National Institute for Health and Care Excellence

Health Technology Evaluation

Acalabrutinib and venetoclax with or without obinutuzumab for untreated chronic lymphocytic leukaemia [ID6232]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Johnson & Johnson Innovative Medicine	Yes, the proposed evaluation route is appropriate.	Comment noted. No action required.
	AbbVie UK	No comment	No action required.
	AstraZeneca UK Ltd	AstraZeneca agrees with the proposed evaluation route of a single technology appraisal (STA). In addition, AstraZeneca consider that acalabrutinib and venetoclax, with or without obinutuzumab (AV/AVO), will be appropriate for a cost-comparison appraisal versus currently available fixed duration treatment regimens used in non-high risk patients (i.e., patients without 17p deletion or TP53 mutation). Acalabrutinib and ibrutinib have previously been demonstrated to be clinically equivalent, as accepted by the Committee in TA891 and TA689. After the addition of venetoclax to the Bruton tyrosine kinase (BTK) inhibitors, AV and	Thank you for your comment. NICE has determined that cost comparison is not an appropriate route for this topic, so it will proceed as an STA.

Section	Stakeholder	Comments [sic]	Action
		venetoclax with ibrutinib (VenI) are also anticipated to be clinically equivalent. Initial feedback from clinical experts confirms that AV may be considered clinically equivalent to VenI in terms of efficacy. Pursuing a cost-comparison appraisal would increase the efficiency of the appraisal and allow faster access to acalabrutinib (and venetoclax with or without obinutuzumab) and patients with untreated chronic lymphocytic leukaemia (CLL).	
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	It is highly appropriate to evaluate acalabrutinib and venetoclax with or without obinutuzumab in untreated chronic lymphocytic leukaemia as this is a potentially valuable treatment option for this patient group. I believe the route of evaluation (single technology appraisal) is likely to be appropriate though the specifics of decision-making about route of evaluation are outside my area of expertise.	Thank you for your comment. No action required.
Wording	Johnson & Johnson Innovative Medicine	Yes, the wording of the remit does reflect the issues	Thank you for your comment. No action required.
	AbbVie UK	No comment	No action required.
	AstraZeneca UK Ltd	As noted under the 'Population' heading below, the population of interest for this appraisal is patients with untreated CLL without 17p deletion or TP53	Thank you for your comment. The population is intentionally kept broad

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		mutation. This aligns with the population included within the pivotal clinical trial for AV/AVO, in this indication (the AMPLIFY trial).	to avoid excluding potentially eligible people. The committee will assess the technology in line with its marketing authorisation. The company will have the opportunity to justify their considerations of the relevant population in their submission.
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	The wording of the remit is appropriate.	Thank you for your comment. No action required.
Additional comments on the draft remit	Johnson & Johnson Innovative Medicine	N/A	No action required.

Section	Stakeholder	Comments [sic]	Action
	AbbVie UK	No comment	No action required.
	AstraZeneca UK Ltd	Timing issues AV/AVO would represent an important additional treatment option for patients with untreated CLL without a 17p deletion or TP53 mutation; AV provides the additional benefit of being an all-oral combination. Moreover, AV/AVO has a more tolerable adverse event profile versus currently available treatments.3 A further option in the treatment armamentarium for untreated CLL would allow clinicians and patients increased flexibility when considering treatment options. As such, AV/AVO should be evaluated with urgency to avoid any delays in access for patients.	Thank you for your comment. No action required.
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	Timing issues This is not of immediate clinical urgency but should be evaluated promptly.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background	Johnson & Johnson Innovative Medicine	N/A	No action required.
	AbbVie UK	No comment	No action required.
	AstraZeneca UK Ltd	The background information is largely accurate and captures the key points related to CLL and its' treatment. However, AstraZeneca wishes to highlight a few minor amendments: • Currently available treatments for CLL are split based on the treatment duration, with treatments being either fixed duration (e.g, VenI and venetoclax with obinutuzumab [VenO]) or treat-to-progression (e.g., acalabrutinib monotherapy and zanubrutinib). The choice between fixed duration or treat-to-progression treatments is a key consideration driving treatment decisions. Due to the relevance of treatment duration in treatment decisions, the background section should include some discussion of fixed duration and treat-to-progression regimens. • The background section mentions specific treatments without listing all other treatments available (e.g., "immunotherapies, such as rituximab" and "targeted therapies, such as acalabrutinib, ibrutinib, idelalisib and venetoclax"). AstraZeneca suggests that it would be more accurate to refer to the classes of treatment (i.e., BTK inhibitors [acalabrutinib, ibrutinib], BCL2 inhibitors [venetoclax] and CD20 targeting monoclonal antibodies [obinutuzumab]), without referring to specific treatment options to ensure all options are encompassed.	Thank you for your comment. The aim of the background and technology sections are to provide a very brief summary of the disease area. Further data and information can be provided at the submission stage of the appraisal. We have updated the scope to include a sentence describing that treatments can be fixed duration or continuous. Further data and information can be provided at the

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		In the section on the technology, three clinical trials are listed as providing evidence for AV/AVO in untreated CLL. AstraZeneca wish to highlight that the submission for AV/AVO will be based on the pivotal clinical trial informing the anticipated marketing authorisation for AV/AVO, the AMPLIFY trial.	submission stage of the appraisal. The committee will assess the technology in line with its marketing authorisation. The company will have the opportunity to justify their considerations of the relevant population in their submission.
	BeiGene UK Ltd.	Page 1, Background section, Paragraph 5, final sentence: In addition to the targeted therapies listed in, Zanubrutinib is also approved and reimbursed and has proven useful in people with a poor prognosis such as those with 17p deletion of TP53 mutation, as reflected in NICE Guidance TA891 referenced elsewhere in the draft scope. We would suggest Zanubrutinib is therefore also added to the sentence for completeness.	Thank you for your comment. Zanubrutinib has been added to the last paragraph of the background section for completeness.
Population	Johnson & Johnson Innovative Medicine	The transplant-eligible population is not included in either the licensed or studied population. Specifically, individuals with previously untreated chronic lymphocytic leukaemia who are eligible for autologous stem cell transplantation are excluded from the study population.	Thank you for your comment. The committee will assess the technology in line with its marketing authorisation.

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			The company will have the opportunity to justify their considerations of the relevant population in their submission.
	AbbVie UK	Yes [population is defined appropriately]	No action required.
	AstraZeneca UK Ltd	The population included with the NICE draft scope is patients with untreated CLL. The clinical evidence base for AV/AVO is the Phase III AMPLIFY trial. The population included within AMPLIFY is **patients with previously untreated CLL without a 17p deletion or TP53 mutation**. The population of interest in this appraisal will align with the clinical evidence base (i.e., the AMPLIFY trial).3	Thank you for your comment. The population is intentionally kept broad to avoid excluding potentially eligible people. The committee will assess the technology in line with its marketing authorisation. The company will have the opportunity to justify their considerations of the relevant population in their submission.
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding	In regard to paragraph 3:	Thank you for your comment. The scope

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	on behalf of British Society of Haematologist, The Royal College of Pathologists	While CLL often progresses slowly, some patients will have rapidly progressive disease. In regard to paragraph 4: In addition to 17p deletion or TP53 gene mutation, there are other genetic features associated with adverse outcomes including presence of unmutated immunoglobulin heavy chain gene (uIGHV), and complex karyotype (Eichorst et al, 2020, Annals of Oncology, currently reference 5 in the scope document would be a suitable reference). These features are commonly tested for in clinical practice in UK. In regard to paragraph 5: CLL is not considered a curable disease and many patients will require more than one line of treatment. When used in the treatment of CLL, chemotherapy is always combined with immunotherapy (such as rituximab or obinutuzumab), in a combination known as chemoimmunotherapy. Reference to 'chemotherapy' should be removed from the background information as chemotherapy is not used alone in the treatment of CLL. Chemoimmunotherapy is very uncommonly used in the treatment of CLL in the UK, as targeted therapies have been demonstrated to be more effective. Chemoimmunotherapy (CIT) is ineffective in patients with deletion 17p and/or TP53 mutation and is never recommended for these patients.	has been updated to reflect that some patients will have rapidly progressive disease. The scope has been updated to reflect that complex karyotypes can also impact treatment decisions and outcomes. The term chemoimmunotherapy has been added. Chemotherapy has been retained as treatments listed in the scope are intended to be broad.

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		Zanubrutinib should be included in the list of targeted therapies. Idelalisib is the least commonly used of these agents and should be moved to the end of the list of targeted therapies to reflect this. Targeted therapies are useful in patients both with and without high risk features (such as deletion 17p, TP53 mutation, uIGHV status).	The scope has been updated to reflect this.
Subgroups	Johnson & Johnson Innovative Medicine	The subgroups suggested in the scope are appropriate.	Comment noted. No action required.
	AbbVie UK	It is appropriate to have subgroups for patients with and without a 17p deletion or TP53 mutation, given that patients with these mutations have a worse prognosis	Comment noted. No action required.
	AstraZeneca UK Ltd	As the population of interest is patients with untreated CLL without a 17p deletion or TP53 mutation, people with and without a 17p deletion or TP53 mutation is not a relevant subgroup. Subgroup analyses by IGHV mutation status were conducted for OS and PFS in AMPLIFY, and the results will be presented as part of subgroup analysis forest plots. Consideration of subgroups by IGHV mutation status in the cost-effectiveness analysis may be limited by availability of comparator data by IGHV mutation status.	Thank you for your comment. The population is intentionally kept broad to avoid excluding potentially eligible people. The committee will assess the technology in line with its marketing authorisation. Where possible analysis of subgroups noted in the scope should be provided. The

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			company will have the opportunity to justify any exclusion of these subgroups or inclusion of additional subgroups in their submission.
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	The two subgroups indicated in the scope (those with and without deletion 17p or TP53 deletion, and according to IGHV status) are appropriate.	Comment noted. No action required.
Comparators	Johnson & Johnson Innovative Medicine	Yes, these seem to represent standard treatments currently used in the NHS	Comment noted. No action required.
	AbbVie UK	AbbVie does not believe FCR/BR to be a relevant comparator for this appraisal given the very low usage in clinical practice.	Thank you for your comment. The comparators have been retained as those listed

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			in the scope are intended to be broad. The most appropriate comparator(s) will be discussed in more detail during the appraisal and by the committee, with input from the company submission and clinical experts.
	AstraZeneca UK Ltd	Classification of comparators by subgroup The comparators included in the draft scope are categorised into three subgroups: 1. Adults with untreated CLL where mutation is not specified 2. Adults with untreated CLL without a 17p deletion or TP53 mutation only 3. Adults with untreated CLL with a 17p deletion or TP53 mutation As outlined above, the population of interest for this appraisal is patients with untreated CLL without a 17p deletion or TP53 mutation. To align with this population, treatments included under subgroup 2 above (adults with untreated CLL without a 17p deletion or TP53 mutation only) represent the relevant comparators to AV/AVO. However, based on treatment guidelines and feedback from UK clinical experts, AstraZeneca believes that VenI (currently included under the first subgroup – adults with untreated CLL where mutation is not specified) is used	Thank you for your comment. The comparators have been retained as those listed in the scope are intended to be broad. A strong and clear rationale should be provided for excluding any comparators from the evidence submission. The most appropriate comparator(s) will be discussed in more detail during the appraisal and by the committee, with input from the company

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		in patients without a 17p deletion or TP53 mutation so would be a relevant comparator to AV/AVO. The current list of comparators in subgroup 2 do not reflect the importance of dosing of regimens, namely fixed duration or treat-to-progression. As fixed duration and treat-to-progression regimens are currently used in distinct patient populations in clinical practice, the list of comparators relevant to AV/AVO should reflect this. Feedback from clinicians indicates that patients currently receiving treat-to-progression regimens (i.e. acalabrutinib [TA689] and zanubrutinib [TA931]) would continue to do so, and the introduction of AV/AVO, which is a fixed duration regimen, would not displace currently available treat-to-progression treatments (and vice versa).2,4 As such, the treat-to-progression regimens included in the scope under the subgroup of "Adults with untreated CLL without a 17p deletion or TP53 mutation only" (i.e., [TA689] and zanubrutinib [TA931])) are not relevant comparators to AV/AVO.2,4 Treatments not used in clinical practice In addition to the above comments regarding classification of the comparators into subgroups, the following treatments should not be included as comparators within any subgroups, for reasons detailed below: • Obinutuzumab with chlorambucil (O-Clb) is rarely used in UK clinical practice since the introduction of targeted treatments for patients for whom FCR/BR are unsuitable (i.e., acalabrutinib, zanubrutinib, VenI and VenO). As such, O-Clb should not be considered a relevant comparator. • Since the introduction of targeted therapies, bendamustine monotherapy is not used in UK clinical practice for untreated CLL. Bendamustine monotherapy was not considered a relevant comparator in recent appraisals of CLL treatments in FCR/BR unsuitable patients (e.g.,	submission and clinical experts. The committee will assess the technology in line with its marketing authorisation. The company will have the opportunity to justify their considerations of the relevant population in their submission.

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		VenO, VenI and zanubrutinib).1,4,5 Bendamustine monotherapy should therefore not be considered a relevant comparator. • FCR/BR are a treatment option for patients without 17p deletion or TP53 mutation. However, use of FCR/BR in UK clinical practice is limited since the introduction of targeted therapies (e.g., VenI and VenO). • Acalabrutinib with obinutuzumab (AO) is included as a comparator, however AO has not been appraised or recommended by NICE. As such, AO should not be included as a comparator in any subgroup.	
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	All relevant comparators have been included. Chemoimmunotherapy: FCR (TA 174); chlorambucil and obinutuzumab (TA343); bendamustine and rituximab; are uncommonly in the UK. Chemotherapy is not used alone in CLL and therefore I believe bendamustine (TA216) is an unsuitable comparator.	Thank you for your comment. The comparators have been retained as those listed in the scope are intended to be broad. The most appropriate comparator(s) will be discussed in more detail during the appraisal and by the committee, with input from the company submission and clinical experts.

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Outcomes	Johnson & Johnson Innovative Medicine	Yes, these outcome measures capture the most important health related benefits and harms of the technology.	Comment noted. No action required.
	AbbVie UK	No Comment	No action required.
	AstraZeneca UK Ltd	The outcomes listed in the draft scope broadly reflect the most relevant outcomes to measure the health-related benefits and harms of treatments for CLL. However, infection-free survival is not a standard outcome for CLL and was not collected in the AMPLIFY trial for AV/AVO. In addition, data on infection-free survival are unlikely to be publicly available for the relevant comparators. As such, infection-free survival should be removed from the draft scope. Information on infections as adverse events will be collected as part of the safety outcomes.	Thanks for your comments. Outcomes listed in the scope are selected on the basis of their importance to patients and carers rather than on their availability in the clinical studies. Infection free survival has been removed from the scope.
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist,	Yes [Outcomes listed are appropriate and will capture the most important health related benefits (and harms) of the technology]	Comment noted. No action required.

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	The Royal College of Pathologists		
Equality	Johnson & Johnson Innovative Medicine	N/A	No action required.
	AbbVie UK	No comment	No action required.
	AstraZeneca UK Ltd	No equality issues associated with the management of untreated CLL have been identified.	No action required.
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	I do not believe there are any issues here.	Thank you for your comment. No action required.
	Johnson & Johnson	N/A	No action required.

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Other considerations	Innovative Medicine		
	AbbVie UK	No comment	No action required.
	AstraZeneca UK Ltd	No further comments.	No action required.
	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	In addition to the three trials listed in 'the technology', please also note the publication of phase 2 expansion cohort of acalabrutinib plus venetoclax and obinutuzumab in previously untreated CLL patients with high risk disease (including del17p/ TP53) (Davids et al, 2024, Journal of Clinical Oncology, https://doi.org/10.1200/JCO-24-02503)	Thank you for your comment. No action required.
Questions for consultation	Johnson & Johnson Innovative Medicine	N/A	No action required.
	AbbVie UK	**Please select from the following, will acalabrutinib and venetoclax with or without obinutuzumab be:** Prescribed in secondary care with routine follow-up in secondary care.	Thank you for your comment. No action required.

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		Where do you consider acalabrutinib and venetoclax with or without obinutuzumab will fit into the existing care pathway for previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma? AbbVie believes that as acalabrutinib and venetoclax is a combination of a bruton's tyrosine kinase inhibitor (BTKI) and a BCL-2 inhibitor, it will Be used in the same positions as the BTKI and BCL-2 inhibitor combination currently reimbursed i.e.ibrutinib in combination with venetoclax.	
	AstraZeneca UK Ltd	**Where do you consider acalabrutinib and venetoclax with or without obinutuzumab will fit into the existing care pathway for previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma?** In line with the AMPLIFY trial, AV/AVO is positioned as a fixed duration treatment for adult patients with untreated CLL without a 17p deletion or TP53 mutation. As outlined under 'comparators', as AV/AVO is a fixed duration treatment, it is anticipated to only displace fixed duration treatments that are currently available for patients without a 17p deletion or TP53 mutation (i.e., VenI and VenO [available via the CDF for fit patients for whom FCR/BR is suitable]). **Please select from the following, will acalabrutinib and venetoclax with or without obinutuzumab be:** C. Prescribed in secondary care with routine follow-up in secondary care	Thank you for your comment. The committee will assess the technology in line with its marketing authorisation. The company will have the opportunity to justify their considerations of the relevant population in their submission No action required.

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		D. Other (please give details): AV/AVO will be prescribed in secondary with routine follow-up in secondary care. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** It is anticipated that all comparators and subsequent treatments for AV/AVO are prescribed in secondary care with routine follow-up in secondary care, in line with the anticipated prescribing and follow-up of AV/AVO. Further detail of the follow-up requirements for comparators and subsequent treatments will be explored with clinical experts to support the appraisal of AV/AVO. **Would acalabrutinib and venetoclax with or without obinutuzumab be a candidate for managed access?** Clinical evidence to support the appraisal of AV/AVO in patients with untreated CLL without 17p deletion or TP53 mutation is from the Phase III AMPLIFY trial. Data from AMPLIFY are anticipated to be suitably mature and reliable to allow the Committee to recommend AV/AVO via routine commissioning. The AMPLIFY trial is ongoing and future data cuts of AMPLIFY are event-driven and subject to change. As such, current timings of upcoming data cuts of the AMPLIFY trial are unknown. However, data with additional follow-up	

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		are anticipated to become available in the future, should the Committee deem managed access necessary. **Do you consider that the use of acalabrutinib and venetoclax with or without obinutuzumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Acalabrutinib and venetoclax are both administered orally, meaning AV is a completely oral treatment option. This contrasts with other fixed duration treatments currently available for untreated CLL (i.e., VenO) which requires IV administration of obinutuzumab. Although the lower resource use of oral administration compared to IV will be reflected in the modelled costs, the non-monetary benefits for patients will not be captured. In particular, fewer hospital visits can minimise disruptions to patients' daily lives and reduce the emotional burden of frequent reminders of their illness, as highlighted in the appraisal of VenI [TA891].1 As a fixed duration treatment, some patients may benefit from reduced treatment exposure and the option for a treatment-free period. Although the adverse events associated with reduced treatment exposure will be captured in the QALYs, the additional emotional benefit of a treatment-free interval will not be.	

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	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	Acalabrutinib and venetoclax with or without obinutuzumab would be both prescribed and routinely followed up in secondary care. The comparators and subsequent treatments would also be prescribed and routinely followed up in secondary care. Acalabrutinib and venetoclax with or without obinutuzumab would be a candidate for managed access. I do not consider that the use of acalabrutinib and venetoclax with or without obinutuzumab is likely to result in health-related benefits that are unlikely to be included in the QALY calculation.	Thank you for your comment. No action required.
Additional comments on the draft scope	Johnson & Johnson Innovative Medicine	N/A	No action required.
	AbbVie UK	No comment	No action required.
	AstraZeneca UK Ltd	No further comments on the draft scope. Comment 3 of the form: The following relevant stakeholders are not included on the provisional stakeholder list: UK CLL Forum and Lymphoma Action.	Thank you for your comment. UK CLL forum and Lymphoma Action have been added to the stakeholder list.

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	BeiGene UK Ltd.	N/A	No action required.
	UK CLL Forum, and responding on behalf of British Society of Haematologist, The Royal College of Pathologists	Comment 3 on the form: Lymphoma Action is a patient/ carer group which would be a suitable additional stakeholder as they offer support to CLL/SLL patients.	Thank you for your comment. Lymphoma Action has been added to the stakeholder list.