National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Acalabrutinib for untreated and treated chronic lymphocytic leukaemia ID1613

Response to consultee and commentator comments on the draft remit and draft scope

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AstraZeneca	No comment received	N/A
	AbbVie	No comment received	N/A
	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	No comment received	N/A
Wording	AstraZeneca	No comment received	N/A
	AbbVie	To reflect the complexity of the appraisal and the different indications being appraised, the draft remit should be changed to: • To appraise the clinical and cost effectiveness of acalabrutinib within its marketing authorisation for untreated chronic lymphocytic leukaemia	Comments noted. In line with the Guide to the Methods of Technology Appraisal 2013, NICE will appraise acalabrutinib in line with its marketing

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		• To appraise the clinical and cost effectiveness of acalabrutinib within its marketing authorisation for treating relapsed or refractory chronic lymphocytic leukaemia This change would also be consistent with previous NICE appraisals in this therapy area	authorisation. Both the untreated and previously treated populations can be appraised within one appraisal. The title and remit of the draft scope has been updated to reflect this more clearly.
	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	Yes	Comment noted. No changes required.
Timing Issues	AstraZeneca	No comment received	N/A
	Abbvie	No comment received	N/A
	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	No comment received	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	No comment. It is important to recognise that the classification of patients (e.g. into fit and unfit) was based on treatment options available more than a decade ago. As more treatment options have become available, this classification has become less and less relevant and clinical practice is moving towards other ways of determining eligibility for treatment options. This evolution in both clinical thinking and practice should be reflected in the scope.	Comments noted. The background section of the scope is intended to provide a broad summery of the condition. The complexity of the condition is highlighted within the draft scope. No changes required.
	Abbvie	No comment	N/A
	Leukaemia Care	CLL is the most common leukaemia in adults in the UK, rather than just one of the most common	Comment noted. The draft scope has now been updated to reflect this.
	RCPath, BSH, UK CLL Forum	The background information is broadly accurate but the sentence “Treatment can also depend on the presence of 17p deletion or TP53 mutation” needs to change. All patients should be assessed prior to treatment for the presence of TP53 mutations or deletions, as patients who carry these genetic changes in their CLL do not respond to conventional CIT. In addition, there is increasing evidence for the role of assessing IgVH mutational status to tailor the most appropriate and efficacious therapy for the individual. In addition, in table 1 for patients Without a 17p deletion (del[17p]) or TP53 mutation I would describe the population who receive FCR as young fit patients (not as currently described “for whom fludarabine in combination with cyclophosphamide is considered appropriate”)	Comments noted. The draft scope has been updated. The wording of “for whom fludarabine in combination with cyclophosphamide is considered appropriate” is used for consistency with past and ongoing NICE appraisals in this area.

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		Also need to add for p53 deleted pts:Venetoclax monotherapy (TA487) in those unsuitable a B-cell receptor pathway inhibitor	The subgroup population list has been updated in the draft scope to include people with unmutated IgHV disease, if evidence allows. Venetoclax monotherapy (TA487) has been recommended as a treatment option within the Cancer Drugs Fund (CDF) and therefore is not considered to be in routine use in the NHS in England. Please see the NICE position statement on CDF treatments as comparators.
The technology/ intervention	AstraZeneca	No comment	N/A
	Abbvie	No comment	N/A
	Leukaemia Care	No comment received	N/A

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	RCPath, BSH, UK CLL Forum	No comments received	N/A
Population	AstraZeneca	No comment	N/A
	Abbvie	As explained above, the population should be changed as follows: 1. People with untreated chronic lymphocytic leukaemia 2. People with relapsed or refractory chronic lymphocytic leukaemia who have had at least one prior therapy	Comment noted. Please see the relevant response above.
	Leukaemia Care	We agree that patients should be separated by genetic status within both the untreated and relapse/refractory group. It is well established that genetic status can change response to treatments and can therefore changes which treatments are available to each group. This in turn creates different needs in each population, and clinicans having choice to meet patient needs is really important. There is evidence about the efficacy of acalabrutinib in both previously treated (ASCEND) and untreated patients (ELEVATE II), therefore we are keen for the scope to remain as broad as possible in respect to the defined patient population.	Comments noted. No changes to the draft scope required.
	RCPath, BSH, UK CLL Forum	CLL patients should be offered genetic analysis not only for TP53 abnormalities but also by IGHV mutation status.	Comment noted. The subgroup population list has been updated in the draft scope to include people with unmutated IgHV disease if evidence allows.

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Comparators	AstraZeneca	AZ is of the opinion that venetoclax with obinutuzumab is not a relevant comparator for the untreated CLL patients of this appraisal. It is noteworthy that venetoclax in previously untreated patients with CLL in the presence of a 17p deletion or TP53 mutation (when a B-cell receptor pathway inhibitor is unsuitable) has not been included in the draft scope due to being in CDF. It is our belief that the combination of venetoclax and obinutuzumab in untreated CLL patients should also be out of scope. Bendamustine (in combination with rituximab) is also used in patients who have had at least one previous therapy and should be considered as a comparator in this appraisal.	Comments noted. venetoclax with obinutuzumab (ID1402) is currently undergoing a NICE appraisal for untreated CLL, and therefore may become standard clinical practice during the process of this appraisal. Therefore, it will be retained in the draft scope as a comparator. Venetoclax monotherapy (TA487) has been recommended as a treatment option within the Cancer Drugs Fund (CDF) and therefore is not considered to be in routine use in the NHS in England.
	AbbVie	No comment	N/A
	Leukaemia Care	Venetoclax monotherapy is available at different points, depending on response to previous treatment and genetic status (TA487):	Venetoclax monotherapy (TA487)

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		• with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor or • without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor Therefore, venetoclax monotherapy needs including in the comparator list. Best alternative care can vary, as there is still some discussion among the community about the right order to give certain novel treatments due to limited experience in using treatments plus the volume of new treatments coming to the market for CLL. However, the most appropriate comparators would be FCR and ibrutinib for untreated patients (just ibrutinib if have high risk genetics), and ibrutinib or venetoclax with rituximab (BSH guidelines 2018).	was recommend as a treatment option in the Cancer Drugs Fund (CDF) and therefore not considered appropriate as a comparator in this appraisal. Please see the NICE position statement on CDF treatments as comparators.
	RCPath, BSH, UK CLL Forum	Have changed comparator list to a different order and added in the Venetoclax monotherapy: For untreated CLL, including (but not limited to): • rituximab with fludarabine and cyclophosphamide • ibrutinib (currently only available I the UK for 17p deletion or TP53 mutation)	Venetoclax monotherapy (TA487) was recommend as a treatment option in the Cancer Drugs Fund (CDF) and therefore not considered appropriate as a comparator in this appraisal. Please see the NICE position

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		• bendamustine with or without rituximab • obinutuzumab with chlorambucil • venetoclax with obinutuzumab (subject to NICE appraisal) • Venetoclax monotherapy (TA487) (17p deletion or TP53 mutation unsuitable for a B-cell receptor pathway inhibitor) • idelalisib with rituximab (17p deletion or TP53 mutation) • chlorambucil with or without rituximab The most important direct comparator will be Ibrutinib monotherapy, there is highly anticipated data of phase 3 direct comparison study of Ibrutinib and Acalabrutinib in relapsed patients (Elevate, NCT02477696), this study primary completion day was June 2019 For previously treated CLL, including (but not limited to): • venetoclax with rituximab • venetoclax monotherapy • ibrutinib • rituximab with fludarabine and cyclophosphamide • idelalisib with rituximab	statement on CDF treatments as comparators. No changes to the draft scope required.
Outcomes	AstraZeneca	No comment	N/A
	Abbvie	No comment	N/A

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	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	Yes	Comment noted. No changes required.
Economic analysis	AstraZeneca	No comment	N/A
	Abbvie	No comment	N/A
	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	It is important to consider the long term outcomes in these patients. Delivering BTK inhibitor therapy as initial treatment in CLL is likely to reduce health care utilisation in addition to the benefits in PFS. For example, patients are likely to have a reduced incidence of recurrent infections in future years; which will not be measured effectively in many trials	Comments noted. The reference case for a submission stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Equality and Diversity	AstraZeneca	No comment	N/A
	Abbvie	No comment	N/A

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	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	No comments received.	N/A
Other considerations	AstraZeneca	AZ believes that people with IGHV unmutated disease are an important subgroup of patients who should be considered in the appraisal.	Comment noted. The subgroup population list has been updated in the draft scope to include people with unmutated IgHV disease.
	Abbvie	No comment	N/A
	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	In draft scope is copied in below: If the evidence allows the following subgroups will be considered: • people with a 17p deletion or TP 53 mutation • people previously untreated • people previously treated • people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the	Comment noted. no changes to the scope required.

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		evidence that has underpinned the marketing authorisation granted by the regulator	
Innovation	AstraZeneca	No comment	N/A
	Abbvie	No comment	N/A
	Leukaemia Care	Given that there is only one other BTK inhibitor on the market, this could be considered a step change in the management of patients. There are limited options for patients who cannot tolerate ibrutinib, so it should be considered a big change in management of relapsed/refractory patients, and in those with high risk genetics and co-morbidities that mean they are unlikely to tolerate ibrutinib, such as those with heart conditions. We have patient survey data that could be analysed further to understand patient preferences about treatments, as well as qualitative focus group data. This may be able to assist the committee in understanding the need for choice in treating CLL.	Comment noted. Committee will consider if acalabrutinib is innovative.
	RCPath, BSH, UK CLL Forum	This submission offers a major advance for the UK patients offering BTK inhibitor as front line and relapse therapy. At present in the UK, only patients with p53 deletion or mutation are eligible to receive BTK inhibitor Ibrutinib as first line therapy, despite it having a licence and good evidence of PFS and OS benefit as monotherapy, N Engl J Med 2018; 379:2517-2528 Trials suggest that Acalabrutinib, a more selective BTK inhibitor than Ibrutinib. It shows similar efficacy and a better side effect profile Patients who were	Comment noted. Committee will consider if acalabrutinib is innovative.

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		intolerant of Ibrutinib were able to tolerate Acalubrutinib and achieve disease control Awan FT et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Adv. 2019 May 14;3(9):1553-1562. There is significantly less cardiac toxicity: Atrial fibrillation occurs only in 3% of patients There is evidence of effectiveness of Acalabrutinib in relapsed CLL: ASCEND study and front line treatment: Elevate TN study	
Questions for consultation	AstraZeneca	All questions for consultation have been addressed in other parts of this response	Comments noted. No changes to the scope required.
	Abbvie	Acalabrutinib is a B cell receptor inhibitor (BCRI) with a similar mechanism of action to Ibrutinib, which is currently reimbursed in the NHS in both the frontline and relapsed/refractory setting. The anticipated positioning of acalabrutinib in clinical practice is: • As an alternative BCRI to ibrutinib • As a salvage BCRI, if patients can't tolerate ibrutinib	Comments noted. No change to the scope required.
	Leukaemia Care	No comments received	N/A
	RCPath, BSH, UK CLL Forum	No comments received.	N/A

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Additional comments on the draft scope	AstraZeneca	AZ is of the opinion that given the complexity of this disease setting (treatment options and definitions of patient types), it is appropriate for this topic to be discussed at a scoping workshop with other consultees.	Comments noted. NICE recognises the complexity of this condition, and this is highlighted in the draft scope. However, this is a disease are with which NICE has had extensive experience. There have been several previous NICE technology appraisals in this area. NICE believes that a consultation on the draft scope is sufficient to finalise the scope for this appraisal.
	Abbvie	Any additional comments on the draft remit We note that two NICE appraisal pages were initially set up (see below) but that these have now been merged into one appraisal. • Acalabrutinib for previously treated chronic lymphocytic leukaemia [ID1613] https://www.nice.org.uk/guidance/indevelopment/gid-ta10500 • Acalabrutinib for Chronic Lymphocytic Leukaemia (CLL)in Elderly and unfit patients, Not specified, First line [ID1614] https://www.nice.org.uk/guidance/indevelopment/gid-ta10501	Comment noted. Please see the relevant response above.

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		We believe that these should be kept as two separate appraisals for the following reasons: • It appears that two pivotal phase III trials; ELEVATE TN and ASCEND will support the marketing authorisation application for the untreated and relapsed/refractory indications respectively. Any differences in regulatory timelines between the two indications will therefore mean the combined NICE appraisal will have to proceed according to the regulatory timelines of the later indication. This would result in a delayed appraisal for one indication relative to its marketing authorisation and impede patient access • As outlined in the draft scope (page 1), "*treatment for CLL is complex and depends on several factors*" The complexity and treatment challenges in the relapsed/refractory CLL indication are different from those in the untreated CLL indication. Furthermore, the poorer prognostic del 17p/TP53 mutated subgroup adds an additional layer of complexity – all of which will be difficult to evaluate in one combined appraisal, thus potentially prolonging the appraisal and delaying patient access.	
	Leukaemia Care	No comment received	N/A
	RCPath, BSH, UK CLL Forum	No comments received.	N/A

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Chronic Lymphocytic Support Association (CLLSA)

Janssen

Lymphoma action