National Institute for Health and Care Excellence

Health Technology Evaluation

Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no minimal residual disease [ID6405]

Response to stakeholder organisation 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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Amgen	The need for an appraisal is appropriate and the Company agrees with the proposed evaluation route (STA).	Thank you for your comment. No action required.
	RCP&Barts Health	Strategies to improve disease-specific and QOL outcomes in this patient group are currently limited, hence the evaluation exercise is of high importance to the clinical community and patient groups,	Thank you for your comment. No action required.
Wording	Amgen	The Company wishes to update the appraisal title to: “Blinatumomab as part of frontline consolidation for the treatment of Philadelphia-chromosome-negative CD19-positive B-precursor MRD-negative acute lymphoblastic leukaemia”	Thank you for your comments. The title and remit/evaluation objective has been updated to ‘Blinatumomab with chemotherapy for consolidation treatment

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			of Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no minimal residual disease.'
	RCP&Barts Health	Yes	Thank you for your comment. The title and remit/evaluation objective has been updated to 'Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no minimal residual disease.' No action required.
Timing issues	Amgen	Current standard of care for patients with Ph- B-ALL who are MRD-negative in frontline consolidation is chemotherapy alone. Despite some patients achieving MRD-negativity with chemotherapy, there is a high unmet need for clinically effective treatments as the remission seen often is not durable and a	Thank you for your comment. NICE has scheduled this topic into its work programme.

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		high proportion of patients relapse. Relapses have negative impacts on the patients and the health care system. The Company therefore wishes to achieve reimbursement for blinatumomab as soon as possible.	For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-hte10035
	RCP&Barts Health	I would support priority review given the lack of strategies currently to improve outcomes in this group.	Thank you for your comment. NICE has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-hte10035
Additional comments on the draft remit	Amgen		No action required.
	RCP&Barts Health		No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Amgen	**Background** - Current wording: “Other treatment options may include stem cell transplantation if a suitable donor can be found”	Thank you for your comment. The scope background provides a brief overview of the condition and treatment

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		- Proposed wording: “Stem cell transplant is reserved for patients with high-risk characteristics, and if a suitable donor can be found, is received prior to consolidation”	pathway. The background section of the scope has been updated to include ‘Stem cell transplant is reserved for patients with high-risk characteristics, and if a suitable donor can be found.’
	RCP&Barts Health	Adequate. Some qualifications are needed around the aim of therapy as curative intent is not always appropriate particularly in older patients or those with signifcant co-morbidities. These patients should be addressed separately (see below)	Thank you for your comment. The scope background provides a brief overview of the condition and treatment pathway. The background section of the scope has been updated to include ‘Stem cell transplant is reserved for patients with high-risk characteristics, and if a suitable donor can be found.’
Population	Amgen	For clarity, the Company wishes to update the wording to: “People with Philadelphia-chromosome-negative CD19-positive MRD-negative B-precursor acute lymphoblastic leukaemia in frontline consolidation”	Thank you for your comment. The population in the scope

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			has been updated to 'People with Philadelphia-chromosome-negative CD19-positive MRD-negative B-precursor acute lymphoblastic leukaemia in frontline consolidation.'
	RCP&Barts Health	Yes	Thank you for your comment. The population in the scope has been updated to 'People with Philadelphia-chromosome-negative CD19-positive MRD-negative B-precursor acute lymphoblastic leukaemia in frontline consolidation.' No other action required.
Subgroups	Amgen	The population in our submission will be aligned with the population of the E1910 Phase 3 RCT primary endpoint [redacted])	Thank you for your comment. No action required.
	RCP&Barts Health	Stratified assessment of older patients should form part of the evaluation. This group are usually treated with a similar chemotherapy paradigm induction, consolidation and maintenance but dose attenuated. The	Thank you for your comment. The

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		evaluation outcome should consider the applicability of the treatment intervention in the context of an age-adjusted chemotherapy backbone.	committee will make decisions based on the evidence presented by the submitting company. It will take into account evidence for specific groups, including age, in its decision making. No action required.
Comparators	Amgen	The only appropriate comparator is consolidation chemotherapy alone, because this is current standard of care (SOC) in frontline consolidation treatment for adults with Ph- MRD-negative B-ALL. This has been validated by UK clinicians. Blinatumomab is not an appropriate comparator as it is not reimbursed in the target population, i.e. frontline consolidation treatment for adults with Ph- MRD-negative B-ALL. (Blinatumomab is only reimbursed in patients with Ph- *MRD-positive* B-ALL). Stem cell transplant (alloSCT) is not an appropriate comparator. In UK clinical practice, in patients with Ph- MRD-negative B-ALL, alloSCT is reserved for patients with high-risk cytogenetics, and is received at the end of induction/ intensification (i.e. prior to the consolidation phase). **Therefore, if blinatumomab is made available in frontline consolidation, alloSCT would not be displaced by blinatumomab.**	Thank you for your comments. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal. The comparators in the scope have been updated by removing 'Blinatumomab'.

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	RCP&Barts Health	Sustained MRD negative disease responses would not routinely be considered for allo-SCT unless for a specific reason – e.g. chemotherapy treatment intolerance. Hence the inclusion of allo-SCT as a comparator is uncertain.	Thank you for your comments. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal. The comparators in the scope have been updated by removing 'Blinatumomab'.
Outcomes	Amgen	Treatment response rate (i.e. minimal residual disease, haematologic responses and complete remission) are not appropriate outcome measures. This is because the target population for this appraisal are patients *who are already in complete remission and who are MRD-negative, at the end of induction/ intensification (i.e. prior to consolidation).* Rate of stem cell transplant is not an appropriate outcome measure. This is because in UK practice, patients with Ph- MRD-negative B-ALL, alloSCT is reserved for those with high-risk cytogenetics, and is given at the end of induction/ intensification (i.e. prior to consolidation). Furthermore, in the E1910 trial, intent to transplant was a stratification factor and the proportion of patients who received alloSCT was low and well-balanced between treatment arms. Therefore, treatment with blinatumomab did not influence whether a patient received alloSCT, and rate of stem cell transplant should therefore not be considered as an outcome measure.	Thank you for your comment. The list of outcomes is not exhaustive. The outcomes in the scope have been kept broad. Stakeholders can provide justification around the most appropriate outcomes and the committee will consider this during the appraisal. No action required.

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		The other outcomes listed are appropriate, although PFS was not collected in the E1910 trial (relapse-free survival (RFS) was collected). Therefore, the economic analysis for this appraisal focuses on OS and RFS for modelling efficacy outcomes and health state occupancy.	
	RCP&Barts Health	Yes	Thank you for your comment. No action required
Equality	Amgen	It is not anticipated that there will be any equality or equity issues with the draft remit and scope.	Thank you for your comment. No action required.
	RCP&Barts Health	As above, the evaluation procedure should consider whether age-restrictions are justifiable. While the licensing study applies an upper age limit, SOC application requires additional considerations. Usually the approach is to individualise treatment decisions based on biologic, personal and clinical parameters, thus the NICE evaluation should reflect and incorporate the complexity of real-life assessments and not necessarily restrict to a clinical trial defined criteria when determining benefit. A further consideration is the small group of patients who will not be evaluable for MRD, for a multitude of factors, from sample failure or lack of an applicable molecular/flow based MRD assay. These patients should be considered within the provisions of the final assessment and care should be taken to not structurally discriminate against this subgroup on the basis of technical factors related to MRD test assessments..	Thank you for your comment. NICE appraises technologies within their licence. NICE welcomes input from stakeholders to give insight into clinical practice. The committee will make decisions based on the evidence presented by the submitting company. It will take into account evidence for specific groups, including age or those not evaluable for

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			MRD, in its decision making.
Other considerations	Amgen	The Company believes that the economic model should not include costs associated with MRD testing. MRD testing is already standard UK practice and is carried out at the end of induction/intensification (i.e. prior to consolidation) for **all patients with Ph- B-ALL.** Therefore, there are no additional MRD tests or costs during frontline consolidation, as the target population are already known to be MRD-negative and therefore have already been tested.	Thank you for your comments. The economic analysis section of the scope has been updated by removing text related to costs associated with testing for minimal residual disease status.
	RCP&Barts Health	I am not aware of the full marketing authorisation conditions and whether the MRD methodology is specified. However I would urgently emphasise that the modality for MRD assessment should consider a country specific context. In the UK and across Europe, MRD evaluations are conducted by molecular evaluations primarily (>90%) which is subject to stringent quality control. Hence, MRD status is expected to be assigned by molecular evaluation for many patients with a smaller group of patients determined by flow cytometry where molecular MRD is not available. Please revise the wording under the economic evaluation subsection since it only mentions flow cytometry.	Thank you for your comments. The economic analysis section of the scope has been updated by removing text related to costs associated with testing for minimal residual disease status.
	Amgen	Q1. Where do you consider blinatumomab with chemotherapy will fit into the existing care pathway for Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia? [redacted]	Thank you for your comments.

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		Q2. Is it anticipated that blinatumomab with chemotherapy will be used for children? - Although the target population for this appraisal are adult patients with Ph- MRD-negative B-ALL in frontline consolidation, we have consulted with the paediatric ALL clinical community and the usage of blinatumomab as part of frontline consolidation is very relevant and would serve a high unmet need to the Ph- MRD-negative paediatric population. Q3. Have all relevant comparators for blinatumomab with chemotherapy been included in the scope? In particular, is stem cell transplant an appropriate comparator. - The only appropriate comparator is consolidation chemotherapy alone. - Stem cell transplant and blinatumomab are not appropriate comparators for frontline consolidation in patients with Ph- MRD-negative B-ALL. Please see our detailed response to the "Comparator" question above Q4. Please select from the following, will blinatumomab with chemotherapy be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care **C. Prescribed in secondary care with routine follow-up in secondary care** D. Other (please give details): Q5. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.	Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal. The compactors in the scope have been updated by removing 'Blinatumomab'.

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		- For comparators and subsequent treatments, the setting for prescribing and routine follow-up does not differ from the intervention Q6. Are the outcomes listed in the draft scope for this appraisal appropriate, particularly the rate of stem cell transplant? - Rate of stem cell transplant and treatment response rate (i.e. minimal residual disease, haematologic responses and complete remission) are not appropriate outcome measures - Please see our detailed response to the “Outcomes” question above Q7. Would blinatumomab with chemotherapy be a candidate for managed access? - Blinatumomab as part of frontline consolidation should be considered for routine baseline commissioning. [redacted] Q8. Do you consider that the use of blinatumomab with chemotherapy can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? - No; the Company expects all benefits to be captured via quality-adjusted life years (QALYs) Q9. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. - N/A	The list of outcomes is not exhaustive. The outcomes in the scope have been kept broad. Stakeholders can provide justification around the most appropriate outcomes and the committee will consider this during the appraisal.

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		Q10. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims - Please see our respond to the “Equality” question above Q11. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. N/A	
	RCP&Barts Health		No action required.
Additional comments on the draft scope	Amgen		No action required.
	RCP&Barts Health		No action required.

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