 19% | 19% | 0% |
| Vomiting | 22% | 21% | 1% | 13.5% | 12.9% | 0.6% | 10% | 9% | 1% |
| Stomatitis | - | - | - | 2.8% | 2.8% | 0% | - | - | - |
| Arthralgia | 22% | 21% | 1% | 21.9% | 20.8% | 1.1% | - | - | - |
| Musculoskeletal Pain | 33% | 32% | 1% | 7.3% | 6.7% | 0.6% | - | - | - |
| Muscle Spasms | 13% | 13% | 0% | 2.8% | 2.8% | 0% | - | - | - |
| Cough | 27% | 26% | 1% | 21.9% | 21.9% | 0% | 16%** | - | - |
| Hemorrhage/Bleed | 25% | 24% | 1% | 42.7% | 41.0% | 1.7% | - | - | - |
| Bruising (via USPI) | 32% | - | 3% | - | - | - | - | - | - |
| Hypertension | 17% | 13% | 4% | 7.3% | 4.5% | 2.8% | - | - | - |
| Pneumonia | 13% | 6% | 7% | 10.7% | 5.1% | 5.6% | 9% | 5% | 4%** |
| Infection | - | - | - | 69.1% | 48.3% | 20.8% | - | - | 18%** |
| URI | 14% | 13% | 1% | 21.3% | 19.1% | 2.2% | 17% | 16% | 1% |
| Skin Infection | 13% | 12% | 1% | 1.7% | 1.7% | 0% | - | - | - |
| UTI | 12% | 9% | 3% | 12.4% | 11.8% | 0.6% | 6% | 6% | |
| Nasopharyngitis | 12% | 12% | 0% | 11.2% | 10.7% | 0.6% | - | - | - |
| Conjunctivitis | 11% | 11% | 0% | 2.8% | 2.8% | 0% | - | - | - |
| Sepsis | - | - | - | 1.7% | 0% | 1.7% | 4% | 4% | |
| Hyperuricemia | 13% | 12% | 1% | 4.5% | 2.8% | 1.7% | - | - | - |
| Hyperglycemia | - | - | - | 5.1% | 3.9% | 1.1% | - | - | 4%** |
| TLS | 1% | 1% | 0% | 1.7% | 0.6% | 1.1% | 1% | 1% | |
| Atrial Fibrillation | 12% | 7% | 5% | 3.4% | 2.8% | 0.6% | - | - | - |
| Pyrexia | 19% | 17% | 2% | 12.9% | 12.9% | 0% | 23%** | - | - |

| | Ibrutinib + Obinutuzumab (iLLUMINATE)[a,b] | | | Acalabrutinib + Obinutuzumab (ACE-CL-007) | | | Venetoclax + Obinutuzumab (CLL-14)[c,d] | | |
|---|---|---|---|---|---|---|---|---|---|
| **Fatigue** | 18% | 0% | 0% | 28.1% | 26.4% | 1.7% | 21% | 19% | 2% |
| **Peripheral Edema** | 12% | 12% | 0% | 12.4% | 11.8% | 0.6% | - | - | - |
| **Insomnia** | 12% | 12% | 0% | 9% | 9% | 0% | - | - | - |
| **Dry eye** | - | - | - | 1.1% | 1.1% | 0% | - | - | - |
| **Lacrimation Increased** | - | - | - | 1.7% | 1.7% | 0% | - | - | - |
| **Vision Blurred** | - | - | - | 2.8% | 2.8% | 0% | - | - | - |
| **Visual Acuity Reduced** | - | - | - | 0% | 0% | 0% | - | - | - |
| **Headache** | - | - | - | 39.9% | 38.8% | 1.1% | 11% | - | - |
| **IRR** | 25% | 23% | 2% | 13.5% | 11.2% | 2.2% | 45%** | 36% | 9%** |

G=grade; IRR=infusion-related reaction; URI=upper respiratory tract infection; UTI=urinary tract infection; TLS=tumor lysis syndrome; USPI=United States prescribing information.
Notes: - indicates not reported.

** included in CLL14 NEJM presentation but not in venetoclax USPI;
Note: Green bold text indicates results favor acalabrutinib; red text indicates results favor comparator.
[a] iLLUMINATE (ASH'18, #691).
[b] Moreno et al. 2018.
[c] Venetoclax USPI
[d] Fischer et al. 2019.

**Statistical considerations**

The sponsor has proposed a weighted approach, assigning weights to individual observations so that there is balance between the compared groups. The sponsor also state that the distributions of weights were inspected to identify potential sensitivity to extreme weights. The weighted t-test for continuous variables and the weighted Chi-square test for categorical variables were used in the comparison. The weights were used to calculate the effective sample size (ESS) achieved after weighting patients. A low ESS may indicate an irregular distribution of weights across patients, meaning that only a small fraction of patients may be utilized to drive the treatment effect.

There is considerable uncertainty with respect to the magnitude and importance of any efficacy differences between acalarutininb and venetoclax. Any improved safety needs to take this possible inferior efficacy into account. In conclusion, the sponsor provided both results of superiority head-to-head comparison as well as a number of cross-trial comparisons comparing acalabrutinib **monotherapy** or in **combination with obinituzumab** to various authorized monotherapy or combination treatments including ibrutinib (same class of BTKi) and venetoclax (among the new SoC for CLL) both in previously untreated or in  The differences with respect to baseline characteristics and trial methods between the trials hamper any firm conclusion.

The COMP therefore considered that the sponsor has not justified sufficiently the basis for significant benefit and should further elaborate on concerns associated with the indirect comparisons.

# 4. COMP list of issues

Prevalence

The sponsor is asked to re-address the prevalence of the proposed condition in the EU, taking into account the "Points to consider on the estimation and reporting of the prevalence of a condition for orphan designation"

The sponsor is asked to recalculate the prevalence as no current data regarding the incidence and overall survival has been provided for this incurable disease. Sensitivity analyses on all assumptions should be conducted as the prevalence of CLL/SLL is very close to the threshold. These should include expectations on contemporary crude incidence and the impact of current treatment on survival and should therefore clarify the complete prevalence of CLL/SLL.

Significant benefit

The sponsor should further elaborate on the robustness of the results of the indirect comparisons presented for acalabrutinib to ibrutinib and venetoclax to demonstrate significant benefit with respect to efficacy and safety by cross-trial comparison, also in view of the reduced effective sample sizes and the unequal distribution of weights in the MAIC. Sensitivity analysis should be provided by omitting individuals with the highest weights.