NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]

**Contents:**

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from AstraZeneca**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Chronic Lymphocytic Leukaemia Support Association-Lymphoma Action
   b. Leukaemia Care
   c. UK Chronic Lymphocytic Leukaemia Forum-British Society of Haematology-Royal College of Pathologists
   d. AbbVie
   e. Janssen-Cilag
   f. National Cancer Research Institute, *endorsed by the Royal College of Physicians*

   *Comments on the Appraisal Consultation Document from experts:*
   *None*

   *Comments on the Appraisal Consultation Document received through the NICE website*
   *None*

4. **Evidence Review Group critique of company comments on the ACD**

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# Acalabrutinib for treating chronic lymphocytic leukaemia

## Single Technology Appraisal

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Type of stakeholder:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

**Commentators –** Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| 1 | Consultee (company) | AstraZeneca | **Summary of the Company's position**<br><br>The Company would like to thank the Committee for the opportunity to respond to the Appraisal Consultation Document (ACD).<br><br>The Company welcome the recommendations made by the Committee for acalabrutinib as a treatment option for:<br><br>1. Previously untreated chronic lymphocytic leukaemia (CLL) in adult patients who have a 17p deletion or TP53 mutation.<br>2. Previously treated CLL in adult patients who have had at least 1 previous treatment if ibrutinib is their only other suitable treatment option.<br><br>However, the Company consider the wording of the recommendation for patients who have received at least 1 previous treatment is restrictive, and that it does not allow clinicians to treat patients who are intolerant to ibrutinib with a Bruton tyrosine kinase inhibitor (BTKi). The Company invite the Committee to consider the alternative wording detailed in comment 2 below.<br><br>Furthermore, the Company are concerned that despite the evidence submitted by the Company and expressed by clinical experts, coupled with the support from CLL patient group representatives, the Committee have not recommended acalabrutinib for the treatment of non-high-risk previously untreated CLL (i.e., patients who do not have a 17p deletion or TP53 mutation) when therapy with fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR) is unsuitable.<br><br>In response to this decision, the Company would like to highlight the following key points for consideration by the Committee:<br><br>1. There is a high unmet need for alternative treatment options, with different mechanisms of action, to the current selection of first-line treatments available for previously untreated CLL in non-high-risk patients unsuitable for FCR or BR therapy.<br>2. The proportion of patients receiving second-line venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab has been overestimated by the Committee | Comments noted. The committee considered your comments and the scenario analyses presented in Table 1. The points raised in this summary comment are addressed below, as they are raised individually in comments 2-7. |

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment<br>Please insert each new comment in a new row</th><th>NICE Response<br>Please respond to each comment</th></tr>
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and does not reflect current National Health Service (NHS) clinical practice in England in the Committee's preferred modelling assumptions.<br>
3. The treatment duration of second-line ibrutinib following treatment with chlorambucil plus obinutuzumab is underestimated and does not consider the confounding effect of previous lines of therapy on progression-free survival (PFS).<br>
4. Clinical support and evidence have not been appropriately considered in decision making when determining the Committee's preferred modelling assumptions for post-progression survival.<br><br>
Comments 3 to 6 detail the Company's position on these points. In addition, the Company noted one factual inaccuracy within the ACD; this is detailed in comment 7.<br><br>
In light of the evidence presented in comments 3 to 6, the Company consider the scenarios presented within Table 1 to be clinically plausible and suitable for decision making. Two additional exploratory scenarios are presented with the aim of alleviating the Committee's concerns on long-term survival estimates.<br><br>
As heard from the Patient Groups and the clinical experts at the Appraisal Committee Meeting (5th November 2020), there is a significant unmet need in non-high-risk previously untreated CLL patients who are ineligible for FCR or BR therapy. Current treatment options are limited, and the Company is committed to addressing this unmet need. Furthermore, acalabrutinib remains a cost-effective treatment option relative to chlorambucil plus obinutuzumab within this patient population at the Patient Access Scheme (PAS) price of £[redacted] per 30-day pack of 100 mg tablets compared to comparator list price, across all scenarios presented in Table 1. Therefore, the Company would like to invite the Committee to consider the evidence presented within this response and to reconsider their decision on acalabrutinib for the treatment of non-high-risk previously untreated CLL (i.e., patients who do not have a 17p deletion or TP53 mutation) when therapy with FCR or BR is unsuitable.<br><br>
Table 1. Cost-effectiveness scenario analyses for acalabrutinib PAS price versus comparator list prices
<table>
<tr><th>Scenario[1]</th><th>Inc. cost (£)</th><th>Inc. QALYs</th><th>ICER (£)</th></tr>
<tr><td>1. Company preferred base-case</td><td>[redacted]</td><td>[redacted]</td><td>Dominating</td></tr>
<tr><td>2. ERG preferred base-case</td><td>[redacted]</td><td>[redacted]</td><td>8,868</td></tr>
<tr><td>3. Company base case (scenario 1) plus 20% V+R usage following first-line C+O</td><td>[redacted]</td><td>[redacted]</td><td>Dominating</td></tr>
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment<br>Please insert each new comment in a new row</th><th>NICE Response<br>Please respond to each comment</th></tr>
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<table>
<tr><td>4. ERG base case (scenario 2) plus 20% V+R usage following first-line C+O</td><td>[redacted]</td><td>[redacted]</td><td>15,320</td></tr>
<tr><td colspan="4">Exploratory scenarios</td></tr>
<tr><td>5. ERG base case (scenario 2) plus 50% reduction in acalabrutinib survival benefit</td><td>[redacted]</td><td>[redacted]</td><td>6,853</td></tr>
<tr><td>6. ERG base case (scenario 2) plus 50% reduction in acalabrutinib survival benefit and 20% V+R usage following first-line C+O</td><td>[redacted]</td><td>[redacted]</td><td>14,996</td></tr>
</table>
Abbreviations: C+O, chlorambucil plus obinutuzumab; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; V+R, venetoclax plus rituximab.<br>1. Please refer to Error! Reference source not found., Appendix 1 for model settings.</td><td></td></tr>
<tr><td>2</td><td>Consultee (company)</td><td>AstraZeneca</td><td>The wording of the recommendation made by the Committee for patients who have received at least 1 previous treatment is restrictive and does not allow clinicians to treat patients who are intolerable to ibrutinib with a BTKi.<br><br>The Company regard the wording within the Committee's recommendation of acalabrutinib in patients who have received at least 1 previous treatment to be unnecessarily restrictive.<br><br>The restriction to patients for whom "ibrutinib is their only other suitable treatment option" does not allow for cases where a clinician would prefer to treat with a BTKi but are unable to do so either because ibrutinib is contraindicated (i.e., due to cardiac comorbidities) or intolerable.<br><br>Therefore, the Company urge the Committee to reconsider the wording of the draft recommendation and amend it to allow for patients for whom a BTKi would be their most suitable treatment option:<br><br>• "Acalabrutinib is recommended as an option for treating previously treated CLL in adult patients who have had at least 1 previous treatment, only if a BTKi is their most suitable treatment option."</td><td>Comment noted. The committee considered your comments. The recommendations in section 1.2 of the FAD have been updated as follows: "Acalabrutinib is recommended as an option for treating CLL in adults who have had at least 1 previous treatment, only if:<br>• the company provides the drug according to the commercial arrangement (see section 2)."</td></tr>
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| 3 | Consultee (company) | AstraZeneca | **There is a high unmet need for alternative treatment options with different mechanisms of action to current first-line treatments, especially in non-high-risk previously untreated CLL patients when FCR or BR is unsuitable.**<br><br>Treatment of patients with previously untreated non-high-risk CLL is currently restricted to chemo-immunotherapies, such as chlorambucil plus obinutuzumab. Chlorambucil plus obinutuzumab is associated with considerable adverse and toxic effects. Patients express that these toxic effects have a large impact on their quality of life and that there is an urgent unmet need for new, more tolerable treatment options.[1]<br><br>• *My husband has been on [this] for a year now and suffers harsh bone pain, difficulty breathing and massive bruising with bleeding on arms. His illness has become our life. His blood counts have improved but the side effects are difficult. We wish there was an alternative therapy".*<br><br>• *"Urgent unmet need for first line treatment in people who are not high risk".*<br><br>As noted in Section 3.1 of the ACD, patient experts explained that the physical and psychological effects of CLL have a debilitating effect on their daily lives. The Committee concluded that CLL substantially affects both physical and psychological aspects of quality of life. In Section 3.2, it is also stated that *"chlorambucil plus obinutuzumab is the only other option so targeted treatments such as acalabrutinib are needed"* and *"the committee concluded that acalabrutinib would be welcomed as a new treatment option for people with CLL."*<br><br>[redacted]<br><br>Clinical experts, patient group representatives, the Committee, and the Company, all recognise the urgent unmet need for alternative, novel, less toxic and more efficacious treatment options, such as acalabrutinib, to diversify the treatment pathway and offer more options to patients in the first-line setting. It is clear that there is heterogeneity within this patient population, highlighted by the intolerability of current options in some patients. This further demonstrates the need for a wider range of alternative effective treatment options. In light of this, the Committee's decision to not recommend | Comment noted. The committee considered your comments. The recommendations in section 1.1 of the FAD have now been updated as follows:<br>"Acalabrutinib is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:<br>• there is a 17p deletion or TP53 mutation, or<br>• there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable, and<br>• the company provides the drug according to the commercial arrangement (see section 2)." |

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| | | | acalabrutinib within this setting continues to limit treatment options to more toxic and less efficacious chemo-immunotherapies. | |
| 4 | Consultee (company) | AstraZeneca | **The proportion of patients receiving second-line venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab is not greater than 20% in current clinical practice for NHS England.**<br><br>In the Committee's preferred modelling assumptions, the proportion of patients receiving second-line venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab is overestimated and does not reflect current clinical practice for NHS England.<br><br>Section 3.13 of the ACD states: *"The clinical experts explained that venetoclax plus rituximab was a relatively recent treatment option. It was likely to account for between 20% and 50% of second-line treatment after chlorambucil plus obinutuzumab and would increase over time."* However, in the public section of the Appraisal Committee Meeting (Part 1) the two clinical experts attending the Meeting did not indicate that the use of venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab would reach 50%. Professor Adrian Bloor stated that he did **not** expect venetoclax plus rituximab use relative to ibrutinib to reach 50:50 in the future, and Professor Anna Schuh stated that she agreed that the Company's estimate of 13% was reflective of current treatment patterns.<br><br>Therefore, the Company are concerned with the Committee's decision to assume that venetoclax plus rituximab use following chlorambucil plus obinutuzumab could reach up to 50%. The Company do not agree with this decision and believe it does not align with the available evidence base or clinical expert opinion.<br><br>**Real-world evidence**<br><br>• Data from a retrospective chart review of 202 UK patients with CLL showed that between October 2019 and September 2020 only [redacted]% of patients received second-line treatment with a venetoclax plus rituximab.[2]<br><br>• Updated UK patient-level prescription data collected by IQVIA in September 2020, indicated that 14% of second-line and subsequent line (2L+) BTKi-naïve patients (n=164) were receiving a venetoclax-based regimen (either venetoclax monotherapy or in combination with rituximab). Of the 14% on venetoclax-based regimens, it was estimated that 20% received venetoclax monotherapy, a treatment option outside the scope of this appraisal. As such, as of September 2020, the split of second-line treatments for BTKi-naïve patients in the UK is estimated to be 11%:89% for venetoclax plus rituximab relative to ibrutinib.[3]<br><br>• In addition, the use of venetoclax-based regimens as 2L+ treatment in BTKi-naïve patients has not increased over time. Nationwide IQVIA prescribing data collected between March | Comments noted. The committee considered your comments and consulted the clinical expert opinion at the second committee meeting. Section 3.13 of the FAD has been revised as follows: "In response to consultation, the company provided more evidence to support it's initial assumption. The clinical experts explained that venetoclax plus rituximab was a relatively recent treatment option. At the second committee meeting, they agreed that it was likely to currently account for between 13% and 20% of second-line treatment after chlorambucil plus obinutuzumab but noted this proportion may increase over time. The committee agreed that the distribution of subsequent treatments after disease progression in the untreated CLL model was uncertain and considered scenarios with a range of proportions. It concluded that it was plausible venetoclax plus rituximab currently accounts for up to 20% of second-line treatment after chlorambucil plus obinutuzumab but that this may increase over time." |

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| | | | and September 2020 indicates that 20% (n=180), 16% (n=160) and 14% (n=164) of BTKi-naïve 2L+ patients received treatment with a venetoclax-based regimen in March, July and September 2020, respectively (Figure 1).[3] Therefore, there is no evidence of increased use of venetoclax over time, and instead the data presents a relatively stable pattern of prescribing.<br><br>• Furthermore, nationwide UK IQVIA prescribing data supports the conclusions made by clinical experts and the Company's assumptions. That is that BTKi-naïve patients often receive treatment with a BTKi followed by a venetoclax-based regimen, whilst patients who have previously received treatment with a BTKi will often receive a venetoclax-based regimen as their 2L+ therapy. Nationwide IQVIA prescribing data shows that 75% (n=28), 80% (n=40) and 76% (n=37) BTKi-treated patients in the first-line setting – a patient population that is not relevant to the scope of this appraisal – received treatment with a venetoclax-based regimen as their 2L+ therapy (based on data received in March, July and September 2020, respectively, Figure 1).[3]<br><br>• These data demonstrate the importance of ensuring that the relevant patient population (i.e., BTKi-naïve patients) is considered rather than the entire 2L+ population when determining an appropriate estimate for second-line venetoclax plus rituximab use for the purpose of decision making.<br><br>**Figure 1. Proportion of patients receiving a venetoclax-based regimen in second- or subsequent-line by BTKi exposure (BTKi-naïve vs BTKi-treated)** | |

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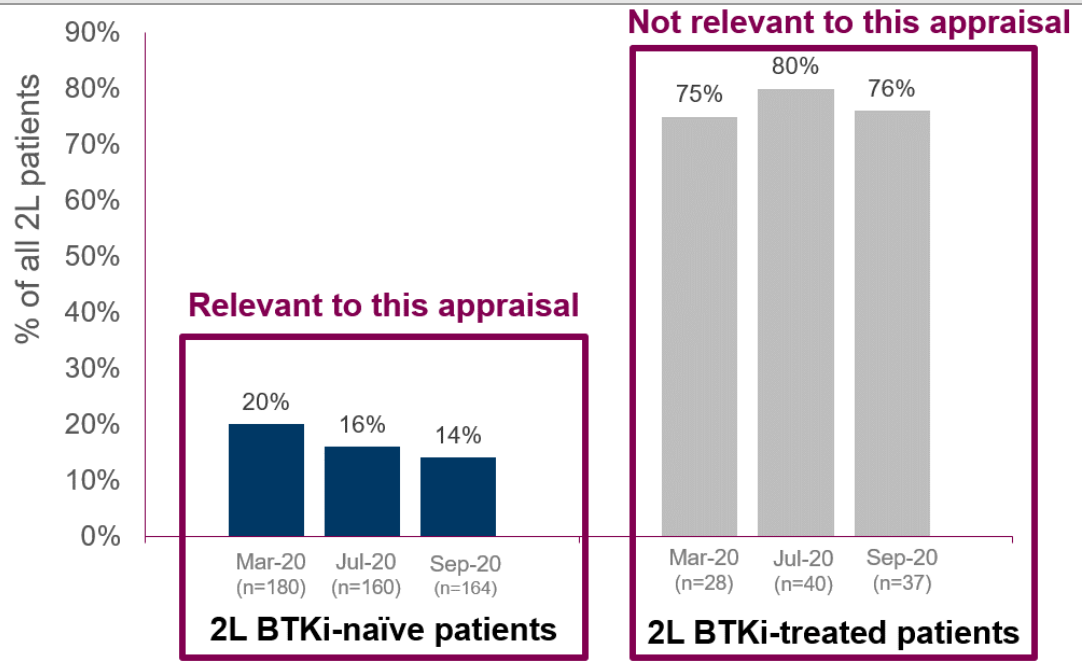
| | | |  <br>Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; 2L, second line; 2L+, second or subsequent line. Note. Venetoclax-based regimens included venetoclax monotherapy.<br><br>**The Company, the Evidence Review Group (ERG), and clinical experts agreed that the proportion of patients receiving venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab is not greater than 20%.**<br><br>• The ERG agreed with the real-world evidence provided by the Company and included a 13%:87% split of venetoclax plus rituximab relative to ibrutinib treatment following first-line chlorambucil plus obinutuzumab in their preferred modelling assumptions (slide 24 of the Appraisal Committee Meeting slides).[1]<br><br>• The ERG's clinical advisors also expect the majority of patients to receive subsequent treatment with ibrutinib following first-line chlorambucil plus obinutuzumab. In the ERG report, one clinical advisor stated that "*there is a general preference for the use of second-line ibrutinib over VenR, with more than 80% of patients receiving ibrutinib and less than 20% of patients receiving VenR*". Furthermore, the clinical advisor did not expect this split to | |

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| | | | change in the *"next few years"* as *"there is no need for ramping up dosage or monitoring for TLS with ibrutinib and fewer hospital attendances are required".*[4]<br><br>The Company acknowledge that the use of venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab may vary geographically across centres, and understand that some centres may primarily prescribe ibrutinib, and others venetoclax plus rituximab. However, NICE decisions should be made on a **national basis and reflect current NHS clinical practice**.<br><br>In conclusion, UK 2020 prescribing data (n=164 patients) from IQVIA does not support the assumption that current venetoclax plus rituximab usage is greater than 20%. When coupled with the data from a retrospective chart review of 202 UK patients (October 2019 – September 2020), the Company firmly believe that the modelled proportion of patients receiving venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab is overestimated in the Committee's preferred modelling assumptions and should not exceed 20% when informing decision making. | |
| 5 | Consultee (company) | AstraZeneca | **Treatment duration of second-line ibrutinib following progression with chlorambucil plus obinutuzumab should be based on evidence relevant to the patient population.**<br><br>In the Committee's preferred modelling assumptions, treatment duration of second-line ibrutinib following progression on chlorambucil plus obinutuzumab is underestimated and does not consider the confounding effect of previous lines of therapy.<br><br>The Committee's preferred scenarios use the ERG's second-line treatment costing model and a Weibull curve (derived from RESONATE PFS data for a cohort of patients who have received 1-2 prior lines of therapy) to estimate mean second-line treatment duration with ibrutinib following first-line chlorambucil plus obinutuzumab. This assumption results in an estimated mean treatment duration with second-line ibrutinib of 4.78 years.<br><br>The Company prefer to estimate the mean treatment duration using a log-normal curve (5.56 years), which was accepted as clinically plausible by the Committee. In Section 3.14 of the ACD it was noted that: *"The committee considered the log-normal parametric model to be plausible but preferred the Weibull [...]".* The Company believe that the Committee's preferred curve underestimates the duration of second-line ibrutinib following first-line chlorambucil plus obinutuzumab treatment.<br><br>• Within the NICE appraisal for venetoclax plus rituximab for previously treated CLL (TA561), mean second-line treatment duration with ibrutinib was estimated at 5.18 years. This estimate was derived from the full RESONATE intention-to-treat (ITT) population where patients received a median of 3 prior lines of treatment.[5] The TA561 Committee accepted this estimate, and it was subsequently used to inform decision making.<br><br>• Long-term data from RESONATE (O'Brien et al. 2019) demonstrates that 74% of patients in | Comments noted. The committee considered your comments. Section 3.14 of the FAD has been revised as follows: "The committee considered the log-normal parametric model to be plausible but preferred the Weibull as it was less constrained by overall survival gains. It agreed that the treatment duration with second-line ibrutinib was uncertain, with the most plausible estimate likely to be between that estimated using the log-normal and the Weibull distributions…. It concluded that the ERG's model for costing subsequent treatments was appropriate, but that it would consider scenarios using the lognormal and Weibull distributions." |

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the ibrutinib cohort who had received 1-2 prior lines remained progression-free at 36 months (Figure 1A O'Brien 2019).[6] In addition, the differences in PFS between treatment-naïve patients versus those receiving ≥3 lines of therapy and patients receiving 1-2 lines versus ≥3 lines of therapy were statistically significant (p-value < 0.0001 and p-value = 0.0109, respectively).[6] The number of prior lines of treatment has been shown to have a large impact on median PFS. RESONATE PFS data split by prior lines of treatment (Munir et al. 2019) demonstrates that median PFS was longer in patients who have had fewer prior lines, with median PFS not reached in patients who had only received 1 prior line (Table 2).[7]<br><br>
Table 2. Median PFS by prior line of therapy (Munir 2019, Figure 2A[7])
<table>
<tr><th>ines of therapy</th><th>1 (n=35)</th><th>2 (n=57)</th><th>3 (n=32)</th><th>4 (n=27)</th><th>≥5 (n=44)</th></tr>
<tr><td>Median PFS (months) (95% CI)</td><td>NR<br>(44.4 – NE)</td><td>67.3<br>(36.0 – NE)</td><td>44.1<br>(25.4 – NE)</td><td>33.0<br>(13.6 – NE)</td><td>27.3<br>(22.0 – 40.8)</td></tr>
</table>
Abbreviations: CI, confidence interval; NE, not estimated; NR, not reached PFS, progression-free survival.<br><br>
• By modelling a mean second-line treatment duration of 4.78 years, the Committee are assuming that patients with previously untreated CLL who will have received first-line chlorambucil plus obinutuzumab will be subject to reduced PFS on subsequent treatment than was observed in the full ITT RESONATE population (who received a median of 3 prior lines of therapy).<br><br>
• It is clear from the data presented in O'Brien et al. 2019 and Munir et al. 2019 that the number of lines of therapy is a confounding factor in duration of PFS on second-line ibrutinib.[6,7] Therefore, it is reasonable to assume that a patient population who have received 1 prior line of therapy should remain progression-free for longer on second-line ibrutinib when compared to the full RESONATE ITT population. Therefore, the Committee's decision to assume a shorter treatment duration than that reported for the full RESONATE ITT population (4.78 years versus 5.18 years [mean duration accepted for decision making during TA561]) unfairly underestimates subsequent treatment costs in the chlorambucil plus obinutuzumab group.
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<tr><td>6</td><td>Consultee (company)</td><td>AstraZeneca</td><td>A survival benefit is expected for acalabrutinib based on clinical evidence and rationale.</td><td>Comments noted. The committee considered your</td></tr>
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| | | | The Company acknowledge the uncertainty surrounding long-term survival benefit, but believe the clinical support and evidence have not been appropriately considered when determining the Committee's preferred modelling assumptions for post-progression survival.<br><br>Section 3.15 of the ACD states:<br><br>• *"The data from ELEVATE-TN showed a trend towards improved overall survival for acalabrutinib compared to chlorambucil plus obinutuzumab. But the data were immature, with a median follow-up at 28 months, and the difference between the groups was not statistically significant."*<br><br>• *"The clinical experts suggested that overall survival was likely to be longer when starting a treatment with acalabrutinib followed by venetoclax plus rituximab. This is because it is more effective and less toxic than chlorambucil plus obinutuzumab followed by ibrutinib".*<br><br>• *"They [the clinical experts] considered it reasonable to use MURANO because it accurately reflects the most likely treatment sequence of acalabrutinib followed by venetoclax plus rituximab. The clinical experts also explained that it was reasonable to expect that people may reach the life expectancy of the general population after treatment with acalabrutinib and may be functionally cured."*<br><br>Despite the statements above, the Committee's preferred modelling scenarios utilise data from the RESONATE trial to inform post-progression survival for both acalabrutinib and chlorambucil plus obinutuzumab. This approach assumes that the risk of death following treatment with acalabrutinib and chlorambucil plus obinutuzumab is equivalent. The Company disagree with this approach for the following reasons:<br><br>• **Clinical experts support the Company's modelling assumptions.** The clinical experts present at the Appraisal Committee Meeting (5th November 2020) fully supported the assumption that patients treated with acalabrutinib followed by venetoclax plus rituximab would benefit from an extension in overall survival compared to those treated with chlorambucil plus obinutuzumab followed by ibrutinib. This is highlighted within Section 3.15 of the ACD.<br><br>• **The introduction of more efficacious treatments earlier on in the pathway will improve long-term survival.** Acalabrutinib is a highly efficacious new treatment for patients with previously untreated CLL. Treatment with acalabrutinib resulted in an 80% reduction in the risk of progression when compared to chlorambucil plus obinutuzumab within the ELEVATE-TN trial (hazard ratio [HR]: 0.20; 95% confidence interval [CI]: 0.13, 0.30; p<0.0001).[8] Data from other novel agents, such as ibrutinib and venetoclax plus rituximab, clearly demonstrate | comments and consulted the clinical expert opinion at the second committee meeting. Section 3.14 of the FAD has been revised as follows: "The clinical experts suggested that overall survival was likely to be longer when starting treatment with acalabrutinib followed by venetoclax plus rituximab. This is because it is more effective and less toxic than chlorambucil plus obinutuzumab followed by ibrutinib. However, long-term data confirming overall survival benefit is lacking at present. They considered it reasonable to use MURANO because it accurately reflects the most likely treatment sequence of acalabrutinib followed by venetoclax plus rituximab. One clinical expert also explained that it was reasonable to expect that many people will reach the life expectancy of the general population after treatment with acalabrutinib and will be functionally cured. The other clinical expert did not consider this plausible. The committee concluded that there was considerable uncertainty in the overall survival estimates for acalabrutinib because of the extrapolation using data from trials for other treatments and the immature data from ELEVATE-TN." |

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| | | | that an early PFS benefit does indeed translate into a long-term survival benefit (ibrutinib vs. ofatumumab: PFS HR: 0.15; CI: 0.11, 0.20; p<0.0001; OS HR [adjusted for cross-over]: 0.64; CI: 0.42, 0.98; p=not reported [NR]; venetoclax plus rituximab vs BR: PFS HR: 0.16; CI: 0.12, 0.23; p<0.001; OS HR: 0.50; CI: 0.30, 0.85; p=0.0093).[7,9] Furthermore, chlorambucil plus obinutuzumab is a highly toxic treatment option. Feedback from UK clinicians was that the use of a non-DNA damaging agent, such as acalabrutinib, are likely to result in reduced mutagenesis compared to chemo-immunotherapies, which in turn, is likely to result in a less aggressive cancer that is easier to treatment at subsequent lines, and hence will translate into improved survival outcomes.<br><br>• **The Committee's preferred modelling assumptions do not reflect the treatment pathway in England.** Patients treated with acalabrutinib in the first-line setting are most likely to receive venetoclax plus rituximab in the second-line setting. The Committee, the ERG, UK clinical experts and the Company are all in agreement with this assumption. However, by choosing to inform post-progression survival following treatment with acalabrutinib based on RESONATE data, the Committee are not appropriately reflecting the outcomes associated with treatment with venetoclax plus rituximab. Instead, the Committee are assuming that patients will incur the cost of venetoclax plus rituximab whilst gaining the outcomes associated with treatment with ibrutinib second-line treatment. The Company consider this assumption inappropriate, and believe that it is more suitable to align outcomes with costs (i.e., use MURANO data [venetoclax plus rituximab survival data] to inform post-progression survival with acalabrutinib).<br><br>**The Committee's approach to base decision making on scenario analyses in which the overall survival gain for acalabrutinib compared to chlorambucil plus obinutuzumab is reduced by 50% is not supported by clinical rationale and is considered clinically implausible by the Company.**<br><br>When combined with the Committee's preferred modelling assumption of using RESONATE to inform post-progression for both treatment arms, this adjustment results in the risk of death following treatment with acalabrutinib being higher than that following treatment with chlorambucil plus obinutuzumab. **There is no clinical rationale for this assumption**.<br><br>The modelling approach forces the overall survival benefit to be 50% lower by increasing the risk of death following progression in the acalabrutinib treatment arm (Figure 2 and<br><br>Figure **3**). Following clarification with the ERG, the Company understand that in order to achieve this reduction the ERG used the 'Goal Seek' Excel function to artificially alter the survival coefficients for risk of death following progression within the model. Therefore, the approach is a not robust or validated method, and it is not driven by any clinical evidence. In light of the clinical support for improved survival following treatment with the highly efficacious non-DNA damaging agent acalabrutinib, the Company consider this scenario to be **clinically implausible**, and hence unfit for | |

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| | | | decision making purposes.<br><br>**Figure 2. Post-progression survival adjusted to reduce acalabrutinib incremental survival gain by 50%***<br><br>  <br><br>Abbreviations: C+O, chlorambucil plus obinutuzumab; PPS, post-progression survival.<br>*Curves constrained by all-cause mortality<br><br>**Figure 3. Risk of post-progression death, adjusted to reduce acalabrutinib incremental survival gain by 50%*** | |

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| | | |  <br>Abbreviations: C+O, chlorambucil plus obinutuzumab; PPS, post-progression survival. *Curves constrained by all-cause mortality | |
| 7 | Consultee (company) | AstraZeneca | **Factual inaccuracies and confidential mark-up**<br><br>European Medicines Association (EMA) approval for acalabrutinib was received on the 5th November 2020.[10] The Company request that the word "anticipated" is removed in the following statements in the ACD to reflect this:<br><br>• Section 2: *"Anticipated marketing authorisation indication"*<br><br>Section 3.5: *"The company's submission did not include people with untreated CLL for whom FCR or BR is suitable, although this population was in the NICE scope and is included in the anticipated marketing authorisation for acalabrutinib."* | Comment noted. The committee considered your comment. The FAD has been updated by removing "anticipated" accordingly. |
| 8 | Consultee | UK CLL Forum/BSH/RCPath | We strongly support the request to use acalabrutinib as first line therapy in elderly patients and those with comorbidity who are not eligible for BR/FCR.<br><br>We are gravely concerned that the recommendations of the Committee will lead to health inequality and unnecessary toxicity in patients with untreated CLL with no high risk cytogenetics for whom BR/FCR is unsuitable for the following reasons:<br><br>Firstly, the recommendation states that in these cases "Chlorambucil and obinutuzumab is the only other option". The majority of patients with CLL who need treatment are not eligible for intensive chemo-immunotherapy (CIT) and therefore this very statement confirms the absence of treatment choice - effectively disenfranchising patients from actively engaging with clinicians. Patients and families are very aware of marketing authorisations and availability of acalabrutinib on the current Early Access Programme. | Comment noted. The committee considered your comment. The recommendations in section 1.1 of the FAD have now been updated as follows:<br>"Acalabrutinib is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:<br>• there is a 17p deletion or TP53 mutation, or<br>• there is no 17p deletion |

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| | | | | or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable, and<br>• the company provides the drug according to the commercial arrangement (see section 2)." |
| 9 | Consultee | UK CLL Forum/BSH/RCPath | Secondly: The Committee accepts that is reasonable to use the full Clinical Trial data from ELEVATE-TN in the untreated CLL model, agreeing with the clinical experts on the assumption that acalabrutinib has a "similar treatment effect for the populations who had untreated CLL whether or not they had high-risk CLL". This clearly creates the situation where patients with high risk TP53 altered CLL have access to treatment associated with a more favourable PFS and toxicity profile than patients without high risk CLL. Given the Committee accepts similar clinical outcomes after acalabrutinib regardless of risk group, we consider iniquitous the relegation of patients without high risk cytogenetics to inferior therapy with chlorambucil and obinutuzumab. | The recommendations in section 1.1 of the FAD have changed - see response to comment 8 |
| 10 | Consultee | UK CLL Forum/BSH/RCPath | Thirdly: The recommendation states that clinical experts suggest that survival is likely longer when starting treatment with acalabrutinib followed by venetoclax-rituximab. The recommendation goes on to state, "This is because it (acalabrutinib) is more effective and less toxic than chlorambucil – obinutuzumab followed by ibrutinib. The Committee accepts that the toxicity profile of acalabrutinib is more favourable than either or both of these therapies but pushes back on issues of overall survival based on immaturity of data without giving due weight to matters concerning toxicity and quality of life. It is the considered clinical experience of many treating haematologists that for many in this patient population quality of life is paramount.<br><br>The Committee accepts a median PFS of around 23 months following chlorambucil and obinutuzumab and models a period of 14 months ("cycles") following disease progression before second line therapy is likely during which time patients are likely to experience increasing symptoms and reduced quality of life. A period of recovery and recuperation after chemotherapy is usual during which persistent fatigue, cytopenia and immune suppression are experienced.<br><br>For many elderly patients, therefore the quality of a significant proportion of their remaining years are entirely determined by the choice of initial therapy and are more compromised by CIT than with BTK inhibitor therapy. | The recommendations in section 1.1 of the FAD have changed - see response to comment 8 |
| 11 | Consultee | UK CLL Forum/BSH/RCPath | Fourthly: We are extremely concerned that infection risk is not taken into full consideration. It is well documented that anti-CD20 antibody therapy exacerbates hypogammaglobulinaemia in CLL and that low immunoglobulin levels are associated with increased risk of infection such as community acquired pneumonia as well as poor dynamic response to vaccination. | The recommendations in section 1.1 of the FAD have changed - see response to comment 8 |

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| | | | There is growing evidence that patients with CLL are at increased risk of developing severe forms of SARS-Cov-2 infection with markedly increased risk of dying from complications of COVID-19. Patients with CLL are considered to be in the Clinically Extremely Vulnerable (CEV) group. Shielding has been an effective mechanism to avoid infection but comes at the price of social isolation and a significant mental health burden.<br><br>The use of first line chlorambucil with obinutuzumab carries significant and specific risks in this regard. We are extremely concerned that such Chemo Immunotherapy will increase COVID risks compared with acalabrutinib.<br><br>Chlorambucil with obinutuzumab is likely to significantly abrogate the effectiveness of any COVID-19 vaccine during therapy and for many months after treatment as well as increasing the risk for our patients of contracting the infection through increased footfall as daycase patients as well as higher likelihood of admission for neutropenic pyrexia or Tumour Lysis Syndrome. Patients will be put at higher risk of COVID and place additional strain on NHS acute beds at a time of national crisis.<br><br>Additionally, in the absence of treatment choice other than CIT, clinicians and patients may decide to defer therapy beyond normal treatment thresholds. This may ultimately increase side effects of therapy and exacerbate disease related symptoms.<br><br>Access to acalabrutinib for all cytogenetic risk groups in the elderly CEV population would, in our opinion, reduce risk of unnecessary treatment delay, mitigate risks around COVID to a significant extent and take some pressure off clinical services. | |
| 12 | Consultee | UK CLL Forum/BSH/RCPath | The published guidelines (BSH, ESMO, NCCN) have become increasingly obsolete in the face of new clinical trial data as well as new NICE Technology appraisal guidance. In particular NICE TA663 Venetoclax with obinutuzumab for untreated CLL. This guidance means that for younger fitter patients, non CIT therapy has become a treatment option. However we are very concerned that TA663 has also exposed considerable inequity of access to a non CIT option in older patients or patients with comorbidity in whom venetoclax-obinutuzumab is not a suitable option.<br><br>We are concerned that patients with high risk cytogenetics or fitter elderly patients will have therapeutic choices denied the more frail and more vulnerable patient population. | The recommendations in section 1.1 of the FAD have changed - see response to comment 8 |
| 13 | Consultee | UK CLL Forum/BSH/RCPath | In summary we believe it is this very group of vulnerable elderly or comorbid patients without high risk cytogenetics who would benefit most from access to acalabrutinib during and beyond this COVID pandemic and we urge the Committee to broaden the scope of TA 1613 to recommend acalabrutinib as an option for patients with untreated CLL without 17p deletion or TP53 mutation in whom BR/FCR and venetoclax with obinutuzumab are unsuitable. | The recommendations in section 1.1 of the FAD have changed - see response to comment 8 |
| 14 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma | A choice of treatment options is vitally important for all CLL patients, both due to the heterogeneity of the disease but also because the comorbidities that are often present in this older population mean that not all treatments are suitable for every patient.<br>The limited approvals granted as a result of this TA are very disappointing to the patient community | Comment noted. The committee considered your comment. The recommendations in section 1.1 of the FAD have now been |

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| | | Action<br>Joint response on behalf of both charities | and the decisions appear to be based predominantly on finance which does not give confidence in NICE's evaluation and decision processes for the clinical and patient communities. | updated as follows:<br>"Acalabrutinib is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:<br>• there is a 17p deletion or TP53 mutation, or<br>• there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable, and<br>the company provides the drug according to the commercial arrangement (see section 2)." |
| 15 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action<br>Joint response on behalf of both charities | We are concerned that the NICE Appraisal recommendations appear to be substantially financially based for the treatment naive patients with TP53 disruption or 17p deletion, **although we welcome the approval for this group.**<br>Acalabrutinib is approved - quote:- "**despite the uncertainties**, because it is likely to be cost-saving compared with ibrutinib. So acalabrutinib is recommended for routine use in the NHS for this group. | Comment noted. The reference to cost-saving is made because of the type of cost-minimisation analysis the company presented. |
| 16 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action<br>Joint response on behalf of both charities | For previously treated CLL we have the same concerns that the recommendation is significantly based on finance again despite uncertainties, **although we welcome the approval for this group.**<br>quote - "**despite the uncertainties,** acalabrutinib is likely to be cost- saving compared with ibrutinib. So acalabrutinib is recommended for routine use in the NHS for people with previously treated CLL. | Comment noted. The reference to cost-saving is made because of the type of cost-minimisation analysis the company presented. |
| 17 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action<br>Joint response on | In addition, the ACD states: "**Acalabrutinib ONLY when Ibrutinib is their ONLY suitable treatment option because it is cheaper".**<br>Ibrutinib will not be a suitable treatment option for patients with cardiac issues or those on anticoagulant therapy and so Acalabrutinib will not be available to that group. Clinically this is one of the main advantages of Acalabrutinib over Ibrutinib, especially for this group of patients but that has now been removed as an option for them. | Comment noted. The committee considered your comments. The recommendations in section 1.2 of the FAD have been updated as follows: "Acalabrutinib is recommended as an option for |

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| | | behalf of both charities | Ibrutinib will rarely be the only suitable treatment option now that VenO has been approved (via the CDF for treatment naïve patients) but we need a range of treatment options as patients often need more than one treatment for their relapsed and remitting CLL. | treating CLL in adults who have had at least 1 previous treatment, only if:<br>• the company provides the drug according to the commercial arrangement (see section 2)."<br>See also section 3.22 of the FAD |
| 18 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action<br>Joint response on behalf of both charities | The final scope included the possibility of various sub-groups of CLL patients to be considered if the evidence allowed for it and patients with unmutated IgHV disease could have been considered.<br>There is mounting evidence that these patients statistically have very much shorter remissions when treated with chemoimmunotherapy.<br>Despite uncertainties, approval was granted for other groups and this group should be considered separately, particularly for treatment naïve patients. A paper in NEJM 2020 by Shanafeldt et al showed considerable survival advantage with Acalabrutinib in this group of patients with unmutated IgHV status. | The committee has recommended acalabrutinib in all the populations the company submitted evidence for. |
| 19 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action<br>Joint response on behalf of both charities | As a patient group we are very disappointed that untreated patients who are suitable for FCR/BR were not within the scope of this TA even though the licence is for all untreated CLL patients.<br>There must be reassurance that this will be reviewed at the earliest opportunity, as soon as evidence becomes available (including real world evidence), rather than wait for the automatic NICE review period to expire. | Comment noted. The company did not present evidence for this population and so the committee could not make any recommendations. NICE will review the guidance if relevant evidence is presented for this population. |
| 20 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action<br>Joint response on behalf of both charities | With the COVID pandemic refusal to grant access to Acalabrutinib for all CLL patients means that many will be denied a safe, oral and effective treatment that will keep them away from the hospital environment. ALL the other treatment options available to treatment naïve and relapsed patients (FCR, BR, ChlO, VenO) with the exception of Ibrutinib require attendance for intravenous treatments and the increased risk of adverse events including infection with associated morbidity and mortality.<br>The free access programme for Acalabrutinib has provided many patients who are unfit for chemoimmunotherapy with a safe, oral treatment during the pandemic and has been welcomed by NHS Consultants. | The recommendations in section 1.1 of the FAD have changed - see response to comment 8. |
| 21 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action | The decision not to approve Acalabrutinib for treatment naive patients who do not have TP53 disruption or 17p deletion has further widened the health inequalities gap with regard to access to targeted treatments for this group of patients. Whilst there is a group of patients for who FCR is likely to give a durable remission, the unmutated IgHV group and those with complex genetics will do particularly badly with this chemotherapy based treatment and suffer toxicities. The first treatment | The recommendations in section 1.1 of the FAD have changed - see response to comment 8 |

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| | | Joint response on behalf of both charities | that patients receive is the most significant in determining their overall survival and quality of life. This cannot be acceptable or justifiable and we ask NICE to consider the use of the CDF for these patients as was done for Ven+O which also had data uncertainties and lacked comparative data. | |
| 22 | Consultee | Chronic Lymphocytic Leukaemia Support and Lymphoma Action<br>Joint response on behalf of both charities | In summary, whilst we welcome the approvals as a result of this TA we feel that they are too limited, are based very significantly on finance considerations and deny access to many patients who would benefit greatly from this treatment. | The recommendations in section 1.1 of the FAD have changed - see response to comment 8 |
| 23 | Commentator | AbbVie Ltd | Section 1.1 page 3 states that acalabrutininb is only recommended as an option if ibrutinib is their only treatment option.<br><br>This is appropriate given that acalabrutinib has not demonstrated cost-effectiveness versus venetoclax plus rituximab. To avoid confusion on the population suitable for acalabrutinib and ensure venetoclax plus rituximab is duly considered within its NICE recommendation we propose the following wording:<br><br>Acalabrutinib is recommended as an option for treating CLL in adults who have had at least 1 previous treatment, only if:<br>• venetoclax plus rituximab is not a suitable treatment option, and<br>• the company provides it according to the commercial arrangement (see section 2).<br><br>The relevant wording should be clearly reflected by NHSE in all commissioning guidance and systems to ensure appropriate implementation. | Comment noted. The recommendations in section 1.2 of the FAD have been updated. See also section 3.22 of the FAD. |
| 24 | Commentator | AbbVie Ltd | Section 4.1 Page 22 states that acalabrutinib has been available through an early access to medicines scheme (EAMS), however there does not appear to be a record of this on the EAMS database. | Comment noted. This was an error and has been corrected. |
| 25 | Commentator | Janssen-Cilag | Section 1.2 of the ACD lays out the Committee's preliminary recommendation on the use of acalabrutinib in CLL patients treated in the relapsed/refractory setting:<br><br>*"Acalabrutinib is recommended as an option for treating CLL in adults who have had at least 1 previous treatment, only if:*<br>*- ibrutinib is their only suitable treatment option, and*<br>*- the company provides it according to the commercial arrangement (see section 2)."*<br><br>The restriction "*ibrutinib is their only suitable treatment option*" may be open to different interpretations. It could be read as acalabrutinib can be used in patients that could receive ibrutinib (a broad interpretation) or for patients that their only option is ibrutinib (narrow interpretation). In this | Comment noted. The recommendations in section 1.2 of the FAD have been updated. See also section 3.22. |

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| | | | second case, patients that are suitable for venetoclax + rituximab could not receive acalabrutinib but could receive ibrutinib. Janssen would welcome further clarity on the wording of the restriction. | |
| 26 | Commentator | Janssen-Cilag | Section 3.16 of the ACD discusses the assumptions retained by the Committee in the base-case cost-effectiveness analyses for untreated CLL patients when FCR or BR is unsuitable.<br><br>With regards to modelling post-progression survival, the Committee explains how, while incorporating the ERG' preferred assumption "*using RESONATE post-progression survival for both treatment arms*", "*it also considered that further assumptions should be included in that base-case*", including "*adjusting the overall survival gain for acalabrutinib compared with chlorambucil plus obinutuzumab such that it was 50% lower, reflecting uncertainty about the immature survival data in ELEVATE-TN*".<br><br>Adjusting the survival gain of acalabrutinib versus chlorambucil plus obinutuzumab to assume that it is 50% lower does not seem appropriate for consideration within the base-case. Janssen acknowledges that the evidence from the ELEVATE-TN trial is still immature and therefore it is important to test uncertainty through survival scenarios. However, Janssen would welcome further clarity on the choice of a 50% adjustment as this does not appear to align with clinical expert opinion as expressed in the ACD document (section 3.15). | The committee considered this a relevant scenario given the immaturity of the data. It is not inconsistent with the clinical experts' comments, as this scenario still assumes a survival benefit with acalabrutinib. |
| 27 | Consultee | Leukaemia Care | We are disappointed to see an optimised recommendation be made. These are increasing in blood cancer appraisals, as outlined in the Blood Cancer Alliance Access to Medicines report. We wish to see treatments made available in all clinically appropriate groups. | Comment noted. The recommendations have changed and the committee has now recommended acalabrutinib in all populations for which the company submitted evidence. |
| 28 | Consultee | Leukaemia Care | The group in which the treatment has not been recommended, those who are untreated and unable to have FCR or BR, require alternative treatment options. There are no other BTK inhibitors available in this population until relapse from another therapy, and there is good evidence of efficacy in this group, as outlined by the clinical experts at the meeting. | Comment noted. The committee considered your comment. The recommendations in section 1.1 of the FAD have now been updated as follows:<br>"Acalabrutinib is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:<br>• there is a 17p deletion or TP53 mutation, or<br>• there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is |

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| | | | | unsuitable, and<br>• the company provides the drug according to the commercial arrangement (see section 2).” |
| 29 | Consultee | Leukaemia Care | Having a range of available treatments is more important than ever in the COVID-19 era. Alternative treatments for those who cannot have FCR or BR often involve time in hospital and/or significant immune suppression is a side effect, both of which are desirable to avoid currently and likely for some time yet. | Comment noted. See response to comment 28. |
| 30 | Consultee | Leukaemia Care | The excluded group may also contain others who not suitable for FCR for reasons that have not been explored in the trials and as subgroups here. Clinical studies state that other genetic changes such as IGHV mutation and chromosome aberrations can affect response to chemoimmunotherapy options. | Comment noted. |
| 31 | Consultee | Leukaemia Care | One uncertainty outlined in the ACD concerns the average length of time a person is treated with ibrutinib. This is something that has been discussed in previous appraisals, such as that of venetoclax and rituximab, and so there is precedence for this that should be considered. We believe 5 years to be a reasonable assumption, which both the clinical experts agreed with in the committee meeting but does not seem to have been taken into account in the decision-making. This is an uncertainty which could be resolved in the CDF as well. | Comment noted. The committee considered this scenario in decision-making see section 3.16 of the FAD. |
| 32 | Consultee | Leukaemia Care | If the committee is not minded recommending this population for the CDF, we ask they consider earlier review as further data is expected. | Comment noted. Acalabrutinib is now recommended in all population the company submitted evidence for. |
| 33 | Consultee | Leukaemia Care | Uncertainty about overall survival is common in appraisals of CLL treatments due to the nature of the disease. Therefore, some flexibility is need in decision making here. The ACD states that the clinical experts supported the company’s modelling for survival after acalabrutinib and that life expectancy could match the general population, but it is unclear how this clinical advice impacted upon the committee’s decision making. Additionally, this could be resolved by use of the CDF as clinical trials are ongoing. | Comment noted. |
| 34 | Consultee | Leukaemia Care | Whilst there may be uncertainty around the proportion of people receiving venetoclax and rituximab second line, NICE make a decision nationally and so the national average needs to be ascertained and considered. This is something that could be done whilst the treatment is in the CDF if necessary. | Comment noted. |
| 35 | Consultee | Leukaemia Care | We ask the committee to reconsider the CDF to resolve the uncertainties listed above. | Comment noted. |
| 36 | Consultee | Leukaemia Care | We disagree with the narrowing of the population who can access acalabrutinib as a second line or subsequent therapy to those who would otherwise have had ibrutinib. We are unclear as to the basis for this decision from the information provided in the ACD. | Comment noted. Acalabrutinib is now recommended in all population the company submitted evidence for. |
| 37 | Commentator | [NCRI] | The decision not to fund acalabrutinib for patients with CLL without TP53 abnormalities (fit or frail) in first-line comes as a great disappointment to the clinical community.<br>We understand that the dominant driver behind this decision is the cost of acalabrutinb for the NHS. When ibrutinib was licenced, Janssen decided not to submit an application for frontline use of ibrutinib | Comment noted. The committee considered your comment. The recommendations in section 1.1 of the FAD have now been |

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| | | | knowing that it would force a significant reduction of its price. We thank AZ for submitting this technology appraisal and for having made acalabrutinib available to UK patients in an Early Access Programme due to close in April 2021.<br>We plea to NICE, AstraZeneca and the NHS to re-consider the decision and to negotiate a pricing solution that is acceptable to all stake holders. | updated as follows:<br>"Acalabrutinib is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:<br>• there is a 17p deletion or TP53 mutation, or<br>• there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable, and<br>• the company provides the drug according to the commercial arrangement (see section 2)." |
| 38 | Commentator | [NCRI] | The Phase 3 data from the ELEVATE study was reviewed by the Committee. The study uses the correct comparator for frail patients i.e: Chlorambucil +Obinutuzumab (CO) that is the current NICE-approved standard of care for patients with treatment naïve CLL in the NHS. The study shows a significant PFS advantage for patients treated with acalabrutinib compared to the current NICE standard. | Comment noted |
| 39 | Commentator | [NCRI] | The drug also shows favourable toxicity profile, and -contrary to CO- is orally available and does not require chair time, which is a major argument with and without a COVID pandemic.<br>There is therefore little uncertainty with respect to the superiority of acalabrutinib in this indication, and this therapy should therefore be given a favourable response for all frail frontline patients. | Comment noted. Acalabrutinib is now recommended in this population. |
| 40 | Commentator | [NCRI] | Irrespective of the model system used, the OS modelling for any highly efficacious therapy will be uncertain in an era when many novel and highly efficacious therapies are given sequentially. As clinicians, we know that this has had already a very significant positive impact on the overall survival of our patients, but we cannot easily quantify the extent of benefit yet. This will only be possible from longer-term real-world data collection. | Comment noted |
| 41 | Commentator | [NCRI] | We echo the patient support organisations' deep regret that fit patients with CLL were not within scope of this TA. We admit that there is theoretical uncertainty about the use of the second-in-class BTKi acalabrutinib in fit patients as the ongoing study results are still awaited. However, it is not plausible to refuse fit patients access to this class of drugs when the first-in-class BTKi ibrutinib showed an overall | Comment noted. The company did not present evidence to show clinical or cost-effectiveness of acalabrutinib for |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | survival advantage compared to FCR (Shanafeldt T et al NEJM 2020) in fit patients, esp those with unmutated IgHV status. This data was not considered in the initial consultation. We would therefore urge NICE to make acalabrutinib available via the CDF for fit patients in the same way as Ven-Obinutuzumab has been made available without data for this patient group. | patients with untreated CLL who are able to receive FCR/BR. |

There were no web comments to the ACD.

NICE National Institute for Health and Care Excellence

**Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]**

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | AstraZeneca |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| Comment number | Comments |
|---|---|
| 1 | **Summary of the Company's position**<br><br>The Company would like to thank the Committee for the opportunity to respond to the Appraisal Consultation Document (ACD).<br><br>The Company welcome the recommendations made by the Committee for acalabrutinib as a treatment option for:<br><br>1. Previously untreated chronic lymphocytic leukaemia (CLL) in adult patients who have a 17p deletion or TP53 mutation.<br>2. Previously treated CLL in adult patients who have had at least 1 previous treatment if ibrutinib is their only other suitable treatment option.<br><br>However, the Company consider the wording of the recommendation for patients who have received at least 1 previous treatment is restrictive, and that it does not allow clinicians to treat patients who are intolerant to ibrutinib with a Bruton tyrosine kinase inhibitor (BTKi). The Company invite the Committee to consider the alternative wording detailed in comment 2 below.<br><br>Furthermore, the Company are concerned that despite the evidence submitted by the Company and expressed by clinical experts, coupled with the support from CLL patient group representatives, the Committee have not recommended acalabrutinib for the treatment of non-high-risk previously untreated CLL (i.e., patients who do not have a |

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| | 17p deletion or TP53 mutation) when therapy with fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR) is unsuitable.<br><br>In response to this decision, the Company would like to highlight the following key points for consideration by the Committee:<br><br>1. There is a high unmet need for alternative treatment options, with different mechanisms of action, to the current selection of first-line treatments available for previously untreated CLL in non-high-risk patients unsuitable for FCR or BR therapy.<br>2. The proportion of patients receiving second-line venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab has been overestimated by the Committee and does not reflect current National Health Service (NHS) clinical practice in England in the Committee's preferred modelling assumptions.<br>3. The treatment duration of second-line ibrutinib following treatment with chlorambucil plus obinutuzumab is underestimated and does not consider the confounding effect of previous lines of therapy on progression-free survival (PFS).<br>4. Clinical support and evidence have not been appropriately considered in decision making when determining the Committee's preferred modelling assumptions for post-progression survival.<br><br>Comments 3 to 6 detail the Company's position on these points. In addition, the Company noted one factual inaccuracy within the ACD; this is detailed in comment 7.<br><br>In light of the evidence presented in comments 3 to 6, the Company consider the scenarios presented within Table 1 to be clinically plausible and suitable for decision making. Two additional exploratory scenarios are presented with the aim of alleviating the Committee's concerns on long-term survival estimates.<br><br>As heard from the Patient Groups and the clinical experts at the Appraisal Committee Meeting (5th November 2020), there is a significant unmet need in non-high-risk previously untreated CLL patients who are ineligible for FCR or BR therapy. Current treatment options are limited, and the Company is committed to addressing this unmet need. Furthermore, acalabrutinib remains a cost-effective treatment option relative to chlorambucil plus obinutuzumab within this patient population at the Patient Access Scheme (PAS) price of £[redacted] per 30-day pack of 100 mg tablets compared to comparator list price, across all scenarios presented in Table 1. Therefore, the Company would like to invite the Committee to consider the evidence presented within this response and to reconsider their decision on acalabrutinib for the treatment of non-high-risk previously untreated CLL (i.e., patients who do not have a 17p deletion or TP53 mutation) when therapy with FCR or BR is unsuitable. |

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**Table 1. Cost-effectiveness scenario analyses for acalabrutinib PAS price versus comparator list prices**

| Scenario[1] | Inc. cost (£) | Inc. QALYs | ICER (£) |
|---|---|---|---|
| 1. Company preferred base-case | [redacted] | [redacted] | Dominating |
| 2. ERG preferred base-case | [redacted] | [redacted] | 8,868 |
| 3. Company base case (scenario 1) plus 20% V+R usage following first-line C+O | [redacted] | [redacted] | Dominating |
| 4. ERG base case (scenario 2) plus 20% V+R usage following first-line C+O | [redacted] | [redacted] | 15,320 |
| ***Exploratory scenarios*** | | | |
| 5. ERG base case (scenario 2) plus 50% reduction in acalabrutinib survival benefit | [redacted] | [redacted] | 6,853 |
| 6. ERG base case (scenario 2) plus 50% reduction in acalabrutinib survival benefit and 20% V+R usage following first-line C+O | [redacted] | [redacted] | 14,996 |

Abbreviations: C+O, chlorambucil plus obinutuzumab; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; V+R, venetoclax plus rituximab.
1. Please refer to Table 3, Appendix 1 for model settings.

2

**The wording of the recommendation made by the Committee for patients who have received at least 1 previous treatment is restrictive and does not allow clinicians to treat patients who are intolerable to ibrutinib with a BTKi.**

The Company regard the wording within the Committee's recommendation of acalabrutinib in patients who have received at least 1 previous treatment to be unnecessarily restrictive.

The restriction to patients for whom *"ibrutinib is their only other suitable treatment option"* does not allow for cases where a clinician would prefer to treat with a BTKi but are unable to do so either because ibrutinib is contraindicated (i.e., due to cardiac comorbidities) or intolerable.

Therefore, the Company urge the Committee to reconsider the wording of the draft recommendation and amend it to allow for patients for whom a BTKi would be their most suitable treatment option:

- *"Acalabrutinib is recommended as an option for treating previously treated CLL in adult patients who have had at least 1 previous treatment, only if a BTKi is their most suitable treatment option."*

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| 3 | **There is a high unmet need for alternative treatment options with different mechanisms of action to current first-line treatments, especially in non-high-risk previously untreated CLL patients when FCR or BR is unsuitable.**<br><br>Treatment of patients with previously untreated non-high-risk CLL is currently restricted to chemo-immunotherapies, such as chlorambucil plus obinutuzumab. Chlorambucil plus obinutuzumab is associated with considerable adverse and toxic effects. Patients express that these toxic effects have a large impact on their quality of life and that there is an urgent unmet need for new, more tolerable treatment options.[1]<br><br>• *My husband has been on [this] for a year now and suffers harsh bone pain, difficulty breathing and massive bruising with bleeding on arms. His illness has become our life. His blood counts have improved but the side effects are difficult. We wish there was an alternative therapy".*<br><br>• *"Urgent unmet need for first line treatment in people who are not high risk".*<br><br>As noted in Section 3.1 of the ACD, patient experts explained that the physical and psychological effects of CLL have a debilitating effect on their daily lives. The Committee concluded that CLL substantially affects both physical and psychological aspects of quality of life. In Section 3.2, it is also stated that *"chlorambucil plus obinutuzumab is the only other option so targeted treatments such as acalabrutinib are needed"* and *"the committee concluded that acalabrutinib would be welcomed as a new treatment option for people with CLL."*<br><br>[redacted]<br><br>Clinical experts, patient group representatives, the Committee, and the Company, all recognise the urgent unmet need for alternative, novel, less toxic and more efficacious treatment options, such as acalabrutinib, to diversify the treatment pathway and offer more options to patients in the first-line setting. It is clear that there is heterogeneity within this patient population, highlighted by the intolerability of current options in some patients. This further demonstrates the need for a wider range of alternative effective treatment options. In light of this, the Committee's decision to not recommend acalabrutinib within this setting continues to limit treatment options to more toxic and less efficacious chemo-immunotherapies. |
| 4 | **The proportion of patients receiving second-line venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab is not greater than 20% in current clinical practice for NHS England.**<br><br>In the Committee's preferred modelling assumptions, the proportion of patients receiving second-line venetoclax plus rituximab following treatment with chlorambucil |

plus obinutuzumab is overestimated and does not reflect current clinical practice for NHS England.

Section 3.13 of the ACD states: *"The clinical experts explained that venetoclax plus rituximab was a relatively recent treatment option. It was likely to account for between 20% and 50% of second-line treatment after chlorambucil plus obinutuzumab and would increase over time."* However, in the public section of the Appraisal Committee Meeting (Part 1) the two clinical experts attending the Meeting did not indicate that the use of venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab would reach 50%. Professor Adrian Bloor stated that he did **not** expect venetoclax plus rituximab use relative to ibrutinib to reach 50:50 in the future, and Professor Anna Schuh stated that she agreed that the Company's estimate of 13% was reflective of current treatment patterns.

Therefore, the Company are concerned with the Committee's decision to assume that venetoclax plus rituximab use following chlorambucil plus obinutuzumab could reach up to 50%. The Company do not agree with this decision and believe it does not align with the available evidence base or clinical expert opinion.

**Real-world evidence**

- Data from a retrospective chart review of 202 UK patients with CLL showed that between October 2019 and September 2020 only [redacted]% of patients received second-line treatment with a venetoclax plus rituximab.[2]

- Updated UK patient-level prescription data collected by IQVIA in September 2020, indicated that 14% of second-line and subsequent line (2L+) BTKi-naïve patients (n=164) were receiving a venetoclax-based regimen (either venetoclax monotherapy or in combination with rituximab). Of the 14% on venetoclax-based regimens, it was estimated that 20% received venetoclax monotherapy, a treatment option outside the scope of this appraisal. As such, as of September 2020, the split of second-line treatments for BTKi-naïve patients in the UK is estimated to be 11%:89% for venetoclax plus rituximab relative to ibrutinib.[3]

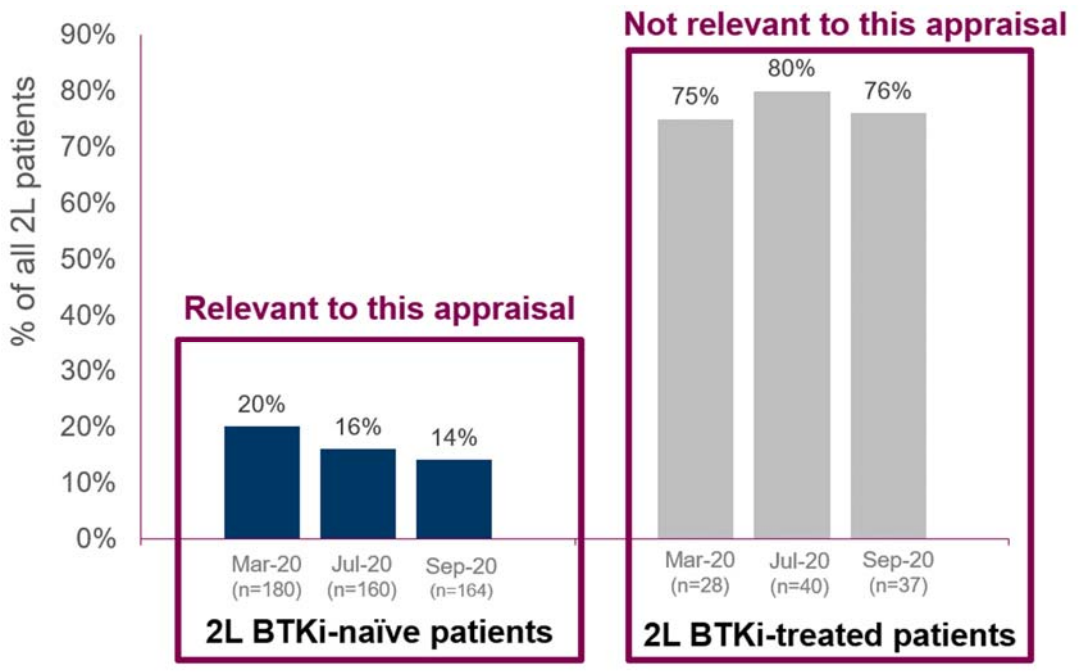
- In addition, the use of venetoclax-based regimens as 2L+ treatment in BTKi-naïve patients has not increased over time. Nationwide IQVIA prescribing data collected between March and September 2020 indicates that 20% (n=180), 16% (n=160) and 14% (n=164) of BTKi-naïve 2L+ patients received treatment with a venetoclax-based regimen in March, July and September 2020, respectively (Figure 1).[3] Therefore, there is no evidence of increased use of venetoclax over time, and instead the data presents a relatively stable pattern of prescribing.

- Furthermore, nationwide UK IQVIA prescribing data supports the conclusions made by clinical experts and the Company's assumptions. That is that BTKi-naïve patients often receive treatment with a BTKi followed by a venetoclax-based regimen, whilst patients who have previously received treatment with a BTKi will often receive a venetoclax-based regimen as their 2L+ therapy. Nationwide IQVIA prescribing data shows that 75% (n=28), 80% (n=40) and 76% (n=37) BTKi-treated patients in the first-line setting – a patient population that is not relevant to the scope of this appraisal – received treatment with a

venetoclax-based regimen as their 2L+ therapy (based on data received in March, July and September 2020, respectively, Figure 1).[3]

- These data demonstrate the importance of ensuring that the relevant patient population (i.e., BTKi-naïve patients) is considered rather than the entire 2L+ population when determining an appropriate estimate for second-line venetoclax plus rituximab use for the purpose of decision making.

**Figure 1. Proportion of patients receiving a venetoclax-based regimen in second- or subsequent-line by BTKi exposure (BTKi-naïve vs BTKi-treated)**




Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; 2L, second line; 2L+, second or subsequent line.
Note. Venetoclax-based regimens included venetoclax monotherapy.

**The Company, the Evidence Review Group (ERG), and clinical experts agreed that the proportion of patients receiving venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab is not greater than 20%.**

- The ERG agreed with the real-world evidence provided by the Company and included a 13%:87% split of venetoclax plus rituximab relative to ibrutinib treatment following first-line chlorambucil plus obinutuzumab in their preferred modelling assumptions (slide 24 of the Appraisal Committee Meeting slides).[1]

- The ERG's clinical advisors also expect the majority of patients to receive subsequent treatment with ibrutinib following first-line chlorambucil plus obinutuzumab. In the ERG report, one clinical advisor stated that "*there is a general preference for the use of second-line ibrutinib over VenR, with more than 80% of patients receiving ibrutinib and less than 20% of patients receiving VenR"*. Furthermore, the clinical advisor did not expect this split to change in the *"next few years"* as *"there is no need for ramping up dosage or monitoring for TLS with ibrutinib and fewer hospital attendances are required".*[4]

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| | The Company acknowledge that the use of venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab may vary geographically across centres, and understand that some centres may primarily prescribe ibrutinib, and others venetoclax plus rituximab. However, NICE decisions should be made on a **national basis and reflect current NHS clinical practice**.<br><br>In conclusion, UK 2020 prescribing data (n=164 patients) from IQVIA does not support the assumption that current venetoclax plus rituximab usage is greater than 20%. When coupled with the data from a retrospective chart review of 202 UK patients (October 2019 – September 2020), the Company firmly believe that the modelled proportion of patients receiving venetoclax plus rituximab following first-line chlorambucil plus obinutuzumab is overestimated in the Committee's preferred modelling assumptions and should not exceed 20% when informing decision making. |
| 5 | **Treatment duration of second-line ibrutinib following progression with chlorambucil plus obinutuzumab should be based on evidence relevant to the patient population.**<br><br>In the Committee's preferred modelling assumptions, treatment duration of second-line ibrutinib following progression on chlorambucil plus obinutuzumab is underestimated and does not consider the confounding effect of previous lines of therapy.<br><br>The Committee's preferred scenarios use the ERG's second-line treatment costing model and a Weibull curve (derived from RESONATE PFS data for a cohort of patients who have received 1-2 prior lines of therapy) to estimate mean second-line treatment duration with ibrutinib following first-line chlorambucil plus obinutuzumab. This assumption results in an estimated mean treatment duration with second-line ibrutinib of 4.78 years.<br><br>The Company prefer to estimate the mean treatment duration using a log-normal curve (5.56 years), which was accepted as clinically plausible by the Committee. In Section 3.14 of the ACD it was noted that: *"The committee considered the log-normal parametric model to be plausible but preferred the Weibull [...]".* The Company believe that the Committee's preferred curve underestimates the duration of second-line ibrutinib following first-line chlorambucil plus obinutuzumab treatment.<br><br>• Within the NICE appraisal for venetoclax plus rituximab for previously treated CLL (TA561), mean second-line treatment duration with ibrutinib was estimated at 5.18 years. This estimate was derived from the full RESONATE intention-to-treat (ITT) population where patients received a median of 3 prior lines of treatment.[5] The TA561 Committee accepted this estimate, and it was subsequently used to inform decision making.<br><br>• Long-term data from RESONATE (O'Brien et al. 2019) demonstrates that 74% of patients in the ibrutinib cohort who had received 1-2 prior lines remained progression-free at 36 months (Figure 1A O'Brien 2019).[6] In addition, the differences in PFS between treatment-naïve patients versus those receiving ≥3 lines of therapy and patients receiving 1-2 lines versus ≥3 lines of therapy were statistically significant (p-value < 0.0001 and p-value = 0.0109, respectively).[6] |

The number of prior lines of treatment has been shown to have a large impact on median PFS. RESONATE PFS data split by prior lines of treatment (Munir et al. 2019) demonstrates that median PFS was longer in patients who have had fewer prior lines, with median PFS not reached in patients who had only received 1 prior line (Table 2).[7]

**Table 2. Median PFS by prior line of therapy (Munir 2019, Figure 2A[7])**

| Lines of therapy | 1 (n=35) | 2 (n=57) | 3 (n=32) | 4 (n=27) | ≥5 (n=44) |
|---|---|---|---|---|---|
| Median PFS (months) (95% CI) | NR (44.4 – NE) | 67.3 (36.0 – NE) | 44.1 (25.4 – NE) | 33.0 (13.6 – NE) | 27.3 (22.0 – 40.8) |

Abbreviations: CI, confidence interval; NE, not estimated; NR, not reached PFS, progression-free survival.

- By modelling a mean second-line treatment duration of 4.78 years, the Committee are assuming that patients with previously untreated CLL who will have received first-line chlorambucil plus obinutuzumab will be subject to reduced PFS on subsequent treatment than was observed in the full ITT RESONATE population (who received a median of 3 prior lines of therapy).

- It is clear from the data presented in O'Brien et al. 2019 and Munir et al. 2019 that the number of lines of therapy is a confounding factor in duration of PFS on second-line ibrutinib.[6,7] Therefore, it is reasonable to assume that a patient population who have received 1 prior line of therapy should remain progression-free for longer on second-line ibrutinib when compared to the full RESONATE ITT population. Therefore, the Committee's decision to assume a shorter treatment duration than that reported for the full RESONATE ITT population (4.78 years versus 5.18 years [mean duration accepted for decision making during TA561]) unfairly underestimates subsequent treatment costs in the chlorambucil plus obinutuzumab group.

6

**A survival benefit is expected for acalabrutinib based on clinical evidence and rationale.**

The Company acknowledge the uncertainty surrounding long-term survival benefit, but believe the clinical support and evidence have not been appropriately considered when determining the Committee's preferred modelling assumptions for post-progression survival.

Section 3.15 of the ACD states:

- *"The data from ELEVATE-TN showed a trend towards improved overall survival for acalabrutinib compared to chlorambucil plus obinutuzumab. But the data were immature, with a median follow-up at 28 months, and the difference between the groups was not statistically significant."*

- *"The clinical experts suggested that overall survival was likely to be longer when starting a treatment with acalabrutinib followed by venetoclax plus rituximab.*

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| | *This is because it is more effective and less toxic than chlorambucil plus obinutuzumab followed by ibrutinib".*<br><br>• *"They [the clinical experts] considered it reasonable to use MURANO because it accurately reflects the most likely treatment sequence of acalabrutinib followed by venetoclax plus rituximab. The clinical experts also explained that it was reasonable to expect that people may reach the life expectancy of the general population after treatment with acalabrutinib and may be functionally cured."*<br><br>Despite the statements above, the Committee's preferred modelling scenarios utilise data from the RESONATE trial to inform post-progression survival for both acalabrutinib and chlorambucil plus obinutuzumab. This approach assumes that the risk of death following treatment with acalabrutinib and chlorambucil plus obinutuzumab is equivalent. The Company disagree with this approach for the following reasons:<br><br>• **Clinical experts support the Company's modelling assumptions.** The clinical experts present at the Appraisal Committee Meeting (5th November 2020) fully supported the assumption that patients treated with acalabrutinib followed by venetoclax plus rituximab would benefit from an extension in overall survival compared to those treated with chlorambucil plus obinutuzumab followed by ibrutinib. This is highlighted within Section 3.15 of the ACD.<br><br>• **The introduction of more efficacious treatments earlier on in the pathway will improve long-term survival.** Acalabrutinib is a highly efficacious new treatment for patients with previously untreated CLL. Treatment with acalabrutinib resulted in an 80% reduction in the risk of progression when compared to chlorambucil plus obinutuzumab within the ELEVATE-TN trial (hazard ratio [HR]: 0.20; 95% confidence interval [CI]: 0.13, 0.30; p<0.0001).[8] Data from other novel agents, such as ibrutinib and venetoclax plus rituximab, clearly demonstrate that an early PFS benefit does indeed translate into a long-term survival benefit (ibrutinib vs. ofatumumab: PFS HR: 0.15; CI: 0.11, 0.20; p<0.0001; OS HR [adjusted for cross-over]: 0.64; CI: 0.42, 0.98; p=not reported [NR]; venetoclax plus rituximab vs BR: PFS HR: 0.16; CI: 0.12, 0.23; p<0.001; OS HR: 0.50; CI: 0.30, 0.85; p=0.0093).[7,9] Furthermore, chlorambucil plus obinutuzumab is a highly toxic treatment option. Feedback from UK clinicians was that the use of a non-DNA damaging agent, such as acalabrutinib, are likely to result in reduced mutagenesis compared to chemo-immunotherapies, which in turn, is likely to result in a less aggressive cancer that is easier to treatment at subsequent lines, and hence will translate into improved survival outcomes.<br><br>• **The Committee's preferred modelling assumptions do not reflect the treatment pathway in England.** Patients treated with acalabrutinib in the first-line setting are most likely to receive venetoclax plus rituximab in the second-line setting. The Committee, the ERG, UK clinical experts and the Company are all in agreement with this assumption. However, by choosing to inform post-progression survival following treatment with acalabrutinib based on RESONATE data, the Committee are not appropriately reflecting the outcomes associated with treatment with venetoclax plus rituximab. Instead, the Committee are assuming that patients will incur the cost of venetoclax plus rituximab whilst gaining the outcomes associated with treatment with ibrutinib second-line treatment. The Company consider this assumption inappropriate, |

and believe that it is more suitable to align outcomes with costs (i.e., use MURANO data [venetoclax plus rituximab survival data] to inform post-progression survival with acalabrutinib).

**The Committee's approach to base decision making on scenario analyses in which the overall survival gain for acalabrutinib compared to chlorambucil plus obinutuzumab is reduced by 50% is not supported by clinical rationale and is considered clinically implausible by the Company.**

When combined with the Committee's preferred modelling assumption of using RESONATE to inform post-progression for both treatment arms, this adjustment results in the risk of death following treatment with acalabrutinib being higher than that following treatment with chlorambucil plus obinutuzumab. **There is no clinical rationale for this assumption**.

The modelling approach forces the overall survival benefit to be 50% lower by increasing the risk of death following progression in the acalabrutinib treatment arm (Figure 2 and Figure 3). Following clarification with the ERG, the Company understand that in order to achieve this reduction the ERG used the 'Goal Seek' Excel function to artificially alter the survival coefficients for risk of death following progression within the model. Therefore, the approach is a not robust or validated method, and it is not driven by any clinical evidence. In light of the clinical support for improved survival following treatment with the highly efficacious non-DNA damaging agent acalabrutinib, the Company consider this scenario to be **clinically implausible**, and hence unfit for decision making purposes.

**Figure 2. Post-progression survival adjusted to reduce acalabrutinib incremental survival gain by 50%***

Abbreviations: C+O, chlorambucil plus obinutuzumab; PPS, post-progression survival. *Curves constrained by all-cause mortality

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| | **Figure 3. Risk of post-progression death, adjusted to reduce acalabrutinib incremental survival gain by 50%***  Abbreviations: C+O, chlorambucil plus obinutuzumab; PPS, post-progression survival. *Curves constrained by all-cause mortality |
| 7 | **Factual inaccuracies and confidential mark-up**<br><br>European Medicines Association (EMA) approval for acalabrutinib was received on the 5th November 2020.[10] The Company request that the word "anticipated" is removed in the following statements in the ACD to reflect this:<br><br>• Section 2: *"Anticipated marketing authorisation indication"*<br><br>• Section 3.5: *"The company's submission did not include people with untreated CLL for whom FCR or BR is suitable, although this population was in the NICE scope and is included in the anticipated marketing authorisation for acalabrutinib."* |

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## Appendix 1

**Table 3. Summary of model settings for non-high-risk previously untreated CLL patients who are ineligible for FCR or BR therapy**

| Setting | Company preferred base case | ERG preferred base case |
|---|---|---|
| **Time horizon** | 30 years | 30 years |
| **Discount rate** | 3.5% per annum for costs and outcomes | 3.5% per annum for costs and outcomes |
| **TTP/TTD distribution (ELEVATE-TN)** | Exponential: acalabrutinib<br>Generalised Gamma: C+O | Exponential: acalabrutinib<br>Generalised Gamma: C+O |
| **PPS data source and distribution** | MURANO PPS: acalabrutinib<br>RESONATE PPS: C+O | RESONATE PPS: acalabrutinib<br>RESONATE PPS: C+O |
| **Utility values** | PF: Age- and sex-matched Ara and Brazier<br>PD: NICE TA561 | PF: Age- and sex-matched Ara and Brazier<br>PD: NICE TA561 |
| **Dose intensity** | Apply RDI for all treatments | Apply RDI for all treatments |
| **Treatment costs** | Acalabrutinib PAS price<br>Comparator and subsequent treatment list price<br>Apply wastage based on ERG methodology | Acalabrutinib PAS price<br>Comparator and subsequent treatment list price<br>Apply wastage based on ERG methodology |
| **Subsequent treatment pathway*** | Acalabrutinib: 100% V+R<br>C+O: 87%:13% ibrutinib: V+R | Acalabrutinib: 100% V+R<br>C+O: 87%:13% ibrutinib: V+R |
| **Subsequent treatment duration** | ERG costing model (Weibull distribution) | ERG costing model (Log-normal distribution) |
| **Delay before initiating subsequent treatment** | 14 cycles | 14 cycles |

Abbreviations: BR, bendamustine plus rituximab; CLL, chronic lymphocytic leukaemia; C+O, chlorambucil plus obinutuzumab; ERG, Evidence Review Group; FCR, fludarabine, cyclophosphamide and rituximab; NICE, National institute for Health and Care Excellence; PAS, PPPS, post-progression survival; TTD, time to pre-progression death; TTP, time to progression

* The Company note that the proportion of ibrutinib: V+R has increased when considering the data presented in comment 4, however for consistency 87%:13% ibrutinib: V+R was modelled.

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**Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]**

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Chronic Lymphocytic Leukaemia Support and Lymphoma Action**<br><br>**Joint response on behalf of both charities** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **None** |
| **Name of commentator person completing form:** | [redacted] |

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| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | A choice of treatment options is vitally important for all CLL patients, both due to the heterogeneity of the disease but also because the comorbidities that are often present in this older population mean that not all treatments are suitable for every patient.<br>The limited approvals granted as a result of this TA are very disappointing to the patient community and the decisions appear to be based predominantly on finance which does not give confidence in NICE's evaluation and decision processes for the clinical and patient communities. |
| 2 | We are concerned that the NICE Appraisal recommendations appear to be substantially financially based for the treatment naive patients with TP53 disruption or 17p deletion, **although we welcome the approval for this group.**<br><br>Acalabrutinib is approved - quote:- "**despite the uncertainties**, because it is likely to be cost-saving compared with ibrutinib. So acalabrutinib is recommended for routine use in the NHS for this group. |
| 3 | For previously treated CLL we have the same concerns that the recommendation is significantly based on finance again despite uncertainties, **although we welcome the approval for this group.**<br>quote - "**despite the uncertainties,** acalabrutinib is likely to be cost- saving compared with ibrutinib. So acalabrutinib is recommended for routine use in the NHS for people with previously treated CLL. |
| 4 | In addition, the ACD states: "**Acalabrutinib ONLY when Ibrutinib is their ONLY suitable treatment option because it is cheaper".**<br>Ibrutinib will not be a suitable treatment option for patients with cardiac issues or those on anticoagulant therapy and so Acalabrutinib will not be available to that group. Clinically this is one of the main advantages of Acalabrutinib over Ibrutinib, especially for this group of patients but that has now been removed as an option for them.<br>Ibrutinib will rarely be the only suitable treatment option now that VenO has been approved (via the CDF for treatment naïve patients) but we need a range of treatment options as patients often need more than one treatment for their relapsed and remitting CLL. |
| 5 | The final scope included the possibility of various sub-groups of CLL patients to be considered if the evidence allowed for it and patients with unmutated IgHV disease could have been considered. There is mounting evidence that these patients statistically have very much shorter remissions when treated with chemoimmunotherapy.<br>Despite uncertainties, approval was granted for other groups and this group should be considered separately, particularly for treatment naïve patients. A paper in NEJM 2020 by Shanafeldt et al showed considerable survival advantage with Acalabrutinib in this group of |

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|---|---|
| | patients with unmutated IgHV status. |
| 6 | As a patient group we are very disappointed that untreated patients who are suitable for FCR/BR were not within the scope of this TA even though the licence is for all untreated CLL patients.<br>There must be reassurance that this will be reviewed at the earliest opportunity, as soon as evidence becomes available (including real world evidence), rather than wait for the automatic NICE review period to expire. |
| 7 | With the COVID pandemic refusal to grant access to Acalabrutinib for all CLL patients means that many will be denied a safe, oral and effective treatment that will keep them away from the hospital environment. ALL the other treatment options available to treatment naïve and relapsed patients (FCR, BR, ChlO, VenO) with the exception of Ibrutinib require attendance for intravenous treatments and the increased risk of adverse events including infection with associated morbidity and mortality.<br>The free access programme for Acalabrutinib has provided many patients who are unfit for chemoimmunotherapy with a safe, oral treatment during the pandemic and has been welcomed by NHS Consultants. |
| 8 | The decision not to approve Acalabrutinib for treatment naive patients who do not have TP53 disruption or 17p deletion has further widened the health inequalities gap with regard to access to targeted treatments for this group of patients. Whilst there is a group of patients for who FCR is likely to give a durable remission, the unmutated IgHV group and those with complex genetics will do particularly badly with this chemotherapy based treatment and suffer toxicities. The first treatment that patients receive is the most significant in determining their overall survival and quality of life.<br>This cannot be acceptable or justifiable and we ask NICE to consider the use of the CDF for these patients as was done for Ven+O which also had data uncertainties and lacked comparative data. |
| 9 | In summary, whilst we welcome the approvals as a result of this TA we feel that they are too limited, are based very significantly on finance considerations and deny access to many patients who would benefit greatly from this treatment. |

Insert extra rows as needed

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Leukaemia Care |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | n/a |
| **Name of commentator person completing form:** | [redacted] |

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|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | We are disappointed to see an optimised recommendation be made. These are increasing in blood cancer appraisals, as outlined in the Blood Cancer Alliance Access to Medicines report. We wish to see treatments made available in all clinically appropriate groups. |
| 2 | The group in which the treatment has not been recommended, those who are untreated and unable to have FCR or BR, require alternative treatment options. There are no other BTK inhibitors available in this population until relapse from another therapy, and there is good evidence of efficacy in this group, as outlined by the clinical experts at the meeting. |
| 3 | Having a range of available treatments is more important than ever in the COVID-19 era. Alternative treatments for those who cannot have FCR or BR often involve time in hospital and/or significant immune suppression is a side effect, both of which are desirable to avoid currently and likely for some time yet. |
| 4 | The excluded group may also contain others who not suitable for FCR for reasons that have not been explored in the trials and as subgroups here. Clinical studies state that other genetic changes such as IGHV mutation and chromosome aberrations can affect response to chemoimmunotherapy options. |
| 5 | One uncertainty outlined in the ACD concerns the average length of time a person is treated with ibrutinib. This is something that has been discussed in previous appraisals, such as that of venetoclax and rituximab, and so there is precedence for this that should be considered. We believe 5 years to be a reasonable assumption, which both the clinical experts agreed with in the committee meeting but does not seem to have been taken into account in the decision-making. This is an uncertainty which could be resolved in the CDF as well. |
| 6 | If the committee is not minded recommending this population for the CDF, we ask they consider earlier review as further data is expected. |
| 7 | Uncertainty about overall survival is common in appraisals of CLL treatments due to the nature of the disease. Therefore, some flexibility is need in decision making here. The ACD states that the clinical experts supported the company's modelling for survival after acalabrutinib and that life expectancy could match the general population, but it is unclear how this clinical advice impacted upon the committee's decision making. Additionally, this could be resolved by use of the CDF as clinical trials are ongoing. |
| 8 | Whilst there may be uncertainty around the proportion of people receiving venetoclax and rituximab second line, NICE make a decision nationally and so the national average needs to be ascertained and considered. This is something that could be done whilst the treatment is in the CDF if necessary. |
| 9 | We ask the committee to reconsider the CDF to resolve the uncertainties listed above. |
| 10 | We disagree with the narrowing of the population who can access acalabrutinib as a second line or subsequent therapy to those who would otherwise have had ibrutinib. We are unclear as to the basis for this decision from the information provided in the ACD. |

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **UK CLL Forum**/BSH/RCPath |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | Yes for CLL Forum: the funds are mainly used to organise educational meetings, provide travel grants for scientists<br>Roche £10,000<br>Janssen £7000<br>Abbvie £10,000<br>AZ £10,000 |
| **Name of commentator person completing form:** | [redacted; redacted; redacted; redacted; redacted; redacted **and** redacted] |

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|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | We strongly support the request to use acalabrutinib as first line therapy in elderly patients and those with comorbidity who are not eligible for BR/FCR.<br><br>We are gravely concerned that the recommendations of the Committee will lead to health inequality and unnecessary toxicity in patients with untreated CLL with no high risk cytogenetics for whom BR/FCR is unsuitable for the following reasons:<br><br>Firstly, the recommendation states that in these cases “Chlorambucil and obinutuzumab is the only other option”. The majority of patients with CLL who need treatment are not eligible for intensive chemo-immunotherapy (CIT) and therefore this very statement confirms the absence of treatment choice - effectively disenfranchising patients from actively engaging with clinicians. Patients and families are very aware of marketing authorisations and availability of acalabrutinib on the current Early Access Programme. |
| 2 | Secondly: The Committee accepts that is reasonable to use the full Clinical Trial data from ELEVATE-TN in the untreated CLL model, agreeing with the clinical experts on the assumption that acalabrutinib has a “similar treatment effect for the populations who had untreated CLL whether or not they had high-risk CLL”. This clearly creates the situation where patients with high risk TP53 altered CLL have access to treatment associated with a more favourable PFS and toxicity profile than patients without high risk CLL. Given the Committee accepts similar clinical outcomes after acalabrutinib regardless of risk group, we consider iniquitous the relegation of patients without high risk cytogenetics to inferior therapy with chlorambucil and obinutuzumab. |
| 3 | Thirdly: The recommendation states that clinical experts suggest that survival is likely longer when starting treatment with acalabrutinib followed by venetoclax-rituximab. The recommendation goes on to state, “This is because it (acalabrutinib) is more effective and less toxic than chlorambucil – obinutuzumab followed by ibrutinib. The Committee accepts that the toxicity profile of acalabrutinib is more favourable than either or both of these therapies but pushes back on issues of overall survival based on immaturity of data without giving due weight to matters concerning toxicity and quality of life. It is the considered clinical experience of many treating haematologists that for many in this patient population quality of life is paramount.<br><br>The Committee accepts a median PFS of around 23 months following chlorambucil and obinutuzumab and models a period of 14 months (“cycles”) following disease progression before second line therapy is likely during which time patients are likely to experience increasing symptoms and reduced quality of life. A period of recovery and recuperation after chemotherapy is usual during which persistent fatigue, cytopenia and immune suppression are experienced.<br><br>For many elderly patients, therefore the quality of a significant proportion of their remaining years are entirely determined by the choice of initial therapy and are more compromised by CIT than with BTK inhibitor therapy. |
| 4 | Fourthly: We are extremely concerned that infection risk is not taken into full consideration. It is well documented that anti-CD20 antibody therapy exacerbates hypogammaglobulinaemia in CLL and that low immunoglobulin levels are associated with increased risk of infection such as community acquired pneumonia as well as poor dynamic response to vaccination.<br><br>There is growing evidence that patients with CLL are at increased risk of developing severe forms of SARS-Cov-2 infection with markedly increased risk of dying from complications of COVID-19. Patients with CLL are considered to be in the Clinically Extremely Vulnerable (CEV) group. Shielding has been an effective mechanism to avoid infection but comes at the price of social isolation and a significant mental health burden. |

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| | The use of first line chlorambucil with obinutuzumab carries significant and specific risks in this regard. We are extremely concerned that such Chemo Immunotherapy will increase COVID risks compared with acalabrutinib.<br><br>Chlorambucil with obinutuzumab is likely to significantly abrogate the effectiveness of any COVID-19 vaccine during therapy and for many months after treatment as well as increasing the risk for our patients of contracting the infection through increased footfall as daycase patients as well as higher likelihood of admission for neutropenic pyrexia or Tumour Lysis Syndrome. Patients will be put at higher risk of COVID and place additional strain on NHS acute beds at a time of national crisis.<br><br>Additionally, in the absence of treatment choice other than CIT, clinicians and patients may decide to defer therapy beyond normal treatment thresholds. This may ultimately increase side effects of therapy and exacerbate disease related symptoms.<br><br>Access to acalabrutinib for all cytogenetic risk groups in the elderly CEV population would, in our opinion, reduce risk of unnecessary treatment delay, mitigate risks around COVID to a significant extent and take some pressure off clinical services. |
| 5 | The published guidelines (BSH, ESMO, NCCN) have become increasingly obsolete in the face of new clinical trial data as well as new NICE Technology appraisal guidance. In particular NICE TA663 Venetoclax with obinutuzumab for untreated CLL. This guidance means that for younger fitter patients, non CIT therapy has become a treatment option. However we are very concerned that TA663 has also exposed considerable inequity of access to a non CIT option in older patients or patients with comorbidity in whom venetoclax-obinutuzumab is not a suitable option.<br><br>We are concerned that patients with high risk cytogenetics or fitter elderly patients will have therapeutic choices denied the more frail and more vulnerable patient population. |
| 6 | In summary we believe it is this very group of vulnerable elderly or comorbid patients without high risk cytogenetics who would benefit most from access to acalabrutinib during and beyond this COVID pandemic and we urge the Committee to broaden the scope of TA 1613 to recommend acalabrutinib as an option for patients with untreated CLL without 17p deletion or TP53 mutation in whom BR/FCR and venetoclax with obinutuzumab are unsuitable. |

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **AbbVie Ltd** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **None** |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
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| 1 | Section 1.1 page 3 states that acalabrutininb is only recommended as an option if *ibrutinib is their only treatment option*.<br><br>This is appropriate given that acalabrutinib has not demonstrated cost-effectiveness versus venetoclax plus rituximab. To avoid confusion on the population suitable for acalabrutinib and ensure venetoclax plus rituximab is duly considered within its NICE recommendation we propose the following wording:<br><br>*Acalabrutinib is recommended as an option for treating CLL in adults who have had at least 1 previous treatment, only if:*<br>• *venetoclax plus rituximab is not a suitable treatment option, and*<br>• *the company provides it according to the commercial arrangement (see section 2).*<br><br>The relevant wording should be clearly reflected by NHSE in all commissioning guidance and systems to ensure appropriate implementation. |
| 2 | Section 4.1 Page 22 states that acalabrutinib has been available through an early access to medicines scheme (EAMS), however there does not appear to be a record of this on the EAMS database. |

Insert extra rows as needed

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not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

**Acalabrutinib for untreated and treated chronic lymphocytic leukaemia [ID1613]**

**Consultation on the appraisal consultation document – deadline for comments by 5pm on Monday 11 January 2021 via NICE Docs.**

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Janssen-Cilag** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **None** |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
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| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
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| | Janssen thanks NICE for the opportunity to comment on the preliminary decision after the consideration of the evidence for acalabrutinib for treating chronic lymphocytic leukaemia (CLL). We believe that all relevant evidence has been taken into account however, we would like to comment on Sections 1.2 and 3.16 of the document. |
| 1 | Section 1.2 of the ACD lays out the Committee's preliminary recommendation on the use of acalabrutinib in CLL patients treated in the relapsed/refractory setting:<br><br>*"Acalabrutinib is recommended as an option for treating CLL in adults who have had at least 1 previous treatment, only if:*<br>*- ibrutinib is their only suitable treatment option, and*<br>*- the company provides it according to the commercial arrangement (see section 2)."*<br><br>The restriction "*ibrutinib is their only suitable treatment option*" may be open to different interpretations. It could be read as acalabrutinib can be used in patients that could receive ibrutinib (a broad interpretation) or for patients that their only option is ibrutinib (narrow interpretation). In this second case, patients that are suitable for venetoclax + rituximab could not receive acalabrutinib but could receive ibrutinib. Janssen would welcome further clarity on the wording of the restriction. |
| 2 | Section 3.16 of the ACD discusses the assumptions retained by the Committee in the base-case cost-effectiveness analyses for untreated CLL patients when FCR or BR is unsuitable.<br><br>With regards to modelling post-progression survival, the Committee explains how, while incorporating the ERG' preferred assumption "*using RESONATE post-progression survival for both treatment arms*", "*it also considered that further assumptions should be included in that base-case*", including "*adjusting the overall survival gain for acalabrutinib compared with chlorambucil plus obinutuzumab such that it was 50% lower, reflecting uncertainty about the immature survival data in ELEVATE-TN*".<br><br>Adjusting the survival gain of acalabrutinib versus chlorambucil plus obinutuzumab to assume that it is 50% lower does not seem appropriate for consideration within the base-case. Janssen acknowledges that the evidence from the ELEVATE-TN trial is still immature and therefore it is important to test uncertainty through survival scenarios. However, Janssen would welcome further clarity on the choice of a 50% adjustment as this does not appear to align with clinical expert opinion as expressed in the ACD document (section 3.15). |

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the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

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| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | [**none**] |
| **Name of commentator person completing form:** | [[redacted], **NCRI CLL** [redacted]] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
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| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
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| Example 1 | |
| 1 | The decision not to fund acalabrutinib for patients with CLL without TP53 abnormalities (fit or frail) in first-line comes as a great disappointment to the clinical community.<br>We understand that the dominant driver behind this decision is the cost of acalabrutinb for the NHS. When ibrutinib was licenced, Janssen decided not to submit an application for frontline use of ibrutinib knowing that it would force a significant reduction of its price. We thank AZ for submitting this technology appraisal and for having made acalabrutinib available to UK patients in an Early Access Programme due to close in April 2021.<br>We plea to NICE, AstraZeneca and the NHS to re-consider the decision and to negotiate a pricing solution that is acceptable to all stake holders. |
| 2 | The Phase 3 data from the ELEVATE study was reviewed by the Committee. The study uses the correct comparator for frail patients i.e: Chlorambucil +Obinutuzumab (CO) that is the current NICE-approved standard of care for patients with treatment naïve CLL in the NHS. The study shows a significant PFS advantage for patients treated with acalabrutinib compared to the current NICE standard. |
| 3 | The drug also shows favourable toxicity profile, and -contrary to CO- is orally available and does not require chair time, which is a major argument with and without a COVID pandemic. There is therefore little uncertainty with respect to the superiority of acalabrutinib in this indication, and this therapy should therefore be given a favourable response for all frail frontline patients. |
| 4 | Irrespective of the model system used, the OS modelling for any highly efficacious therapy will be uncertain in an era when many novel and highly efficacious therapies are given sequentially. As clinicians, we know that this has had already a very significant positive impact on the overall survival of our patients, but we cannot easily quantify the extent of benefit yet. This will only be possible from longer-term real-world data collection. |
| 5 | We echo the patient support organisations' deep regret that fit patients with CLL were not within scope of this TA. We admit that there is theoretical uncertainty about the use of the second-in-class BTKi acalabrutinib in fit patients as the ongoing study results are still awaited. However, it is not plausible to refuse fit patients access to this class of drugs when the first-in-class BTKi ibrutinib showed an overall survival advantage compared to FCR (Shanafeldt T et al NEJM 2020) in fit patients, esp those with unmutated IgHV status. This data was not considered in the initial consultation. We would therefore urge NICE to make acalabrutinib available via the CDF for fit patients in the same way as Ven-Obinutuzumab has been made available without data for this patient group. |
| 6 | |

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Insert extra rows as needed

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# Acalabrutinib for treating chronic lymphocytic leukaemia: A Single Technology Appraisal

## ERG comments on company's ACD response


| | |
|---|---|
| Produced by | The School of Health and Related Research (ScHARR), The University of Sheffield |
| Authors | Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK<br><br>Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK |
| Correspondence Author | Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK |
| Date completed | 25th January 2021 |

## 1. Introduction

In December 2020, NICE published its Appraisal Consultation Document (ACD) for acalabrutinib for the treatment of chronic lymphocytic leukaemia (CLL).[1] The ACD recommendations are shown in Box 1.

**Box 1: NICE ACD recommendations for acalabrutinib for the treatment of CLL[1]**

*1.1 Acalabrutinib is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:*

- *they have a 17p deletion or TP53 mutation and*
- *the company provides it according to the commercial arrangement (see section 2).*

*1.2 Acalabrutinib is recommended as an option for treating CLL in adults who have had at least 1 previous treatment, only if:*

- *ibrutinib is their only suitable treatment option, and*
- *the company provides it according to the commercial arrangement (see section 2).*

*1.3 These recommendations are not intended to affect treatment with acalabrutinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop*

Acalabrutinib was not recommended for people with untreated CLL that is not high risk for whom fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR) is unsuitable (see ACD,[1] Section 3.20). The Appraisal Committee concluded that, in all scenarios considered for the untreated CLL population without high risk cytogenetic features, the incremental cost-effectiveness ratios (ICERs) for acalabrutinib would not be considered an acceptable use of NHS resources.

In January 2021, the company submitted a response to the NICE ACD.[2] The company's response includes a summary of the company's position and six main issues. This addendum provides a brief commentary from the ERG on the company's ACD response.

## 2. Summary of company's ACD response and comments from the ERG

### Company's comment 1: Summary of the company's position

The first comment within the company's ACD response[2] provides a summary of the company's position, together with a table of model results for the untreated CLL population which includes a Patient Access Scheme (PAS) discount for acalabrutinib of [redacted] and the list prices of comparator and downstream treatment regimens. The ERG notes that these ICERs are not relevant for decision-making as they do not include the confidential price discounts for comparator and downstream therapies. After

submitting their ACD response, the company increased their PAS discount to [redacted]. The results of the company's key ACD analyses including the updated acalabrutinib PAS and the cPAS discounts for comparator and downstream treatments are presented in a separate confidential appendix. The ERG's comments on the specific issues raised in the company's ACD response are presented in the subsequent sections.

For the sake of clarity, the ERG has highlighted the differences between the analyses which are preferred by the company, the ERG and the Appraisal Committee in Table 1.

**Table 1: Summary of differences in assumptions preferred by the company, the ERG and the Appraisal Committee**

| Aspect of company's model | Company[2] | ERG[3] | NICE Appraisal Committee[1] | Company ACD response comment number |
|---|---|---|---|---|
| Proportion of patients who receive second-line VenR | 13% | 13%.<br>ERG Additional Sensitivity Analysis 1 indicates that second-line ibrutinib is dominated by VenR. Greater use of VenR would increase the ICER for acalabrutinib. It is uncertain whether use of VenR will increase in the future. | At least 20% and possibly up to 40% | Comment 4 |
| Parametric survival model used to estimate PFS for second-line ibrutinib | Log-normal (applied in ERG costing model) | Weibull (applied in ERG costing model) | Log-normal plausible but Weibull preferred (applied in ERG costing model) | Comment 5 |
| PPS source | VenR – MURANO;[4] Ibrutinib - RESONATE[5] | Same PPS for both groups - RESONATE[5] | Same PPS for both groups - RESONATE[5] | Comment 6 |
| Adjustment of modelled incremental OS gain | No adjustment | No adjustment included in ERG's preferred analysis. ERG Additional Sensitivity Analysis 2 explores scenarios in which incremental OS gains are reduced by 50% and 100% by inflating the PPS rate parameter in the acalabrutinib group. | 50% reduction to account for uncertainty associated with immaturity of OS data in ELEVATE-TN[6] | Comment 6 |

*ERG - Evidence Review Group; ACD - Appraisal Consultation Document; VenR - venetoclax plus rituximab; PFS - progression-free survival; PPS – post-progression survival; OS - overall survival*

**Company's comment 2: The wording of the recommendation made by the Committee for patients who have received at least 1 previous treatment is restrictive and does not allow clinicians to treat patients who are intolerable to ibrutinib with a Bruton's Tyrosine Kinase inhibitor (BTKi)**

The company's ACD response[2] argues that the wording of NICE ACD Recommendation 1.2, which states that acalabrutinib is recommended only for previously treated CLL patients for whom "*ibrutinib is their only suitable treatment option*", is unnecessarily restrictive. The company has instead proposed that the wording of this recommendation should be amended to read *"Acalabrutinib is recommended as an option for treating previously treated CLL in adult patients who have had at least 1 previous treatment, only if a BTKi is their most suitable treatment option."*

The ERG believes that the existing wording of ACD Recommendation 1.2 is appropriate, as the economic comparison presented in the company's submission[7] (CS) for this population is limited to a cost-minimisation analysis (CMA) which compares the costs of acalabrutinib and ibrutinib, based on an assumption of equivalent health outcomes for each regimen. The results of the company's CMA are relevant only to patients who would otherwise receive ibrutinib. The incremental costs and health outcomes for acalabrutinib versus other second-line therapies, such as venetoclax plus rituximab (VenR), are not presented in the CS.[7] As previously noted in the ERG report[3] (Executive Summary, Issue 1, page 7), it is likely that acalabrutinib is more expensive than VenR in the second-line setting (based on list prices for these regimens), as acalabrutinib is not subject to a maximum fixed treatment duration.

**Company's comment 3: There is a high unmet need for alternative treatment options with different mechanisms of action to current first-line treatments, especially in non-high-risk previously untreated CLL patients when FCR or BR is unsuitable**

The company's ACD response[2] highlights the significant unmet need amongst people with untreated CLL. The company's response comments that current treatments are restricted to chemo-immunotherapies, such as chlorambucil plus obinutuzumab (GClb) which is associated with considerable toxicity.

The ERG agrees that the availability of a new effective and less toxic therapy for CLL would be welcomed by patients and clinicians. This view is also reflected in Section 3.2 of the ACD. [1] The ERG also notes that in December 2020, NICE issued a positive recommendation for the use of venetoclax plus obinutuzumab (VenG) for the treatment of people with untreated CLL (with or without high-risk cytogenetic features), which will provide an alternative to chemo-immunotherapy within this patient population.[8]

**Company's comment 4: The proportion of patients receiving second-line venetoclax plus rituximab following treatment with chlorambucil plus obinutuzumab is not greater than 20% in current clinical practice for NHS England**

The company's ACD response[2] raises concerns regarding the Appraisal Committee's decision to assume that the use of VenR following GClb could reach up to 50%, as they do not believe that this is reflective of the available evidence base or clinical expert opinion. The company's response includes summaries of unpublished data from a retrospective chart review and prescription data collected by IQVIA which both indicate that less than 20% of untreated CLL patients go on to receive a venetoclax-based second-line regimen. The company's response also argues that NICE decisions should be made on a national basis and should reflect current NHS clinical practice.

The ERG highlights that the proportion of patients who receive VenR as second-line therapy (following GClb) is a key driver of the ICER, as in the company's original base case model, more than 78% of the total treatment costs in the comparator group were attributable to the use of second-line ibrutinib. Increasing the proportion of patients in the comparator group who receive VenR reduces the cost of the comparator group sequence and increases the ICER for acalabrutinib. This is because VenR is given for a maximum of 26 cycles (2 years) whereas ibrutinib does not have a maximum fixed treatment duration. The ERG report[3] also highlighted that the company's model is predisposed to advantage any sequence in which VenR (rather than ibrutinib) is used in the second-line position and that fully incremental analyses suggest that GClb followed by ibrutinib is dominated by GClb followed by VenR, thereby leading to higher ICERs for acalabrutinib followed by VenR (see ERG report, ERG Additional Sensitivity Analysis 1, Table 63, page 142).

As discussed in the ERG report[3] (Section 5.3.4, critical appraisal point [3d], page 118), there is uncertainty around the proportion of CLL patients who currently receive VenR as second-line therapy. The ERG's clinical advisors agreed that currently less than 20% of patients currently receive VenR (with the remainder receiving ibrutinib), but did not fully agree about whether this proportion should be expected to remain stable in the future:

- The first clinical advisor stated that the use of VenR was unlikely to change in the next few years and that this preferential use of ibrutinib was because there is no need for ramping up dosage or monitoring for tumour lysis syndrome (TLS) with ibrutinib and because fewer hospital attendances are required.
- The second advisor commented that whilst the COVID-19 pandemic continues, there would be a continued preference towards ibrutinib rather than VenR as patients do not need to attend hospital as frequently. They also noted that a number of units have developed outpatient-based dose escalation for VenR; hence, they would use this regimen as well. The advisor further

commented that emerging data suggest that ibrutinib works well in patients who have had VenR without a prior BTKi, which may lead to an increase in the use of VenR in the future.[3]

The ERG's preferred analysis within the original ERG report (submitted prior to the factual accuracy check) assumed that 20% of patients in the GClb group receive VenR as second-line treatment and that the remaining 80% of patients receive ibrutinib, based on the advice received from the ERG's clinical advisors. As part of their factual accuracy response to the ERG report, the company provided data from IQVIA which suggest that around 13% of patients receive VenR. Following the factual accuracy check, the ERG amended its preferred analysis to include this estimate as it reflects data rather than an assumption. The ERG believes that there is uncertainty regarding whether this proportion would remain stable in the future; if the proportion increases, the ICER for acalabrutinib will be higher than that reflected in the company's and the ERG's preferred analyses. However, the ERG agrees with the company that if the Appraisal Committee wishes to make recommendations on the basis of current NHS practice, it would be inappropriate to assume higher levels of second-line VenR use.

**Company's comment 5: Treatment duration of second-line ibrutinib following progression with chlorambucil plus obinutuzumab should be based on evidence relevant to the patient population**

The company's ACD response[2] argues that mean treatment duration on second-line ibrutinib is underestimated, based on the ERG's preferred Weibull model for second-line PFS (mean time on ibrutinib = 4.78 years). The company's response states that their preferred model for second-line PFS for ibrutinib is the log-normal model (mean time on ibrutinib = 5.56 years). The company's ACD response makes four points:

(i) In TA561[9] (VenR for previously treated CLL), mean time on treatment with ibrutinib was estimated to be 5.18 years.

(ii) Analyses of data from the RESONATE trial[5] (ibrutinib for relapsed/refractory [R/R] CLL) indicate that median PFS is longer for patients with fewer prior lines of therapy.

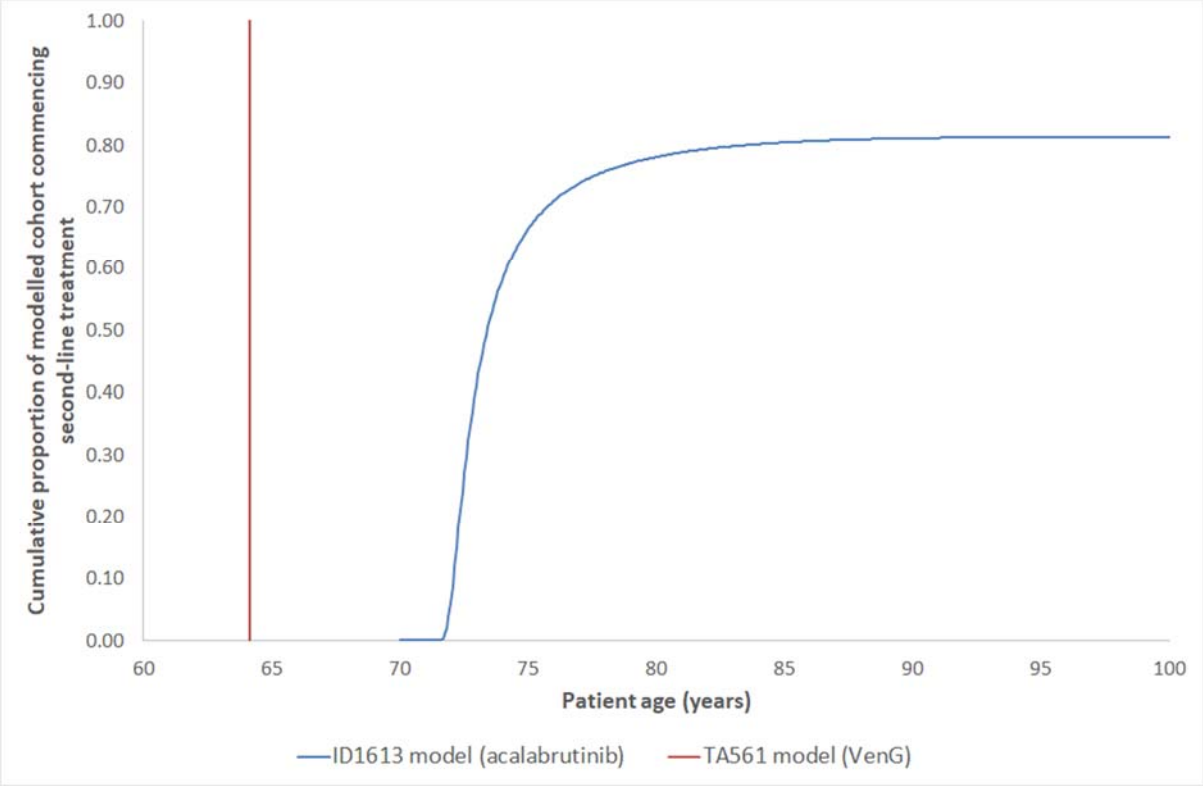
(iii) By modelling a mean second-line treatment duration of 4.78 years (based on the ERG's preferred Weibull PFS model), the Committee is assuming that patients with previously untreated CLL who have received first-line GClb will have a lower mean PFS on subsequent treatment than was observed in the full intention-to-treat (ITT) RESONATE population (who received a median of 3 prior lines of therapy).

(iv) The Appraisal Committee's decision to assume a shorter treatment duration than that reported for the full RESONATE ITT population (4.78 years versus 5.18 years) unfairly underestimates subsequent treatment costs in the GClb group.

The ERG agrees that there is uncertainty regarding second-line treatment duration. The ERG has three main observations regarding the company's comments:

- The treatment duration applied in the model used to inform TA561[9] (VenR for previously treated CLL) is a model-based estimate, rather than observed data.
- As noted in the ERG report[3] (Section 5.4.1.1, page 136), the ERG selected the Weibull distribution to represent second-line PFS in the ERG's preferred analysis, as this was the company's preferred model in TA561[10] and because, unlike the exponential, log-normal, log-logistic and generalised gamma models, it was not strongly influenced by the general population and disease-specific mortality constraint included in the economic model. The impact of the mortality constraint can be seen in Figure 25 and Table 69 of the ERG report (pages 155-156). Assuming a 70-year old population, the Weibull model suggests a mean PFS duration of 7.53 years without the mortality constraint and 7.48 years with the mortality constraint included. The equivalent estimates for the log-normal model are 11.06 and 9.72 years, respectively. For patients who progress at older ages, the impact of this constraint becomes more substantial, as general population mortality rates increase and maximum remaining treatment time decreases. The ERG's concerns regarding the log-normal model remain unchanged.
- As discussed by the ERG during the Appraisal Committee meeting, the population of CLL patients receiving second-line treatment in the acalabrutinib model is older than the population of R/R CLL patients included in the TA561 model.[9] In TA561, the company's model assumed that all patients enter the model and begin treatment with VenR or ibrutinib for their R/R disease at the age of 64.18 years, based on the characteristics of the population enrolled in the MURANO trial.[4] In the acalabrutinib model, the target population with previously untreated CLL is assumed to be aged 70 years at model entry, based on the mean age of patients in ELEVATE-TN,[6] and patients who survive their PFS event begin their second-line treatment according to their time to progression together with an assumed lag of [redacted] cycles (median age of modelled population starting second-line treatment ~73 years; see Figure 1). As the patients in the acalabrutinib model are several years older than those in the TA561 model, this means that patients have a comparatively lower remaining life expectancy and therefore less time alive in which they can receive second-line treatment. For a population of patients aged 70 years, the Weibull PFS model fitted to the 1-2 prior lines ibrutinib data from RESONATE[5] leads to mean PFS duration of 7.48 years. This is longer than that the mean estimate of 5.18 years used for the ITT population in TA561.

**Figure 1: Age at which patients start second-/subsequent-line therapy in the TA561 model (VenG for R/R CLL) and the ID1613 model (acalabrutinib for untreated CLL)**




**Company's comment 6: A survival benefit is expected for acalabrutinib based on clinical evidence and rationale**

The company's ACD response[2] acknowledges that the available evidence to support an overall survival (OS) advantage for acalabrutinib versus GClb is uncertain. The company disagrees with the Appraisal Committee's preferred base case, which reflects the ERG's Additional Sensitivity Analysis 2 (incremental modelled OS gain for acalabrutinib estimated in the ERG's preferred analysis halved). The company also disagrees with the ERG's preferred approach of applying the same post-progression survival (PPS) risk in both treatment groups. The company's ACD response makes four main points to support their argument:

1. The clinical experts at the Appraisal Committee Meeting fully supported the assumption that patients treated with acalabrutinib followed by VenR would have an OS gain compared to those treated with GClb followed by ibrutinib.
2. The introduction of more efficacious treatments earlier on in the pathway will improve long-term survival. The company highlights that the ELEVATE-TN trial[6] demonstrated a statistically significant improvement in PFS for acalabrutinib versus GClb (hazard ratio [HR]: 0.20; 95% confidence interval [CI]: 0.13, 0.30; $p<0.0001$) and suggests that this will translate into an OS gain.

3. The Appraisal Committee's preferred modelling assumptions do not reflect the treatment pathway in England. The company argues that it is inappropriate to assume the same PPS risk from RESONATE[5] in both groups and that MURANO[4] should instead be used to estimate PPS for second-line VenR (following acalabrutinib).
4. The Appraisal Committee's preferred scenario in which the modelled OS gain for acalabrutinib versus GClb is reduced by 50% is not supported by clinical rationale and is considered clinically implausible. The company also argues that the approach used by the ERG to implement Additional Sensitivity Analysis 2 is not a *"robust or validated method."*

The ERG's concerns regarding the limitations of the clinical evidence and the company's approach for modelling OS remain unchanged. Further details of these concerns can be found in the ERG report[3] (Section 5.3.4, critical appraisal point [5] pages 122-128). Briefly, the ERG report highlights the following concerns:

- There is limited evidence to demonstrate an OS advantage for acalabrutinib versus GClb (HR for OS for acalabrutinib versus GClb of 0.60 (95% CI 0.28, 1.27; *p*=0.16).
- The CS[7] does not present any randomised evidence to support estimates of OS relating to the specific sequences of treatments included in the model (acalabrutinib followed by VenR versus GClb followed by ibrutinib).
- Modelled OS is strongly influenced by general population mortality risks.
- Apparent differences between PPS for VenR and ibrutinib from MURANO[4] and RESONATE[5] may be a consequence of confounding resulting from the use of unadjusted (naïve) arm-based comparisons across trials.
- The company's model implies that a large proportion (at least [redacted]) of patients treated with acalabrutinib are cured.
- Predicted OS for the acalabrutinib group is similar to that for the general population, with only a minimal loss of life expectancy (modelled acalabrutinib OS = [redacted] years; general population OS = 15.56 years). Thus, as well as assuming that most patients are cured, the company's model also suggests that uncured patients do not lose much life expectancy.

In addition, the ERG makes the following comments:

- The Appraisal Committee's preferred assumption reflects ERG Additional Sensitivity Analysis 2. This is not the ERG's preferred analysis, which instead applied the PPS model from RESONATE[5] to both treatment groups without adjustment of the incremental OS gain. The ERG's preferred analysis suggests a less optimistic OS projection for acalabrutinib compared with the company's model; however, this is still highly uncertain.

- Neither the ERG's preferred analysis nor the Appraisal Committee's preferred base case is inconsistent with the clinical experts' view that acalabrutinib followed by VenR would confer an OS advantage over GClb followed by ibrutinib. Both of these scenarios assume an OS gain for the acalabrutinib group.
- In TA663[8] (VenG for untreated CLL), the available OS data from the CLL14 trial were also immature (HR=1.24, 95% CI: 0.64 to 2.40; *p*=0.52). The model used to inform this appraisal conservatively assumed zero incremental OS gain between VenG and GClb, despite a statistically significant difference in PFS between the groups. The ERG's preferred analysis and the Appraisal Committee's base case for acalabrutinib each reflect scenarios which are considerably more favourable to the intervention than the model used to inform TA663.
- As described in the ERG report,[3] Additional Sensitivity Analysis 2 was undertaken by manually calibrating the PPS rate parameter in the acalabrutinib group until the undiscounted incremental OS gain was equal to 50% of the value estimated in the ERG's preferred analysis. The ERG believes that the simplest way of exploring the uncertainty around the incremental OS gain predicted by the company's model is by modifying this PPS rate parameter. This necessarily requires the assumption that VenR is less effective than ibrutinib, which may not hold. An alternative approach could have involved modifying the pre-progression survival model for acalabrutinib; however, the ERG considers it unlikely that the company would have considered this alternative approach to be clinically plausible either. Whilst neither approach is ideal, the ERG maintains that it is important to assess the uncertainty surrounding modelled incremental OS given the limitations of the empirical data from ELEVATE-TN.[6]

**Comment 7: Factual inaccuracies and confidential mark-up**

The company's response highlights two sentences in the ACD which require amendment. The ERG agrees that the word "anticipated" should be removed as full marketing authorisation was granted in November 2020.[11]

## 3. References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