13 July 2015
EMA/480192/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the use of minimal residue disease as an endpoint in chronic lymphocytic leukaemia studies' (EMA/629967/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Professor Peter Hillmen, Leeds Institute of Cancer and Pathology, University of Leeds, UK on behalf of the United Kingdom National Cancer Research Institute (NCRI) CLL sub-group
2	Paolo Ghia, President of ERIC (European Research Initiative on CLL)
3	EFPIA – Sini Eskola
4	Medicines Evaluation Board, The Netherlands
5	Gilead Sciences International Ltd
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We highly recommend the implementation of these guidelines to speed the identification of effective therapy for patients with CLL. We believe that the gold standard should be the assessment of MRD in the bone marrow with a threshold of 1 CLL cell in 10,000 cells (10^{-4}) as indicated in the current guidance. This is essential as using progression free survival is too late an end-point with current therapy and leads to the failure to develop therapies for patients who are fit for fludarabine-based therapies, given their long median PFS, but that the vast majority of these patients relapse and that most eventually die of their CLL. Also outcomes are better after the first line of therapy rather than in the salvage setting so it is important that therapies are developed and approved in this patient setting.	
2	This guideline is very timely and will be welcomed by the entire CLL scientific community as well as the affected patients. It will help to foster clinical research and obtain meaningful results in shorter time.	
3	This draft guideline is seen as a positive step for the development in CLL and we appreciate the efforts made by the oncology working party to draft a very helpful and very pragmatic guidance. As more effective treatments become available, it is becoming crucial to develop and use surrogate endpoints such as MRD that are predictive of the long term outcome and in this context, implementation of MRD will participate in bringing safe and effective drugs earlier to patients. The guidance brings a number of key points to favour a shorter development timeline, with the use of MRD to show primary evidence of clinical benefit in support of a potential early licensure. We would like however to highlight a number of important comments:	

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	• This guideline might give the impression that some data are still missing in order to use MRD as a primary endpoint in a clinical trial and also points out areas where uncertainty seem to remain. Although we acknowledge that it will be important to continue gathering additional information and run further exploratory analyses to consolidate our understanding on the correlation between MRD and PFS, we are also of the opinion that there is now solid evidence supporting the use of MRD as a primary endpoint in pivotal clinical trials in chronic lymphocytic leukaemia. Comments and clarifications have therefore been proposed considering that MRD can be used as a primary endpoint in a CLL trial as long as long term benefit can be confirmed. • Additional statistical analyses (enclosed) have also been performed showing that measuring MRD in CR patients does not improve the surrogacy as defined per the Prentice criteria. This data supports the recommendation to measure MRD in all patients when used as a primary endpoint in a pivotal CLL trial. • The value of MRD-negativity as a surrogate endpoint may depend on the type of investigational therapy. We recommend clarifying within the guidance the need and value of achieving MRD-negativity in the context of targeted therapies like Imbruvica (ibrutinib) and Zydelig (idelalisib). Both therapies were recently approved by the European Commission for the treatment of chronic lymphocytic leukaemia and both demonstrated clinical benefit by improvement of PFS over standard salvage therapy with only few complete remissions achieved in patients. It appears that in the context of specific targeted therapies clinical benefit like improvement in PFS may not be reflected by MRD-	

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	negativity. We suggest clarifying the limits of correlation of achieving MRD-negativity and clinical benefit in the context of the guidance, for example in the section 'utility'. • The draft guideline does not describe the appropriate regulatory approval route/mechanism that would be used if a drug treatment arm demonstrated a MRD improvement over a control arm. Discussion of the appropriate Regulatory approval mechanism (Conditional Marketing Authorisation [CMA] or full approval), would be appreciated. There is recognition that a CMA is reserved for the initial MAA only. Discussion of the regulatory mechanism to approve a drug for the 2nd or 3rd indication based upon a MRD surrogate endpoint would be helpful. • Following discussions at the Biotherapy Development Association (BDA) multi stakeholder meeting in London in May 2014, to discuss the draft guidance on minimal residual disease (MRD) in chronic lymphocytic leukaemia (CLL) and other haematological malignancies, it is hoped that there will be additional follow up and hopefully additional draft guidance in other haematological malignancies such as multiple myeloma or acute myeloid lymphoma. The guideline should address current or future plans to recommend MRD in those clinical settings. Similarly, the guidance could address aspects related to the use of MRD as a treatment decision tool.	
4	This document on the use of MRD as an endpoint on phase III trials is welcomed. It is agreed that MRD is a useful tool to evaluate the effect of induction therapy in CLL. It is also agreed that it is too early to use MRD as a surrogate endpoint, and that, as an alternative, the response rate of MRD negativity might be used as an intermediate	

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	endpoint for early licensure for CLL therapies awaiting confirmation by PFS data post licensure. However, for a guidance document more explicit guidance on the use and interpretation of MRD as an intermediate endpoint is expected. Issues that need further clarification include: - how to evaluate whether a difference in MRD negativity response is large enough to predict a clinically relevant PFS benefit, and – interpretation of differences in kinetics of MRD negativity and its impact on clinical benefit (e.g. achieving MRD negativity early vs late, the depth of MRD response and kinetics of the MRD value below threshold level). Furthermore, the paragraph on the purpose of this document (lines 38-40), while well written, states that also regulatory requirements will be described. Yet only little attention is paid to this subject in the main guideline text. It is suggested to include a separate section on regulatory requirements/considerations in this document discussing the type of licensure that can be granted in case this guideline is successfully applied by sponsors (assumed to be conditional approval), and the regulatory consequences when PFS benefit expectations are not met (due to patient drop out or disappointing efficacy). It is recognised that it may be difficult to provide guidance on the issues raised above. If so, then it may be currently too early to publish a stand-alone guideline on the use of MRD. Which may also be true for a supplement of the condition-specific guidance in appendix 4 of the guideline on the valuation of anticancer products in man. Instead, another type of document with a different scope (e.g. reflection paper/position paper), might be better suited to discuss (the possibilities and limitations of) the current knowledge on the	

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	value of MRD assessment in CLL.	
5	We welcome this consultation and strongly encourage the finalisation of guidance on this important topic. Guidance on the use of MRD as an intermediate endpoint is likely to further drug development for CLL.	
6	While the use of MRD as an endpoint is very welcomed, one aspect that is confusing within this proposed guideline, or missing, is a clear position on the use of MRD versus CR (and CR/CRi for that matter) as endpoints. The guideline specifies that MRD response would be a proportion of patients who achieve CR and MRD negative status. It also indicates that all patients with clinical CR should be assessed for MRD. However, not all patients achieving CR are MRD negative. Thus, the question becomes whether having both CR and MRD as endpoints requires an acknowledgement or definition of an acceptable threshold of difference between treatment arms for CR and for MRD. The risk is that if the endpoint is based only on MRD, it would be more difficult to show a statistical difference between arms based on that endpoint. Also, the guideline does not include CR/CRi and how this relates to MRD. Clarification of the importance of CR/CRi in light of MRD as an endpoint would be welcomed.	
6	A difference in MRD response rate is required to support early licensure (we assume a conditional approval, although this is not explicitly stated), and according to line 130 this includes both CR and MRD negative status. However, true confirmation of clinical benefit still requires PFS and a supporting evaluation of OS. It would be helpful to discuss MRD response rate earlier in the document which could avoid some of the confusion.	
6	We are encouraged that the EMA seeks to incorporate MRD response	

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	as an intermediate endpoint in clinical trials of CLL-directed therapy. As has been demonstrated in CML and ALL, there is a growing recognition for many hematologic malignancies that MRD responses are prognostic for time-dependent endpoints such as progression free survival. Moreover, MRD will likely emerge as a recognized indication for treatment, particularly with agents that are most efficacious with lower tumour burdens and have improved safety relative to conventional chemotherapy. We are hopeful that this guideline will serve as a basis for broader inclusion of MRD-based endpoints in clinical trials. It is anticipated that the technology of MRD detection will advance rapidly, and we support a forward-looking inclusion of emerging technologies, i.e., not limited to ASO-PCR or flow cytometry (FC). For example, MRD detection by next-generation sequencing (NGS) offers sensitivity beyond that of ASO-PCR and FC. This may be particularly useful in important exploratory endpoints in future clinical trials as recommended in this document. Specifically, NGS may allow more precise thresholds for MRD positivity. Additionally, NGS better captures clonal evolution due to its insensitivity to target sequence loss.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
4	6	The document uses the terms residue and residual. Are these terms interchangeable?	Typo error corrected (should read as residual).
19-20	1	Comments: The term “MRD negativity” is inappropriate because currently all patients relapse, i.e. there is persistent disease in patients with no detectable MRD. There is variation in the detection limit for different assays, for example 4-CLR flow can detect 10^{-4} (i.e. less than 1 CLL cell in 10,000 cells), other flow assays and qPCR can detect 10^{-5}, and high-throughput sequencing can detect 10^{-6}. There appear to be improvements in outcome per log depletion and therefore the specific threshold for detection is important when comparing outcomes. Proposed change: Suggest that “MRD negativity” is replaced by “MRD $<10^{-4}$” or “MRD <0.01%” or “absence of detectable MRD” throughout. However 10^{-4} has been validated as an assay, is widely applicable and is associated with outcome so is an appropriate end-point for regulatory approval.	Accepted. “MRD negativity” has been replaced by “undetectable MRD”. As a consequence, “MRD positivity” has been replaced by “detectable MRD”.

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19-20	2	Comments: The term “MRD negativity” can cause confusion because patients who are MRD negative by one technique may be MRD positive by another. “Undetectable MRD” or “absence of detectable MRD” may be more appropriate terms because the individual techniques used to quantify MRD each have their own detection limit. Proposed change: Proposed change from “Minimal residual disease (MRD) negativity in patients in clinical complete remission (= MRD response rate)” to “The absence of detectable minimal residual disease (MRD) in patients in clinical complete remission (= MRD response rate)”	Accepted (see previous comment).
20-21 *Minimal residual disease (MRD) negativity in patients in clinical complete remission (= MRD response rate) after induction therapy may be used as an intermediate endpoint for licensure in randomised well controlled studies designed to show superiority in terms of PFS.*	3	We suggest using standard terminology regarding the classification of endpoints. Introducing the concept of “intermediate” endpoint may create some interpretation issues. We believe that the results of CLL8, CLL10 and CLL11 (see attached report) supported by data from the literature provide sufficient evidence to be able to use MRD as a primary endpoint and therefore, we recommend using the term “primary endpoint” in this sentence. Furthermore, the prediction of the PFS HR for a given relative MRD difference may still be improved and it is acknowledged that PFS data from future studies are	Not accepted. The term intermediate endpoint is widely used and should not create confusion. There is not sufficient data at present to consider MRD response a “full” primary endpoint. PFS is still considered the primary endpoint for CLL trials and should be provided from the pivotal clinical trial(s) that support early licensing based on MRD response. Unless fully justified it is recommended PFS data to be provided from the clinical trial that supported the licensure based on MRD clinical endpoint.

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		necessary to continue building the database and the statistical model supporting MRD. We therefore acknowledge that PFS should be provided e.g. as a long-term follow up measure in order to confirm the results observed with the primary endpoint. Although we agree that confirmatory PFS data should be submitted after early licensure using MRD, we are also of the opinion that PFS data does not necessarily need to be provided from the clinical trial which supported the initial Marketing Authorisation. Confirmatory PFS data from a separate well conducted clinical trial can be used to support long-term benefit. See also additional changes proposed on line 102. We also consider that MRD should be measured in all patients, and not only in patients in complete remission. Statistical analysis performed on CLL8, CLL10 and CLL11 studies (enclosed report) show that restricting the definition of MRD response to CR patients does not improve the surrogacy according to Prentice criteria. Additionally, we consider that MRD is a more objective measurement of disease status than clinical response and therefore, restricting the definition of MRD response to only the subgroup of patients with CR might introduce some subjectivity in the MRD analysis. A thorough analysis of this aspect is presented in the attached document. Proposed change :	Based on current available data it is not acceptable at present to include patients with a clinical partial response and undetectable MRD status as MRD responders. A sentence has been added to the text. A recommendation to assess MRD status in all patients with response to treatment, and not limited to those with CR, is already included in the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Minimal residual disease (MRD) negativity (= MRD response rate) after induction therapy may be used as a **primary** endpoint for licensure in randomised well controlled studies. ~~designed to show superiority in terms of PFS~~. ~~This requires that the benefit/risk of the experimental regimen is well characterised in CLL and that these data would support the superiority of the regimen over established regimens used as induction therapy in CLL.~~ **As MRD offers the possibility to submit results earlier based on a shorter follow up time than with the standard PFS endpoint, it is required that the benefit/risk of the experimental regimen is well characterised in CLL and that these data would support the superiority of the regimen over established regimens used as induction therapy in CLL**.	
20, 23, 127-128, 130-133	3	The guideline refers to assessment of MRD at the end of induction therapy. CLL therapy is currently changing from chemotherapy-based induction regimens towards long term treatment until progression with targeted drugs. MRD might serve as an endpoint also with targeted therapy to assess the quality of response. We suggest consideration of MRD as an endpoint also during long term treatment with targeted agents, as a deep response as indicated by MRD negativity may prevent development of resistance to targeted therapy	Not accepted. It is acknowledged MRD may also be an appropriate intermediate endpoint with targeted therapy but there is currently insufficient data available. As new data become available pertinent revisions of this guideline will be conducted.

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		and ultimately prolong PFS. Proposed change : Delete "~~after end of induction~~"	
21-23	4	It is not clear what is meant with '*this*' at the beginning of the second sentence. Furthermore, benefit/risk (B/R) is an assessment issue so when discussed here. it is preferred to use 'efficacy' and 'safety' as terminology. However as efficacy and safety are not discussed in this document these should not be part of the executive summary of this GL. Instead, the most important requirements for the use of MRD as an endpoint should be mentioned here (e.g. threshold of MRD negativity, inclusion in statistical analysis plan, and adequate assay and quality management system, need for powering on PFS). Proposed change (if any): Remove the sentence (*This requires…therapy in CLL*.), mention target population (CLL) in the first sentence and add the most important requirements for the use of MRD.	Accepted. No details on MRD assessment requirements have been included but a general reference as "Regulatory recommendations with regards to laboratory aspects for MRD measurements, definition as a clinical intermediate efficacy endpoint and the inclusion in the statistical analysis plan should be followed".
21-23	6	"This requires that the benefit/risk of the experimental regimen is well characterised in CLL and that these data would support the superiority of the regimen over established regimens used as induction therapy in CLL." Recommend that "induction" be excluded, as this is	Not accepted. Data supporting the use of MRD as a clinical endpoint is available following induction therapy. The term induction is not expected to be confused with line of therapy by treating physicians.

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		frequently interpreted as first line therapy. From the arguments presented in this guidance, as well as from the existing literature, MRD negativity may also be prognostic in later lines of therapy. This point is reaffirmed in lines 95-96.	Note the text has been amended (see previous comment).
28-32 *With the introduction of new immune-chemotherapeutic combinations over the last decade the efficacy of treating patients with CLL has greatly improved and median PFS now ranges from 3.5 to 6.7 years after first line therapy whilst median OS for patients with advanced stages (Binet C or Rai IV) is approximately 6.5 years. Allogeneic stem cell transplant remains the only curative therapy and it is recommended for patients with very high risk and/or refractory disease.*	3	We suggest highlighting that the validation of MRD as an accepted primary endpoint is necessary to continue developing drugs in CLL in view of the median PFS currently achieved with approved therapies. Proposed change : With the introduction of new immune-chemotherapeutic combinations over the last decade, the efficacy of treating patients with CLL has greatly improved and median PFS now ranges from 3.5 to 6.7 years after first line therapy whilst median OS for patients with advanced stages (Binet C or Rai IV) is approximately 6.5 years. **Despite these significant advances, the disease remains incurable when treated with chemotherapy and monoclonal antibodies alone**. Allogeneic stem cell transplant remains the only curative therapy and it is recommended for patients with very high risk and/or refractory disease. **Currently, PFS is considered an appropriate primary endpoint to demonstrate clinically meaningful patient benefit in randomised phase III CLL studies. However, with such an endpoint**	Accepted. Proposed text has been included in the guideline.

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		the timeframe to achieve meaningful statistical and clinical results from pivotal studies with new therapies in earlier treatment lines is well over 5 years. In the effort to develop efficacious treatment options to address the unmet medical need of CLL patients, there is an urgent need to find alternatives to the currently used time-to-event variables so that the efficacy of novel therapies can be evaluated at an earlier time point.	
33-35 *Because patients achieving clinical complete remission (CR) according to international guidelines will eventually relapse, minimal residual disease (MRD) undetectable at clinical and morphological level must have been present.*	3	Using the term MRD is misleading here. We recommend to refer only to residual disease Proposed change : Because patients achieving clinical complete remission (CR) according to international guidelines will eventually relapse, ~~minimal~~ residual disease ~~(MRD)~~ undetectable at clinical and morphological level must have been present.	Not accepted. The residual disease has to be minimal because it cannot be detected by conventional morphology/clinical measures.
33-36	4	Comment: In our view these sentences could be phrased more accurately. Proposed change (if any)(**BOLD** is added text and ~~strikethrough~~ is text removed): *Because patients achieving clinical complete remission (CR) according to international guidelines will eventually relapse,*	Partly accepted. See also previous comments. As this is an introduction to the guideline the reference to the assays is not included.

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		*~~minimal~~ residual disease ~~(MRD),~~ undetectable at clinical and morphological level**,** must have been present at **the time of CR**. Therefore, the quality of CR should be also assessed for the **presence or** absence of **minimal residual disease (***MRD***) with sensitive bioanalytical assays**.	
35	1	Comments: The data from the UK ADMIRE and ARCTIC trials are consistent with DCLLSG data showing that PR patients with undetectable MRD have the same outcome as CR patients with undetectable MRD. It is therefore important not to restrict MRD assessments to CR patients, but also to investigate patients in PR.	Accepted. The text “Therefore, the quality of response to treatment should be also assessed for the absence of detectable MRD” is included and does not refer only to CR response. A recommendation to investigate MRD status in patients in PR is already included under “additional recommendations”.
35	2	Comments: The current data indicates that patients with undetectable MRD but with a clinical partial response have a similarly good outcome compared to those with undetectable MRD in CR. It is not clear whether this reflects overestimation of residual tumour by the current response criteria or underestimation of MRD levels. While it may be appropriate that the MRD response rate should be limited to patients achieving CR with undetectable MRD, it would be inappropriate to restrict MRD assessments to patients with a clinical CR, particularly as MRD assessments are often performed on the bone marrow sample taken to	Accepted.

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		assess response. Proposed change from “the quality of CR should be also assessed for the absence of MRD” to “the quality of response should be also assessed for the absence of detectable MRD”.	
35	6	“Therefore, the quality of CR should be also assessed for the absence of MRD levels below 10-4.” Recommend that “absence of MRD” be replaced by “MRD levels below 10-4” or “MRD negativity.” This is especially applicable given that assays are increasingly sensitive and may detect cells or DNA below this level.	Accepted. However, the text has been amended to “absence of detectable MRD” (see previous comment).
35	6	“Therefore, the quality of CR should be also assessed for the absence of MRD.” CR criteria from the IWG (Hallek et al, Blood 111:5446-5456) indicate criteria for CR, including peripheral blood cell reconstitution. The authors highlight the challenges of understanding CRi, or incomplete marrow recovery. Recommend clarifying how CRi AND MRD negativity would be handled.	Published data refers mainly to CR responses in relation to MRD undetectable. No further guidance can be given on CRi. Patients with CR (not CRi) and undetectable MRD can be considered MRD responders.
36	3	In line with our recommendation to measure MRD in all patients, we suggest to delete this sentence: ~~Therefore, the quality of CR should be also assessed for the absence of MRD.~~	The text has been amended (see previous comments).

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38-40 *The scope of this document is to describe the basis and regulatory requirements for the use of MRD as an intermediate endpoint to predict clinical benefit in trials in CLL.*	3	As mentioned, above, we consider that there is sufficient data to use MRD as a primary endpoint and would suggest using the standard term “primary endpoint” to avoid any interpretation issue. This does not prevent the requirement to provide long term PFS data as part of post approval commitments. Additionally, the objective of using MRD as a primary end point is to register new effective drugs in a timely manner. It is now widely recognized that MRD is a good predictor of clinical benefit in CLL. Proposed change : The scope of this document is to describe the basis and regulatory requirements for the use of MRD as a primary ~~intermediate~~ endpoint to register new safe and effective treatments ~~predict clinical benefit in trials~~ in CLL.	Not accepted. See previous comment.
38-40	4	Comment: While implicitly mentioned in the scope of this GL, it is suggested to explicitly mention here that it is **not** the purpose of the document to provide guidance on the use of MRD evaluations as basis for therapy. Furthermore, as CLL and SLL are essentially the same disease, with the only difference the site where the cancer primarily occurs, it should be clarified that this document only discusses the use of MRD evaluation for CLL and not SLL.	Accepted. Please note reference is made broader to other B cell lymphomas.

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		Proposed change (if any): (**BOLD** is added text): *… to other clinical settings* ***such as SLL. Of note, this document is not intended to discuss MRD-guided treatment of CLL.***	
39-40	6	"At present, this guidance is not applicable to other clinical settings." Any clarification of why the guidance is not applicable to other clinical settings would be welcomed. For example, the concept of MRD as a predictor of long term outcome is also applicable to ALL. Therefore, it is unclear why this guidance would not be applicable to other settings.	Although the concept and use of MRD may be applicable to other haematological malignancies, the definitions and criteria for its use as an endpoint in clinical trials will vary depending on the nature of the disease. For example, unlike other haematological malignancies, CLL is not linked to a specific structural chromosomal abnormality and cytogenetic methods cannot be used to detect MRD. However, molecular or genetic assays can be used to identify a malignant clone in CLL using IGH gene rearrangements or a specific surface antigen combination. This guideline is written with specific regulatory recommendations applicable only to CLL.
41	4	Comment: The text on the scope is placed before the "scope" heading. The heading: 'main guideline text' is missing. Proposed change (if any): Heading '*scope'* should be moved upwards in the text (before lines 38-40), and heading '*main guideline tex*t' should be inserted here.	Accepted. Additional subheadings in the guideline have been included for clarity.
45-47	1	Comments: Suggest replace "MRD negativity" as discussed above	Accepted.

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45-47	2	Comments: We suggest replacing the term “MRD negativity” as discussed above and amending the sentence to ensure consistency with the guidelines. Proposed change from “According to current international definitions MRD negativity equals a quantitative detection of less than 1 CLL cell in 10000 leukocytes (MRD level < 10 -4)” to “According to current international definitions, the absence of MRD equals a quantitative detection of less than 1 CLL cell in 10000 leukocytes (MRD level < 10 -4)”	Accepted (see previous comment).
45-47 *According to current international definitions MRD negativity equals a quantitative detection of less than 1 CLL cell in 10000 leukocytes (MRD level < 10 -4).*	3	We propose to add a reference to the International Workshop on CLL (iwCLL)’s updated guidelines for the diagnosis and treatment of CLL. Proposed change: According to current international definitions **(Hallek et al., Blood 2008)** MRD negativity equals a quantitative detection of less than 1 CLL cell in 10000 leukocytes (MRD level < 10^{-4}). **References:** **Hallek M et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from the International Workshop on Chronic Lymphocytic Leukaemia updating the National Cancer Institute Working Group 1996**	Partly accepted. The reference is included only in the references section at the end of the document.

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		guidelines. Blood. 2008;111: 5446 – 5456.	
45, 89	3	There is a need to understand whether 'following treatment', 'shortly after treatment' mean the same thing. If not, the guidance should include more information on the expected timing to measure MRD response.	Information on the expected timing to measure MRD response is already included under "MRD definitions as clinical endpoint and methods" subheading.
48-49	2	Comments: Proposed change from "There is no data currently available to support a MRD level below the 10 -4 threshold would provide added clinical benefit" to "There is no prospective data currently available to support a MRD level below the 10 -4 threshold would provide added clinical benefit".	Accepted.
48 and 91	3	The wording might be misread and is only fully clarified in the context of line 91. It would also be important to describe the interest in acquiring data that explore lower MRD threshold levels. Proposed change: "There is no data currently available to support **that a further reduction of** MRD level below 10^{-4} would provide added clinical benefit. **Exploratory analyses at different thresholds (from 10^{-4} to 10^{-6}) could provide data to gain more insights.**	Partly accepted. The proposed change "There is no data currently available to support that a further reduction of MRD level below 10^{-4} would provide added clinical benefit" has been added. Regarding exploratory analyses it is already addressed in the text under "additional recommendations and considerations".

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51-52	2	Comments: We agree that MRD analysis is not generally available but the ERIC group has performed extensive harmonisation of the flow cytometry with recent submission of an approach applicable to the vast majority of cytometry laboratories. In addition the qPCR approach has been standardised by the EuroMRD group (http://www.ncbi.nlm.nih.gov/pubmed/17287850) Proposed change from “Although MRD evaluation is still not widely standardized there are currently two analytical methods capable of assessing MRD status at the required threshold” to “Although MRD evaluation is still not widely available there are currently two analytical methods capable of assessing MRD status at the required threshold”	Accepted.
51-52	6	“Although MRD evaluation is still not widely standardized there are currently two analytical methods capable of assessing MRD status at the required threshold.” NGS is rapidly emerging as a useful technique to monitor MRD in CLL and other lymphoid malignancies. It is conceivable that in the near future, NGS will be supplanting both ASO-PCR and FC. Please consider including NGS as a potential modality for the assessment of MRD. Additionally, NGS will be extremely helpful in defining the cut-offs for MRD	Not accepted. It is acknowledged NGS is an emerging and promising technique but data currently available is not considered sufficient for a recommendation in the context of a clinical trial. NGS still needs to be fully evaluated in clinical samples against the recommended flow cytometry/ASO RQ PCR methods. Note the sentence “Additional methods for which equivalent sensitivity, specificity and quantitative ranges have been demonstrated may be used in the future” is included in the

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		negativity as outlined in lines 137-138.	text (see comment below).
52 and 81	3	It would be important to avoid that the guidance appears too restrictive with regards to the methodology to be used and introduce aspects related to methods which may be routinely used in the future e.g. Next generation Sequencing. Proposed change: There is no specific recommendation on the method to be used as both are considered appropriate. **Additional methods for which equivalent sensitivity, specificity and quantitative ranges have been demonstrated may be used in the future.**	Accepted.
52	4	Comment: Suggestion to mention the two analytical methods referred to. Proposed change (if any)(BOLD is added text): … capable of assessing MRD status at the required threshold, i.e. real-time quantitative PCR and four (or more)-colour flow cytometry. There is no specific recommendation on the…	Accepted.
53	4	Comment: It is agreed that both methods may be used for evaluation of MRD, however, it is preferred that within a study the same analytical method is used. Proposed change (if any): (BOLD is added text):…	Not accepted. At the BDA workshop on MRD held in London on 13-14 May 2014, experts on this field agreed that within a clinical study both methods could be used providing the same threshold applies for undetectable MRD.

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		both are considered appropriate. However, it is recommended to use one analytical method for MRD on all samples within one study.	
54-56	4	Comment: It is agreed that a quality management system is needed; however, the text seems rather descriptive and is not explicit enough for a GL. Proposed change (if any): It is recommended that MRD should be evaluated under GLP, or an equivalent quality management system, and that the analytical method should be appropriately validated.	Accepted.
54 -57 *A quality management system that includes the laboratory(s) organisational structure, responsibilities, policies and standards needed to ensure accuracy and satisfactory quality of the MRD evaluation assay would be required. The use of central laboratories is not considered a*	3	Since in accordance with GLP/GCP all labs used in clinical trials are required to have quality management systems in place, does this sentence refer to something above and beyond the usual GLP/GCP? If so the guidance should clarify this point and provide details, considering also the reference to technical guidelines. While it may not be appropriate to give this level of detail here, Sponsors and HA's do need some agreed criteria to propose robust study designs. If no central laboratories are required, all local labs within a clinical trial should undergo interlaboratorial comparisons (round-robin tests) in order to normalize results between different laboratories and thereby render them comparable, also maybe even between different trials.	Accepted. See also previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
regulatory requirement provided a robust quality system is in place.			
56-57	4	Comment: It is agreed that the use of a central lab is not required, however, it is recommended that all testing laboratories use the same protocol/SOP for the analytical method of choice. Proposed change (if any)(BOLD is added text):… a robust quality system is in place and that the same protocol **is used for that particular analytical method.**	Accepted. The text has been amended taking into account also previous comments.
58-80	4	Comment: In this section, the two analytical methods that can be used for MRD are described. However, the description is very brief, and does not appear to cover all the major issues. In particular, how to deal with clonal drift of the leukaemia, with oligoclonal disease and with the development of new (sub)clones are issues that require further attention. Proposed change (if any): Expand the section to provide further guidance on the technical considerations/design (limitations and challenges, see above) of these assays. Alternatively, it could be stated briefly which aspects need to be considered, and let the company 'solve' these uncertainties as part of the design of the assay of choice.	Not accepted. Ongoing rearrangements/somatic mutations and oligoclonality are rare in CLL. The guideline is not intended to describe in detail the two methods as both are acceptable. The main advantages/disadvantages have been mentioned and it is up to the company to address any limitation of chosen method and how to handle any uncertainty.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
61-62	4	Comment: The added value of mentioning that the RQ-PCR method is labour intensive is questioned. Sequencing needs to be performed prior to induction therapy. Proposed change (if any)(BOLD is added text and strikethrough is text removed): … PCR (ASO IGH RQ-PCR) is labour intensive as it requires the sequencing of each clone-specific rearrangement prior to induction therapy. It but has sensitivity in…	Accepted.
63-64	6	"Limitations of the method apply in case of changes in phenotype between baseline and follow up investigations." Recommend acknowledgement that there may be both phenotypic and genotypic changes between baseline and follow-up investigations.	Accepted.
64-68 *Since specific primers address a single rearranged IgH gene sequence, there is a certain risk of target gene loss due to ongoing rearrangements in the IgH region which would result in reduced sensitivity. In order to minimize false negative MRD measurements, two*	3	Target gene loss may be caused by somatic mutations in the IG target region. This could lead to different primer binding properties and reduced sensitivity. However this is thought to be rare events in CLL. False negative rate could be estimated by comparing MRD levels measured by two different methods. Boettcher et al. (Leukaemia 2009 Nov;23(11):2007-17) have shown that MRD could not be detected in 4/530 (0.8%) samples by ASO-PCR but by Flow cytometry. Flow cytometry did not detect MRD in 7/530 (1.3%) samples whereas ASO-PCR did.	Partly accepted. The proposed change of text is accepted but the words "at diagnosis" have been changed to "at baseline" as MRD may be used as an endpoint in trials with patients with either newly diagnosed or previously treated CLL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Ig PCR targets should be used if oligoclonal clones are found at the time of diagnosis		The risk and impact of having false negative results due to changes in the IGH/IGK regions may be considered low due to the following reasons: o Ongoing rearrangements (or somatic mutations) in the IGH/IGK region are thought to be very rare events in CLL. o Randomized studies may have similar false negative rates in both study arms o As a “control”, false negative results can be identified by comparing MRD status and clinical response (MRD negative patients must not have progressive disease) Occurrence of “true” Oligo- or biclonality happens rarely in CLL (5% of patients; Langerak AW et al., Leukaemia 2012 26, 2159-2171) and is typically observed at study start when IGH/IGK rearrangement patterns and clonality is assessed. In case of oligoclonality, a patient requires to have multiple PCR assays designed covering all existing clones. This may only be feasible for biclonal disease where two PCR assays are required. Proposed change : ~~In order to minimize false negative MRD measurements, two Ig PCR targets should be used~~ If biclonal disease is found at the time of diagnosis,	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		two IG PCR targets should be used to accurately quantify MRD. Patients with oligoclonal disease where accurate quantification of the CLL cell count of all clones is not possible should not be assessed for MRD by ASO-PCR.	
63-67	4	Comment: It appears that two separate issues are discussed here (clonal rearrangement/drift, and oligoclonal disease) and these should be separately addressed. Proposed change (if any): (BOLD is added text and strikethrough is text removed) In order to minimize false negative MRD measurements due to this clonal drift, multiple two Ig PCR targets should be used. If oligoclonal disease is clones are found at the time of diagnosis, primer sets should be designed for each clone.	See previous comments.
65		Comment: while new IG rearrangements are rarely if ever occurring, one should consider the possibility of additional somatic mutations occurring in the sequence of primer binding site. Proposed change (if any): "….due to the ongoing rearrangements/somatic mutations in the …."	Accepted.
64-65-66	2	Comment: According to the international gene nomenclature (http://www.genenames.org/) the Immunoglobulin gene acronym is "IG" and not "Ig"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): IGH, IG	
68- 69 *A major advantage is that the samples do not need to be fresh and can be shipped to a single centre for analysis*	3	We recommend deleting this statement as it is not considered appropriate. Once a patient enters the study, a fresh blood sample requires to be shipped to a central laboratory for quantification of CLL cells by flow cytometry. This is required for a dilution curve and absolute quantification. All following blood samples require to be shipped as fresh samples to a central laboratory for DNA extraction. Advantages of ASO RQ PCR include batched analysis of MRD by ASO-PCR (and not online flow cytometry) and ability to store DNA samples for re-analysis or bridging studies (comparison/validation of different technologies) if required. Proposed change : ~~A major advantage **of this method** is that the samples do not need to be fresh and can be shipped to a single centre for analysis~~	Not accepted. See reference number 5 (International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. A.C. Rawstron et al; Leukaemia (2007) 21, 956-964)
71 *In addition, ASO RQ-PCR offers a higher qualitative sensitivity below the threshold of 10-4 which might be relevant in clinical trials exploring complete eradication of the disease.*	3	This statement is considered correct for small subsets of patients only where assays are sensitive enough. It may not be helpful for the assessment of MRD as an efficacy endpoint (primary or secondary). Proposed change : ~~*In addition, ASO RQ-PCR offers a higher qualitative sensitivity below the threshold of 10-4 which might be relevant in clinical trials exploring complete eradication*~~	Not accepted. The sentence is to be taken into account for exploratory objectives.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~*of the disease.*~~	
72	4	Comment: Slight rearrangement in text. Proposed change (if any)(BOLD is added text and strikethrough is text removed): Four (or more)-colour or more flow cytometry.	Accepted
73	4	Comment: Correction in formulation. Proposed change (if any): (BOLD is added text and strikethrough is text removed)… unique phenotype, low number amount of leukaemic cells…	Not accepted
76-80	4	Comment: Also for MRD assessment by flow cytometry knowledge on the type of clone(s) at time of diagnosis (i.e. prior to treatment) is needed. Proposed change (if any): Please address this in the text.	Accepted. Sequence analysis of the IGH gene is expected in the context of a clinical trial to assess mutational status as a prognostic marker. A sentence has been included in the text.
78-80 *Appropriate handling and transport to central laboratories may be difficult to establish in multi-centre, multi-national clinical trials.*	3	We suggest referring to regional labs as alternative. Proposed change : Appropriate handling and transport to a single central laboratory may be difficult to establish in multi-centre, multi-national clinical trials. **Implementation of regional labs may offer an acceptable solution as long as data handling and analysis are consistent across labs.**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
82-84	1	Comments: MRD data from several different UK trials, presented at EHA June 2015, demonstrates that Peripheral Blood MRD can be highly informative with some treatments but poorly predictive of outcome with other treatments. Bone Marrow MRD is the gold standard. Therefore we believe it is appropriate that the gold standard remains MRD in the Bone Marrow as the current draft guidance suggests.	Accepted.
82-84	2	Comment: As assessed, the gold standard for MRD assessment is BM. The sentence “MRD status can be assessed either from peripheral blood (PB) or bone marrow (BM).” May create confusion and allow for loose practise. The following sentence should be modified in order to reinforce the need of BM confirmation. Proposed change from: “If MRD negativity is shown, this should be confirmed in the BM” to “If MRD is shown to be absent from PB, it is mandatory to confirm MRD status in the BM”.	Accepted. Text amended to “If MRD is not detectable in PB, it is mandatory to confirm MRD status in the BM”.`
83-84 *It is recommended that for all medicinal products irrespective of drug class, patients are screened for CLL eradication in PB first. If MRD negativity is shown,*	3	We consider that measuring MRD in BM does not improve the surrogacy and recommend not to follow this approach for the primary analysis. We recommend to measure MRD in all patients in peripheral blood for the purpose of the primary analysis. A BM sampling is an invasive technique which may raise some ethical concerns if it is rendered mandatory and performed in	Not accepted. Although BM is normally not required for assessment of a response to treatment in clinical practice, it is recommended in the context of clinical trials, especially if CR has been achieved. (*Reference: Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
this should be confirmed in the BM		all patients rather than for confirmation of CR in accordance with the iWCLL guideline. Furthermore, statistical analyses have shown that measuring MRD in bone marrow would not improve the correlation with PFS (see attached report). There is therefore no reason to mandate a bone marrow sample in all patients for the primary analysis. Analysis of MRD using available bone marrow samples should however be part of secondary analysis and support the primary analysis. Proposed change : It is recommended that for all medicinal products irrespective of drug class ~~patients are screened for CLL eradication in PB first. If MRD negativity is shown, this should be confirmed in the BM.~~ **MRD response be evaluated based on a peripheral blood sample as part of the primary analysis. MRD measurement should also be performed in BM (for patients in whom a BM sample has been taken for confirmation of CR) as part of the secondary analysis in order to complement the primary analysis. This 2 step approach will also further expand the body of evidence supporting the use of MRD in CLL trials.**	*the International Workshop on Chronic Lymphocytic Leukaemia updating the National Cancer Institute–Working Group 1996 guidelines. Michael Hallek, Blood. 2008 Jun 15; 111(12): 5446–5456).*
84	4	Comment: Minor clarification. Proposed change (if any)(BOLD is added text): If MRD negativity is shown in PB, this should be confirmed in	Accepted. See also previous comment

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the BM.	
86-87 *It is accepted that in case of disease progression, response to therapy is the most important prognostic factor for survival.*	3	The sentence starts with “in case of disease progression,” but the rest of the sentence indicates response is the most important prognostic factor for survival. It may not be clear how this follows. <u>Proposed change :</u> Please clarify.	Accepted. For clarity the reference to disease progression has been deleted as, overall, response to therapy in CLL is the most important prognostic factor for survival (*New prognostic markers in chronic lymphocytic leukaemia, Carol Moreno; Blood reviews, Volume 22, Issue 4, July 2008, Pages 211–219).*
89-90 *The availability of MRD data shortly after treatment is important because with more effective treatment regimens PFS will only be evaluable after a long observation period.*	3	Proposed change : The availability of MRD data shortly after treatment is important because with more effective treatment regimens PFS will ~~only~~ be evaluable **only** after a long observation period.	Accepted.
87	4	Comment: Minor clarification. Proposed change (if any)(BOLD is added text):… profound reduction of tumour load, as evaluated with the MRD assay, and not the treatment regimen…	Accepted.
89-92	4	Comment: It is suggested remove the conclusion here (i.e. MRD data shortly after treatment is important, because with more effective treatment regimens PFS	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		will only be evaluable after a long observation period) and place it further below. Proposed change (is any) (strikethrough is text removed): … the key factor for durable remission. The availability of MRD data shortly after treatment is important because with more effective treatment regimens PFS will only be evaluable after a long observation period. Available data has shown that MRD negativity at the end of induction treatment is a strong predictor of PFS and OS irrespective of the following: …	
91	1	Comments: Suggest replace “MRD negativity” as discussed above	Accepted.
91	2	Proposed change from “Available data has shown that MRD negativity at the end of induction treatment” to “Available data has shown that the absence of detectable MRD at the end of induction treatment”	Accepted. See previous comment. “MRD negativity” has been changed to “undetectable MRD” throughout the text.
94-96	1	Comments: Suggest replace “MRD negativity” as discussed above	Accepted.
94-96	2	Proposed change from “Although patients are more likely to reach MRD negativity with some therapies compared to others, for those patients that achieved MRD negativity by different therapies there appear to be no differences in terms of PFS or OS” to “Although patients are more likely to achieve undetectable MRD	Accepted. See previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		with some therapies compared to others, for those patients that achieved absence of detectable MRD by different therapies there appear to be no differences in terms of PFS or OS".	
94 - 96 *Although patients are more likely to reach MRD negativity with some therapies compared to others, for those patients that achieved MRD negativity by different therapies there appear to be no differences in terms of PFS or OS.*	3	The sentence should be rephrased to better understand the correlation made between gain on MRD and PFS throughout treatments. Proposed change : Although patients are more likely to reach MRD negativity with some therapies compared to others, ~~for those patients that achieved MRD negativity by different therapies there appear to be no differences in terms of PFS or OS~~ **MRD negative patients reach similar gains in terms of PFS or OS regardless of therapy received.**	Accepted. See also previous comments.
98	2	Comment: According to international gene nomenclature (http://www.genenames.org/) the appropriate acronym for ZAP70 is without hyphen: Proposed change: ZAP70	Accepted.
99-100	1	Comments: Data from the UK ARCTIC and ADMIRE trials, submitted for presentation at the IWCLL meeting show median PFS for BM MRD <0.01% not reached (95% alive and progression-free at 24 months, 87% alive and progression-free at 36 months, 82% alive and	Comment is acknowledged but mature data from both trials are still awaited. See also comment below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		progression-free at 48 months), median PFS for 0.01-1% 48.5 months, median PFS for >1% 24.3 months.	
99-100	2	DCLLSG data (PMID 22331940): Median PFS is estimated at 68.7, 40.5, and 15.4 months for MRD low- (< 10−4), intermediate- (≥ 10−4 to <10−2), and high-level (≥ 10−2) groups. Proposed change from "Current evidence suggests that in unselected patient cohorts an MRD level ≥ 10 -4is associated to a median PFS of about 2 years, whereas a MRD level < 10 -4 predicts a median PFS of around 6 years" to "Current evidence suggests that in unselected patient cohorts an MRD level ≥ 10 -2 is associated to a median PFS of about 2 years, whereas a MRD level < 10 -4predicts a median PFS of around 6 years."	Accepted. The sentence has been phrased as "Current evidence suggests that an MRD level ≥ 10 -2 is associated to a median PFS of about 2 years, whereas a MRD level < 10 -4 predicts a median PFS of around 6 years".
100	3	Comment: We suggest to clarify what is meant by "*unselected patient cohorts"*	See previous comment
101-102 *The validation of MRD negativity as a surrogate endpoint requires that the treatment effect on this marker can explain quantitatively the treatment effect in terms of PFS. This*	3	The statement "This remains to be shown" implies that the guideline doesn't fully consider MRD as an accepted endpoint and that more data are needed before considering a definitive use of MRD as primary endpoint. Although it is acknowledged that additional data are required to more precisely predict PFS for a given MRD response rate, current data allow to quantitatively predict the PFS HR with a confidence	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
remains to be shown.		interval acceptable to appropriately design phase 3 clinical trials. Proposed change : It is proposed to remove the following statement: ~~This remains to be shown.~~	
101-104	1	Comments: Suggest replace “MRD negativity” as discussed above	Accepted.
101-104	2	Proposed change from “The validation of MRD negativity as a surrogate endpoint requires that the treatment effect on this marker can explain quantitatively the treatment effect in terms of PFS. This remains to be shown. Qualitatively available data are sufficiently convincing for MDR negativity to be used as an intermediate endpoint in randomised controlled trials” to “The validation of MRD response as a surrogate endpoint requires that the treatment effect on this marker can explain quantitatively the treatment effect in terms of PFS. This remains to be shown. Qualitatively available data are sufficiently convincing for the MRD response rate to be used as an intermediate endpoint in randomised controlled trials.”	Partly accepted. The term “MRD response rate” has been used as it is later defined as surrogate endpoint for licensing. See also previous comment.
101-104	4	Comment: To include here the conclusion as to why MRD could be used as intermediate endpoint. Proposed change (if any)(BOLD is added text): The availability of MRD data shortly after treatment is	Partly accepted. The conclusion has been inserted in previous paragraph. See also previous comments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		important, as upon development of more effective treatment regimens PFS will only be evaluable after a long observation period. Yet, the validation of MRD negativity as a surrogate endpoint requires that the treatment effect on this marker can explain quantitatively the treatment effect in terms of PFS. This remains to be shown.	
103-104 *Qualitatively available data are sufficiently convincing for MDR negativity to be used as an intermediate endpoint in randomised controlled trials.*	3	Propose to rephrase as follows indicating which references used to support this statement: ~~Qualitatively~~ **Currently** available data are **qualitatively** sufficiently convincing for MRD negativity to be used as a **primary** ~~intermediate~~ endpoint in randomised controlled trials (**Boettcher et al, 2012**) **as long as the benefit in terms of long term efficacy can eventually be confirmed.**	Partly accepted. MRD status cannot be used as primary endpoint. See previous comments. References are listed at the end of the document. Text has been amended to include ….*as long as the benefit in terms of long term efficacy can eventually be confirmed*.
105-108	6	"MRD as endpoint for licensure A difference in MRD response rates can be used as primary evidence of clinical benefit to obtain early licensure in randomised CLL trials designed to show superiority in terms of PFS provided all the following conditions are met:" In trials with patients with very advanced disease, there may not be an adequate comparator arm. Randomized trials may neither be feasible nor ethical. It is conceivable that in such a setting, MRD response may further support approval based on clinical	Accepted. Included " any deviations should be fully justified".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		response.	
106-107 *A difference in MRD response rates can be used as primary evidence of clinical benefit to obtain early licensure in randomised CLL trials…*	3	The guidance should elaborate on the meaning of early licensure based on the current EU regulatory framework.	Early licensure refers to approval before PFS data become available. It does not refer to the marketing application legal basis or other regulatory considerations for centralised procedures (conditional, accelerated assessment, exceptional circumstances). The sentence "….but where mature PFS data will only become available at a later stage. Regulatory considerations (e.g. legal basis of the marketing authorisation application or other considerations, for example conditional approval) should be decided on a case by case basis." has been added for clarity.
106-107 *A difference in MRD response rates can be used as primary evidence of clinical benefit to obtain early licensure in randomised CLL trials…*	3	The guideline indicates that "*PFS confirmation will be obtained at a further analysis with the trial being prospectively powered for this purpose.*" This statement implies that PFS would have to be determined in the same study and does not allow for flexibility to confirm PFS benefit in a separate study. In addition, enrolling a large number of patients to be able to confirm PFS in the same study years after MRD has been determined could be problematic in terms of patient retention. Confirmation of clinical benefit in a separate study has been typically used for previously authorised products that have used surrogate endpoints for conditional marketing authorisation and should be considered in this context as well.	Not accepted. See previous comments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change : A difference in MRD response rates can be used as primary evidence of clinical benefit to obtain early licensure~~. in randomised CLL trials designed to show superiority in terms of PFS provided all the following conditions are met:~~ *Study design and results* • The difference in MRD response rate between study arms is large enough to predict that a relevant PFS benefit will appear on mature data • PFS confirmation will be **provided as a post approval measure** ~~at a further analysis with the trial being prospectively powered for this purpose~~ **or by the means of another well conducted trial to confirm the benefit in the initial trial.**	
106 and 110 and 116 and…	4	Comment: Measuring MRD and achieving MRD negativity are two different things. It is assumed that it is the differences in the rate of MRD negativity that can be used as primary evidence. Suggestion: The whole document should be carefully checked for appropriate use of the wording MRD and MRD negativity. Proposed change (if any): (BOLD is added text) A difference in MRD negativity response rates can be used as primary…	Partly accepted. Clarification on term “MRD negativity” has been addressed in previous comment and amended throughout the text. A definition of MRD response rate is included in the text in the prior paragraph and later under MRD definitions and method. Therefore no further changes are considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
109	4	Comment: In this section further clarification could be included on what time point the MRD intermediate endpoint should be based, and whether there are consequences for interpretation of the data if the patient had reached MRD negativity earlier or later in terms of clinical benefit. Proposed change (if any): Please address this comment in the text.	Partly accepted. Note new subheadings have been incorporated to text for clarity. Time point for MRD assessment is described in 3.2.2 (under MRD definitions as clinical endpoint and method). The interpretation of data regarding time taken to achieve undetectable MRD is considered exploratory. There is not sufficient data available to provider further guidance on this aspect.
110	4	Comment: Some guidance on how to assess whether an observed difference in MRD negativity response rate is sufficient for prediction of relevant PFS benefit would be welcomed. As it is stated now it raises the question on how large is large enough, and how do we known whether the difference is large enough. Proposed change (if any): See general comments.	The comment is acknowledged but unfortunately it is not possible to provide a specific difference in magnitude of effect needed to predict PFS, as it also occurs with other CHMP guidance (e.g. points to consider on applications based on single pivotal trial….efficacy is expected to be compelling….).
110-111 *The difference in MRD response rate between study arms is large enough to predict that a relevant PFS benefit will appear on mature data*	3	The guidance should provide some indication regarding the magnitude of the effect that the agency would expect to see between the study arms (e.g. minimal absolute difference to be observed) or advice whether this should be discussed as part of a product specific scientific advice.	See previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
110-111	6	"The difference in MRD response rate between study arms is large enough to predict that a relevant PFS benefit will appear on mature data." It would be helpful if some additional guidance could be provided on what such a difference is or how a sponsor would justify such a difference.	See previous comment.
116-117 *In case of early approval based on MRD response rate, an analysis of PFS would be required from the holder of the marketing authorisation in an agreed timeframe.*	3	Depending on timing, early approval could make it difficult to complete the study. Proposed change : If possible, it would be helpful to include guidance on how to maintain study compliance after approval.	Comment is acknowledged but in general, early approval (e.g. when studies are approved on an interim analysis but mature data is expected to follow after authorisation) poses a risk to maintain study compliance after licensing. It is outside the scope of this guidance how it should be handled.
119	1	Comments: See comment on MRD in PR above: only assessing patients in confirmed CR would risk missing valuable response data.	Accepted (see comment below).
119	2	See comments on the absence of MRD in patients achieving PR above and the timing of bone marrow assessments to minimise invasive biopsy. Even if the MRD response rate is limited to patients in CR, only assessing patients in confirmed CR would risk missing valuable response data. Proposed change from "All patients with clinical CR should be assessed for MRD" to "All patients with	Partially accepted. All patients with clinical response (not restricted to CR) should be assessed for MRD in PB. Only patients with undetectable MRD in PB should have confirmation of MRD status in BM.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical CR or PR should be assessed for MRD. BM MRD assessment is not informative for patients with $>10^{-2}$ MRD in the PB "	
119 *All patients with clinical CR should be assessed for MRD*	3	The guideline describes the option to use MRD as an 'intermediate' endpoint, with confirmation of benefit through an adequately powered endpoint. However, in line 117 it is recommended that MRD should only be analysed in patients with clinical CR, which would results in a combined endpoint of clinical CR with MRD negative status. As data have demonstrated that MRD negative status is also of benefit in patients with clinical PR, and MRD is rarely negative in patients with clinical SD or PD, we suggests consideration of MRD as an endpoint independent of clinical response. This recommendation is also supported by statistical analysis (see attached report) showing that including CR in the MRD definition does not improve the surrogacy vis a vis PFS. Proposed change : All **patients should** be assessed for MRD **in blood. MRD analysis in bone marrow when available should be provided as part of the secondary analysis.**	Not accepted. It is expected very few patients achieving PR will achieve undetectable MRD. Until further data from randomized controlled studies are available to support the use of MRD on its own as a surrogate/ primary endpoint consideration is given to clinical response. See also previous comment.
122-135	4	Comment: The need for this section could be reconsidered: some of these points are already mentioned elsewhere in the document, while other	Partially accepted. The section has been reorganized for clarity. New subheadings are introduced.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		points could be placed somewhere else (see below). Proposed change (if any): Please, reconsider this paragraph.	
124	4	Comment: This technical requirement should be mentioned in the section on the analytical methods/laboratory assays. Proposed change (if any): Please, move text to paragraph laboratory assays.	See previous comment.
124 *MRD status should be measured by a standardised method with a quantitative lower limit of at least < 10-4*	3	We consider that not only the sensitivity requires to be defined but also other parameters, like specificity and reproducibility. For each accepted method, there is a need for clear technical guidelines (similar to ESG-MRD-ALL guidelines for example) Proposed change : MRD status should be measured by a standardised method **following guidelines that define specificity, sensitivity and reproducibility**	Accepted.
127 *Measurement of MRD should be conducted at end-of-treatment response final staging assessment (around 3 months after end of treatment) to fully represent the effect of treatment.*	3	This wording is based on the experience with historical chemotherapy regimens. Duration of therapy for newer targeted therapies may not have as directed timing for assessment. In continuous oral treatment regimens, e.g. Ibrutinib, Idelalisib formal end-of-treatment analysis is not possible as treatment is continuous. The selection of time point for assessment of MRD should be driven by mechanism of action of	Partly accepted. The proposed change has been slightly modified: "Deviations from the recommended time point for MRD assessment may be acceptable if justified by appropriate clinical data on the mechanism of action of the drug and prior knowledge on the kinetics of responses". Data supporting the use of MRD as a clinical endpoint is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the drug and prior knowledge on the kinetics of responses of the drug from earlier clinical research and other timepoints should be defined as well. This principle should also apply to the setting of maintenance/ consolidation therapy. Proposed change : **The time point for assessment of MRD should also take into account the mechanism of action of the drug and prior knowledge on the kinetics of responses of the drug from earlier clinical research. This principle should also apply to the setting of maintenance / consolidation therapy**.	currently available in the induction setting. Reference to consolidation therapy is mentioned under “additional areas of uncertainty” and reference for maintenance will be included.
126 *A quality control scheme for all laboratories providing CLL MRD analysis will be required*	3	We would also propose to clarify that the quality control scheme refers to a specific lab. Proposed change : A quality control scheme for **each**~~all~~ laborator**y**~~ies~~ providing CLL MRD analysis **in the clinical trial** will be required.	Accepted.
126, 129	4	Comment: This is a repetition of what is stated earlier in the document (lines 46 and 54). Proposed change (if any): Remove the repetition from the text.	Partially accepted. The section has been reorganized for clarity. New subheadings are introduced.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
127	4	Comment: This requirement might be better fit in the paragraph on the samples. Proposed change (if any): Please, move text to paragraph on samples.	Partially accepted. The section has been reorganized for clarity. New subheadings are introduced.
127-128	5	Comment: It is not clear how the proposed timing for MRD measurement would apply to non-cyclic therapies taken continuously until disease progression or unacceptable toxicity.	This guideline is based on available knowledge of MRD assessment during cyclic therapies. Deviations of timing for MRD measurements, such as in continuous (non-cyclic) therapy, will need to be justified. The text has been modified (see previous comment).
127-128	6	“Measurement of MRD should be conducted at end-of-treatment response final staging assessment (around 3 months after end of treatment) to fully represent the effect of treatment.” If a patient receives allogenic hematopoietic stem cell transplantation (HSCT), how is the end of treatment defined?	A recommendation on MRD assessment following allogenic hematopoietic stem cell transplantation (HSCT) is included under the heading “additional recommendations/considerations”. A specific time point cannot be provided in this guidance.
130-133	2	Comment: as discussed above, it has been shown that also patients achieving PR and MRD negativity have overlapping clinical outcome as the CR. Proposed change: Add PR patients in the response rate or consider them separately and create 2 distinct categories “CR MRD response rate” and “Total MRD rate”	See previous comments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
130 – 131 *MRD response rate is defined as the proportion of patients in the ITT population in whom a clinical complete response (CR) and MRD negative status is achieved following induction treatment in CLL.*	3	Comment: In a Global context of clinical development (specially in Orphan indication) it is important to recommend the guideline to clarify which International Guideline (s) are to be applied for response assessment with clear guidance on the requirement of imaging tests in the context of physical examination, symptoms, and blood tests <u>Proposed change :</u> Statement on the International Guidelines to be applied	Not accepted. International guidelines do change overtime. There is no need to clarify a specific guideline provided there is a reasonable justification on the method used for assessment response to a therapy in a clinical trial.
130-134 *MRD response rate is defined as the proportion of patients in the ITT population in whom a clinical complete response (CR) and MRD negative status is achieved following induction treatment in CLL.* *Patients who achieve clinical CR and MRD negative status at the end of treatment will be counted as MRD responders*	3	As previously mentioned, it is proposed to amend the definition of MRD. <u>Proposed change :</u> MRD response rate is defined as the proportion of patients in the ITT population in whom ~~complete response (CR) and~~ MRD negative status is achieved following ~~induction~~ treatment in CLL.	Not accepted. See previous comments.

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130-135	4	Comment: These definitions might be better included in the section on study design and results. Proposed change (if any): Please, move text to paragraph on study design and results.	The section has been reorganized for clarity. New subheadings are introduced and order of bullet points changed.
130-131	6	"MRD response rate is defined as the proportion of patients in the ITT population in whom a clinical complete response (CR) and MRD negative status is achieved following induction treatment in CLL." How would those patients for whom a suitable MRD marker could not be found be analysed? From a statistical standpoint, such patients may be considered missing completely at random (MCAR), so to assume that such patients are MRD nonresponders may be very conservative. As an option to consider, at least possibly as a sensitivity analysis, if MRD status is to be used as a primary endpoint for early licensure, the population could be based on a modified ITT population consisting only of randomized patients for whom a suitable MRD marker could be found.	Partly accepted. The sentence "A sensitivity analysis in patients with missing bone marrow samples may be conducted" has been included.
132-133	6	"Patients who achieve clinical CR and MRD negative status at the end of treatment will be counted as MRD responders" As above, in lines 127-128, it is unclear whether end of treatment is after induction or consolidation. It may be before allogenic HSCT, as not all patients except high risk refractory patients will receive this therapy.	End of treatment refers to induction treatment.

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		Just as ORR is usually based on the best response achieved during treatment (or within a certain number of cycles), Amgen recommends that the MRD response rate also be based on those who achieve an MRD response at any point during treatment or during a certain number of cycles, rather than at just one assessment at the end of treatment.	Not accepted. The definition of MRD response rate has a different basis than ORR and currently available data recommends assessment of MRD after end of treatment.
134-135 *Patients with missing MRD assessment and with MRD-positive status will be counted as MRD non-responders*	3	Comment: Definition on patients in whom a MRD assessment is technically not possible, e.g. because no informative PCR / immune phenotype could be defined, should also be given. <u>Proposed change :</u> Include after missing MRD assessment: "(technically impossible, missing specimen)"	Accepted. The text has been changed to "missing MRD assessment(any cause)…." to cover any possible reasons for missing MRD assessment.
136	3	Comment: It is of interest to study the correlation in between MRD assessment in PB and BM. A recommendation should be provided to investigate such a correlation in future trials. <u>Proposed change :</u> **For exploratory purposes, it is recommend to assess correlation between MRD in PB and BM systematically in new clinical trials.**	Accepted.

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136-143	3	It is recommended to consider all settings as prospective trials are needed to determine whether additional therapy to convert CR/PR MRD positive into MRD negative is of significant clinical benefit. For example, improvement in MRD should be also investigated in maintenance/consolidation treatment after first line or second line treatment, particularly among patients with high risk CLL (e.g. deletion 17p and 11q, p53 mutation, IGVH and β2 microglobulin). Proposed change : **For exploratory purposes, it is recommended that MRD status be assessed in all settings including maintenance and consolidation treatment after first line or second line therapy, particularly in patients with high risk CLL.**	Accepted. A sentence has been added under “areas of uncertainty”.
137-138	1	Comments: Suggest replace “MRD negativity” as discussed above	Accepted.
137-138	2	Proposed change from “Exploratory analyses are recommended using different cut-offs for “MRD negativity” in patients with CR as well as PR. The prognostic value of different levels of MRD may also be explored” to “Exploratory analyses are recommended using different cut-offs for MRD response in patients with CR as well as PR. The prognostic value of different levels of MRD may also be explored”	Accepted. The text has been amended according to previous comment.

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137	4	Comment: The prognostic value of the timing of MRD achievement should be discussed as well. Proposed change (if any): See also general comments.	The timing of MRD assessment is after end of induction treatment. The prognostic value of MRD is not related to the timing of assessment. The prognostic value is linked to achieving (or not) the required undetectable level after end of treatment. See previous comments.
139-140	1	Comments: See comment on MRD in PR above: propose that MRD assessments are performed in responding patients with the additional comment that BM MRD assessment is not informative for patients with >10-2 MRD in the PB	See previous comments.
139-140	2	See comments on the absence of MRD in patients achieving PR above and the timing of bone marrow assessments to minimise invasive biopsy. Proposed change: delete “For exploratory purposes, it is recommended that all patients responding to therapy (including PR) should have their MRD status assessed at least in peripheral blood” and, as noted above, propose that MRD assessments are performed in responding patients with the additional comment that BM MRD assessment is not informative for patients with >10-2 MRD in the PB	Accepted.
140 *For exploratory purposes, it is*	3	We suggest to delete this sentence given that the recommendation is to measure MRD in peripheral	See previous comments.

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recommended that all patients responding to therapy (including PR) should have their MRD status assessed at least in peripheral blood.		blood in all patients in the primary analysis. ~~For exploratory purposes, it is recommended that all patients responding to therapy (including PR) should have their MRD status assessed at least in peripheral blood.~~	
141-143	1	Comments: Suggest replace “MRD negativity” as discussed above	Accepted.
141-143	2	Proposed change: “For patients that undergo allogeneic SCT, early MRD positivity is common probably due to the fact the onset of graft-versus-leukaemia is not immediate. MRD negativity can be achieved several months after allogeneic SCT” to “For patients that undergo allogeneic SCT, persistence of detectable MRD is common, probably due to the fact the onset of graft-versus-leukaemia is not immediate. Absence of detectable MRD can be achieved several months after allogeneic SCT”.	Accepted. See previous comment.
141-143	6	“For patients that undergo allogeneic SCT, early MRD positivity is common probably due to the fact the onset of graft-versus-leukaemia is not immediate. MRD negativity can be achieved several months after allogeneic SCT.” When to measure MRD in case of HSCT is unclear. This statement seems to indicate that MRD measurements will be conducted prior to and after HSCT.	See previous comment.

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142-144 *For patients that undergo allogeneic SCT, early MRD positivity is common probably due to the fact the onset of graft-versus-leukaemia is not immediate. MRD negativity can be achieved several months after allogeneic SCT.*	3	We suggest to state '*SCT*' in full and rephrase as below: Proposed change: '*For patients that undergo allogeneic SCT, early MRD positivity is common probably due to the fact* ***that*** *the onset of graft-versus-leukaemia is not immediate. MRD negativity can be achieved several months after allogeneic SCT.*'	Accepted.
145-147	4	Comment: Clarification of the text is suggested. Proposed change (if any): It has been suggested that the kinetics of MRD levels rather than a single MRD assessment may be more meaningful because it is the increase of MRD over time and not only its persistence of MRD negativity that is eventually followed by clinical relapse.	MRD levels achieved after therapy represent the nadir of a tumour burden in a patient, which might be independent from the speed of regrowth. The text refers to the persistence of residual disease (either below or above detectable levels) and the importance of the kinetics of the malignant cells. So, to evaluate the potential of relapse one single MRD level may not be informative (the MRD level may be just detectable but may stay at that level over some time) but repeated values of MRD over time will show if there is regrowth of malignant cells (with eventual relapse) because the increase in malignant cells is expected to be exponential. Note this text is placed under "additional areas of uncertainty" until there is more knowledge in this field.

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147-148	4	Comment: Unclear what is meant with the text: The kinetics of relapse is exponential even at the lowest evaluable levels of the disease. Is it a reminder that the scale of the MRD evaluation is logarithmic, or the it the cell expansion which is, in principle, exponential, or is the course of disease development exponential? Proposed change (if any): Please, clarify.	The text refers to the exponential kinetics of the regrowth of malignant cells. See previous comment.
147-148	6	“The kinetics of relapse is exponential even at the lowest evaluable levels of the disease.” An additional area of uncertainty is the prognostic significance of kinetics of MRD response. In ALL, more rapid MRD response is associated with improved survival parameters.	Accepted. A sentence has been included: The prognostic significance of MRD assessments during induction therapy is unknown, in particular, for tailoring treatment according to MRD response aiming to reduce duration of treatment and subsequent reduction of toxicity.
150-151	4	Comment: This text is not fully clear. However, when the proposal is accepted to explicitly mention that MRD-guided treatment does not fall within the scope of this document in the section on the scope, this text can be removed here. Proposed change (if any): Please, clarify or remove text here.	The text refers to the uncertainties on the use of MRD from a scientific point of view that may be considered for exploratory purpose only.