National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia

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
Wording	Janssen	Yes, the wording of the remit does reflect the issues.	Comment noted.
	British Society of Haematology, Royal College of Pathologists	Yes	Comment noted.
	AbbVie Ltd	Yes	Comment noted.
	Leukaemia Care	None	Comment noted.
	Chronic Lymphocytic Leukaemia Support Association	Yes	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Janssen	None	Comment noted.
	British Society of Haematology, Royal College of Pathologists	Three to six months	Comment noted.
	AbbVie Ltd	The NHS would benefit from early appraisal of this technology as there are limited treatment options in relapsed/refractory CLL	Comment noted.
	Leukaemia Care	None	Comment noted.
	Chronic Lymphocytic Leukaemia Support Association	This appraisal is urgent as there are very few truly effective alternatives for relapsed and refractory patients, particularly those that have received prior Ibrutinib or Idelasalib. This combination is a step change in outcomes and should be appraised as soon as possible.	Comment noted.
Additional comments on the draft remit	Janssen	None	Comment noted.
	British Society of Haematology, Royal College of Pathologists	None	Comment noted.
	AbbVie Ltd	None	Comment noted.
	Leukaemia Care	None	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Chronic Lymphocytic Leukaemia Support Association	None	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Janssen	None	Comment noted. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	Accurate	Comment noted. No changes to the scope are needed.
	AbbVie Ltd	AbbVie suggest adding the full recommendation of TA487: "*Venetoclax is recommended for use within the Cancer Drugs Fund, as an option for treating CLL, in adults with a 17p deletion or TP53 mutation when a BCRi is unsuitable, or whose disease has progressed after a B‑cell receptor pathway inhibitor, or without a 17p deletion or TP53 mutation whose disease has progressed after both chemo‑immunotherapy and a BCRi*" AbbVie also suggest adding the full recommendation of TA429: "*Ibrutinib alone is recommended as an option for treating CLL in adults who have had*	Comment noted. The scope is only intended to provide a general overview of the available treatment options to the NHS for the treatment of relapsed or refractory chronic lymphocytic leukaemia in people

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		at least 1 prior therapy or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable".	who have had at least 1 therapy. Hence any recommendations in populations outside this scope are not included. However, for information, the technology appraisal guidance 487 and 429 are acknowledged in the relevant NICE recommendations section of the scope.
	Leukaemia Care	None	Comment noted. No changes to the scope are needed.
	Chronic Lymphocytic Leukaemia Support Association	Yes	Comment noted. No changes to the scope are needed.
The technology/ intervention	Janssen	None	Comment noted. No changes to the scope are needed.

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	British Society of Haematology, Royal College of Pathologists	Yes	Comment noted. No changes to the scope are needed.
	AbbVie Ltd	The EU brand name of venetoclax is Venclyxto®. Venclexta, is the US brand name.	Comment noted. The brand name of venetoclax has been updated to reflect the EU brand name.
	Leukaemia Care	The reference to “Rituximab (MabThera, Roche Products” should be amended to “Rituximab” to allow for usage of biosimilar rituximab.	Comment noted. The technology/intervention section has been amended accordingly.
	Chronic Lymphocytic Leukaemia Support Association	Yes	Comment noted. No changes to the scope are needed.
Population	Janssen	Yes, the population seems appropriately defined	Comment noted. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	TP53 deleted or mutated patients. This patient group will not normally be given Bendamustine and rituximab which is comparator arm used in this trial. The ideal comparator for this group of patients is B-cell receptor antagonist such as ibrutinib and idelalsib with rituximab.	Comment noted. No changes to the scope are needed.

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	AbbVie Ltd	The population is defined appropriately	Comment noted. No changes to the scope are needed.
	Leukaemia Care	None	Comment noted. No changes to the scope are needed.
	Chronic Lymphocytic Leukaemia Support Association	Patients who have been treated as first line with a B cell receptor pathway inhibitor should be considered as a priority. These patients will have been in a clinical trial (inc FLAIR) and have contributed to research. If they progress on treatment then their outlook is very bleak in the absence of Venetoclax (reported as only 72 days survival). However, these patients are not covered by TA 487 and are ineligible for Venetoclax mono therapy so this appraisal is very important for them. The subgroup analysis proposed currently includes only patients with deletion of chromosome 17p and should be widened to include patients with aberrations in TP53.	Comment noted. The remit states that venetoclax in combination with rituximab will be appraised within its marketing authorisation. Therefore, the appraisal will focus on the specific population covered by the marketing authorisation. Patients with TP53 mutations have now been added as a subgroup in the scope.

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Comparators	Janssen	Yes, these seem to represent standard treatments currently used in the NHS.	Comment noted. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	Yes. The mentioned drugs are currently the standard of therapy. Venetoclax with rituximab can be considered as “best alternative care”.	Comment noted. No changes to the scope are needed.
	AbbVie Ltd	AbbVie agree that **ibrutinib**, **idelalisib in combination with rituximab** and **venetoclax monotherapy** can be considered as comparators to venetoclax in combination with rituximab. AbbVie consider that **chemo-immunotherapy** is not a comparator for venetoclax in combination with rituximab since most of the chemo-immunotherapy options are not reimbursed. Furthermore the advent of BCRi has changed the treatment landscape such that BCRis are more commonly used after 1 line of prior treatment. Finally, this was considered in the Ibrutinib NICE appraisal (TA429 –pages 6-9 of the Final Appraisal Determination) and it was concluded that chemo-immunotherapy is not a comparator in this patient population. AbbVie consider **best supportive care** not to be a comparator to venetoclax in combination with rituximab. It is reserved for latter lines of therapy after all	Comments noted. Venetoclax monotherapy has not been included as a comparator because it is currently in the CDF and CDF treatments are not routinely considered as established practise. Chemo-immunotherapy is not included as a comparator in the scope. No change required. Comment noted. The list of comparators have been kept broad to

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		treatment options (including venetoclax+rituximab and ibrutinib) have been exhausted.	ensure it captures all possible lines of therapy.
	Leukaemia Care	Ibrutinib, idelalisib in combination with rituximab and venetoclax monotherapy are appropriate comparators. Best supportive care is not an appropriate comparator as anyone clinically suitable for venetoclax in combination with rituximab (VR) would currently receive venetoclax monotherapy instead of BSC.	Comments noted. Venetoclax monotherapy has not been included as a comparator because it is currently in the CDF and CDF treatments are not routinely considered as established practise. Comment noted. The list of comparators have been kept broad to ensure it captures all possible lines of therapy.
	Chronic Lymphocytic Leukaemia Support Association	Yes but Bendamustine+Rituximab has been ommitted and should be included in order to consider the results of the MURANO phase III study, the preliminary 2 year results were reported December 2017. However, this combination is not NICE approved and not part of UK practice. Venetoclax monotherapy TA 487 could be described as best alternative care but this does not cover all the required groups of patients as set out in this appraisal.	Comments noted. Bendamustine + Rituximab has not been included as a comparator because it is not considered established practice in the NHS for treating relapsed or refractory

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		Best supportive care would only be considered for patients who had received prior Venetoclax monotherapy.	chronic lymphocytic leukaemia. Please see section 4.8 of TA429. Venetoclax monotherapy has not been included as a comparator because it is currently in the CDF and CDF treatments are not routinely considered as established practise. Comment noted. The list of comparators have been kept broad to ensure it captures all possible lines of therapy.
Outcomes	Janssen	Yes, these outcome measures capture the most important health related benefits and harms of the technology.	Comment noted. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	Yes. One of the important end-points is minimal residual disease(MRD) which was a secondary end point in this trial. It would be unfair to compare the MRD results of Venetoclax with B-cell receptor antagonists due to contrasting mechanism of actions. However, comparison of MRD negative rate with Venetoclax alone vs venetoclax with rituximab should be very useful.	Comment noted. Minimal residual disease negative rate has been included as an outcome measure in the scope.

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	AbbVie Ltd	None	Comment noted. No changes to the scope are needed.
	Leukaemia Care	Outcomes should include proportion of patients who are MRD (minimal residual disease) negative, as a surrogate for OS (Overall Survival).	Comment noted. Minimal residual disease negative rate has been included as an outcome measure in the scope.
	Chronic Lymphocytic Leukaemia Support Association	The rates of Minimal Residual Disease (MRD) negativity should also be considered as a surrogate marker of benefit as this will differentiate the comparators and the subject technology.	Comment noted. Minimal residual disease negative rate has been included as an outcome measure in the scope.
Economic analysis	Janssen	A lifetime horizon would seem appropriate.	Comment noted. The reference case 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

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			compared. No changes to the scope needed.
	British Society of Haematology, Royal College of Pathologists	It makes economic sense to introduce a finite duration of therapy. However, the length of therapy with venetoclax should be determined by the depth of response rather than finite duration as suggested in the trial protocol e.g. stopping the therapy at achievement of deep remission.	Comment noted. The reference case 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. No changes to the scope needed.
	AbbVie Ltd	None	Comment noted.
	Leukaemia Care	None	Comment noted.
	Chronic Lymphocytic Leukaemia Support Association	None	Comment noted.
Equality and Diversity	Janssen	None	Comment noted.
	British Society of Haematology,	None	Comment noted.

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	Royal College of Pathologists		
	AbbVie Ltd	None	Comment noted.
	Leukaemia Care	None	Comment noted.
	Chronic Lymphocytic Leukaemia Support Association	Although Venetoclax is an oral treatment, Rituximab is administered by intravenous or subcutaneous infusion. This requires hospital attendance and may inhibit some elderly or less mobile patients from access.	Comment noted. No changes to the scope are needed.
Other considerations	Janssen	None	Comment noted. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	Risk of tumour lysis syndrome and need for hospital admissions for high risk group during dose escalation.	Comment noted. No changes to the scope are needed.
	AbbVie Ltd	Consider clarifying the inclusion/exclusion of TP53 patients in the subgroup of patients with 17p deletion.	Comment noted. Patients TP53 mutations have now been added as subgroup in the scope.

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	Leukaemia Care	17p/TP53 was used as a sub-group in previous NICE CLL appraisals. VR has been shown to have consistent effect in all risk subsets. There is also an unmet need in all subsets.	Comment noted. Patients with TP53 mutations have now been added as subgroup in the scope.
	Chronic Lymphocytic Leukaemia Support Association	None	Comment noted. No changes to the scope are needed.
Innovation	Janssen	Yes, we consider the technology to be innovative. No, we do not believe that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	Yes. This combination is very beneficial in achieving deep remissions for CLL patients. Addition of monoclonal antibody such as rituximab to venetoclax enhances the depth of response and may become the standard of care in selected patients. It is important to consider the achievement of complete remissions and MRD negative rates in this appraisal.	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.
	AbbVie Ltd	There are limited options for treating relapsed/refractory CLL. The advent of B Cell receptor inhibitors (BCRi) such as ibrutinib has reduced the reliance on	Comment noted. The committee will consider

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		toxic chemo-based regimens. Venetoclax in combination with rituximab further improves the range of treatment options and provides substantial health-related benefits in the form of: • **Fixed treatment duration chemo-free therapy**, enabling significant proportions of patients prolonged time without therapy, reducing the overall significant cost burden of therapy, especially when contrasted to daily, treatment-to-progression alternative therapies such as BCRIs • **Avoids the need for further chemo-immunotherapy,** which creates mutations/clonal evolution • **A well tolerated treatment regimen** • **Significant rates of Minimal Residual Disease (MRD) negativity** being achieved from a targeted, chemo-free therapy combination, indicating deep responses to treatment	the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.
	Leukaemia Care	None	Comment noted. No changes to the scope are needed.
	Chronic Lymphocytic Leukaemia Support Association	We consider Venetoclax + Rituximab to be a step change for relapsed/refractory patients who have had at least one prior therapy. The MURANO study has shown that the rate of MRD negativity and progression free survival (PFS) is very significantly higher in this patient group. For patients with relapsed CLL, V+R will provide an alternative to Ibrutinib and Idelalisib, both of which have significant side effects. For some patients it will also the offer the potential benefit of MRD negativity and consequent stopping of treatment.	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.

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		For patients who relapse after Ibrutinib or Idelalisib therapy, the combination of venetoclax and rituximab is likely to provide significant improved overall survival and definitely improved progression free survival. This combination of V+R should lead to an increase quality of life, which may not be reflected in the QALY calculation as the benefits will be mainly psychological due to a reduction in anxiety regarding possible early future relapse. Ref: Data to be considered; The primary analysis of the MURANO trial (NCT02005471) https://ash.confex.com/ash/2017/webprogram/Paper109076.html	
Questions for consultation	Janssen	None	Comment noted. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	None	Comment noted. No changes to the scope are needed.
	AbbVie Ltd	The anticipated position of venetoclax + rituximab is after 1 prior line of therapy, which could be either chemo-immunotherapy or a BCRi	Comment noted. No changes to the scope are needed.

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	Leukaemia Care	None	Comment noted. No changes to the scope are needed.
	Chronic Lymphocytic Leukaemia Support Association	Venetoclax + Rituximab should be available for ALL relapsed or refractory CLL patients. The "Person with blood or bone marrow cancer / Leukaemia / Lymphoid Leukaemia / Treatment for relapsed or refractory disease" pathway.	Comment noted. No changes to the scope are needed.
	UK CLL Forum	1. Have all relevant comparators for venetoclax in combination with rituximab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory chronic lymphocytic leukaemia after 1 prior therapy? *The comparators currently listed in the draft scope are: Ibrutinib, Idelalisib in combination with rituximab, Venetoclax monotherapy and Best supportive care. Re-treatment with CIT following prior CIT therapy would only be considered for patients who achieved a very prolonged PFS (over 5 years) from CIT therapy. This would only occur in a minority of the patients treated in first relapse. The preferred therapy would be bendamustine in combination with rituximab. This combination is not NICE approved and is therefore not part of routine UK practice. Furthermore, the advent of BCRi has changed the treatment landscape such that BCRis are now the preferred therapy even for these patients as most patients are considered too frail for re-treatment with purine-analogues if better tolerated therapies are available. Finally, question was considered in the Ibrutinib NICE appraisal (TA429) (see pages 6 to 9 of this document https://www.nice.org.uk/guidance/ta429/documents/final-appraisal-*	Comments noted. 1. Chemo-immunotherapy is not included as a comparator in the scope. No change needed. 2. Best supportive care has been included in the scope to include people who are unsuitable for or have relapsed following any of the listed active treatment options (in the comparator section).

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		determination-document) and it was concluded that chemo-immunotherapy is not a comparator in this patient population. 2. How should best supportive care be defined? *Without the availability of venetoclax and rituximab combination therapy, patients relapsing following Ibrutinib would go on to receive venetoclax single agent, not best supportive care. Best supportive care would be offered in patients relapsing following venetoclax monotherapy or following the venetoclax and rituximab combination. Therefore, best supportive care is not the right comparator. If NICE decides to include it nevertheless, then the evaluation of cost should include as least:* • *Provision of transfusion (red cell and platelet) support* • *Prophylaxis of infections as CLL leads to severe secondary immunosuppression: regular immunoglobulin infusions, various prophylactic antibiotics regimen* • *Investigations for infections: bronchoscopies, colonoscopies, CT scans, microbiology* • *Treatment of infections: hospital admissions to treat community acquired and atypical infections with often prolonged therapies that sometimes require high dependency care and certainly lead to prolonged hospitalisation, but excluding intensive care.* 3. Are the outcomes listed appropriate? *YES*	3. Comment noted. No change needed 4. People with TP53 mutations have now also been added as a subgroup in the scope. 5 - 8: Comments noted. No changes to the scope are needed.

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		4. Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom venetoclax in combination with rituximab is expected to be more clinically effective and cost effective or other groups that should be examined separately? *It would be desirable if NICE appraisals were to become more precise regarding the genetic abnormalities and nomenclature used in the NICE appraisal process and we would therefore recommend to involve diagnosticians in the appraisal process. The subgroup analysis proposed here currently includes only patients with deletion of chromosome 17p. This is incorrect. Patients with single nucleotide mutations or small insertions/deletions in TP53 should also be included in this subgroup analysis as both the Murano data and many other studies now identify these patients.* *For reference: the gene TP53 is located on chromosome 17p and its function is disrupted not just when it is lost (ie via deletion of the 17p) but also when it is mutated. In the relapsed/refractory setting, up to 25% of patients have deletions, but an additional 25% might have mutations of TP53 that confer resistance to chemotherapy in exactly the same way as deletions do. Clinically accredited tests to test for deletions and mutations are routinely available in the UK.* 5. Where do you consider venetoclax in combination with rituximab will fit into the existing NICE pathway on blood and bone marrow cancers? *Venetoclax in combination with rituximab should be made available for all patients with relapsed CLL irrespective of whether they have previously received BCRi or not. It should be available for patients with TP53 disruption*	

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		(deletion of 17p or TP53 mutation), for patients who had prior therapy with chemo-immunotherapy only and for patients who have relapsed or are intolerant to Ibrutinib or Idelalisib in combination with rituximab. The sequencing of therapy should not be imposed on clinicians by the NICE decision, but should be left to physician's discretion and patients' choice as both Ibrutinib and venetoclax & rituximab are highly effective, but differ in their side-effect profile. 6. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. *There are no issues here.* 7. Do you consider venetoclax in combination with rituximab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *We consider this combination a significant step change forward:* • *For patients with relapsed CLL, it will provide an alternative to Ibrutinib and Idelalisib. Although both of these drugs have improved overall survival very significantly, they also have significant side-effects (cardiac, bleeding, muscle cramps, pneumonitis, colitis, atypical infections) leading to intolerance and permanent discontinuation in about 20-30% and 50% of patients in the first year for Ibrutinib and*	

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		Idelalisib, resp. Besides, dosing of both drugs is continuous until disease progression. • *The venetoclax-rituximab combination is extremely well tolerated and would represent a better choice for patients in this setting. Fewer side-effects would translate into fewer hospital admissions and out-patient attendance.* • *As the venetoclax & rituximab combination leads to the cessation of therapy after 2 years in the MRD negative patients (i.e. the majority), it will be more cost effective and preferred by many patients who are reluctant to be on continuous therapy and might become non-compliant.* • *The venetoclax-rituxmab combination also appears more effective than venetoclax monotherapy that is currently available via the CDF for patients relapsing after BCRi or who are intolerant to BCRi.* • *For patients who relapse after Ibrutinib or Idelalisib therapy, the combination of venetoclax and rituximab is likely to provide improved overall survival and definitely improved progression free survival and will be used as a bridge to transplantation in transplant-eligible patients.* 8. Do you consider that the use of venetoclax in combination with rituximab can result in any potential significant and 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 Appraisal Committee to take account of these benefits *The Murano trial data demonstrates the benefits of venetoclax in combination with rituximab compared to chemo-immunotherapy. There is no data available*	

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		directly comparing the venetoclax & rituximab combination against Ibrutinib or Idelalisib & rituximab. Clinical trial data on single agent venetoclax should also be considered in the appraisal. Real-world data on venetoclax single agent is currently being collected across Europe and the UK by Abbvie. In addition, the data relating to the compassionate use Ibrutinib programme of over 300 UK patients also includes a cohort of patients who subsequently went on to receive venetoclax single agent. These data should be considered.	
Additional comments on the draft scope	Janssen	None	Comment noted. No changes to the scope are needed.
	British Society of Haematology, Royal College of Pathologists	Is combination therapy of venetoclax with rituximab superior to comparators as bridge to allogeneic transplantation in selected patients Combination therapy in patients where B-cell receptor antagonist therapy is considered unsuitable due to side effect profile e.g uncontrolled atrial fibrillation or history of inflammatory bowel disease.	Comment noted. No changes to the scope are needed.
	AbbVie Ltd	None	Comment noted. No changes to the scope are needed.
	Leukaemia Care	None	Comment noted. No changes to the scope are needed.

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	Chronic Lymphocytic Leukaemia Support Association	None	Comment noted. No changes to the scope are needed.

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

Clinical Commissioning Group
DHSC