Single Technology Appraisal

Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-cell precursor acute lymphoblastic leukaemia without minimal residual disease [ID6405]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive B-cell precursor acute lymphoblastic leukaemia without minimal residual disease [ID6405]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Amgen:**
   a. Company submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Leukaemia Care

4. **Expert personal perspectives** from:
   a. Dr Nick Morley – clinical expert, nominated by Amgen UK
   b. Dr Bela Wrench – clinical expert, nominated by the Royal College of Pathologists
   c. Ariana Ortiz – patient expert, nominated by Leukaemia Care

5. **External Assessment Report** prepared by ScHARR

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

July 2024

File name	Version	Contains confidential information	Date
ID6405_Blinatumomab in Ph-negative MRD-negative ALL_Document B_CON	V1.0	Yes	26th July 2024

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Abbreviations

Acronym	Definition
ACRIN	American College of Radiology Imaging Network
AFT	Accelerated Failure Time
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
AlloSCT	Allogeneic stem cell transplant
BCP	B-cell precursor
BCR-ABL	Breakpoint Cluster Region Abelson (Philadelphia chromosome)
BFM	Berlin-Frankfurt-Münster
BIC	Bayesian information criterion
BIM	Budget impact model
BLINCYTO	Blinatumomab
BMT	Bone marrow transplantation
BNF	British National Formulary
BSA	Body surface area
CAR	Chimeric antigen receptor-T cell
CDF	Cancer drugs fund
CEM	Cost-effectiveness model
CNS	Central nervous system
CR	Complete remission
CRS	Cytokine release syndrome
CSR	Clinical study report
DCO	Data cutoff
DSA	Deterministic sensitivity analysis
DSU	Data service users
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOI	Event of interest
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment reports
ERG	Evidence Review Group
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLAG-IDA	Fludarabine, cytarabine, idarubicin, and filgrastim
GMALL	German Multicentre Study Group
HCRU	Healthcare resource use

Acronym	Definition
ICER	Incremental Cost-effectiveness Ratio
ICU	Intensive care unit
KM	Kaplan Meier
LCH	Log-cumulative hazard plot
LYG	Life years gained
MCM	Mixture cure models
MFC	Multiparameter Flow Cytometry
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Monthly Specialities
MRD	Minimal residual disease
NHB	Net health benefit
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NSAIDS	Nonsteroidal anti-inflammatory drugs
ONS	Office for National Statistics
PAS	Patient access scheme
PCR	Polymerase Chain Reaction
PEG	PEG-asparaginase
PFS	Progression-free survival
POMP	Purinethol (6-mercaptopurine), oncovin (vincristine), methotrexate and prednisone
PRO	Patient reported outcomes
PRS	Post-relapse survival
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QLQ	Quality of Life Questionnaire
RCT	Randomised controlled trials
RFS	Relapse-free survival
SAS	Safety Analysis Set
SCT	Stem cell transplant
SLR	Systematic literature review
SMR	Standardised mortality ratio
SOC	Standard of care
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document

Acronym	Definition
UKALL	UK National Cancer Research Institute Acute Lymphoblastic Leukaemia study
WBC	White blood cell
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The decision problem addressed in this submission, compared to that defined in the final scope issued by NICE, is summarised in Table 1. As outlined below, the marketing authorisation of blinatumomab is anticipated to be extended to include the population of [redacted]. This submission covers adults in this patient population and is broadly aligned with the NICE final scope (see Table 1).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with Philadelphia-chromosome-negative CD19- positive MRD-negative B-precursor ALL in frontline consolidation.	Adult patients with CD19-positive Ph-negative precursor B-cell ALL that is MRD-negative at the start of the consolidation phase.	The population of focus is narrower than the NICE final scope and the anticipated full license as it focuses on adults only. This is in line with the available clinical evidence base for blinatumomab in this indication and with the anticipated positioning of blinatumomab in UK clinical practice.
Intervention	Blinatumomab with chemotherapy	Blinatumomab plus SOC consolidation chemotherapy	N/A – in line with NICE final scope
Comparator(s)	Established clinical management without blinatumomab with chemotherapy, which may include chemotherapy (with or without corticosteroids) and stem cell transplant	SOC consolidation chemotherapy	The NICE final scope includes stem cell transplant as part of established clinical management. However, UK clinicians stated that in practice, for patients with Ph- MRD-negative B-ALL, alloSCT is reserved only for high-risk patients (e.g., those with adverse cytogenetics).[1] Further, if eligible and a suitable donor is available, alloSCT is received at the end of the induction/ intensification phase, prior to the consolidation phase. As such, should blinatumomab (plus SOC consolidation chemotherapy) be made available in the frontline consolidation phase, it would not displace alloSCT. Therefore, alloSCT is not considered a comparator in this submission.

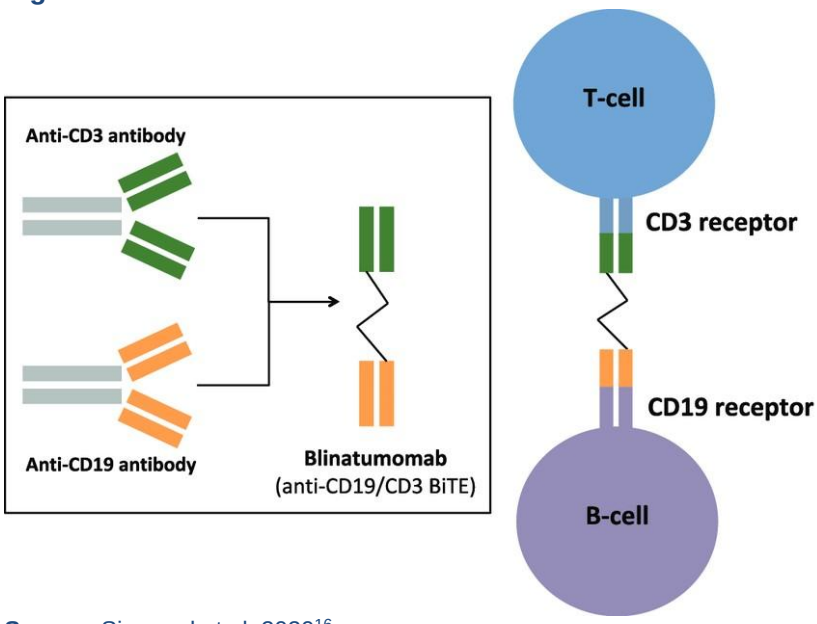
Outcomes	The outcome measures to be considered include: • OS • PFS (including RFS and EFS) • Treatment response rate (including MRD, haematologic responses and complete remission) • Rate of stem cell transplant • AEs of treatment • HRQoL.	The outcome measures to be considered include: • OS • RFS • AEs of treatment	Treatment response rate is not considered in this appraisal as it does not represent an appropriate outcome measure. 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 also does not represent an appropriate outcome measure for consideration. This is because in UK clinical practice in the target population (patients with Ph- MRD-negative B-ALL), alloSCT is reserved for those with high-risk features (e.g. adverse cytogenetics) who are eligible for transplant and for whom a suitable donor is available, and it would be received at the end of induction/intensification treatment (i.e. prior to the consolidation phase. Furthermore, in the E1910 trial, intent to transplant was a stratification factor during randomisation. The proportion of patients who received alloSCT was low and well-balanced between treatment arms, so treatment with blinatumomab did not influence whether a patient received alloSCT. HRQoL was not collected in the E1910 trial, therefore utility values in this submission are aligned with TA589.[2]

Abbreviations: ALL: acute lymphoblastic leukaemia; AlloSCT: allogeneic stem cell transplant; EFS: event-free survival; HRQoL; health-related quality of life; MRD: minimal residual disease; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; Ph: Philadelphia chromosome; RFS: relapse-free survival; SOC: standard of care; UK: United Kingdom.

B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with blinatumomab are presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Blinatumomab (Blincyto®)
Mechanism of action	Blinatumomab is a bispecific T-cell engager (BiTE®) that binds specifically to B-lineage surface antigen, CD19, on CD19-positive diseased B-cell ALL blasts, while simultaneously binding CD3 on the immune system T cells (Figure 1).[3] This leads to T cell-mediated elimination of CD19-positive B cells, and has demonstrated an ability to improve survival in patients with B-cell precursor ALL irrespective of baseline MRD status.[3-6] Blinatumomab was designed to target CD19 due to its near universal expression as a B-cell surface antigen at all stages of maturation and presumed importance for proliferation and survival.[7] Therefore, the mechanism of action and efficacy of blinatumomab are independent of age, consolidation ccuhemotherapy backbone, and Ph status, which has been confirmed in clinical trials and real-world settings across different B-cell precursor ALL subpopulations.[6, 8-15] **Figure 1: Blinatumomab mechanism of action**  **Source:** Sigmund et al. 2020[16]
Marketing authorisation /CE mark status	Blinatumomab was granted orphan designation by the EC in 2009.[17] The EMA and MHRA have approved the marketing authorisation for blinatumomab as a monotherapy treatment in four indications to date (see row below). An extension to the current license is anticipated [redacted] for the following population: [redacted].
Indications and any restriction(s)	Blinatumomab holds a marketing authorisation for monotherapy treatment in the following patient populations:[17, 18] • Adults with CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome

<table>
<tr><td>as described in the SmPC</td><td>positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options (September 2015)
• Adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% (November 2018)
• Paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation (alloSCT; July 2018)
• Paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy (October 2021)[17]</td></tr>
<tr><td>Method of administration and dosage</td><td>Blinatumomab is administered by cIV infusion delivered at a constant rate using an infusion pump over a period of up to 96 hours. A single cycle of blinatumomab treatment comprises cIV infusion at the doses indicated in Table 3, followed by a 14-day treatment-free interval.[17, 18]

Table 3: Recommended dosage of blinatumomab in this indication[17, 18]
<table>
<tr><th>Consolidation cycles</th><th>Patients >45 kg</th><th>Patients <45 kg</th></tr>
<tr><td>Days 1–28</td><td>28 mcg daily</td><td>15 mcg/m^2 (body surface area-based dose) daily[a]</td></tr>
<tr><td>Days 29–42</td><td>14-day treatment-free interval</td><td>14-day treatment-free interval</td></tr>
</table>
Footnotes: [a]This dose should not exceed 28 mcg daily.
Abbreviations: kg: kilogram; mcg: microgram.</td></tr>
<tr><td>Additional tests or investigations</td><td>Within this submission, blinatumomab is positioned for use in a subpopulation of adult patients who are CD19-positive, Ph-negative and MRD-negative in the frontline consolidation phase. Therefore, an accurate and validated assay for the Philadelphia chromosome identification and MRD testing is necessary to determine eligibility for blinatumomab use.

Immunophenotyping (confirmation of CD19 status), Philadelphia chromosome (BCR-ABL fusion gene) testing, and MRD status testing are already routine clinical practice in the diagnosis, risk stratification and monitoring of B-cell precursor ALL in the UK.[19] Therefore no additional tests or investigations are anticipated to be required for treatment with blinatumomab.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The list price of a vial of blinatumomab (38.5 mcg) is £2,017. The average cost of blinatumomab per cycle at the list price is £56,476 (28 mcg/day for Days 1–28, 28 vials).</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A confidential simple PAS discount of [redacted] will apply to blinatumomab in this indication. This equates to a with-PAS price for blinatumomab of [redacted] per vial.</td></tr>
</table>

Abbreviations: *BCR-ABL:* Breakpoint Cluster Region Abelson (Philadelphia chromosome); BiTE: bispecific T-cell engager; cIV: continuous intravenous; EC: European Commission; EMA: European Medicines Agency; MHRA: Medicines and Healthcare products Regulatory Agency; MRD: minimal residual disease; Ph: Philadelphia chromosome; SmPC: summary of product characteristics.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary of MRD-negative B-cell ALL

- B-cell precursor ALL is type of leukaemia characterised by the excessive proliferation of lymphoblastic B-cells and rapid onset of disease.[20] The diseased precursor B-cells near-universally express CD19 on their surface and leads to bone marrow failure and subsequent disease complications that severely impact the quality of life of patients.[21-23]
- After undergoing the first phases of treatment, patients in the UK with B-cell precursor ALL receive testing to investigate their response to treatment. Haematological complete remission (CR) refers to a return to normal blood count and an absence of leukaemia cells in the blood/bone marrow determined via traditional microscopy.[24]
- Despite achieving haematological CR after induction therapy, minimal residual disease (MRD), can remain. This refers to a level of disease activity not detectable using traditional microscopy in which cancerous cells can still be identified within the bone marrow during remission by using more sensitive analytical methods, including PCR and flow cytometry.[25-27]
- MRD status is an independent predictor of survival for B-cell precursor ALL. Patients with MRD-positive ALL experience higher rates of relapse and mortality than patients with MRD-negative ALL. Nevertheless, a considerable proportion of MRD-negative patients still experience relapse (36%) or have died (40%) at the 10 year timepoint and as a result there remains an unmet need in this population to prevent relapse and improve survivial.[28]

Current treatment pathway and unmet need

- A large proportion of patients with ALL achieve haematological CR without exhibiting MRD (64%).[29] In the current frontline UK treatment pathway (informed by the UKALL14 protocol), patients with Ph-negative, precursor B-cell ALL that is MRD-negative in the consolidation phase of the treatment pathway receive standard of care consolidation chemotherapy and subsequent maintenance therapy.
- In contrast, patients with MRD-positive disease with a haematological CR in frontline consolidation phase can be treated with blinatumomab, which has been shown to achieve a MRD response (i.e. reducing leukemic burden, from MRD-positive to MRD-negative status) in the majority of patients in the BLAST trial.[24]
- For patients with Ph-negative, MRD-negative, B-ALL, allogeneic stem cell transplantation (alloSCT) is typically offered to a small subset of these patients, with high-risk features (e.g. owing to adverse cytogenetics. For high-risk patients, alloSCT is carried out at the end of the induction phase, and therefore these patients do not proceed to the consolidation phase.[30]
- The majority of adult patients with Ph- MRD-negative B ALL will proceed to the consolidation phase. However, the risk of relapse remains high and hence there remains a pressing unmet medical need for novel treatments that increase the current efficacy seen with the standard consolidation chemotherapy alone, and to reduce risk of relapse and improve survival.

Blinatumomab and its proposed positioning in this appraisal within the frontline adult treatment pathway

- Blinatumomab is positioned for patients with CD19-positive, Ph-negative B-cell precursor ALL that is MRD-negative at the end of induction/intensification i.e. the start of the consolidation phase
- If recommended, adding blinatumomab to SOC consolidation chemotherapy would help address the current unmet need for an effective and targeted therapy that can avoid/reduce the risk of relapse, offering patients a new therapeutic option in frontline consolidation.

B.1.3.1 Health condition

Acute lymphoblastic leukaemia

Leukaemia is the overarching term for a group of haematological malignancies that are characterised by aberrant and excessive production of immature or abnormal cells by bone marrow or other blood-forming organs.[20] Leukaemia is classified into acute and chronic forms of the disease and further subdivided according to the type of cell that is affected. Acute leukaemia is characterised by the excessive, aberrant proliferation of immature blood cells which leads to rapid onset of disease, whereas chronic leukaemia is associated with slower disease onset and progression.[20] ALL is a form of acute leukaemia specifically involving the neoplastic proliferation of lymphoblasts, an immune cell type that are precursors of lymphocytes and which hold an important role in immunity. The proliferation of these immature lymphoid cells in the bone marrow subsequently disrupts the production of normal bone marrow elements, ultimately resulting in decreased red blood cells (anaemia), white blood cells (leukopenia) and platelet counts (thrombocytopenia).[21, 31] Consequently, patients with ALL typically acutely present with bone marrow failure and symptoms including tiredness, pale skin, fever, bruising, bleeding, bone pain and enlarged lymph nodes.[31]

ALL sub-classifications

B-cell ALL is the most common subtype of ALL, representing approximately 76% of all cases.[20] Of the clinically recognised phenotypes of B-cell ALL, the most common subtype is B-cell precursor ALL (representing ~93% of B-cell ALL cases), and these precursor B-cells near-universally express CD19 on their surface, among other surface antigens.[2, 20, 32]

Beyond these broad phenotypes, molecular sub-typing can be carried out for more detailed diagnostic evaluation and risk stratification. For example, B-cell precursor ALL can be further subclassified according to the molecular mechanisms and genetic modifications underlying the disease. The ALL subtype with an *ABL1-BCR* gene fusion mutation is termed Philadelphia chromosome positive (“Ph positive”) ALL, and it affects approximately 20−30% of adult patients and 2–3% of children with ALL.[33] Patients who do not have this genetic mutation are referred to as Philadelphia negative (Ph-).

Epidemiology

In the UK, there are approximately 8,500 new cases of adult leukaemia every year based on the average incidence between 2016 and 2018, with an estimated 300 new cases of adult ALL annually. It is estimated that 8,200 people were diagnosed with ALL between 1991 and 2010, while around 250 people die from ALL each year; the highest rates of mortality are observed in older patients.[34]

Prognosis

Overall, leukaemia accounted for approximately 3% of all cancer deaths in the UK between 2017 and 2019.[34] Whilst limited research has been conducted on UK-wide survival rates, a study performed in England reported that only two-thirds of patients are still alive after 5 years of being diagnosed with ALL, while five-year survival for B-cell ALL is estimated to be 40–50% in adult patients. With current multi-agent chemotherapy regimens, up to 90% of frontline adult patients

will achieve an initial haematologic CR, but up to 50% of patients will experience relapse and need a second line of therapy (treatment for disease relapse).[35-38]

There are several factors that influence disease progression and prognosis. Poor prognostic factors include young or advanced age (<1 year and >65 years), the presence of leukaemic blasts in the central nervous system (CNS) at diagnosis, high white blood cell count (WBC) at diagnosis, slow response to initial treatment and having MRD positive status.[39]

MRD status and disease progression

Frontline standard of care for newly diagnosed adult patients with Ph- B-cell precursor ALL begins with induction chemotherapy. The main clinical objective of the induction phase is to achieve haematological CR and normalisation of bone marrow function, i.e. <5% blasts in the bone marrow by standard microscopy, no circulating blasts outside the bone marrow and normal blood counts for neutrophils, platelets and haemoglobin.[40]

However, patients in haematological CR may still have minimal residual disease (MRD), which refers to residual blast cells present at levels below the detection sensitivity of standard microscopy but that are detectable using more sensitive molecular techniques (polymerase chain reaction [PCR] and flow cytometry).[41] Patients with MRD are referred to as MRD-positive (MRD+), and those without MRD are referred to as MRD-negative (MRD-).

MRD-negative status is generally defined as the presence of a small number leukaemic cells in the bone marrow during remission, although thresholds used to define MRD-negativity in previous clinical studies have varied.[42] Nonetheless, relapse is still a significant risk in patients with MRD-negative disease, which highlights the unmet need for an efficacious targeted therapy that deepens remission and prevents disease relapse in these patients.[28]

B.1.3.2 Disease burden

Symptom burden

ALL represents a considerable burden on patients' health-related quality of life (HRQoL). The disease symptoms caused by ALL and adverse events associated with some currently available ALL treatment options can considerably impact the emotional and physical functioning of patients and their families.[22] Nevertheless, there is a paucity of data available that quantifies the effect of ALL on patient HRQoL, including UK-specific data. The most relevant data sources are provided below, derived from studies in Europe and UK-based studies in similar indications.

HRQoL is measured using patient-reported outcomes (PRO), such as The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30).[43] Using this measure, a previous study performed in Sweden found that in comparison with the general adult population, patients with ALL (N=225) had lower global health status, with lower physical and psychological functions and higher symptom burden.[23] These findings align with the outcomes of studies performed in other comparable countries.[44, 45] Moreover, a UK-based study has reported differences in utility values across health states for patients with relapsed or refractory precursor B-cell ALL. Using a time trade-off survey, mean utility values were highest for treatment response states, including complete remission (0.86) and complete remission with partial haematological recovery (0.75).[22] Other health states, indicative

of poorer response to treatment, were associated with lower utility values, including aplastic bone marrow (0.59), partial remission (0.50), and progressive disease (0.30).[22]

Economic burden

Moreover, the economic burden of precursor B-cell ALL is considered to be high due to increased healthcare resource use and the recurrent hospitalisation of patients. Patients with a comparable disease state, relapsed or refractory precursor B-cell ALL, spend an average of 46% of their time in hospital whilst receiving chemotherapy, which contributes to significant economic burden on the healthcare system and its resources.[46] Therefore treatments that sustain long term remission and prevent relapse would be expected to provide economic benefits. ALL is also associated with a wider societal cost. This is because, understandably, working people with ALL may need to miss work and/or be less productive at work due to their disease. For example, Leukaemia Care (UK) reported, of the patients who were working or studying prior to their ALL diagnosis, 70% experienced a decrease in their productivity.[47] In addition, ALL can lead to an early death and result in an average of 23 to 39 years of life lost.[48] As some of these years would have been working years, this is also associated with adverse societal economic consequences.

B.1.3.3 Clinical pathway of care

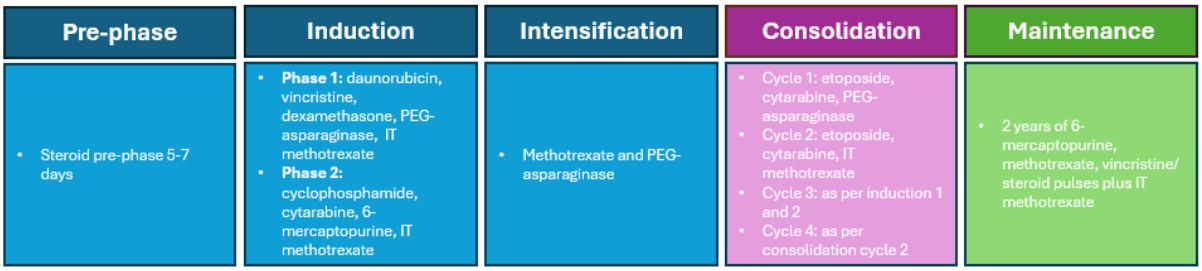
Current treatment pathway

The current frontline treatment pathway for newly diagnosed patients with Ph-negative, MRD-negative, B-cell precursor ALL in the UK follows a structured protocol, called UKALL14, that is comprised of several phases, as summarised in Figure 2 and below:

- Pre-phase: Steroids, which aim to reduce the blast count and reduce the risk of complications, such as tumour lysis syndrome and cytokine release syndrome
- Induction therapy (Phases I and II): An intensive phase of chemotherapy that aims to induce complete remission.
- Intensification therapy: Typically comprises methotrexate and PEG-asparaginase. For the minority of Ph-negative, MRD-negative, B-cell precursor ALL patients with high-risk characteristics (e.g. adverse cytogenetics) and if a suitable donor can be found, allogeneic stem cell transplantation (alloSCT) may be considered after intensification therapy (before consolidation therapy) if the patients achieve a haematological CR after induction.
- Consolidation therapy: Consolidation chemotherapy alone is the current standard of care for patients with Ph-negative, MRD-negative, B-cell precursor ALL. The aim of consolidation treatment for B-cell ALL encompasses the consolidation of the initial response achieved through induction chemotherapy, eradicating any remaining leukaemia cells that persist and thus reducing the risk of subsequent relapse.
- Maintenance therapy: Following consolidation therapy, patients receive long-term maintenance therapy with the aim of maintaining remission and preventing leukaemia regrowth, which involves low doses of chemotherapy over an extended period of approximately two years.

Clinical experts have confirmed that this treatment pathway is aligned with the UKALL14 protocol and that it is representative of the typical care received by patients in current UK clinical practice.[24, 49]

Figure 2: UK frontline treatment pathway overview for Ph-negative MRD-negative B-ALL



Source: Cancer Research UK. UKALL14: a randomised trial for adults with frontline acute lymphoblastic leukaemia: trial protocol, 2012.[24]

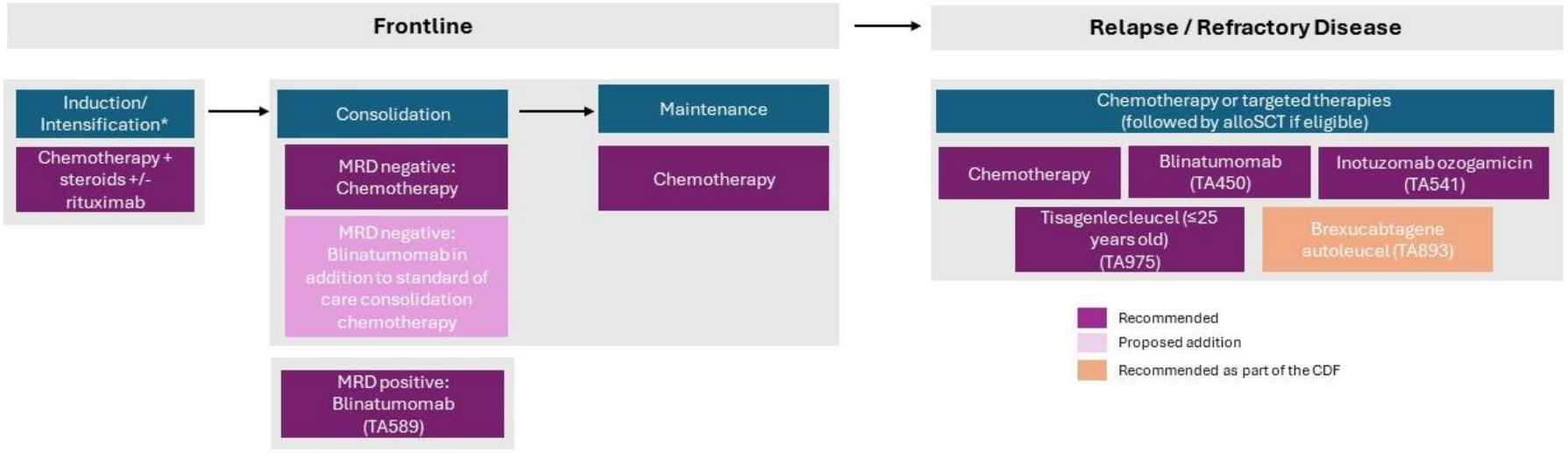
MRD testing and defining a specific treatment pathway

MRD testing is imperative post-induction within the frontline treatment pathway for risk stratification and guiding the later stages of therapy.[29] Following MRD testing after induction, the treatment approach for the consolidation phase is determined, as outlined in Figure 3.[2, 24, 49, 50]

Frontline patients who have MRD-positive disease may receive blinatumomab followed by alloSCT, if eligible.[2] In contrast, frontline patients with MRD-negative disease after induction/intensification continue to receive standard of care multiagent chemotherapy. Due to the significant risk of relapse in patients who are MRD-negative, there remains an unmet need for a targeted treatment in the consolidation phase to deepen remission and to reduce the risk of subsequent relapse.

If patients relapse, they are eligible to receive blinatumomab, inotuzumab or tisagenlecleucel (for patients aged 25 years or younger), or brexucabtagene autoleucel (available via the Cancer Drugs Fund), followed by alloSCT, as clinically appropriate.[51, 52]

Figure 3: Frontline and relapse/refractory pathway for adult patients with Ph- B-Cell ALL



*If eligible (e.g. adverse cytogenetics), patients may proceed to alloSCT after intensification and before consolidation phase
Abbreviations: alloSCT: allogenic stem cell transplant; CDF: cancer drugs fund; MRD: minimal residual disease; Ph: Philadelphia chromosome.
Source: NICE TA589;[2] Cancer Research UK;[24] E1910 CSR. Amgen Data on File;[53] NICE TA975;[52] NICE TA450;[54] NICE TA541;[54] NICE TA893.[50]

Unmet need

B-cell precursor ALL is a serious, life-threatening illness associated with a poor prognosis. Adults with frontline acute B-cell ALL can achieve a high rate of complete remission with conventional chemotherapy but frequently relapse. With current multi-agent standard of care (SOC) chemotherapy regimens, up to 90% of frontline adult patients will achieve an initial hematologic CR; however, up to 50% of patients will experience relapse and need a subsequent therapy.[35-38]

Meta-analyses have shown that a considerable proportion of patients with MRD-negative disease will relapse (36%) or die (40%) within 10 years.[28] Hence there remains an unmet need to improve survival, achieve long term remission and reduce relapse in MRD-negative patients.

Blinatumomab

Blinatumomab is a bispecific T-cell engager antibody that simultaneously binds specifically to CD19 expressed on the surface of cancerous B-cell lymphocytes and to CD3 which is expressed on the surface of the immune system T-cells.[3] This results in activated endogenous T-cells being brought into proximity with cancerous lymphocytes, leading to their destruction via T-cell cytotoxicity directed towards the cancer cells.[3] Therefore, the mechanism of action of blinatumomab takes advantage of existing immune pathways to improve the immune response to cancer. CD19 is selected as the target surface antigen due to its near universal expression on B cells at all stages of maturation and its importance for cell proliferation and survival.

Blinatumomab has received NICE recommendations in the treatment of relapsed or refractory, Ph-negative, precursor B-cell ALL in adults, as well as for the treatment of adults with MRD-positive B-cell precursor ALL.[2] Whilst blinatumomab has been recommended for use in MRD-positive disease, there are no targeted agents specifically indicated for the treatment of Ph-negative, B-cell precursor ALL that is MRD-negative in frontline consolidation phase. A recommendation by NICE for blinatumomab in this population would therefore fulfil a significant unmet need for an effective and well-tolerated treatment option in this MRD-negative patient population that deepens remission and prevents relapse.

B.1.4 *Equality considerations*

It is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was performed on 27th July 2023, and updated on 12th April 2024, to identify all relevant clinical evidence from clinical trials on the efficacy and safety of blinatumomab as part of frontline treatment for newly diagnosed patients with Ph-negative B-cellALL. Searches were restricted by date of publication from 2012 onwards. Congress abstracts published earlier than 2021 were excluded from electronic searches because it is expected that meaningful trial results published as abstracts prior to the last four years have since been published as manuscripts, and thus would have been captured in the electronic database searches.

The SLR identified 4,881 publications. In total, 241 publications were included as primary literature; 235 publications underwent data extraction and 6 SLRs and meta-analyses were identified for reference checking.

Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical systematic literature review (SLR) identified 14 studies investigating the safety and efficacy of blinatumomab as part of frontline treatment for newly diagnosed adult patients with Ph-negative B-cell precursor ALL (see Appendix D). Two of the 14 identified studies were randomised controlled trials (RCTs; E1910 [Litzow et al.][55-57] and Golden Gate (Jabbour et al. 2022).[58] However, the Jabbour et al. 2022 publication only reported results of the single-arm, safety run-in phase of the trial and results for the Phase III RCT part of the study are not yet published. The remaining 12 of these studies were single-armed trials (SATs). Given that the E1910 study was the only RCT identified that considered the population of relevance (minimal residual disease [MRD]-negative adult patients) and has relevant data published, it alone represents the main clinical evidence base for this submission.

The E1910 study was an investigator-sponsored study (also known as an investigator-initiated study), with a Phase III RCT design, that investigated the efficacy and safety of consolidation chemotherapy (henceforth termed standard of care [SOC] consolidation chemotherapy) with or without blinatumomab in treating adult patients with Ph-negative B-cell precursor ALL in the frontline consolidation setting. In September 2022, a planned interim analysis showed that the E1910 study had achieved its primary objective of demonstrating that blinatumomab plus consolidation chemotherapy improves OS compared with SOC consolidation chemotherapy alone in patients who were MRD-negative after frontline induction/intensification. As such, it was recommended that the trial be halted due to statistically superior treatment benefit to OS when adding blinatumomab to SOC consolidation chemotherapy. The primary analysis was subsequently conducted, per the ECOG-ACRIN study group's requirements, with a June 2023 data cut. Patients had a median follow-up of 4.5 years in both treatment arms, resulting in mature long-term efficacy estimates. Further details of the E1910 study are presented in Table 4 and the clinical study report, and efficacy results are presented in Section B.2.6.[49]

All data presented in this submission are from the Full Analysis Set (FAS) from the E1910 study, which included all randomised patients who were assessed as MRD-negative centrally after induction and intensification chemotherapy, as this represents the population indicated in the decision problem. The E1910 study was powered to compare OS between the blinatumomab and SOC chemotherapy arm versus the SOC chemotherapy alone arm among patients who were MRD-negative after induction therapy. This is related to the design change upon the US FDA accelerated approval of blinatumomab in MRD-positive ALL in 2018, where, following the 2018 approval, all patients who were still MRD-positive after induction therapy were no longer randomised, and instead were assigned to the blinatumomab arm. Therefore, data from the MRD-positive and MRD-agnostic population are not presented in this section. However, the combined MRD-positive and MRD-negative data can be found in the E1910 clinical study report (CSR) provided in the reference pack.[53]

Table 4: Clinical effectiveness evidence

Study	E1910
Study design	Phase III, randomised controlled study which investigated the efficacy and safety of chemotherapy with or without blinatumomab in treating Ph-negative B-cell precursor ALL in the frontline consolidation phase.
Population	Adult patients with Ph-negative B-cell precursor ALL that is MRD-negative after frontline induction and intensification chemotherapy.
Intervention(s)	Blinatumomab + SOC consolidation chemotherapy.
Comparator(s)	SOC consolidation chemotherapy alone (i.e. modified UKALLXII/E2993 regimen).
Indicate if study supports application for marketing authorisation	Yes, a license extension for blinatumomab is supported by the E1910 trial, and anticipated [redacted] for the following population: [redacted].
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	For the MRD-negative population, the following endpoints were considered in line with the decision problem:[a] **Primary endpoint**: OS **Secondary endpoints:** • RFS • AEs
All other reported outcomes	For the MRD-negative population: • OS and RFS censored at alloSCT (sensitivity analyses) The prespecified secondary endpoint OS and RFS from alloSCT for the combined MRD-negative and MRD-positive population are provided in Appendix M[a]

Footnotes: [a] Given the population indicated in the decision problem, only data from the MRD-negative population of the E1910 study are presented in this submission. However, results from the combined MRD-positive and MRD-negative population population are available in the E1910 CSR which has been provided as part of the reference pack for this submission.[53]
Abbreviations: AE: adverse event; ALL: acute lymphoblastic leukaemia; alloSCT: allogeneic SCT; MRD: minimal residual disease; N/A: not applicable; OS: overall survival; Ph: Philadelphia chromosome; RFS: relapse-free survival; SCT: stem cell transplant; SOC: standard of care.
Source: E1910 CSR. Amgen Data on File.[53]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

E1910 is a Phase III, randomised controlled study conducted at 77 centres in the United States, Canada, and Israel. The study investigated the efficacy and safety of SOC consolidation chemotherapy with or without blinatumomab in treating adult patients with Ph-negative precursor B-cell ALL in the frontline setting. During an advisory board conducted by Amgen in October 2023 that focused on adult B-cell ALL, UK expert clinicians confirmed that the SOC consolidation chemotherapy regimen used in both treatment arms is very similar to the UKALL14 protocol used in the frontline Ph- MRD negative setting in UK clinical practice .[1, 24]

A summary of the trial design is illustrated in Figure 4 and included the following steps:

- **Step 1 (Induction), Arm A:** Eligible patients initially receive 2 cycles of induction chemotherapy, with the addition of peg-asparaginase for patients <55 years of age, and the addition of rituximab for CD20 positive patients.
- **Step 2 (Intensification), Arm B:** After the induction phase, patients in haematologic CR/CRi with incomplete peripheral blood count recovery continue on-study and receive 1 cycle of intensification chemotherapy of high-dose methotrexate for central nervous system prophylaxis, with the addition of peg-asparaginase for patients <55 years of age. Subsequently, remission status was assessed, and MRD status was determined centrally by six colour flow cytometry with MRD negativity defined as ≤1 x 10^{-4} (0.01%).
- **Step 3 (Consolidation; randomisation time-point):** Both MRD-negative and MRD-positive patients were then randomised to receive either the following:
    - **Arm C, blinatumomab plus SOC chemotherapy:** two cycles of blinatumomab (four weeks per cycle), followed by three cycles of consolidation chemotherapy, another cycle of blinatumomab (third cycle of blinatumomab), followed by an additional cycle of chemotherapy, and then a fourth cycle of blinatumomab
    - **Arm D, SOC chemotherapy alone:** four cycles of consolidation chemotherapy alone.

    Patients in each arm receive the same number of cycles and doses of chemotherapy.

Note:

- *Randomisation was stratified by MRD status, age (<55 years vs ≤55 years), CD20 status (positive vs negative), rituximab use (yes vs no), and intent to receive alloSCT (yes vs no).*
- *In lieu of consolidation and maintenance chemotherapy, as intent to transplant was a stratification factor, patients could proceed to alloSCT at the discretion of the treating*

physician. If alloSCT was to be performed, the protocol suggested it should be done after the first two cycles of blinatumomab in the blinatumomab arm or at any time following intensification chemotherapy in the SOC consolidation chemotherapy arm.

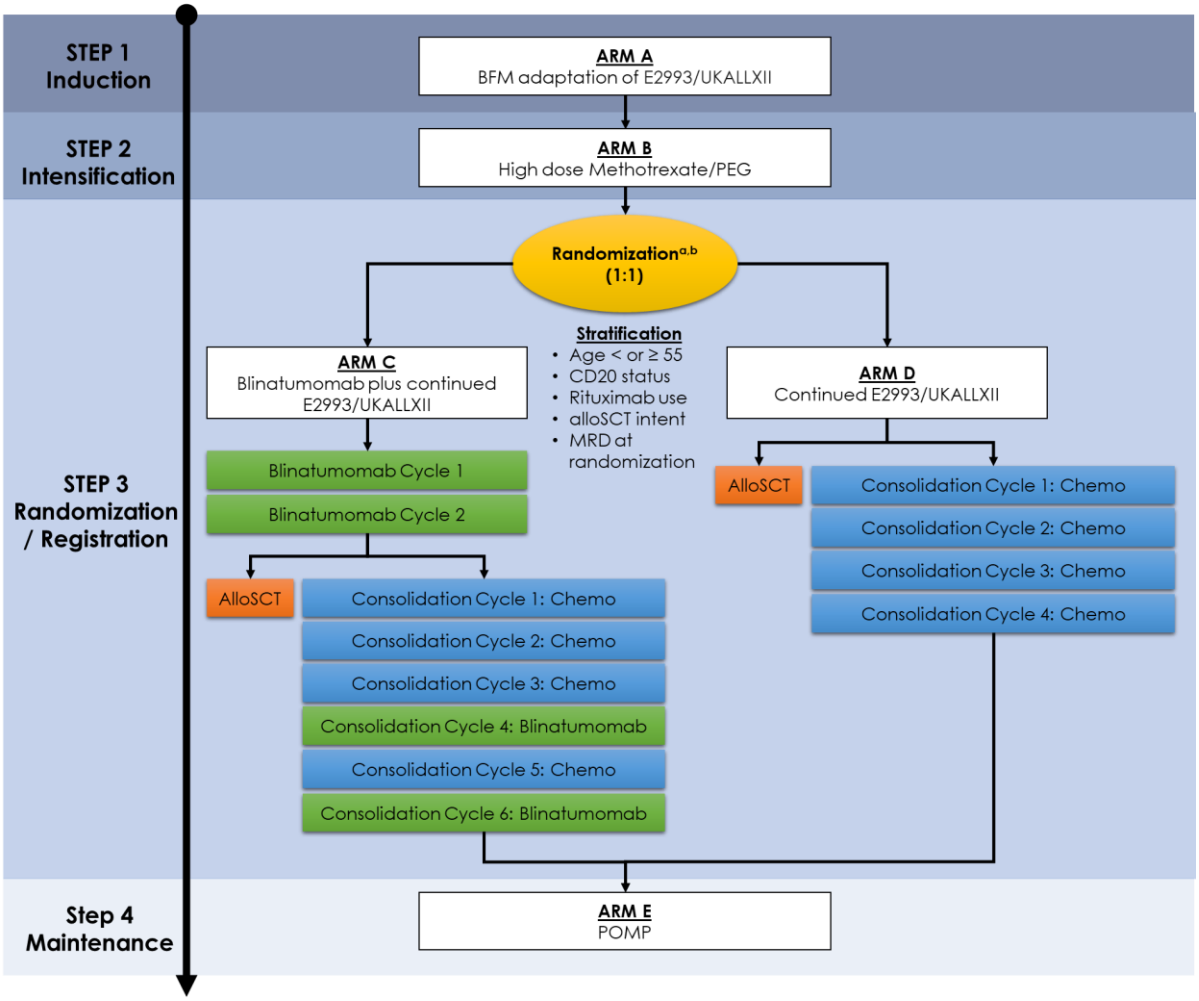
- *Following the Food and Drug Administration (FDA) accelerated approval of blinatumomab for MRD-positive ALL in March 2018, patients who were MRD-positive after intensification therapy (**Step 2**) were no longer randomised and instead were assigned to the blinatumomab arm (**Arm C**) of the study and received blinatumomab plus chemotherapy.*

- **Step 4 (Maintenance), Arm E:** Following completion of consolidation chemotherapy with or without blinatumomab, patients are given 2.5 years of POMP maintenance therapy (6-mercaptopurine,vincristine, methotrexate, and prednisone) timed from the start of the intensification cycle.

Please see Appendix M for the full study schematics.

All data presented in this submission are from the Full Analysis Set (FAS) from the E1910 study, which included all Step 3 randomised patients who were assessed as MRD-negative centrally after induction and intensification chemotherapy, as this represents the population of interest in the decision problem. Therefore, data from the MRD-positive and MRD-agnostic population are not presented. However, these data can be found in the E1910 study CSR provided as part of the reference pack for this submission.

Figure 4: E1910 trial design



Footnotes: [a] Following the FDA accelerated approval of blinatumomab for MRD-positive disease in March 2018, patients who were MRD-positive after intensification were assigned to Arm C and received blinatumomab plus chemotherapy. [b] Intent to transplant was a stratification factor. Patients could proceed to alloSCT at the discretion of the treating physician, which was suggested to be done after the first 2 cycles of blinatumomab in the blinatumomab plus SOC chemotherapy arm or at any time following intensification chemotherapy in the SOC chemotherapy arm.
Abbreviations: alloSCT: allogeneic stem cell transplant; BFM: Berlin-Frankfurt-Münster; CD: cluster of differentiation; Chemo: chemotherapy; FDA: Food and Drug Administration; MRD: minimal residual disease; PEG: peg- asparaginase; POMP: purinethol (6-mercaptopurine), oncovin (vincristine), methotrexate and prednisone.
Source: E1910 CSR. Amgen Data on File.[53]

B.2.3.2 Trial methodology

A summary of the methodology and trial design of the E1910 study is presented in Table 5.

Table 5: Summary of E1910 trial methodology

Trial name	E1910 (NCT02003222).
Location	This study is being conducted at 77 centres in the United States, Canada, and Israel.
Trial design	Phase III, randomised controlled study.
Key eligibility criteria for participants[a]	The key criteria for eligibility for each study step can be found below; • **Step 1 (Induction):** ○ Patients ≥30 years and ≤70 years of age with newly diagnosed Ph-negative B cell precursor ALL were eligible for the induction phase of this study. ○ New diagnosis of B-cell precursor ALL was based upon bone marrow or peripheral blood immunophenotyping. ○ Patients with Philadelphia chromosome-positive/PH1-positive ALL, Burkitt leukaemia/lymphoma, or mature B-cell leukaemia were not eligible. ○ Patients must not have had an antecedent haematologic disorder, history of recent myocardial infarction, or uncontrolled heart failure. ○ Patients with pre-existing significant CNS pathology or uncontrollable seizure disorders were not eligible. ○ Patients with an ECOG performance status 0–3 were eligible for the induction phase of this study. • **Step 2 (Intensification):** ○ Patients with an ECOG performance status of 0–2 were eligible for post-induction therapy. ○ These patients must have had achieved CR or CRi, must have been CNS-negative for leukaemia, and must have had resolved any serious infections or significant medical complications related to induction. • **Step 3 (Randomisation):** ○ Patients eligible for randomisation or assignment to the SOC consolidation chemotherapy plus blinatumomab arm or SOC consolidation chemotherapy arm must have had an ECOG performance status of 0–2. ○ Patients must have maintained peripheral blood evidence of a remission, must have a CR or CRi, and must have resolved any serious infections or medical complications related to therapy. A full list of eligibility criteria is provided in Appendix M.

Method of study drug administration	Blinatumomab 28 mcg daily by continuous infusion (28-day cycle) interspersed with SOC consolidation chemotherapy[b], for a total of 8 cycles: • 2 cycles blinatumomab • 3 cycles SOC consolidation chemotherapy • 1 cycle blinatumomab • 1 cycle SOC consolidation chemotherapy • 1 cycle blinatumomab

Permitted and disallowed concomitant medication	**Within one hour prior to start of treatment in each treatment cycle:**
	For the prevention of acute reactions to blinatumomab, mandatory administration of dexamethasone (20 mg IV) was required.
	During treatment period:
	• NSAIDs should be avoided if possible because they are a potential cause of endothelial stress.
	• Recommended first choice medications for fever management are paracetamol/acetaminophen and/or dexamethasone.
	  ○ The dexamethasone dose should be reduced step-wise as soon as the fever resolves.
	• If these medications are not sufficiently effective, pethidine/meperidine was recommended.
	  ○ For pethidine/meperidine, adequate anti-emetic prophylaxis should be administered.
	Fluid intake/output monitoring:
	• Close monitoring of fluid status by intake and output should be undertaken for the first week of blinatumomab infusion.
	• Efforts to keep patients balanced between intake and output should be maintained, even if diuretic therapy (furosemide or similar) was needed to do this.
	• Careful attention to fluid status may prevent deterioration from capillary leak, however even with meticulous attention, some patients will experience pulmonary oedema and require more aggressive respiratory support.
	  ○ Treating physicians should use their clinical judgment and institutional standards for whatever supportive care measures are needed during this period of time.
	Monitoring of disseminated intravascular coagulation
	• In the first days of treatment, transient disseminated intravascular coagulation-like presentations may develop.
	• Because patients are at risk for capillary leak syndrome and cytokine release syndrome, appropriate supportive care with dexamethasone, blood products and factors (packed red cells, platelets, cryoprecipitate, fresh frozen plasma), vitamin K, and/or albumin should be considered according to institutional standards of care.

	Haematological Monitoring: • In the first days of treatment, a rapid transient drop in platelets, neutrophils and/or haemoglobin may be observed. These effects are not necessarily cytokine-mediated and counts typically recover to baseline during treatment, and usually within two weeks of starting blinatumomab. • However, transfusion of blood and platelets should be performed according to appropriate institutional standards.
Primary outcome	OS of blinatumomab in conjunction with SOC consolidation chemotherapy versus SOC consolidation chemotherapy alone in patients with Ph-negative B cell precursor ALL who are MRD-negative after induction and intensification chemotherapy. OS was measured as time from randomisation until death due to any cause. Patients alive were censored at the date last known to be alive.
Secondary outcomes	• RFS of blinatumomab in conjunction with SOC consolidation chemotherapy versus SOC consolidation chemotherapy alone in MRD-negative patients after induction and intensification chemotherapy. ○ RFS was measured as the time from randomisation until relapse or death due to any cause. Patients who are alive and relapse-free were censored at their last contact date. • OS and RFS in patients who are MRD-positive at Step 3 randomisation/registration and then convert to MRD-negative after two cycles of blinatumomab to those patients who are MRD-negative at randomisation and remain MRD-negative after two cycles of blinatumomab or consolidation chemotherapy.[c] • Toxicities of blinatumomab. • Toxicities of the modified E2993 trial chemotherapy regimen.[37] • OS and RFS of MRD-agnostic population (i.e. MRD-positive and MRD-negative) who proceed to alloSCT after treatment with or without blinatumomab. • Laboratory: Incidence of anti-blinatumomab antibody formation.
Pre-planned subgroups	**Planned subgroups:** • Gender (Female vs. Male) • Race • Ethnicity • Age (≥18 and <35 years, ≥35 and <55 years, ≥55 and <65 years, ≥65 years)
Duration of study and follow-up	All patients, including those who discontinue protocol therapy early, will be followed for 10 years from the start of treatment, even if non protocol therapy is initiated, and for survival.

Footnotes: [a] CD19-positivity was not mandated for eligibility given its high incidence at B-cell ALL diagnosis; [b] Cytarabine (75 mg/m^2 Iv or SC d 1-5), Etoposide (100 mg/m^2 IV d1-5), Methotrexate (12.5 mg IT d1 +/- 1), Peg-asparaginase (2000 IU/m^2 IV or IM, d5, 1000 IU/m2 if age ≥ 55 years (cap dose at 1 via or 3750 IU), Rituximab (375 mg/m^2 IV d5 if CD20 positive [optional]). [c] As the target population of the NICE submission are patients who are MRD-negative, results for MRD-positive patients are not discussed further.
Abbreviations: ALL: acute lymphoblastic leukaemia; BMT: bone marrow transplantation; CNS: central nervous system; CR: complete remission; CRi: Complete Remission with incomplete blood count recovery; ECOG: Eastern Cooperative Oncology Group; IV: intravenous; MFC: Multiparameter Flow Cytometry; MRD: minimal residual disease; NICE: National Institute of Health and Care Excellence; NSAIDS: Nonsteroidal anti-inflammatory drugs; Ph: Philadelphia chromosome; SCT: stem cell transplant; SOC: standard of care.
Source: E1910 CSR. Amgen Data on File.[53]

B.2.3.3 Baseline characteristics

Demographic characteristics

The baseline demographic characteristics for MRD-negative patients at Step 3 (i.e. FAS) are provided in Table 6.

For the SOC consolidation chemotherapy plus blinatumomab arm (N=112) and SOC consolidation chemotherapy arm (N=112),[59] 49.1% and 50.0% of patients, respectively, were male; median (Q1, Q3) age at enrolment was 51.5 (41.0, 59.0) years and 50.0 (40.0, 60.5) years, respectively. Patients enrolled in the study were ≥30 and ≤70 years old. However, clinical expert opinion elicited by Amgen indicated that blinatumomab should be made available in the frontline setting to all patients 18 years old and above, as some younger or older patients are likely to benefit.[1]

Of the patients who had data on race, 87 (77.7%) and 89 (79.5%) in the SOC consolidation chemotherapy plus blinatumomab arm and SOC consolidation chemotherapy arm, respectively, were white. Also, of the patients who provided ethnicity, 95 (84.8%) and 95 (84.8), respectively, were not Hispanic or Latino. The primary country of residence for both arms was the United States.

Overall, baseline demographics characteristics were generally well balanced between the two treatment arms, particularly for age which is an important prognostic factor.[39] Further, they are generalisable to UK clinical practice, as confirmed by clinical experts during an advisory board conducted by Amgen in October 2023.[1]

Table 6: Key demographic characteristics for MRD-negative patients at Step 3

Characteristics	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Sex, n (%)		
Male	55 (49.1)	56 (50.0)
Female	57 (50.9)	56 (50.0)
Race, n (%)		
American Indian or Alaska Native	2 (1.8)	1 (0.9)
Asian	3 (2.7)	2 (1.8)
Black or African American	9 (8.0)	4 (3.6)
Native Hawaiian or Other Pacific Islander	1 (0.9)	0 (0.0)
White	87 (77.7)	89 (79.5)
Not Reported	5 (4.5)	6 (5.4)
Unknown	5 (4.5)	10 (8.9)
Age at enrolment, years		

Mean	50.1	50.0
SD	11.0	11.9
Median	51.5	50.0
Q1, Q3	41.0, 59.0	40.0, 60.5
Min, Max	30, 69	30, 70
Age group, n (%)		
<55 years	66 (58.9)	65 (58.0)
≥55 years	46 (41.1)	47 (42.0)
Unknown	0 (0.0)	0 (0.0)
Age group, n (%)		
≥18 and <35 years	13 (11.6)	17 (15.2)
≥35 and <55 years	53 (47.3)	48 (42.9)
≥55 and < 65 years	37 (33.0)	31 (27.7)
≥65 years	9 (8.0)	16 (14.3)
Country of residence, n (%)		
Canada	7 (6.3)	7 (6.3)
Israel	2 (1.8)	6 (5.4)
United States	103 (92.0)	99 (88.4)

Abbreviations: FAS: Full Analysis Set; MRD: minimal residual disease; SD: standard deviation; SOC: standard of care.
Source: Table 14-2.1 E1910 CSR. Amgen Data on File.[53]

Disease characteristics

The baseline disease characteristics for MRD-negative patients at Step 3 are provided in Table 7.

For both arms, all patients had an ECOG performance status of 0–2 at baseline. In the SOC consolidation chemotherapy plus blinatumomab (N=112) and SOC consolidation chemotherapy (N=112) arms, respectively,[59] 40.2% and 41.4% of patients had a CD20 positive status at enrolment and 29.5% and 32.1% had previously used rituximab. Regarding prior treatments in the SOC consolidation chemotherapy plus blinatumomab and SOC consolidation chemotherapy arms, respectively, a small number of patients had prior surgery (3.6% and 5.4%) and/or prior radiation therapy (1.8% and 3.6%), and approximately a third of patients were intended to receive alloSCT (32.1% and 31.3%, respectively).

Overall, disease demographics were generally well balanced between the two treatment arms. Furthermore, they are generalisable to UK clinical practice, as confirmed by clinical experts during an advisory board conducted by Amgen in October 2023.[1]

Table 7: Key disease characteristics for MRD-negative patients at Step 3

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
ECOG performance status, n (%)		
0	39 (34.8)	40 (35.7)
1	67 (59.8)	69 (61.6)
2	6 (5.4)	3 (2.7)
CD20 status at enrolment, n (%)		
Positive	45 (40.2)	46 (41.4)
Negative	26 (23.2)	26 (23.2)
Not collected	41 (36.6)	40 (35.7)
Rituximab use, n (%)		
Yes	33 (29.5)	36 (32.1)
No	38 (33.9)	36 (32.1)
Not collected	41 (36.6)	40 (35.7)
Prior surgery,[a] n (%)		
Yes	4 (3.6)	6 (5.4)
No	108 (96.4)	106 (94.6)
Prior radiation therapy, n (%)		
Yes	2 (1.8)	4 (3.6)
No	110 (98.2)	108 (96.4)
Intent to receive alloSCT, n (%)		
Yes	36 (32.1)	35 (31.3)
No	76 (67.9)	77 (68.8)

Footnotes: [a] Prior surgery refers to prior cancer treatment with therapeutic intent.
Abbreviations: alloSCT: allogeneic stem cell transplant; CD: cluster of differentiation; ECOG: Eastern Cooperative Oncology Group; FAS: Full Analysis Set; MRD: minimal residual disease; SD: standard deviation; SOC: standard of care.
Source: Table 14-2.5, 14.2.6, and 14-2.7, E1910 CSR. Amgen Data on File.[53]

B.2.3.4 Patient disposition

The patient disposition in the MRD-negative population is provided in Figure 5. Among the 286 randomised patients in the E1910 trial, 224 patients (78.3%) were MRD-negative: 112 patients (73.7%) in the SOC consolidation chemotherapy plus blinatumomab arm and 112 patients (83.6%) in the SOC consolidation chemotherapy arm. Among the 224 randomised MRD-negative patients, 38 patients (33.9%) in the SOC consolidation chemotherapy plus blinatumomab arm and 48 patients (42.9%) in the SOC consolidation chemotherapy arm discontinued treatment and 22 patients (19.6%) in both arms received alloSCT.[60]

Data from the MRD-negative population of the E1910 study are presented in the following sections, as this represents the population indicated in the decision problem. Results from the combined MRD-positive and MRD-negative population are not relevant to the decision problem,

and therefore not considered within this submission. The patient disposition in the overall population of the E1910 trial (MRD-negative and MRD-positive) is provided in Appendix D.

Figure 5: Patient disposition in the MRD-negative population at Step 3

Abbreviations: AlloSCT: allogeneic stem cell transplant; DCO: data cutoff; MRD: minimal residual disease; SOC: standard of care.
Source: E1910 CSR. Amgen Data on File.[53]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

A summary of the analysis populations for efficacy and safety outcomes for the E1910 clinical trial relevant to this submission is presented in Table 8.

Table 8: Summary of analysis populations

Analysis set	Definition
Full analysis set	Full analysis set includes all Step 3 randomised patients who are assessed as MRD-negative centrally after induction and intensification chemotherapy.
Safety analysis set	Includes all patients in the full analysis set who received at least one dose of protocol-specified therapies.

Abbreviations: MRD: minimal residual disease.
Source: Table 8-10. E1910 CSR. Amgen Data on File.[53]

Summary of statistical analyses for the primary efficacy analysis in E1910

The primary objective of the study was to compare OS in MRD-negative patients who received blinatumomab in conjunction with SOC consolidation chemotherapy to that of MRD-negative patients who received SOC consolidation chemotherapy alone. The study was powered to compare OS between the blinatumomab and SOC chemotherapy arm versus the SOC chemotherapy-alone arm among patients who were MRD-negative after induction therapy. This is related to the design change upon the US FDA accelerated approval of blinatumomab in MRD+ ALL in 2018, where, following the 2018 approval, all patients who were still MRD+ after induction therapy were assigned to the blinatumomab arm (Arm C) and were no longer randomised.

As a secondary objective, the relapse-free survival (RFS) in MRD-negative patients who received blinatumomab in conjunction with SOC consolidation chemotherapy was compared to that of MRD-negative patients who received SOC consolidation chemotherapy alone.

A total of 488 Ph-negative B cell precursor ALL patients aged 30-70 years were planned to enter this study. Based on E2993 trial, it was assumed that the survival function of this ALL patient population can be described by a cure rate model.[37] For MRD-negative patients, a 35% long-term cure rate and 13-month median OS in the non-cured group in the control arm was assumed. Adjusted for sequential monitoring, with 190 randomised MRD-negative patients, the study had 80% power to detect 45% reduction in hazard rate in the blinatumomab arm relative to the no blinatumomab arm, using one-sided log rank test at the significance level of 0.025 and assuming two years of follow-up. This is equivalent to detecting an improvement in the three-year OS rate from 45% to 64%. In total, 94 OS events were required.

The primary analyses were completed once the full information for MRD-negative patients (94 events) was reached. Estimates of OS, including medians and confidence intervals, were calculated using the Kaplan-Meier method. Comparison of OS between treatment arms was conducted using the one-sided stratified log-rank test with, age, CD20 status, rituximab use, and whether patients intended to receive allogeneic stem cell transplant (alloSCT) or not as

stratification factors at overall one-sided type I error of 0.025. The primary comparisons of OS was based on the intent-to-treat principle, including all patients that were randomised. The critical values at the primary analyses for each comparison conducted were determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O'Brien-Fleming boundary, taking into account the errors spent at the interim efficacy analyses for that comparison. Cox proportional hazards models, stratified on age, CD20 status, rituximab use, and whether patients intend to receive alloSCT or not, were used to assess the treatment effect by adjusting other possible clinical and biological risk factors, including cytogenetic abnormalities.

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

A summary of the quality assessment for the E1910 study is presented in Table 9.

Table 9: Quality assessment results for the E1910 trial

Study question	Risk of bias	E1910
Was randomisation carried out appropriately?	Low	Randomisation was assigned using a permuted blocks within strata algorithm and stratified by MRD status, age, CD20 status, rituximab use and whether patients intend to receive SCTs.
Was the concealment of treatment allocation adequate?	High	E1910 was an open-label study and therefore treatment allocations were not concealed.
Were the groups similar at the outset of the study in terms of prognostic factors?	Low	Baseline characteristics were well-balanced between treatment groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	High	E1910 was an open-label study and therefore treatment allocations were not concealed.
Were there any unexpected imbalances in drop-outs between groups?	Low	There were no unexpected imbalances in the randomised MRD negative population. 224 patients were randomised (112 into the blinatumomab and SOC chemotherapy arm and 112 into the SOC chemotherapy arm).[56] One patient did not receive any Step 3 treatment in the blinatumomab and SOC chemotherapy arm. In the SOC chemotherapy alone arm there were no patients that did not receive any Step 3 treatment.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low	All pre-specified outcomes were measured and reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and	Low	The primary

were appropriate methods used to account for missing data?		comparisons of OS were based on the intention-to-treat (ITT) principle, including all patients as randomised. All outcomes reported in the methods were described in the results.

Abbreviations: MRD: minimal residual disease; SOC: standard of care; SCT: stem cell transplant.
Source: E1910 CSR. Amgen Data on File;[53] York CRD (2009).[61]

B.2.6 *Clinical effectiveness results of the relevant studies*

Summary of clinical effectiveness results

- The results presented in this submission are from the 23rd June 2023, primary analysis data cut off of the E1910 study.
- Overall, baseline demographic and disease characteristics were generally well balanced between the two treatment arms, and the majority of patients in the E1910 trial were MRD-negative in the SOC consolidation chemotherapy plus blinatumomab arm and in the SOC consolidation chemotherapy arm (112/152 patients [73.7%] and 112/134 patients [83.6%], respectively).[59]
- The study achieved its primary endpoint, with OS in MRD-negative patients being significantly improved in the SOC consolidation chemotherapy plus blinatumomab arm compared with the SOC consolidation chemotherapy arm (log-rank test treatment difference [TD]: p=0.001).
    - At a median follow-up time of 4.5 years, the OS hazard ratio (HR) from a stratified Cox proportional hazard model was 0.44 (95% CI: 0.25, 0.76), indicating a 56% reduction in the hazard rate for OS (death due to any cause) in the blinatumomab plus SOC consolidation chemotherapy arm compared with the SOC consolidation chemotherapy arm.
    - The 5-year Kaplan-Meier OS rate was 82.4% (95% confidence interval [CI]: 73.7, 88.4) in the SOC consolidation chemotherapy plus blinatumomab arm and 62.5% (95% CI: 52.0, 71.3) in the SOC consolidation chemotherapy arm.
    - The median OS was not reached in either treatment arm.
- Similar statistically significant improvements in RFS (a secondary endpoint) were observed (log-rank test TD: p=0.006; treatment difference [TD]) in MRD-negative patients.
    - The 5-year Kaplan-Meier RFS rate was 77.0% (95% CI: 67.8, 83.8) in the SOC consolidation chemotherapy plus blinatumomab arm and 60.5% (95% CI: 50.1, 69.4) in the SOC consolidation chemotherapy arm.
        - The RFS HR from a stratified Cox proportional hazard model was 0.53 (95% CI: 0.32, 0.88), indicating a 47% reduction in the hazard rate for the RFS in the SOC consolidation chemotherapy plus blinatumomab arm compared with the SOC consolidation chemotherapy arm.
        - The median RFS was not reached in either treatment arm.
- Additionally, the effect size seen for OS (HR: 0.46; 95% CI: 0.24, 0.90), and RFS (HR: 0.60; 95% CI: 0.34, 1.04) in patients who were censored upon receiving alloSCT were similar to that seen in the primary analysis. This suggests that the survival benefit of blinatumomab as part of consolidation chemotherapy was consistent regardless of whether

patients received alloSCT or not. Therefore, one can deduce that alloSCT was not the main driver of efficacy in the blinatumomab and SOC chemotherapy arm.
- No new RFS events were observed from 4 years onwards in the blinatumomab with SOC chemotherapy arm, and therefore this could represent a potential curative therapy in some patients.
- In summary, the results presented in the clinical evidence base demonstrate that blinatumomab added to frontline consolidation SOC consolidation chemotherapy represents a potential paradigm shift in how patients with frontline Ph-negative precursor CD19 positive B-cell ALL that is MRD-negative could be treated in routine clinical practice

All results presented for the E1910 study in the following sections are from the 23 June 2023 data cut off. Only data from the MRD-negative population of the E1910 study are presented in the following sections, given the MRD-negative population indicated in the current decision problem, and that blinatumomab for the MRD-positive patients with B-precursor ALL is already recommended by NICE (TA589).[2] However, MRD-positive data are available within the E1910 Clinical Study Report, which has been provided as part of the reference pack for this submission.[53]

B.2.6.1 Primary endpoint: OS from Step 3 in the MRD-negative population (FAS)

The results of OS from Step 3 in the MRD-negative population (FAS) are presented in Table 10 and the corresponding KM plot comparing the two treatment arms is provided in Figure 6.

As of the primary analysis data cutoff date (23 June 2023), the median follow-up time for OS was 4.5 years in both treatment arms. Statistically significant improvements (log-rank test TD: p=0.001) in OS were observed. The 5-year Kaplan-Meier OS rate was 82.4% (95% CI: 73.7, 88.4) in the SOC consolidation chemotherapy plus blinatumomab arm and 62.5% (95% CI: 52.0, 71.3) in the SOC consolidation chemotherapy arm. The OS HR from a stratified Cox proportional hazard model was 0.44 (95% CI: 0.25, 0.76), indicating a 56% reduction in the hazard rate for OS in the SOC consolidation chemotherapy plus blinatumomab arm compared with the SOC consolidation chemotherapy alone arm. The median OS was not reached in either treatment arm.

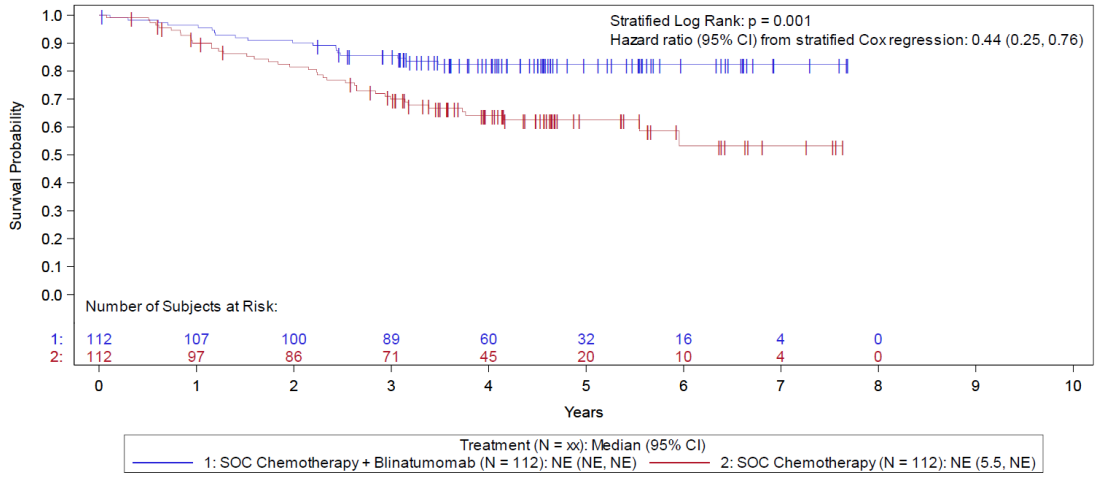
Table 10: OS from Step 3 for MRD-negative patients (FAS)

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Number of events (deaths), n (%)	19 (17.0)	40 (35.7)
Censored, n (%)	93 (83.0)	72 (64.3)
Completed study without event	0 (0.0)	0 (0.0)
Continued on study	88 (78.6)	64 (57.1)
Discontinued study	5 (4.5)	8 (7.1)

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Consent withdrawn	4 (3.6)	6 (5.4)
Lost to follow-up	1 (0.9)	2 (1.8)
Treatment difference (stratified log-rank test)[a,b]		
Normal score	3.02	
p-value	0.001	
Time to event (KM) (yrs)[c]		
Median (95% CI)	NE (NE, NE)	NE (5.5, NE)
KM estimate, % (95% CI)		
0.5 yrs	98.2 (93.0, 99.5)	99.1 (93.8, 99.9)
1 yr	96.4 (90.7, 98.6)	90.0 (82.6, 94.3)
2 yrs	90.1 (82.8, 94.4)	81.5 (72.8, 87.6)
3 yrs	85.5 (77.5, 90.9)	70.0 (60.3, 77.7)
4 yrs	82.4 (73.7, 88.4)	64.1 (53.9, 72.7)
5 yrs	82.4 (73.7, 88.4)	62.5 (52.0, 71.3)
6 yrs	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)
7 yrs	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)
Stratified HR[a,d] (95% CI)	0.44 (0.25, 0.76)	
Time to censoring (KM)for OS (yrs)[c, e]		
Median (95% CI)	4.5 (4.1, 4.6)	4.5 (4.0, 4.6)

Footnotes: [a] Stratification factors: age (<55 years vs. ≥55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive alloSCT (yes vs. no). [b] 1-sided stratified log-rank test p-value is provided. [c] Years are calculated as days from randomisation date to event/censor date, divided by 365.25. [d] Time to censoring measures follow-up time by reversing the status indicator for censored and events. [e] The HR estimates are obtained from a stratified Cox regression model. A HR <1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab + SOC consolidation chemotherapy arm relative to patients in the SOC consolidation chemotherapy arm.
Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio: MRD: minimal residual disease; OS: overall survival; SOC: standard of care.
Source: Table 14-4.1.1. E1910 CSR. Amgen Data on File.[53]

Figure 6: KM for OS from Step 3 for MRD-negative patients (FAS)



Footnotes: Censor indicated by vertical bar.
Abbreviations: CI: confidence interval; FAS: full analysis set; KM: Kaplan Meier; MRD: minimal residual disease; NE: non evaluable; OS: overall survival; SOC: standard of care.
Source: Figure 10-1. E1910 CSR. Amgen Data on File.[53]

B.2.6.2 Secondary endpoint: RFS from Step 3 in the MRD-negative population (FAS)

The results of RFS from Step 3 in the MRD-negative population (FAS) are presented in Table 11 and the corresponding KM plot comparing the two treatment arms is provided in Figure 7.

As of the primary analysis data cutoff date (23 June 2023), the median follow-up time for RFS was 4.5 years for both the SOC consolidation chemotherapy plus blinatumomab arm and the SOC consolidation chemotherapy arm. Statistically significant improvements (log-rank test TD: p=0.006) in RFS were observed in the SOC consolidation chemotherapy plus blinatumomab arm; the 5-year Kaplan-Meier RFS rate was 77.0% (95% CI: 67.8, 83.8) in the SOC consolidation chemotherapy plus blinatumomab arm and 60.5% (95% CI: 50.1, 69.4) in the SOC consolidation chemotherapy arm. The RFS HR from a stratified Cox proportional hazard model was 0.53 (95% CI: 0.32, 0.88), indicating a 47% reduction in the hazard rate for the RFS in the SOC consolidation chemotherapy plus blinatumomab arm. The median RFS was not reached in either treatment arm.

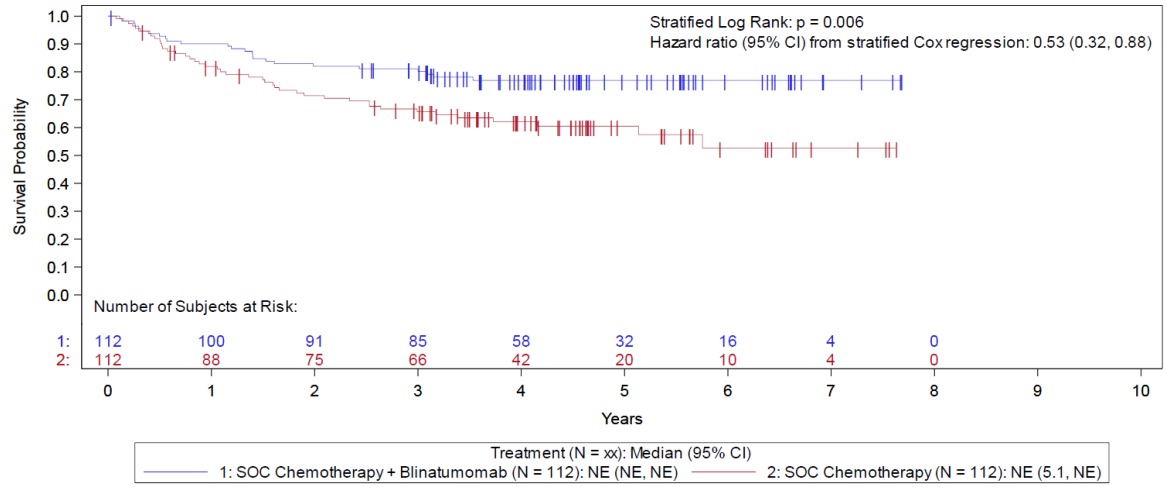
Table 11: RFS from Step 3 for MRD-negative patients (FAS)

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Number of events, n (%)	25 (22.3)	43 (38.4)
Relapse	15 (13.4)	32 (28.6)
Death due to any cause	10 (8.9)	11 (9.8)
Censored, n (%)	87 (77.7)	69 (61.6)
Completed study without event	0 (0.0)	0 (0.0)

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Continued on study	84 (75.0)	61 (54.5)
Discontinued study	3 (2.7)	8 (7.1)
Consent withdrawn	3 (2.7)	6 (5.4)
Lost to follow-up	0 (0.0)	2 (1.8)
Treatment difference (stratified log-rank test)[a,b]		
Normal score	2.51	
p-value	0.006	
Time to event (KM) (yrs)[c]		
Median (95% CI)	NE (NE, NE)	NE (5.1, NE)
KM estimate (yrs), % (95% CI)		
0.5	92.8 (86.1, 96.3)	91.9 (85.1, 95.7)
1	90.1 (82.8, 94.4)	81.9 (73.4, 87.9)
2	82.0 (73.5, 88.0)	71.5 (61.9, 79.0)
3	81.1 (72.5, 87.2)	65.7 (55.9, 73.8)
4	77.0 (67.8, 83.8)	62.1 (52.0, 70.7)
5	77.0 (67.8, 83.8)	60.5 (50.1, 69.4)
6	77.0 (67.8, 83.8)	52.7 (38.5, 65.0)
7	77.0 (67.8, 83.8)	52.7 (38.5, 65.0)
Stratified hazard HR[a,d] (95% CI)	0.53 (0.32, 0.88)	
Time to censoring (KM) for RFS (yrs)[a,e]		
Median (95% CI)	4.5 (4.1, 4.7)	4.5 (4.0, 4.6)

Footnotes: [a] Stratification factors: age (<55 years vs. ≥55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive alloSCT (yes vs. no). [b] 1-sided stratified log-rank test p-value is provided. [c] Years are calculated as days from randomisation date to event/censor date, divided by 365.25. [d] Time to censoring measures follow-up time by reversing the status indicator for censored and events. [e] The HR estimates are obtained from a stratified Cox regression model. A HR <1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab + SOC consolidation chemotherapy arm relative to patients in the SOC consolidation chemotherapy arm.
Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; MRD: minimal residual disease; RFS: relapse-free survival; SOC: standard of care.
Source: Table 14-4.2.1 E1910 CSR. Amgen Data on File.[53]

Figure 7: KM for RFS from Step 3 for MRD-negative patients (FAS)



Footnotes: Censor indicated by vertical bar.
Abbreviations: CI: confidence interval; FAS: full analysis set; KM: Kaplan Meier; MRD: minimal residual disease; NE: non evaluable; RFS: relapse-free survival; SOC: standard of care.
Source: Figure 10-2. E1910 CSR. Amgen Data on File.[53]

B.2.6.3 Sensitivity Analysis: OS from Step 3 censored at alloSCT in the MRD-negative population (FAS)

To investigate the effect of alloSCT on OS, a sensitivity analysis was conducted in which patients who received alloSCT were censored at the time of alloSCT. The results of a sensitivity analysis of OS from Step 3 censored at alloSCT in the MRD-negative population (FAS) are presented in Table 12 and the corresponding KM plot comparing the two treatment arms is provided in Figure 8.

The sensitivity analysis of OS censored at alloSCT also favoured the blinatumomab plus SOC arm, with a [redacted] reduction in the risk of death vs the SOC consolidation chemotherapy arm (HR: [redacted]; 95% CI: [redacted]), consistent with the effect size seen in the primary OS analysis results (Section B.2.6.1). Median OS was [redacted] in either treatment arm. The KM estimate of OS at 5 years was [redacted] (95% CI: [redacted]) in the blinatumomab plus SOC consolidation chemotherapy arm and [redacted] (95% CI: [redacted]) in the SOC consolidation chemotherapy arm.

With the above considered, the robustness of blinatumomab plus SOC consolidation chemotherapy in improving OS is further strengthened by the OS censored at alloSCT (FAS) data. The survival benefit of blinatumomab plus SOC consolidation chemotherapy was consistent with the primary OS analysis, regardless of whether patients received alloSCT.

Table 12: OS from Step 3 censored at alloSCT for MRD-negative patients (FAS)

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Number of events (death due to any cause), n (%)	[redacted]	[redacted]

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Censored, n (%)	[redacted]	[redacted]
Completed study without event	[redacted]	[redacted]
Continued on study	[redacted]	[redacted]
Received alloSCT	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Time to event (KM) (yrs)[a]		
Median (95% CI)	[redacted]	[redacted]
Treatment difference (stratified log-rank test)[b]		
Normal score	[redacted]	
p-value	[redacted]	
KM estimate, % (95% CI)		
0.5 yrs	[redacted]	[redacted]
1 yrs	[redacted]	[redacted]
2 yrs	[redacted]	[redacted]
3 yrs	[redacted]	[redacted]
4 yrs	[redacted]	[redacted]
5 yrs	[redacted]	[redacted]
6 yrs	[redacted]	[redacted]
7 yrs	[redacted]	[redacted]
Stratified HR[c,d] (95% CI)	[redacted]	
Time to censoring (KM) for OS (yrs)[a,d]		
Median (95% CI)	[redacted]	[redacted]

Footnotes: [a] Years are calculated as days from randomisation date to event/censor date, divided by 365.25. [b] 1-sided stratified log-rank test p-value is provided. The HR estimates are obtained from a stratified Cox regression model. An HR < 1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab plus SOC consolidation chemotherapy arm relative to patients in the SOC consolidation chemotherapy arm. [c] Stratification factors: age (< 55 years vs. ≥ 55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive alloSCT (yes vs. no). [d] Time to censoring, measured by reversing the status indicator for censored and events.
Abbreviations: alloSCT: allogeneic stem cell transplant; CI: confidence interval; DCO: data cutoff; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; MRD: minimal residual disease; NE: not estimable; OS: overall survival; SOC: standard of care; yrs: years.
Source: Table 14-4.1.5. E1910 CSR. Amgen Data on File.[53]

Figure 8: KM for OS from Step 3 censored at alloSCT for MRD-negative patients (FAS)

Footnotes: Censor indicated by vertical bar.
Abbreviations: alloSCT, allogeneic stem cell transplant; CI, confidence interval; DCO, data cutoff; FAS: full analysis set; KM, Kaplan-Meier; MRD, minimal residual disease; NE, not estimable; OS, overall survival; SOC, standard of care.
Source: Figure 14-4.1.3. E1910 CSR. Amgen Data on File.[53]

B.2.6.4 Sensitivity Analysis: RFS from Step 3 censored at alloSCT in the MRD-negative population (FAS)

To investigate the effect of alloSCT on RFS, a sensitivity analysis was conducted in which patients who received alloSCT were censored at the time of alloSCT. The results of a sensitivity analysis of RFS from Step 3 censored at alloSCT in the MRD-negative population (FAS) are presented in Table 13 and the corresponding KM plot comparing the two treatment arms is provided in Figure 9.

The sensitivity analysis of RFS censored at alloSCT numerically favoured the blinatumomab plus SOC arm, with a [redacted] reduction in the risk of relapse or death vs the SOC consolidation chemotherapy arm (HR: [redacted]; 95% CI: [redacted]). Median RFS was [redacted] in the blinatumomab plus SOC consolidation chemotherapy arm and was [redacted] (95% CI: [redacted]) in the SOC consolidation chemotherapy arm. The KM estimate of RFS at 5 years was [redacted] (95% CI: [redacted]) in the blinatumomab plus SOC consolidation chemotherapy arm and [redacted] (95% CI: [redacted]) in the SOC consolidation chemotherapy arm. No new RFS events were observed from 4 years onwards in the blinatumomab with SOC consolidation chemotherapy arm.

With the above considered, the robustness of blinatumomab plus SOC consolidation chemotherapy in improving RFS in the primary analysis is further strengthened by the RFS censored at alloSCT (FAS) data.

Table 13: RFS from Step 3 censored at alloSCT for MRD-negative patients (FAS)

	Blinatumomab + SOC consolidation chemotherapy (N=112)	SOC consolidation chemotherapy (N=112)
Number of events, n (%)	[redacted]	[redacted]
Relapse	[redacted]	[redacted]
Death due to any cause	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Relapsed before start of RFS assessment	[redacted]	[redacted]
Completed study without event	[redacted]	[redacted]
Continued on study	[redacted]	[redacted]
Received alloSCT	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Time to event (KM) (yrs)[a]		
Median (95% CI)	[redacted]	[redacted]
Treatment difference (stratified log-rank test)[b]		
Normal score	[redacted]	
p-value	[redacted]	
KM estimate, % (95% CI)		
0.5 yrs	[redacted]	[redacted]
1 yrs	[redacted]	[redacted]
2 yrs	[redacted]	[redacted]
3 yrs	[redacted]	[redacted]
4 yrs	[redacted]	[redacted]
5 yrs	[redacted]	[redacted]
6 yrs	[redacted]	[redacted]
7 yrs	[redacted]	[redacted]
Stratified HR[c,d] (95% CI)	[redacted]	
Time to censoring (KM) for RFS (yrs)[a,d]		
Median (95% CI)	[redacted]	[redacted]

Footnotes: [a] Years are calculated as days from randomisation date to event/censor date, divided by 365.25. [b] 1-sided stratified log-rank test p-value is provided. The HR estimates are obtained from a stratified Cox regression model. An HR < 1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab plus SOC consolidation chemotherapy arm relative to patients in the SOC consolidation chemotherapy arm.[c] Stratification factors: age (< 55 years vs. ≥ 55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive allogeneic SCT (yes vs. no). [d] Time to censoring, measured by reversing the status indicator for censored and events.
Abbreviations: alloSCT: allogeneic stem cell transplant; CI: confidence interval; DCO: data cutoff; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; MRD: minimal residual disease; NE: not estimable; RFS: relapse-free survival; RFS: relapse-free survival; SOC: standard of care; yrs: years.

Source: Table 14-4.2.5. E1910 CSR. Amgen Data on File.[53]

Figure 9: KM for RFS from Step 3 censored at alloSCT for MRD-negative patients (FAS)

Footnotes: Censor indicated by vertical bar.
Abbreviations: alloSCT: allogeneic stem cell transplant; CI: confidence interval; DCO: data cutoff; KM: Kaplan-Meier; MRD: minimal residual disease; NE: not estimable; OS: overall survival; RFS: relapse-free survival; SOC: standard of care.
Source: Figure 14-4.2.3. E1910 CSR. Amgen Data on File.[53]

B.2.6.5 Conclusions

Despite advances in chemotherapy regimens, there remains an unmet need when treating adults with Ph-negative precursor B-cell ALL that is MRD-negative. Patients MRD-negative disease still have a significant risk of relapse, which is associated with poor prognosis and substantial burden on patients and their families, as well as economic burdens. The efficacy results from Study E1910 have demonstrated that in MRD-negative patients blinatumomab significantly improves survival when added to SOC consolidation chemotherapy in the frontline consolidation phase, compared with SOC consolidation chemotherapy alone.

In the prespecified OS (primary endpoint) and RFS (secondary endpoint) analyses among MRD-negative patients, blinatumomab given as part of consolidation chemotherapy led to a statistically and clinically significant reduction in death (OS: HR 0.44; 95% CI 0.25, 0.76) and relapse or death (RFS: HR 0.53; 95% CI 0.32, 0.88), relative to SOC consolidation chemotherapy alone. Additionally, transplant rates were similar and well-balanced in both arms, and the OS HR between treatment arms in the overall MRD-negative patient population was [redacted] to that for patients who were censored upon receiving alloSCT. This suggests that the survival benefit of blinatumomab as part of consolidation chemotherapy was consistent regardless of whether patients received alloSCT or not, and that alloSCT was not the main driver of efficacy in the blinatumomab and SOC chemotherapy arm.

In conclusion, the clinical evidence base from the E1910 trial demonstrates that blinatumomab added to frontline consolidation chemotherapy represents a potential paradigm shift in how patients with Ph-negative MRD-negative precursor B-cell ALL could be managed in routine clinical practice, offering the potential for a curative therapy.

B.2.7 *Meta-analysis*

A meta-analysis is a common statistical method used to aggregate measures of effect from individual trials. As only one trial of blinatumomab relevant to the population of interest in the decision problem was performed (i.e. the E1910 study), a meta-analysis was not necessary and would not have been possible to complete.

B.2.8 *Indirect and mixed treatment comparisons*

The E1910 trial provides a head-to-head comparison between blinatumomab with SOC consolidation chemotherapy and SOC consolidation chemotherapy alone. Therefore, indirect treatment comparisons were not necessary to conduct and this section is not applicable.

B.2.9 *Adverse reactions*

Summary of safety analysis

- Overall, there were [redacted] patients in the Safety Analysis Set (SAS; all MRD-negative patients in the FAS who received at least one dose of protocol-specified therapies): [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients in the SOC consolidation chemotherapy arm.
  - Of the MRD-negative patients in the SOC consolidation chemotherapy plus blinatumomab arm [redacted] reported a Step 3 treatment-emergent adverse event (TEAE). This is comparable to the [redacted] patients who reported a Step 3 TEAE for the MRD-negative patients in the SOC consolidation chemotherapy arm.
  - The incidence of grade ≥3 AEs was also similar between the two treatment arms (blinatumomab plus SOC consolidation chemotherapy arm: [redacted]; SOC consolidation chemotherapy arm: [redacted]
  - The most frequently reported grade ≥3 TEAEs in the SOC consolidation chemotherapy plus blinatumomab arm were neutrophil count decreased ([redacted]), platelet count decreased ([redacted]), white blood cell count decreased ([redacted]), lymphocyte count decreased ([redacted]), anaemia ([redacted]), and febrile neutropenia ([redacted]) which aligned with the SOC consolidation chemotherapy arm.
  - In total, [redacted] patients [redacted] discontinued SOC consolidation chemotherapy plus blinatumomab treatment due to AEs; [redacted] patients ([redacted]) discontinued SOC consolidation chemotherapy treatment due to AEs.
  - TEAEs of interest were reported for [redacted] MRD-negative patients ([redacted]) in the SOC consolidation chemotherapy plus blinatumomab arm (cytokine release syndrome; [redacted] patients [redacted]; medication error: [redacted] patient [redacted]; neurologic: [redacted] patients [redacted]) and [redacted] patients ([redacted]) in the SOC consolidation chemotherapy arm (cytokine release syndrome: [redacted] patients [redacted]; medication error: [redacted] patients [redacted]; neurologic [redacted] patients [redacted]).
- Overall, the safety data were consistent with the safety profile of consolidation chemotherapy, as well as the well-characterised safety profile of blinatumomab described in previous clinical trials.[5, 6] The number and severity of observed AEs were similar across both treatment arms.
  - No new safety signals were observed for blinatumomab plus SOC consolidation chemotherapy in Study E1910.
  - The main safety risks associated with blinatumomab (neurological events, cytokine release syndrome (CRS), and medication errors) are well documented and can be effectively managed through detailed guidance provided in the blinatumomab label.
- In conclusion, the findings of Study E1910 demonstrate that blinatumomab added to frontline consolidation chemotherapy has a [redacted] benefit-risk profile.

B.2.9.1 Safety analysis

The following sections report the data from the Safety Analysis Set (SAS). Overall, there were [redacted] patients in the SAS, which comprised all Step 3 randomised patients who are MRD-negative after induction and intensification SOC consolidation chemotherapy and received at least one dose of protocol-specific therapies.

In the SAS, [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients in the SOC consolidation chemotherapy arm. Of the [redacted] patients who received SOC consolidation chemotherapy plus blinatumomab, [redacted] patients [redacted] received on protocol alloSCT. Of the [redacted] patients who received SOC consolidation chemotherapy, [redacted] patients [redacted] received on protocol alloSCT. Of the [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm, [redacted] patients received SOC consolidation chemotherapy during Consolidation and [redacted] patients received SOC chemotherapy during Maintenance (Step 4). Of the [redacted] patients in the SOC consolidation chemotherapy arm, [redacted] patients received SOC consolidation chemotherapy during Consolidation and [redacted] patients received SOC chemotherapy during Maintenance (Step 4).

B.2.9.2 TEAEs

There were [redacted] patients in the SAS (Step 3 randomised MRD-negative patients): [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients in the SOC consolidation chemotherapy arm. Of the MRD-negative patients in the SOC consolidation chemotherapy plus blinatumomab arm, [redacted] reported a Step 3 TEAE, [redacted] patients [redacted] reported expedited TEAEs, [redacted] reported grade ≥3 TEAEs, [redacted] patients [redacted] reported grade ≥4 TEAEs, and [redacted] patients [redacted] reported a fatal TEAE. Of the MRD-negative patients in the SOC consolidation chemotherapy arm, [redacted] reported a Step 3 TEAE, [redacted] patients [redacted] reported expedited TEAEs, [redacted] reported grade ≥3 TEAEs, [redacted] patients ([redacted] reported grade ≥4 TEAEs, and [redacted] reported a fatal TEAE.

Table 14 provides an overview of the TEAE data for MRD-negative patients at Step 3.

There were [redacted] patients in the SAS (Step 3 randomised MRD-negative patients): [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients in the SOC consolidation chemotherapy arm. Of the MRD-negative patients in the SOC consolidation chemotherapy plus blinatumomab arm, [redacted] reported a Step 3 TEAE, [redacted] patients [redacted] reported expedited TEAEs, [redacted] reported grade ≥3 TEAEs, [redacted] patients [redacted] reported grade ≥4 TEAEs, and [redacted] patients [redacted] reported a fatal TEAE. Of the MRD-negative patients in the SOC consolidation chemotherapy arm, [redacted] reported a Step 3 TEAE, [redacted] patients [redacted] reported expedited TEAEs, [redacted] reported grade ≥3 TEAEs, [redacted] patients ([redacted] reported grade ≥4 TEAEs, and [redacted] reported a fatal TEAE.

Table 14: Incidence of TEAE (SAS)

	Blinatumomab + SOC consolidation chemotherapy ([redacted])	SOC consolidation chemotherapy ([redacted])	Overall ([redacted])

All Step 3 TEAE, n (%)	[redacted]	[redacted]	[redacted]
Expedited events	[redacted]	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]	[redacted]
Grade ≥4	[redacted]	[redacted]	[redacted]
Fatal	[redacted]	[redacted]	[redacted]

Abbreviations: SAS: safety analysis set; SOC: standard of care: TEAE: treatment-emergent adverse event.
Source: Table 14-6.6.1. E1910 CSR. Amgen Data on File.[53]

TEAEs were reported for [redacted] MRD-negative patients [redacted] in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients [redacted] in the SOC consolidation chemotherapy arm (Table 15). In the SOC consolidation chemotherapy plus blinatumomab arm, the most frequently reported TEAEs (patient incidence ≥30%) were neutrophil count decreased ([redacted]), platelet count decreased ([redacted]), anaemia ([redacted]), white blood cell count decreased ([redacted]), and headache ([redacted]), lymphocyte count decreased ([redacted]), vomiting ([redacted]), and diarrhoea ([redacted]). In the SOC consolidation chemotherapy arm, the most frequently reported TEAEs (patient incidence ≥30%) were neutrophil count decreased ([redacted]), platelet count decreased ([redacted]), white blood cell count decreased ([redacted]), anaemia ([redacted]), and headache ([redacted]).

Table 15: TEAE by system organ class and PT reported in ≥30 of patients within any treatment category (SAS)

System organ class PT, n (%)	Blinatumomab + SOC consolidation chemotherapy ([redacted])	SOC consolidation chemotherapy ([redacted])	Overall ([redacted])
Number of patients reporting Step 3 TEAEs	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]

Abbreviations: PT: preferred term ; SAS: safety analysis set; SOC: standard of care: TEAE: treatment-emergent adverse event.
Source: Table 14-6.6.2 E1910 CSR. Amgen Data on File.[53]

B.2.9.3 Grade 3–4 TEAEs

An overview of Grade ≥3 TEAEs by system organ class and PT reported in ≥5% of patients within any treatment category for the SAS is reported in Table 16.

Grade ≥3 TEAEs were reported for [redacted] MRD-negative patients ([redacted]) in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients [redacted] in the SOC consolidation chemotherapy arm. In the SOC consolidation chemotherapy plus blinatumomab arm, the most frequently reported grade ≥3 TEAEs were neutrophil count decreased ([redacted]), platelet count decreased ([redacted]), white blood cell count decreased ([redacted]), lymphocyte count decreased ([redacted]), anaemia ([redacted]), and febrile neutropenia ([redacted]). In the SOC consolidation chemotherapy arm, the most frequently reported grade ≥3 TEAEs (patient incidence ≥20%) were neutrophil count decreased ([redacted]), platelet count decreased ([redacted]), white blood cell count decreased ([redacted]), anaemia ([redacted]), febrile neutropenia ([redacted]), and lymphocyte count decreased ([redacted]).

Table 16: ≥Grade 3 TEAEs by system organ class and PT reported in ≥5% of patients within any treatment category (SAS)

System organ class PT, n (%)	Blinatumomab + SOC consolidation chemotherapy ([redacted])	SOC Consolidation chemotherapy ([redacted])	Overall ([redacted])
Number of patients reporting grade 3 and above Step 3 TEAEs	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]

Hypertriglyceridaemia	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]

Abbreviations: PT: preferred term ; SAS: safety analysis set; SOC: standard of care: TEAE: treatment-emergent adverse event.
Source: Table 14-6.6.4. E1910 CSR. Amgen Data on File.[53]

B.2.9.4 Withdrawals due to AEs

AEs leading to study discontinuation were not provided in the dataset. Based on the patient disposition data, there were [redacted] who did not receive Step 3 treatment (SOC consolidation chemotherapy plus blinatumomab or SOC consolidation chemotherapy) due to AEs. In total , [redacted] patients [redacted] discontinued SOC consolidation chemotherapy plus blinatumomab treatment due to AEs and [redacted] patients [redacted] discontinued SOC consolidation chemotherapy treatment due to AEs.

B.2.9.5 Fatal AEs

In the SOC consolidation chemotherapy plus blinatumomab arm, fatal AEs were reported for [redacted] patients [redacted]: [redacted] of sepsis and [redacted] of intracranial haemorrhage were reported, all of which were in MRD-negative patients. In the SOC consolidation chemotherapy arm, fatal AEs were reported for [redacted] who was MRD negative (sepsis).

B.2.9.6 Safety events of interest

Table 17 provides an overview of TEAEs of interest by event of interest category and PT.

TEAEs of interest were reported for [redacted] MRD-negative patients [redacted] in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients [redacted] in the SOC consolidation chemotherapy arm. Cytokine release syndrome was reported for [redacted] patients ([redacted] in the SOC consolidation chemotherapy plus blinatumomab arm, of which [redacted] patients ([redacted]%) experienced a Grade ≥3 event, and [redacted] in the SOC consolidation chemotherapy arm. Medication error (device malfunction) was reported for [redacted] in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] in the SOC consolidation chemotherapy arm.

Neurologic events were reported for [redacted] patients ([redacted] in the SOC consolidation chemotherapy plus blinatumomab arm, of which [redacted] patients [redacted] experienced a Grade ≥3 event. The most frequently reported neurologic events (patient incidence ≥10%) were headache ([redacted]) and tremor

([redacted]). Neurologic events were reported for [redacted] patients[redacted] in the SOC consolidation chemotherapy arm, of which [redacted]patients[redacted] experienced a Grade ≥3 event. The most frequently reported neurologic event (patient incidence ≥10%) was headache ([redacted]).

Table 17: TEAEs of interest by EOI category and PT (SAS)

EOI category PT, n (%)	Blinatumomab + SOC consolidation chemotherapy ([redacted])	SOC consolidation chemotherapy ([redacted])	Overall ([redacted])
Number of patients reporting Step 3 treatment-emergent adverse EOI (on protocol)	[redacted]	[redacted]	[redacted]
Cytokine release syndrome (Narrow)	[redacted]	[redacted]	[redacted]
Cytokine release syndrome	[redacted]	[redacted]	[redacted]
Medication errors (Broad)	[redacted]	[redacted]	[redacted]
Device malfunction	[redacted]	[redacted]	[redacted]
Neurologic events (Narrow)	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]
Ataxia	[redacted]	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]	[redacted]
Disturbance in attention	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]
Depressed level of consciousness	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]	[redacted]
Hypoesthesia	[redacted]	[redacted]	[redacted]
Mental status changes	[redacted]	[redacted]	[redacted]
Neurotoxicity	[redacted]	[redacted]	[redacted]
Memory impairment	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]	[redacted]
Seizure	[redacted]	[redacted]	[redacted]

Tinnitus	[redacted]	[redacted]	[redacted]
Agitation	[redacted]	[redacted]	[redacted]
Amnesia	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]
Failure to thrive	[redacted]	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]	[redacted]
Lethargy	[redacted]	[redacted]	[redacted]
Oral dysaesthesia	[redacted]	[redacted]	[redacted]
Sleep apnoea syndrome	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]
Trismus	[redacted]	[redacted]	[redacted]

Abbreviations: EOI: event of interest; PT: preferred term ; SAS: safety analysis set; SOC: standard of care: TEAE: treatment-emergent adverse event.
Source: Table 14-6.6.8 E1910 CSR. Amgen Data on File.[53]

B.2.9.7 Anti-blinatumomab antibody assays

[redacted] patients were included in the blinatumomab immunogenicity analysis. Of the [redacted] patients, [redacted] patients were considered on-study after providing informed consent for the testing of blinatumomab immunogenicity (Table 16). Of these, [redacted] patients had at least one post-baseline result. No patients developed anti-blinatumomab antibodies.

Table 18: Anti-blinatumomab antibody assays (Blinatumomab SAS)

	Blinatumomab + SOC consolidation chemotherapy (N=147) n (%)
Patients with an on-study result[a]	[redacted]
Antibody positive at any time (ADA prevalence)	[redacted]
Neutralizing antibody positive at any time	[redacted]
Patients with a post-baseline result	[redacted]
Treatment-induced antibody positive[b]	[redacted]
Treatment-induced neutralizing antibody positive[c]	[redacted]
Transient[d]	[redacted]

Footnotes: Baseline samples were used to calculate the assay cut point and were therefore not resulted. [a] patients are considered on-study after signing informed consent. [b] Antibody positive post-baseline with negative or no result at baseline. [c] Neutralizing antibody positive post-baseline with a negative or no result at baseline. [d] Negative result at the patient's last time point tested within the study period.
Abbreviations: SOC: standard of care; SAS: Safety Analysis Set.
Source: Table 14-8.1. E1910 CSR. Amgen Data on File.[53]

B.2.9.8 Safety conclusions

Overall, there were [redacted] patients in the SAS, which comprised all patients in the FAS who received at least one dose of protocol-specified therapies: [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm and [redacted] patients in the SOC consolidation chemotherapy

arm.[49] It is important to note that blinatumomab was used alongside SOC consolidation chemotherapy in the experimental arm, meaning that both treatment arms received the same amount of SOC consolidation chemotherapy. It is therefore expected that the addition of blinatumomab would somewhat increase the number of TEAEs in the blinatumomab with SOC consolidation chemotherapy arm. However, the number and severity of observed TEAEs in the blinatumomab with SOC consolidation chemotherapy arm were similar to what was observed in the SOC consolidation chemotherapy arm alone in the MRD-negative population.

Overall, blinatumomab plus SOC consolidation chemotherapy was generally well tolerated, and the safety data were consistent with the safety profile of consolidation chemotherapy, as well as the well-characterised safety profile of blinatumomab in adult patients with Ph-negative precursor B-cell ALL. No new safety signals were observed for blinatumomab plus SOC consolidation chemotherapy in the E1910 study.[62, 63] The main safety risks associated with blinatumomab (neurological events, cytokine release syndrome (CRS), and medication errors) are already well documented and can be managed through the risk management plan provided in the blinatumomab label.[64, 65]

In conclusion, the totality of the safety evidence base demonstrates that blinatumomab added to consolidation chemotherapy has a [redacted] benefit-risk profile owing to the superior efficacy seen in terms of OS and RFS compared with consolidation chemotherapy alone, and blinatumomab was generally well tolerated.

B.2.10 *Ongoing studies*

There is currently one ongoing randomised controlled trial for blinatumomab in adult patients who are Ph-negative and in the frontline setting:

- Golden Gate (NCT04994717): a Phase 3 randomised, controlled study of blinatumomab alternating with low-intensity chemotherapy versus SOC for older adults with frontline Ph-negative precursor B-cell ALL.[66]

Data from the primary analysis of the Golden Gate study is anticipated to become available in [redacted] and are therefore unavailable for inclusion in the present submission.

B.2.11 *Interpretation of clinical effectiveness and safety evidence*

The results from Study E1910 demonstrate that blinatumomab has a superior OS and RFS profile when added to frontline SOC consolidation chemotherapy, compared with SOC consolidation chemotherapy alone. In the pre-specified OS (primary endpoint) and RFS (secondary endpoint) analyses among MRD-negative patients, blinatumomab given as part of frontline consolidation chemotherapy led to a statistically and clinically significant reduction in death (OS: HR 0.44; 95% CI 0.25, 0.76; log-rank test TD: p=0.001) and relapse or death (RFS: HR 0.53; 95% CI 0.32, 0.88; log-rank test TD: p=0.006), relative to SOC consolidation chemotherapy alone. These outcomes are objective and are clinically relevant measures of disease. Alongside these robust clinical efficacy results, no new safety signals for blinatumomab were identified in the E1910 trial; the results were consistent with the established safety profile of blinatumomab.

As a multinational Phase 3 RCT, the E1910 study represents the highest quality of evidence for an individual trial evaluating clinical efficacy. In the context of a rare disease (orphan condition), E1910 had a relatively large sample size (N=224 in Full Analysis Set). The study was statistically powered to detect differences in survival among the MRD-negative patients at Step 3, in full alignment with the decision problem of this submission. The trial was not powered to detect differences for subgroups stratified by the prognostic factors of age or performance status, however these characteristics were well-balanced between the two arms owing to pre-specified stratification. As such, the E1910 trial provides data that are both statistically robust and highly relevant to the decision problem of this submission.

In summary, the clinical and safety evidence base provided by Study E1910 demonstrates that blinatumomab added to consolidation chemotherapy represents a potential paradigm shift in how patients with Ph-negative MRD-negative precursor B-cell ALL in the frontline consolidation setting are managed in routine clinical practice, offering the potential for a curative therapy. Moreover, Study E1910 provides a robust clinical evidence package that is broadly generalisable to UK clinical practice and thus is appropriate for decision making.

B.3 Cost effectiveness

Summary of cost effectiveness results

- A cost-utility model was developed to estimate the cost-effectiveness of blinatumomab with SOC consolidation chemotherapy versus the only relevant comparator, SOC consolidation chemotherapy alone (Section B.1.3.3), for the treatment of adult patients with CD19-positive Ph-negative precursor B-cell ALL that is MRD-negative in the frontline consolidation phase.
- The model was a partitioned survival model consisting of three mutually exclusive health states: relapse-free survival (RFS), post-relapse survival (PRS), and death. This analysis was consistent with the NICE reference case and took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% in the base case and a lifetime time horizon was adopted.
- Baseline characteristics were informed by the E1910 trial. Extrapolations of RFS and OS data for both treatment arms were performed using patient-level data from the E1910 trial and mixture-cure models were used for both arms. Extrapolations generated similar estimates of both RFS and OS, reflecting the robustness of the extrapolations and low uncertainty associated with the choice of curve.
- As HRQoL data were not collected in the E1910 trial, the utility values were aligned to those used in TA589.[2] Thus, utility values from the BLAST (TA589) and TOWER (TA450) trials were used to inform health-state utility values, applying the utility for MRD responders from BLAST for patients in the pre-relapse health state, and the post-relapse utility used in the BLAST CEM (matched to the no prior salvage therapy subgroup of patients in the TOWER trial) for patients in the post-relapse health state. As the BLAST trial included frontline adult patients with Ph- CD19+ B-cell ALL in CR, these data were deemed most suitable for use in this appraisal [5, 6] These utilities were confirmed by UK clinical experts to represent the expected quality of life for the modelled population. AE disutilities were informed by the literature and previous NICE appraisals. Additionally, we assume that patients remaining relapse-free for 5 years are no longer at risk of ALL-related disutilities (i.e. they switch to general population utilities).
- The costs of chemotherapy treatment were based on the drug acquisition and administration costs, and adverse event costs associated with the regimens used in the E1910 trial, as well as alloSCT.
- Additional costs included maintenance therapy costs, based on the regimens received in the E1910 trial and subsequent treatment costs, based on estimates of the proportion of patients receiving these therapies provided by UK clinical experts. AlloSCT as a subsequent treatment was informed by the E1910 trial. Finally, the model included adverse event costs and the costs of end-of-life care. Additionally, patients remaining relapse-free for 5 years are no longer at risk of ALL-related costs (i.e. they no longer received subsequent therapy and terminal care costs).

Base case cost-effectiveness results

- In the base case probabilistic analysis, blinatumomab at PAS price was associated with a substantial increase in QALYs gained ([redacted]) and total costs ([redacted]) versus SOC

consolidation chemotherapy. Therefore, blinatumomab at PAS price was associated with a base case probabilistic ICER of £32,311 versus SOC consolidation chemotherapy. All other treatments were modelled at list price, including all subsequent treatments.

- In the base case probabilistic analysis, considering the combined parameter uncertainty in the model, the ICER for blinatumomab versus SOC was seen to be in line with the deterministic base case, indicating low parameter uncertainty.
- The DSA results identified a small number of key influential parameters, including the proportion of patients receiving blinatumomab medication, and the proportion of patients receiving alloSCT in the pre-relapse health state in the SOC consolidation chemotherapy arm; overall the model was robust to uncertainty in the majority of parameters.

B.3.1 *Published cost-effectiveness studies*

An economic systematic literature review was conducted on 12th September 2023, and an update was conducted on 16th April 2024, to identify all relevant literature published on previous economic models of frontline treatments in patients with Ph-negative B-cell precursor ALL. In total, three economic evaluations were identified by the SLR. Full details of the economic SLR search strategy, study selection process and results are reported in Appendix G.

B.3.2 *Economic analysis*

A *de novo* cost-effectiveness model (CEM) was developed to assess the cost-effectiveness of blinatumomab in adult patients with Ph-negative B-cell precursor ALL that are MRD-negative in frontline consolidation. The analysis was conducted from an NHS/Personal Social Services (PSS) perspective, and the CEM adopted a lifetime time horizon (50 years) – see Section B.3.2.2 for further details.

B.3.2.1 Patient population

The CEM evaluated the use of blinatumomab with SOC consolidation chemotherapy as part of frontline consolidation therapy in adult patients with Ph-negative precursor B-cell ALL who are MRD-negative.[49] It is important to note that while the E1910 trial included patients who were both MRD-negative and MRD-positive, the CEM considered the MRD-negative patients only, in line with the decision problem for this appraisal (see Section B.1.1) and the FAS population in the E1910 clinical trial (see Section B.2.4). The E1910 study was powered to compare OS between blinatumomab plus SOC consolidation chemotherapy versus the SOC consolidation chemotherapy alone arm in patients who were MRD-negative after induction therapy. This is related to the protocol amendment, after the US FDA accelerated approval of blinatumomab in MRD-positive ALL in 2018, where, following the 2018 approval, all patients who were still MRD-positive after induction therapy were no longer randomised and instead were assigned to the blinatumomab plus SOC chemotherapy arm.

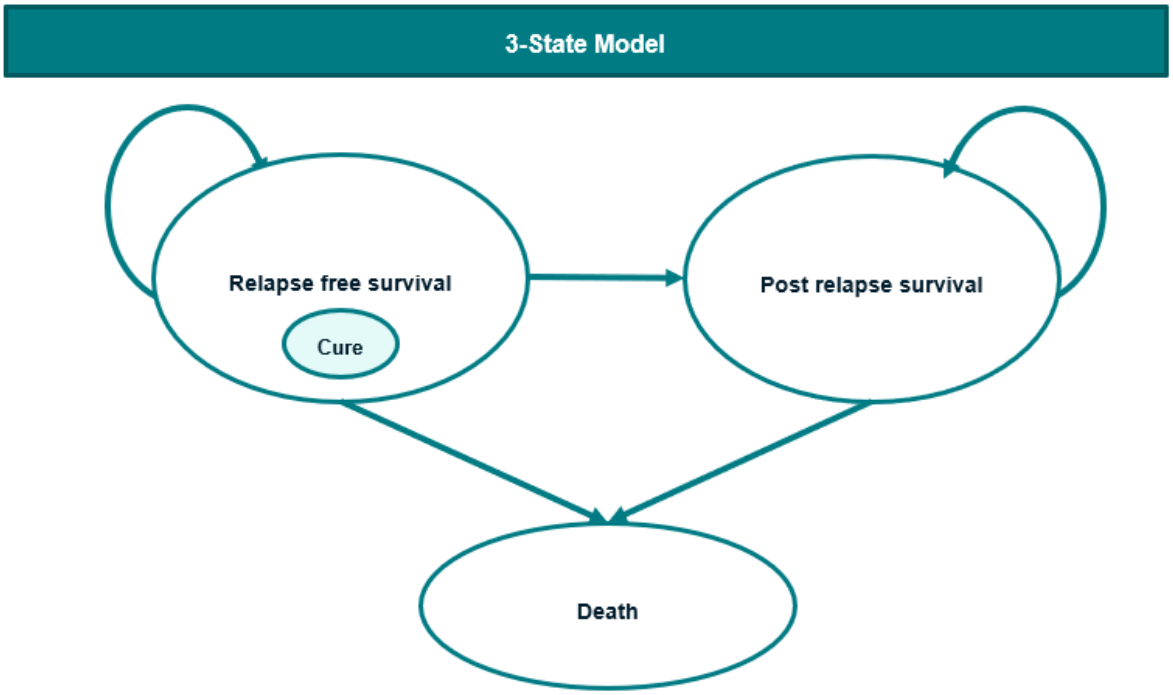
B.3.2.2 Model structure

The CEM was implemented as a Microsoft Excel workbook and designed as a three-state partitioned survival model (PSM) comprising three mutually exclusive health states: RFS, post-

relapse survival (PRS), and death (Figure 10). Model structure selection is discussed further below.

All patients were modelled to enter the CEM in the RFS state. Within the RFS state, it was assumed that all patients have disease that is stable or not actively progressing. Patients could thereafter transition to either the PRS or death states, the latter of which represented an absorbing health state. In line with the definition in the E1910 trial, relapse was defined as reappearance or persistence of blasts in the blood or the presence of >5% blasts that are not attributable to another cause (e.g. bone marrow regeneration).[49] Patients in the PRS state were assumed to have relapsed and could move to second-line treatment. Patients in the PRS state could either stay within the PRS state, or transition to the death state.

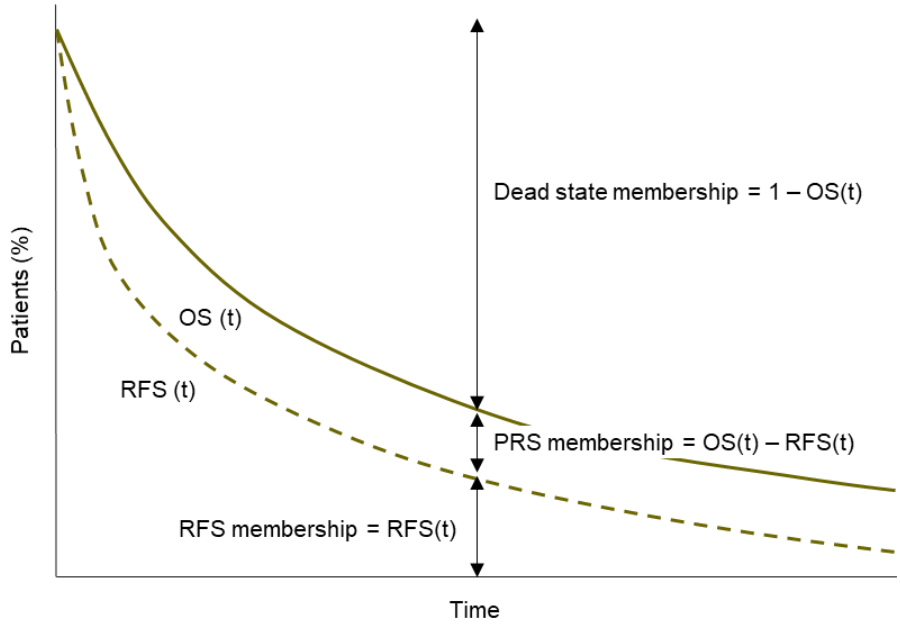
Figure 10: Model structure



Footnotes: The PSM contains a cure health state. As such, patients remaining relapse-free for 5 years are assumed to be cured and follow the general population utilities. Further, they no longer receive costs associated with relapse and terminal care.

Health state occupancy at each model cycle was determined from the cumulative survival probabilities derived from independently modelled OS and RFS curves for both the intervention and comparator arms (Figure 11). The proportion of patients in the RFS state was calculated as the proportion of patients that are alive and event-free on the RFS curve. The proportion of patients in the PRS state was estimated by subtracting the proportion of patients that were alive and event-free (RFS curve) from the proportion of alive patients (OS curve), while the proportion of patients in the death state was estimated by subtracting the proportion of alive patients from the total cohort. In the cure health state, patients remaining relapse-free for 5 years were assumed cured and therefore follow general population utilities and no longer receive costs associated with relapse and terminal care.

Figure 11: Partitioned survival model



Abbreviations: OS: overall survival; PRS: post-relapse survival; RFS: relapse-free survival.

Model structure selection

The PSM approach has been presented in prior economic analyses of treatments for oncology therapies including haematologic malignancies, as well as in the previous NICE submissions for the treatment of Ph-negative precursor B-cell ALL (TA450, TA975 and TA893).[50, 54, 67] .

It is important to note that for a previous submission of blinatumomab in a similar indication (TA589; blinatumomab in MRD-positive ALL), a semi-Markov CEM ultimately represented the decision-making CEM, despite a PSM being originally presented. This was due to the Evidence Review Group (ERG) request to explicitly model alloSCT efficacy, as the majority of patients in the BLAST trial proceeded to alloSCT.[2] Ultimately, both the semi-Markov model and PSM yielded consistent results. However, the semi-Markov model required more assumptions due to limited data for estimating transition probabilities.[68] In the E1910 trial, the proportion of patients in the MRD-negative population who received alloSCT during consolidation was low and comparable between the blinatumomab plus SOC consolidation chemotherapy and SOC consolidation chemotherapy only treatment arms ([redacted] and [redacted], respectively). Therefore, a three-state PSM was selected to model E1910 as it makes use of survival curves directly fitted to RFS and OS, therefore producing efficacy estimates that are close to the observed comparative survival data.[69, 70]

Features of the cost-effectiveness analysis

A summary of the key features of the de novo analysis is provided in Table 19.The analysis was conducted from a UK NHS and PSS perspective over a lifetime (50-year) time horizon. A weekly cycle length was utilised in order to accommodate chemotherapy regimens with varying cycle durations; a half-cycle correction was not applied as a result of the short cycle length. In the base case, costs and effectiveness (life years [LYs] and quality-adjusted life years [QALYs]) were both discounted at 3.5% annually (as per guidance from the UK NICE),[71] but scenario analyses

assessing the impact of assuming discount rates of 1.5% and 5% are presented (see Section B.3.10.3). All costs retrieved were adjusted to 2022/2023 prices using the NHSCII inflation index, when appropriate.[72]

Table 19: De novo model features

Factor	Previous submissions		Current submission	
	TA450[54]	TA589[2]	Chosen values	Justification
Modelling approach	PSM	PSM[a]	PSM	PSM is a transparent, intuitive approach which yields estimates of survival that closely correspond to those observed during the pivotal E1910 trial. This approach has been used and accepted in other submissions for Ph-negative precursor B-cell ALL (TA450, TA975 and TA893).[50, 54, 67] Further, the PSM directly uses data from the E1910 trial, enabling accurate reflection of disease progression and survival of patients treated with blinatumomab and the comparator in this economic analysis.[49] Further discussion of the selection of a PSM approach is presented above.
Time horizon	Lifetime (50 years)	Lifetime (50 years)	Lifetime (50 years)	Sufficiently long period of time to track differences in costs and outcomes between treatments, and to capture health implications from a cured population.
Cycle length	1 week	1 week	1 week	This allows for granularity to capture all necessary events and allows for the flexibility to model the dosing schedules of treatments in the model.
Discounting	3.5%	3.5%	3.5%	In accordance with NICE guidance.[71]
Perspective	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	In accordance with NICE guidance.[71]
Source of utilities	Utility values were based on EQ-5D utility values mapped from the EORTC QLQ-C30 collected from patients in the TOWER trial. Utility values for the cured health state were based on	Utility values for the RFS health state were based on data on EQ-5D utility values from the BLAST trial. Utility values for patients in PRS health state were based on EQ-5D utility values mapped from the EORTC QLQ-C30 among for patients receiving SOC	Utility values for the RFS health state were based on data on EQ-5D utility values from the BLAST trial in MRD responders (i.e. patients converting from MRD-positive to MRD-negative status). Utility values for patients in PRS health state were based on EQ-5D utility values mapped from the EORTC QLQ-C30 among	As HRQoL data were not collected in the E1910 trial, the utility values in this appraisal were aligned to those used in TA589.[2] Thus, utility values from the BLAST (TA589) and TOWER (TA450) trials were used to inform health-state utility values, applying the utility for MRD responders from BLAST for patients in the pre-relapse health state, and the post-relapse utility used in the BLAST CEM (matched to the no prior salvage therapy subgroup of patients in the TOWER trial) for patients in the post-relapse health state. As the BLAST trial included frontline adult patients with Ph-CD19+ B-cell ALL in CR, these data were deemed most suitable for use in this appraisal.[5, 6]

Factor	Previous submissions		Current submission	
	TA450[54]	TA589[2]	Chosen values	Justification
	general population norm utility values.	chemotherapy in the TOWER trial.[5, 6] Utility values for the cured health state were based on general population norm utility values.	for patients receiving SOC chemotherapy in the TOWER trial.[5, 6] Utility values for the cured health state were based on general population norm utility values.	
Source of costs	BNF;[73] eMIT;[74] NHS 2015 Reference Costs;[75] FLAG-IDA protocol;[76] PSSRU 2015[77]	BNF;[78] eMIT;[74] NHS 2015/2016 Reference Costs;[9]clinical validation reference costs.	NHS 2021/2022 Reference Costs;[79] PSSRU 2022;[80] BNF;[78] eMIT[74]	Generic and non-generic drug costs were sourced from eMIT[74] and BNF[78], respectively. All other cost inputs were obtained from NHS reference costs[81] and PSSRU.[80] Costs that were not reported in these sources were retrieved from appropriate literature.
Year of costs	2015[75]	2015/2016[82]	2021/2022[80]	All costs retrieved were adjusted to 2022/2023 prices using the NHSCII inflation index, when appropriate.[72]

Footnotes: [a]A semi-Markov model was later presented and used for decision-making.
Abbreviations: ALL: acute lymphoblastic leukaemia; alloSCT: allogeneic stem cell transplant; BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; EQ-5D: EuroQol Five Dimensions; EORTC-QLQ-C30: quality of life of cancer patients questionnaire; HRQoL: Health-related quality-of-life; MRD: minimal residual disease; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSM: partitioned survival model; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; SOC: standard of care.

B.3.2.3 Intervention technology and comparators

Intervention: blinatumomab

The intervention of interest is blinatumomab, which is first administered for two consecutive cycles of 28 µg/day as a continuous intravenous (IV) infusion over 28 days followed by an infusion-free interval of 14 days. After this, patients may have the option of receiving an alloSCT (based on eligibility and intent to receive an alloSCT at randomisation) or proceeding with consolidation chemotherapy alternating with an additional two cycles of blinatumomab. The consolidation chemotherapy regimen is based on the UKALL XII/ECOG E2993 protocol.[37] The full details of this schedule and its associated costs are provided in Section B.3.5.

Comparator: SOC consolidation chemotherapy

The comparator considered in this CEM is represented by the SOC consolidation chemotherapy regimen used in E1910, which is the conventional consolidation chemotherapy for patients with Ph- MRD-negative disease. During an advisory board UK expert clinicians confirmed that the SOC consolidation chemotherapy regimen used in E1910 aligns with the UKALL14 protocol used in UK clinical practice.[1, 24] Similar to blinatumomab, the full details of this schedule and its associated costs are presented in Section B.3.5.

As intent to transplant was a stratification factor, patients could proceed to alloSCT at the discretion of the treating physician. If alloSCT was to be performed, the E1910 protocol suggested it should be done after the first two cycles of blinatumomab in the blinatumomab arm, or at any time following intensification chemotherapy in the SOC consolidation chemotherapy arm.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The baseline characteristics for the model population are provided in Table 20. The population is characterised at model entry based on mean age, sex, body weight and body surface area (BSA) derived from data from the E1910 Phase 3 randomised controlled trial.

Table 20. Population characteristics

Model parameter	Value
Mean age, years (SD)	50.1 (11.5)
Proportion male, %	49.6%
Mean weight, kg (SD)	86.6 (22.0)
BSA (SD)	2.0 (0.3)

Abbreviations: BSA: body surface area; SD: standard deviation.
Source: Table 14-2.1 and Table 14-2.3. E1910 CSR. Amgen Data on File.[53]

B.3.3.2 Survival inputs and assumptions

The CEM makes direct use of observed RFS and OS events from the E1910 clinical trial to inform health state occupancy.[53] Although the survival data from the E1910 trial were sufficiently long to inform short- to medium-term clinical trajectories (median follow-up time of 4.5 years), they do not provide any

information beyond the end of the study period. Consequently, extrapolation of the underlying survival data beyond the study period is needed to obtain accurate estimates of long-term survival.

Cure has not been formally defined in treatment guidelines, however, an ALL patient (with or without MRD) who remains in remission for around 3 to 5 years is considered likely to have achieved a cure, based on clinical expert opinion (Adelphi Study 2019).[83] This 3 to 5 year cure assumption was confirmed by UK clinical experts during the clinical validation meeting.[84] As such, to accommodate for the possibility of deep clinical remission, patients who can be considered "cured" are considered in the modelling approach using mixture cure modelling. Additionally, it is assumed that for patients remaining relapse-free for 5 years are no longer at risk of ALL-related disutilities (i.e. they switch to general population utilities) and costs (i.e. they no longer receive subsequent therapy and terminal care costs).

Mixture cure models (MCMs)

MCMs are useful to describe survival data where a subgroup of patients experiences long-term survival. There is precedent for curative therapies in haematological oncology indications; AlloSCT is considered curative in ALL, and CAR-T therapies are considered curative when treating later lines of blood cancers.[85, 86] These treatments can induce deep remission often by altering underlying pathophysiology, thereby leading to increased OS.

In MCMs, long-term survival is modelled by estimating an implicit "cure fraction" (i.e. the proportion of patients "cured"). The survival of patients who are "cured" is then modelled assuming age- and sex-matched general population mortality. To account for any residual ALL complications and treatments (e.g. alloSCT), a standardised mortality ratio (SMR) of 1.09 was applied to the general population mortality.[90] The survival of non-cured patients (i.e. 1 – cure fraction) is modelled using a parametric survival model. The "flexsurvcure" R package was used to fit MCMs.[87] Both jointly and separately fitted MCMs were explored.

Using MCMs to extrapolate the OS and RFS outcomes of E1910 is considered justifiable given:

- A plateau in the KM curves of RFS of blinatumomab plus SOC chemotherapy and SOC alone is emerges from 48 and 72 months onwards, respectively, where patients are no longer relapsing and dying. This suggests that a proportion of patients may no longer be at risk of relapse or death due to ALL. Additionally, median survival was not reached in either arm in the E1910 trial.
- MCMs have been accepted by NICE in previous technology appraisals in ALL (TA554), including for blinatumomab (TA589), and this approach was supported by the durable response observed from the respective pivotal trials.[2, 79]
- MCMs are recommended in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 21 in situations where a proportion of patients were effectively "cured" and should be subjected to background mortality.[88]

Modelling the cured population

When modelling cure using MCMs, cured patients, as defined by the cure fraction, follow general population survival (including any additional excess mortality due to residual effects of ALL), while the remaining patients follow a standard parametric survival trajectory. Additionally, in the base case, the model considers patients clinically cured at five years. Thus, patients no longer receive ALL-related costs (subsequent therapy and terminal care costs) and are assumed to have the same utility as the age- and sex-matched general population.

While cured patients are assumed to experience outcomes similar to those of the general population, a standardised mortality ratio (SMR) is applied to the age- and sex-matched general population mortality to model mortality of the cured population in the cost-effectiveness model, to account for any potential lingering complications due to ALL disease or alloSCT. No evidence in the literature was identified regarding the level of excess mortality in cured patients with frontline ALL. The SMRs accepted by NICE in previous submissions are presented in Table 21.

Table 21: SMRs accepted by NICE in previous ALL submissions

SMR	Context	Source
1.09	Accepted by the EAG and Committee during TA895 in second-line R/R diffuse large B-cell lymphoma and was the SMR preferred by the EAG in TA567 (tisagenlecleucel in R/R diffuse large B-cell lymphoma)	TA895, TA567 (sourced from Maurer et al).[79, 89, 90]
3.00	The Committee for TA893 made their decision using a base case SMR of 3.00 in R/R B-cell ALL. Notably, the company had also used the above SMR of 1.09 as their base case, but the EAG considered that this related to a different population and that patients with ALL are at an excess mortality risk of 4–9 times as informed by Martin et al.[91] In this publication, the survival of patients with haematologic malignancies who remained alive and disease-free for five years following alloSCT was captured, with long-term mortality post-alloSCT estimated to be between 4 and 9 times greater than the general population. Ultimately, an SMR of 3.00 was agreed for use in TA893.[50]	TA893 (based on Martin et al).[50, 91]
4.00	An SMR of 4.00 was used in TA541 and TA589 based on Martin et al. as the primary source, where survival of patients with haematologic malignancies who remained alive and disease-free for five years following HSCT was captured.[91]	TA541, TA589 (based on Martin et al).[2, 91, 92]

Abbreviations: ALL: acute lymphoblastic leukaemia; alloSCT: allogenic stem cell transplant; EAG: Evidence Assessment Group; NICE: National Institute for Health and Care Excellence; R/R: relapsed and/or refractory; SMR: standardised mortality ratio.

The model uses a base case SMR of 1.09. This assumption was validated by clinical experts, who argued that the SMRs of 3 and 4 used in previous NICE TAs were too conservative for frontline ALL patients who are MRD-negative.[93] The SMR of 4.00 used in TA589 was considered to be too high for this CEM, as it is based on a study evaluating survival post-transplant.[91] Considering that the majority of MRD-negative patients in the E1910 trial did not receive alloSCT ([redacted] and [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm and the SOC consolidation chemotherapy arm, respectively), an SMR of 4.0 was therefore considered too high.[2] The clinical experts also considered that the three-times mortality risk assumption used in TA893 (KTE-X19) was too high for modelling the cured population in this CEM. This is because the pivotal trial used in TA893 included patients in the relapse/refractory setting (who had also been immunosuppressed after CAR-T therapy), whereas the E1910 trial included frontline patients with MRD-negative disease, who have better survival outcomes than relapse/refractory B-ALL patients.[94] Based on this, the clinical experts indicated an SMR of 1.09 would be plausible.[93]

Scenario analysis: standard parametric survival models

As outlined above, the base case considered a MCM approach. Compared to MCMs, standard parametric distribution may be less accurate in predicting long-term survival in the presence of complex hazards due to clinical cure. Considering that the observed hazards for OS and RFS indicate a general decreasing trajectory, standard parametric models were considered insufficiently flexible to model the

observed hazards in the long term. Therefore, and based on NICE precedence, MCMs were selected for the base case.

However, in line with the guidance in NICE DSU TSD 14, parametric survival models were also considered for extrapolating E1910 data in scenario analyses (see Section B.3.10.3).[95, 96] The recommended distributions (exponential, Weibull, log-logistic, log-normal, Gompertz, and generalised gamma), along with the gamma model, were fitted to the RFS and OS data from E1910. The fitting was performed using the "flexsurv" package in R.[97, 98]

The log-normal extrapolation was ultimately selected for this scenario analysis, as shown in Section B.3.3.4.

Adjusting for extrapolated RFS and OS curves crossing and post-relapse survival

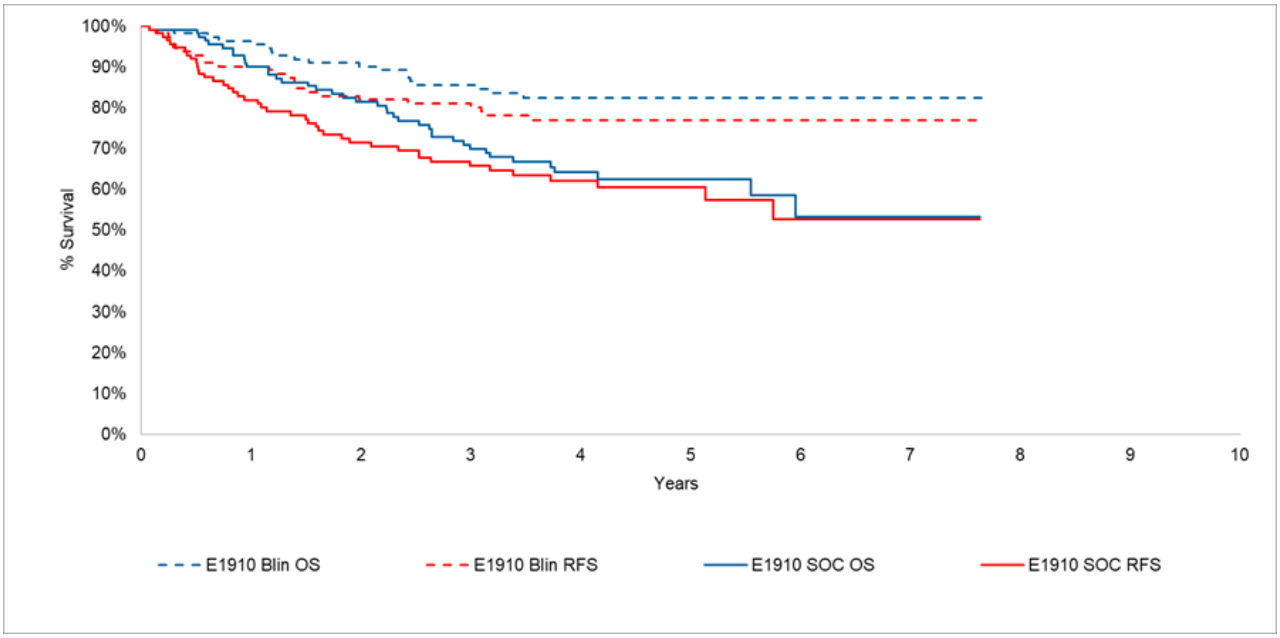
The KM curves for RFS and OS in the E1910 trial are presented in Figure 12.

In the SOC arm, the RFS and OS curves start to converge after three years, but this is likely due to relapse events not being well-documented during long-term follow-up of the E1910 trial. Per the E1910 trial protocol, patients were followed every 3 months if the patient was within the first two years of study entry, every 6 months if a patient was within two to five years of study entry, and every 12 months if a patient was six to 10 years from study entry. This is consistent with clinicians' definition of cure, where patients in long-term remission require less disease monitoring and are at a lower risk of relapse. As such, the E1910 study group did not systematically capture disease assessment during long-term follow-up, with only a patients' alive/death status systematically captured during this period. Thus, the recorded time of relapse may not reflect the time of relapse in full and therefore may have been recorded at the same time as a death event. This is particularly prominent in the SOC arm due to the higher number of RFS and OS events after three years.

Additionally, the convergence of the RFS and OS KM curves may also be due to a low risk of relapse or ALL-related deaths beyond the cure timepoint combined with low patient numbers towards the end of follow-up. However, when presenting the KM curves to clinicians, they stated that in the frontline setting, they would expect that patients would enter the post-relapse state and receive subsequent therapies prior to death.[93]

To correct for any overestimation of RFS due to missed relapse events, the RFS hazard rates in the model are modelled in the base case never to be lower than the risk of an OS event (OS hazard rates). Additionally, survival extrapolations that maximised the separation of the RFS and OS curves were selected for the base case, as described in Section B.3.3.3.

Figure 12: E1910 trial RFS and OS Kaplan-Meier curves



Abbreviations: OS: overall survival; PFS: progression-free survival; SOC: standard of care.

B.3.3.3 Survival extrapolations

In line with the recommendations in NICE DSU TSD 14[95], the choice of the most appropriate survival model for each arm was guided by the following:

- Clinical plausibility, which stipulates that the OS should neither underestimate nor exceed the general population mortality with added SMR and that there should be sufficient separation between the RFS and OS curves to reflect the possibility of post-relapse survival with subsequent therapies.
- Visual inspection against the observed KM curve and hazard plot. The fitted curves were overlaid onto the KM curve from the trial to assess similarity with the observed data.
- Goodness-of-fit statistics using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), where the lower the AIC or BIC, the better the model fit to the observed data. The goodness-of-fit statistics from the two arms of the same endpoint (i.e. OS or RFS) were added and subsequently ranked to determine which model had the best statistical fit.
- The same distribution was applied across both arms for the same endpoint for consistency in the assumption that different distributions make about the shape of the hazard rate (shape of the time dependency).

Overall survival

Assessment of the proportional hazard (PH) assumption

The Log-cumulative hazard plot (LCH) and Schoenfeld residual plots for OS are presented in Figure 13 and Figure 14. The LCH plot showed that curves crossed at the start of the follow-up period, suggesting violation of the PH assumption. After around 6 months, the curves appeared to be approximately parallel. Additionally, the Schoenfeld residual plot formed an approximately horizontal line up to around 34 months, but the gradient after 34 months raised some concerns. However, the Schoenfeld individual

test provided no evidence against the PH assumption (p>0.05). Given that there was some evidence that the PH assumption was violated, the analyses focused on fitting separate effect models to the data.

When assessing the appropriateness of the accelerated failure time (AFT) assumption using a Q–Q plot (Figure 15), the quantile pairs formed an approximately straight line. Nevertheless, additional follow-up was required to assess the AFT assumption more robustly. However, interpretation of the Q–Q plots is subjective, and these tests for PH and AFT are not conclusive and required additional follow-up to provide definitive answers. Therefore, the analyses focused on fitting separate AFT models, in alignment with the PH models.

Figure 13: Log-cumulative hazard plot for OS in the MRD-negative population

Abbreviations: Blin: blinatumomab; MRD: minimal residual disease; OS: overall survival; SOC: standard of care.

Figure 14: Schoenfeld residual plot for OS in the MRD-negative population

Footnotes: The blue dots indicate Schoenfeld residuals; the solid black line indicates time-varying log HR; the dashed black line indicates log-HR ± 2 standard errors; and the solid blue line indicates constant log-HR.
Abbreviations: Blin: blinatumomab; HR: hazard ratio; MRD: minimal residual disease; OS: overall survival; SOC: standard of care.

Figure 15: Quantile–quantile plot for OS in the MRD-negative population

Footnotes: The dotted black line indicates reference line (acceleration factor of 1).
Abbreviations: Blin: blinatumomab; MRD: minimal residual disease; OS: overall survival; SOC: standard of care.

Extrapolation selection

A variety of MCM models were fitted to the observed clinical trial data. Table 22 summarises the model fit statistics associated with the MCM across both blinatumomab plus consolidation chemotherapy and SOC arms for the OS endpoint. The generalised gamma distribution did not converge for OS, so was excluded from the model. Figure 16 and Figure 17 present the extrapolated curves, along with the KM data presented as the black solid line, extrapolated by assuming patients follow SMR-adjusted general population mortality after the end of follow up, shown as the black dotted line.

The best statistically fitting MCM curve based on goodness-of-fit statistics overall was the Weibull MCM. However, none of the models were associated with AIC or BIC values more than 5 points different from the best-fitting model, suggesting that all models fit the KM data well. While all extrapolations appeared to align closely with the original KM curve up to Year 4, all curves underestimated the OS in the blinatumomab arm at its tail. This was likely to happen due to the low numbers at risk in the tail, so the end of the curve was not weighted as highly as the initial period when fitting the models. The exponential, log-logistic and log-normal significantly underestimated the long-term survival compared to the SMR-adjusted general population mortality. This also resulted in the SOC OS estimate converging with RFS estimate for these extrapolations. Consequently, the Weibull, Gompertz and Gamma MCMs were deemed to provide the most plausible OS extrapolations. The Gompertz and Weibull MCMs have very similar survival estimates and were both validated by UK clinician input.[93] The Weibull MCM was ultimately selected for the base case as the cure fraction was more stable when varied in the PSA versus the Gompertz MCM. The gamma and log-logistic MCMs were explored in scenario analyses (see Section B.3.10.3).

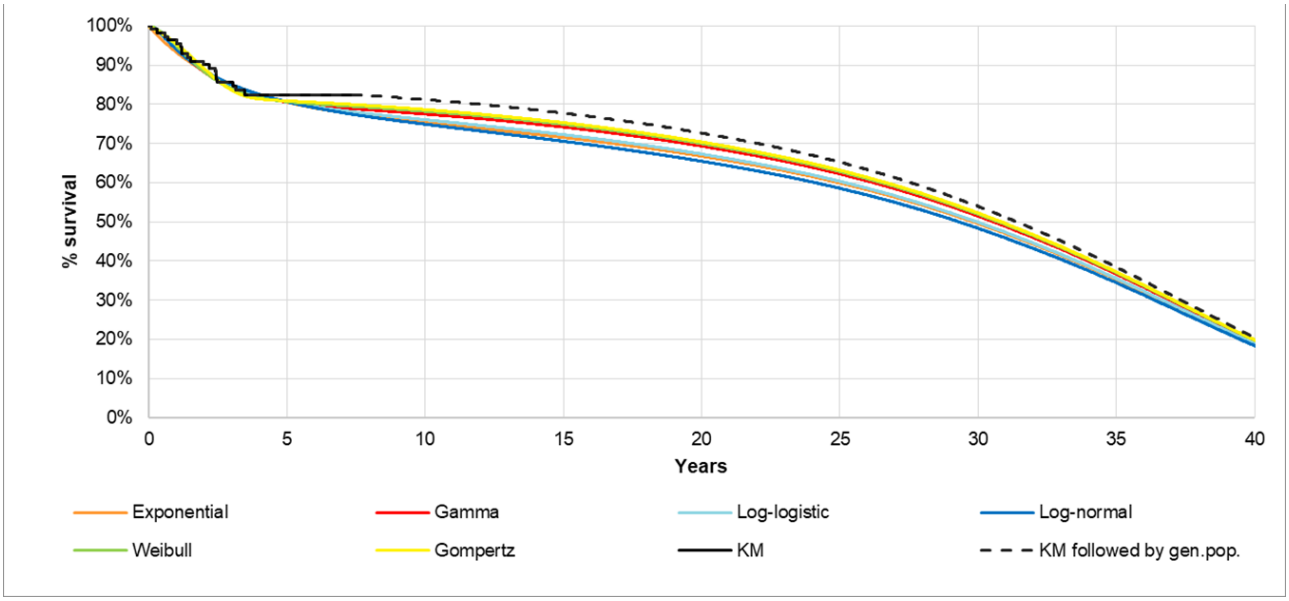
The landmark survival at different time periods versus the KM OS estimates are presented in Table 23. Cure fractions for the OS MCMs are presented in Table 24, with the Weibull MCM cure fraction having been validated by UK clinician input for both the blinatumomab plus SOC and SOC alone treatment arms.

Table 22: Goodness-of-fit statistics – OS in MRD-negative population

Model	Separate MCM fit			
	AIC	AIC rank	BIC	BIC rank
Exponential	718.58	5	729.46	1
Gamma	716.40	3	732.71	4
Gompertz	716.15	2	732.46	3
Log-logistic	717.06	4	733.37	5
Log-normal	719.31	6	735.62	6
Weibull	715.74	1	732.05	2

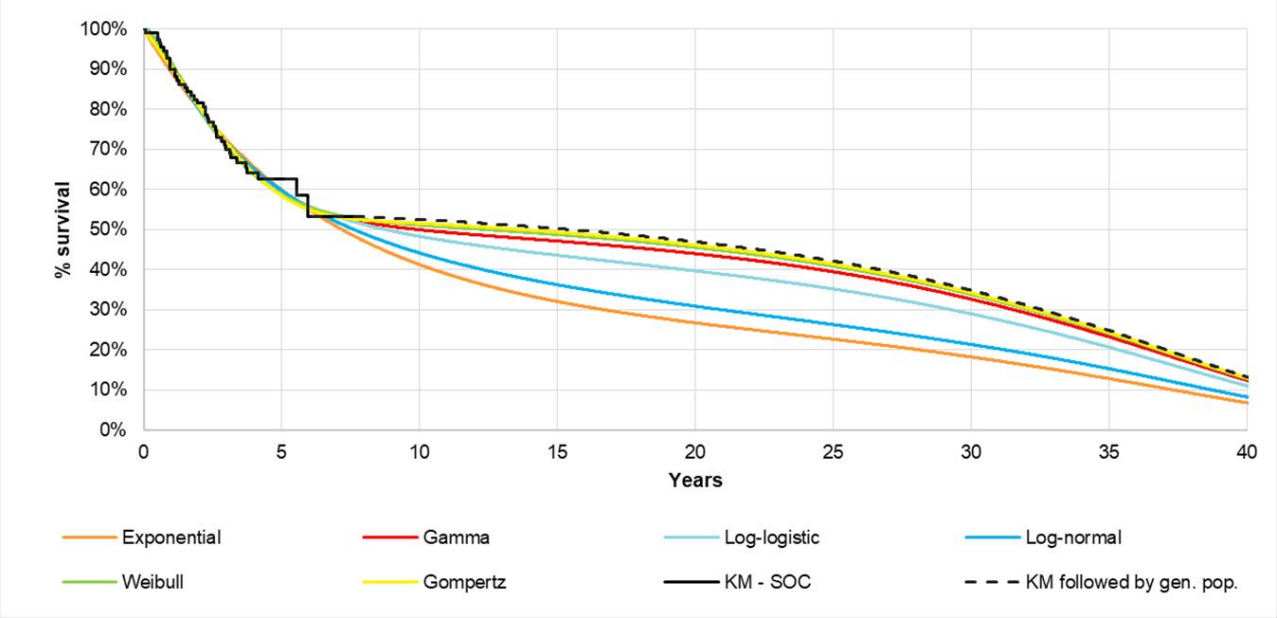
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; MCM, mixture cure model; OS, overall survival.

Figure 16: Extrapolated MCM (OS) – blinatumomab + SOC in MRD-negative population



Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; MRD: minimal residual disease; OS, overall survival; SOC, standard of care.

Figure 17: Extrapolated MCM (OS) – SOC in MRD-negative population



Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; MRD: minimal residual disease: OS, overall survival; SOC, standard of care.

Table 23: Landmark survival estimates for OS in MRD-negative population

Year	Blinatumomab + SOC				SOC			
	KM	Weibull	Log-logistic	Gamma	KM	Weibull	Log-logistic	Gamma
1	96.4%	94.9%	94.7%	94.5%	90.0%	91.5%	91.5%	91.5%
2	90.1%	88.4%	88.6%	88.3%	81.5%	80.5%	79.9%	80.2%
3	85.5%	84.0%	84.7%	84.3%	70.0%	70.9%	70.7%	70.8%
4	82.4%	81.7%	82.3%	82.0%	64.1%	63.7%	64.0%	63.8%
5	82.4%	80.7%	80.7%	80.6%	62.5%	58.8%	59.3%	59.0%
10	-	78.3%	76.2%	77.6%	-	51.2%	48.4%	50.0%
20	-	70.2%	67.6%	69.6%	-	45.7%	39.8%	44.2%
30	-	52.4%	50.3%	51.9%	-	34.1%	29.2%	32.9%

Abbreviations: KM, Kaplan–Meier; OS: overall survival; MRD: minimal residual disease: SOC, standard of care.

Table 24: Cure fractions for MCMs for OS in MRD-negative population

Treatment Arm	Exponential	Gamma	Gompertz	Log-Logistic	Log-Normal	Weibull
Blinatumomab + SOC	0.781	0.811	0.823	0.783	0.756	0.819
SOC	0.278	0.515	0.540	0.439	0.257	0.533

Abbreviations: OS: overall survival; MCM, mixture cure model; MRD: minimal residual disease: SOC, standard of care.

Relapse-free survival

Assessment of the proportional hazard (PH) assumption

The LCH and Schoenfeld residual plots for RFS are presented in Figure 18 and Figure 19, respectively. Similar to OS, the LCH plot displayed curves that cross at the start of the follow-up period, suggesting that the PH assumption was violated. After around 3 months, the curves appeared to be approximately parallel. The Schoenfeld residual plot formed an approximately horizontal line up to around 23 months, supporting the PH assumption. The gradient after 23 months raised some concerns; however, the Schoenfeld individual test provided no evidence against the PH assumption ($p > 0.05$). Given that there was evidence that the PH assumption is violated, the analyses focused on fitting separate effect models to the data.

To assess whether the AFT assumption is appropriate, Q–Q plots were generated (Figure 20). As seen with OS, the quantile pairs formed an approximately straight line. However, to assess the AFT assumption more robustly, extended follow-up was necessary. Given the current dataset's limitations, the tests performed to evaluate the PH and AFT assumptions were inconclusive. To ensure more robust and definitive findings, additional follow-up was required. In keeping with our approach for the analysis of OS, our analyses focused on fitting separate AFT models in conjunction with the PH approach.

Figure 18: Log-cumulative hazard plot for RFS in the MRD-negative population

Abbreviations: Blin: blinatumomab; MRD: minimal residual disease; RFS: relapse-free survival; SOC: standard of care.

Figure 19: Schoenfeld residual plot for RFS in the MRD-negative population

Abbreviations: Blin: blinatumomab; MRD: minimal residual disease; RFS: relapse-free survival.

Figure 20: Quantile–quantile plot for RFS in the MRD-negative population

Abbreviations: Blin: blinatumomab; MRD: minimal residual disease; RFS: relapse-free survival; SOC: standard of care.

Extrapolation selection

A variety of MCM models were fitted to the observed clinical trial data. Table 25 summarises the model fit statistics associated with MCMs across both the blinatumomab + SOC and SOC arms for the RFS endpoint. Figure 21 and Figure 22 present the extrapolated curves.

While the generalised gamma MCM was included when running the survival analysis, it is not considered in the model as it appeared to be over-fitting the data, leading to implausible results (with a low cure fraction) for the RFS distribution and it did not converge when fitting to the OS KM curve, leading to errors. Additionally, the Gompertz MCM cure fraction was unstable when running the probabilistic scenario analysis (PSA) and therefore was also not considered for the base case.

All remaining models provided a good statistical and visual fit to the trial data in both arms but underestimated RFS towards the tail of the KM curve for blinatumomab + SOC, while overestimating

the tail of the SOC KM curve. The exponential, log-normal, and log-logistic distributions had the three best statistical fits. Landmark survival at different time periods for each of the top three MCMs versus the E1910 KM RFS data are presented in Table 26 and the cure fractions for the MCMs are presented in Table 27.

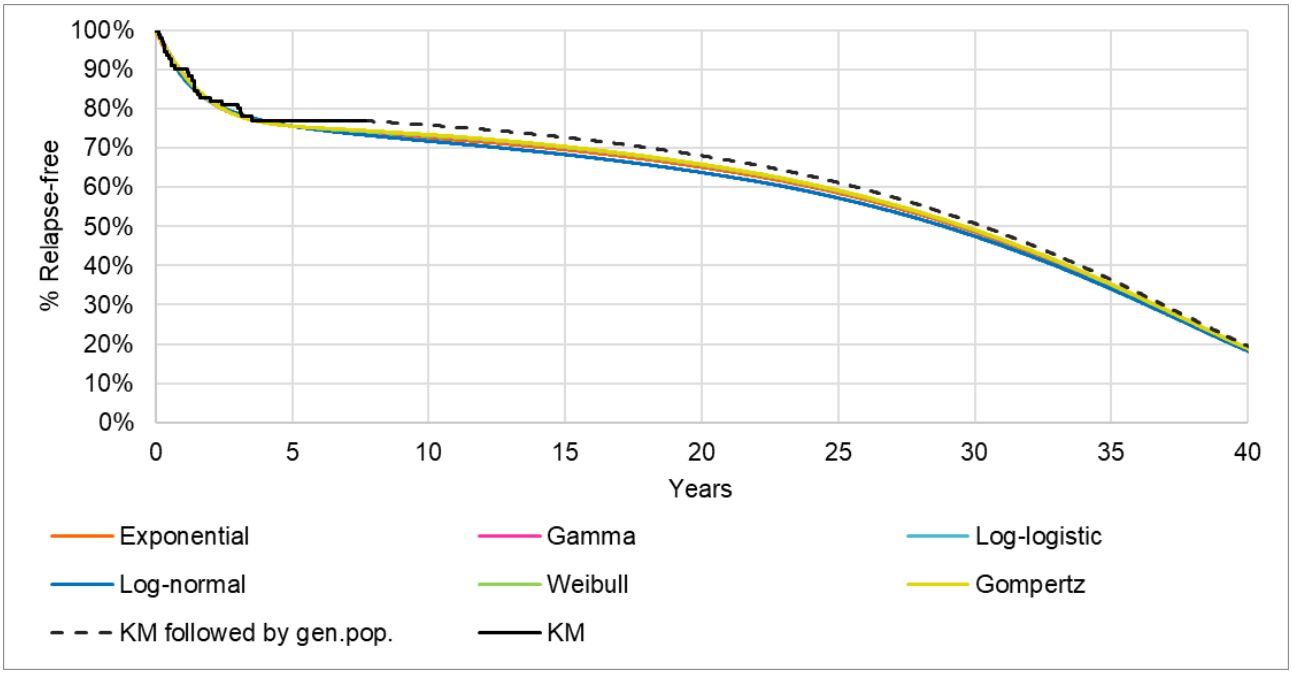
Of these, log-normal was selected as the base case RFS curve, as it provides a plausible survival in both treatment arms, while ensuring that RFS and OS crossing for SOC is kept to a minimum. While all MCMs appear to overestimate RFS in the SOC arm, the log-normal provides the closest fit to the SOC RFS KM curve, with the least overestimate of the KM curve at the tail. Exponential and log-logistic RFS extrapolations were explored in a scenario analysis (see Section B.3.10.3).

Table 25: Goodness-of-fit statistics – RFS in MRD-negative population

Model	Separate MCM fit			
	AIC	AIC rank	BIC	BIC rank
Exponential	784.84	2	795.72	1
Gamma	787.80	4	804.11	4
Generalised gamma	787.81	5	809.56	7
Gompertz	788.15	6	804.46	5
Log-logistic	786.58	3	802.89	3
Log-normal	784.43	1	800.74	2
Weibull	788.17	7	804.48	6

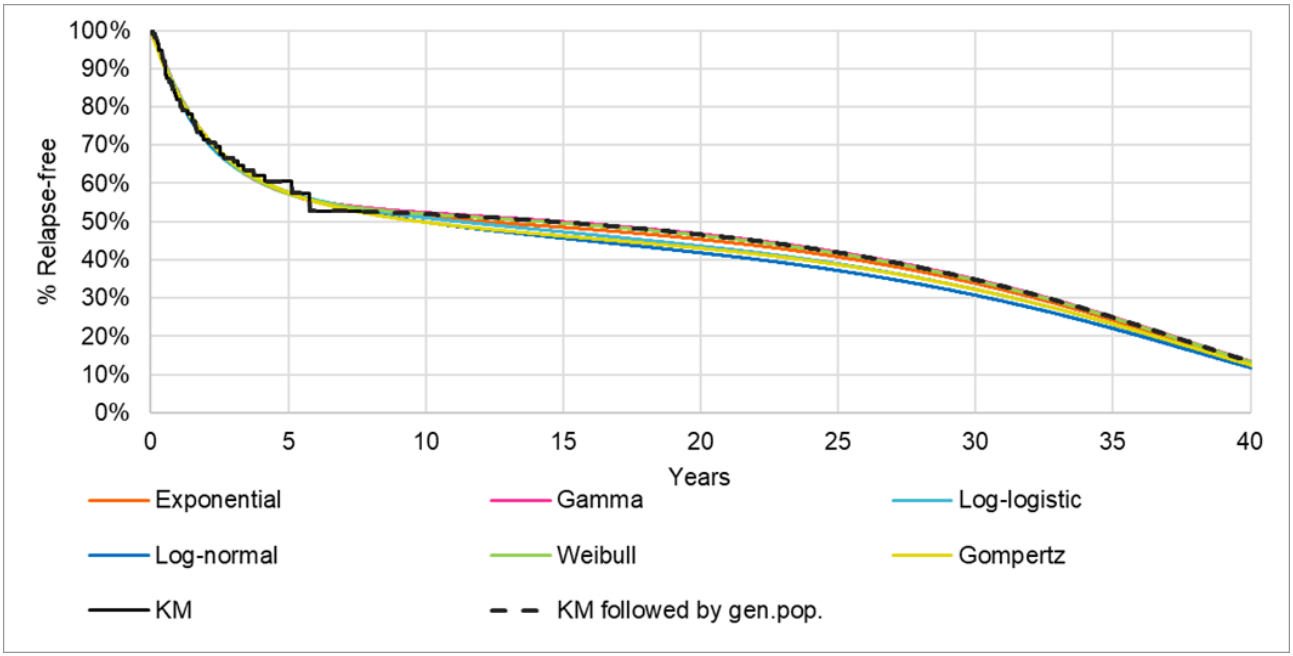
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; MCM, mixture cure model; RFS, relapse-free survival

Figure 21: Extrapolated MCM (RFS) – blinatumomab + SOC in MRD-negative population



Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; MRD: minimal residual disease; RFS, relapse-free survival.

Figure 22: Extrapolated MCM (RFS) – SOC in MRD-negative population



Abbreviations: gen.pop: general population; KM, Kaplan–Meier; MCM, mixture cure model; MRD: minimal residual disease; RFS, relapse-free survival; SOC, standard of care.

Table 26: Landmark survival estimates for RFS in MRD-negative population

Year	Blinatumomab + SOC				SOC			
	KM	Log-Normal	Exponential	Log-Logistic	KM	Log-Normal	Exponential	Log-Logistic
1	90.1%	87.9%	88.3%	88.1%	81.9%	82.2%	83.0%	82.4%
2	82.0%	81.9%	82.1%	81.9%	71.5%	71.4%	72.2%	71.0%
3	81.1%	78.8%	78.7%	78.8%	65.7%	64.9%	65.1%	64.5%
4	77.0%	76.9%	76.7%	76.9%	62.1%	60.6%	60.4%	60.4%
5	77.0%	75.6%	75.5%	75.6%	60.5%	57.6%	57.3%	57.6%
10	-	71.8%	72.6%	71.8%	-	49.8%	51.1%	51.0%
20	-	63.8%	65.1%	63.8%	-	41.8%	45.3%	43.6%
30	-	47.5%	48.6%	47.5%	-	30.7%	33.8%	32.2%

Abbreviations: KM, Kaplan–Meier; MCM, mixture cure model; MRD: minimal residual disease; RFS, relapse-free survival; SOC, standard of care.

Table 27: Cure fractions for MCMs for RFS in MRD-negative population

Treatment Arm	Exponential	Gamma	Gompertz	Log-Logistic	Log-Normal	Weibull
Blinatumomab + SOC	0.759	0.764	0.768	0.737	0.740	0.765
SOC	0.528	0.544	0.425	0.486	0.465	0.540

Abbreviations: MCM, mixture cure model; MRD: minimal residual disease; RFS, relapse-free survival; SOC, standard of care.

B.3.3.4 Summary of survival approaches

An overview of the modelling approaches adopted to extrapolate RFS and OS for each treatment arm in the base case cost-effectiveness analyses are presented in Table 28. As noted previously, the same distribution was applied across both treatment arms.

Table 28: Summary of selected base case survival approaches

Endpoint	Base case extrapolation[a]
RFS	Log-normal mixture cure
OS	Weibull mixture cure

Footnote: [a]The same distribution was applied across both treatment arms.
Abbreviations: OS: overall survival; RFS: relapse-free survival.

Scenario analyses were explored for alternative MCMs distributions (see Section B.3.3.3) as well as using parametric survival models (outlined in Section B.3.3.2). A summary of the survival approaches for these scenarios is provided in Table 29.

Table 29: Summary of scenario analysis survival approaches

Scenario	Endpoint	Scenario extrapolation[a]
Alternative MCM distribution	RFS	Exponential
	RFS	Log-logistic
	OS	Gamma
	OS	Log-logistic
Parametric survival models	RFS	Log-normal
	OS	Log-normal

Footnote: [a]The same distribution was applied across both treatment arms for the same endpoint for consistency in the assumption that different distributions make about the shape of the hazards rate.
Abbreviations: MCM: mixture cure model; OS: overall survival; RFS: relapse-free survival.

B.3.3.5 Adverse events

Probabilities of individual AEs for each intervention were based on trial data from the MRD-negative SAS patient population of the E1910 trial (N=223) as shown in Table 16 in Section B.2.9.3. Grade ≥3 TEAEs that occurred in ≥5% of patients in either trial arm were included in the CEM.[53] Additionally, grade ≥3 CRS was also included despite only affecting [redacted]% of patients in the SOC consolidation chemotherapy with blinatumomab treatment arm because it is a known AE specific to blinatumomab.[53]

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

As health-related quality of life (HRQoL) data were not collected in the E1910 trial, the utility values were aligned to those used in TA589.[2] These utility values were in turn based on data on EQ-5D utility values from trials in populations comparable to the current appraisal: BLAST (blinatumomab for adults with Ph- MRD+ B-ALL in CR)) and TOWER (blinatumomab versus chemotherapy for adults with relapse/refractory Ph-negative B-ALL):[5, 6]

- Utility values for MRD-responders (i.e. patients converting from MRD-positive to MRD-negative status) from the BLAST trial were used to estimate pre-relapse utilities for both treatment arms in

the E1910 trial – i.e. blinatumomab plus SOC consolidation chemotherapy and SOC consolidation chemotherapy alone (TA589).[2]

- As post-relapse utility assessments were limited in the BLAST trial, utility values of patients who were receiving SOC salvage chemotherapy (no prior salvage subgroup only) in the TOWER trial of blinatumomab versus chemotherapy in R/R B-cell ALL were used instead (TA589).[2]

These data were deemed suitable for use in this appraisal given that the BLAST and TOWER populations were similar to the population of interest in this analysis.[5, 6] The utilities from BLAST and TOWER were validated with UK clinical experts, who confirmed these utilities reasonably represent the quality of life of the modelled population.[93]

Utility values for the cured health state were based on general population norm utility values, and this was assumed to be starting at 5 years.

A summary of the health state utility values used in the base case is presented in Table 31.

B.3.4.2 Health-related quality-of-life studies

As detailed in Section B.3.4.1 the utility values align with TA589 and therefore no mapping was required.[2]

B.3.4.3 Adverse reactions

It is well accepted that AEs have a negative impact on patients' HRQoL. Relevant literature has previously explored the negative impact of AEs associated with treatment in patients with ALL, as discussed in Section B.1.3.2. As such, disutility values were applied to those experiencing AEs to estimate the reduction in HRQoL due to the event for its duration. All adverse reactions were assumed to occur in the first cycle of the model and last for a specified duration.

Disutilities associated with AEs were incorporated in the CEM by first multiplying the disutility decrement for each AE with its respective duration and the proportion of patients who had experienced these AEs, and thereafter summed across all AEs to determine a one-off value that was applied in the first cycle of the model. Utility decrements were derived from literature and previous TAs and are listed in Table 30 with the corresponding duration in days and source.

Table 30: Utility decrements associated with AEs included in the model

Adverse event	Utility (SE)	Duration (days)	Source
Alanine aminotransferase increased	−0.000 (0.000)	20.0	Assumed no disutility for abnormal lab tests
Anaemia	−0.120 (0.020)	14.9	Swinburn 2010[99]
Aphasia	−0.000 (0.000)	0.0	Assumption
Aspartate aminotransferase increased	−0.000 (0.000)	20.0	Assumed no disutility for abnormal lab tests
Cytokine release syndrome	−0.230 (0.023)	4.3	Howell et al. 2020[100]
Device-related infection	−0.200 (0.040)	15.1	Assumed same as sepsis
Diarrhoea	−0.050 (0.005)	7.0	Nafees et al. 2008[101]
Fatigue	−0.115 (0.012)	7.0	Lloyd et al. 2006[102]

Adverse event	Utility (SE)	Duration (days)	Source
Febrile neutropenia	−0.090 (0.020)	6.2	Nafees et al. 2008[101]
Headache	−0.027 (0.003)	2.0	Sullivan 2011[103]
Hyperglycaemia	−0.062 (0.010)	7.5	Sullivan 2011[103]
Hypertension	−0.070 (0.010)	4.0	Assumed same as hypotension
Hypertriglyceridemia	−0.000 (0.000)	0.0	Assumed no disutility for abnormal lab tests
Hypotension	−0.070 (0.010)	2.3	TA783[104]
Lymphocyte count decreased	−0.070 (0.010)	19.0	TA783[104]
Nausea	−0.050 (0.010)	7.0	Assumed same as diarrhoea
Neutrophil count decreased	−0.000 (0.000)	9.8	TA520[105]
Platelet count decreased	−0.050 (0.010)	11.9	TA653[106]
Sepsis	−0.200 (0.040)	15.1	Tolley 2013[107]
White blood cell count decreased	−0.050 (0.010)	16.9	TA520[105]

Abbreviations: AE: adverse event; SE: standard error.

Furthermore, patients who had received alloSCT were assumed to incur utility decrements to reflect known AEs or complications associated with alloSCT. A utility decrement of −0.57 was applied for one year, as informed by Sung et al. and in line with previous NICE submissions.[50, 79, 108] The alloSCT-related disutility is applied as a one-off decrement in the first cycle of the model and applied to the proportion of patients who received alloSCT pre-relapse. For patients who received alloSCT after relapse, the alloSCT-related disutility is applied as a one-off decrement at the time of relapse up to the cure timepoint of five years.

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the health state utility values used in the base case is presented in Table 31.

Table 31: Base case health state utilities in MRD-negative population

Health-state utilities	Mean utility value	Source
Relapse free		
Blinatumomab (off-treatment)	0.850	BLAST NICE TA589[2]
Blinatumomab (on-treatment)	0.840	BLAST NICE TA589. A utility decrement of 0.01045 was applied to account for any disutility associated with continuous IV infusion [2]
SOC consolidation chemotherapy	0.850	BLAST NICE TA589[2]
Post-relapse	0.692	TOWER, in line with NICE TA589[2, 109]
Death within ≤ 6 months	−0.129	BLAST, in line with NICE TA589[2]

Abbreviations: MRD: minimal residual disease; SOC: standard of care.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

The CEM included costs for the following categories:

- Consolidation therapy drug acquisition and administration
- alloSCT
- Maintenance therapy drug acquisition and administration
- Subsequent therapy drug acquisition and administration
- Adverse events
- Terminal care

As patients remaining in remission for five years can be considered cured,[83] patients no longer incur ALL-related costs (specifically subsequent therapy and terminal care costs, as all other costs are incurred within the first five years of the model) from five years onwards in the base case of the CEM. Details on the cost estimation in the model are provided in the sections below.

B.3.5.1 Intervention and comparator costs and resource use

Intervention: Blinatumomab with SOC consolidation chemotherapy

Drug acquisition resource use

The intervention of interest is blinatumomab with SOC consolidation chemotherapy, where blinatumomab is first administered for two consecutive cycles at a dose of 28 µg/day as a continuous intravenous infusion over 28 days followed by an infusion-free interval of 14 days.

After this, patients may go on to receive an alloSCT (based on eligibility and intention to receive an alloSCT at randomisation) or continue with consolidation chemotherapy alternating with an additional two cycles of blinatumomab. The consolidation chemotherapy regimen is based on the UKALL XII/ECOG E2993 protocol.[37] The schedule and dosing of this regimen is displayed in Table 32.

Table 32: Drug and dosing regimen for the blinatumomab with SOC consolidation chemotherapy arm

Cycle	Cycle length	Drug	Dose	Administration
Blinatumomab Cycle 1	42 days	Blinatumomab	28 µg/day	Days 1–28, followed by a 14-day treatment-free period
Blinatumomab Cycle 2	42 days	Blinatumomab	28 µg/day	Days 1–28, followed by a 14-day treatment-free period
Consolidation Cycle 1	28 days	Cytarabine	75 mg/m^2	IV on Days 1–5
		Etoposide	100 mg/m^2	IV on Days 1–5
		Methotrexate	12.5 mg	IT on Day 1
		Pegaspargase	2,000 IU/m^2, max dose of 3,750 IU	IV on Day 5
Consolidation Cycle 2	28 days	Cytarabine	75 mg/m^2	IV on Days 1–5
		Etoposide	100 mg/m^2	IV on Days 1–5
		Methotrexate	12.5 mg	IT on Day 1
Consolidation Cycle 3	42 days	Daunorubicin	25 mg/m^2	IV on Days 1, 8, 15, and 22
		Vincristine	1.4 mg/m^2, max dose of 2 mg	IV on Days 1, 8, 15, and 22
		Dexamethasone	10 mg/m^2, max dose of 20 mg	PO on Days 1–7, and 15–21
		Methotrexate	12.5 mg	IT on Day 2
		Cyclophosphamide	650 mg/m^2	IV on Day 29
		Cytarabine	75 mg/m^2	IV on Days 30–33, and 37–40
		6-mercaptopurine	60 mg/m^2	PO on Days 29–42
Blinatumomab Cycle 3	42 days	Blinatumomab	28 µg/day	Days 1–28, followed by a 14-day treatment-free period
Consolidation Cycle 4	28 days	Cytarabine	75 mg/m^2	IV on Days 1–5
		Etoposide	100 mg/m^2	IV on Days 1–5
		Methotrexate	12.5 mg	IT on Day 1
Blinatumomab Cycle 4	42 days	Blinatumomab	28 µg/day	Days 1–28, followed by a 14-day treatment-free period

Abbreviations: IT: intrathecal; IU: international units; IV: intravenous; PO: per oral.

The list price of blinatumomab is £2,017 per vial. The unit costs of cytarabine, etoposide, intrathecal methotrexate (IT), pegaspargase, daunorubicin, vincristine, cyclophosphamide, 6-mercaptopurine, and

dexamethasone were retrieved from the drugs and pharmaceutical drugs and pharmaceutical electronic market information tool (eMIT) database or British National Formulary (BNF; Table 33).[74, 78]

The cost of each drug was derived using the method of moments approach, in which a distribution of the BSA or weight of the patient population is assumed, rather than a point estimate. Using the point estimate and variation of BSA and weight in the E1910 population, normal and log-normal distributions were fitted, respectively, and were thereafter used to calculate a distribution of plausible doses. The average number of vials required was then computed and subsequently multiplied by the cost per vial to obtain the cost per treatment.

Table 33: Unit cost of drug used in consolidation chemotherapy

Drug		Pack size	Unit cost	Dose	Cost per administration	Source
Cytarabine	100 mg/ml vial	5	£13.76	75mg/m²	£2.75	eMIT [110]
Etoposide	20 mg/ml vial	10	£13.40	100mg/m²	£1.34	eMIT [110]
Methotrexate	50 mg/2 ml vial	2	£14.72	12.5mg	£2.94	eMIT [110]
Pegaspargase	3,750 mg/5 ml vial	1	£1,296.79	2000IU/m²	£1,296.36	BNF [78]
Daunorubicin	20 mg/ml vial	10	£715.00	25mg/m²	£214.50	BNF [78]
Vincristine	2 mg/2 ml vial	5	£12.09	1.4mg/m²	£2.42	eMIT [110]
Cyclophosphamide	500 mg powder for injection	1	£9.32	650mg/m²	£22.53	eMIT [110]
	1,000 mg powder for injection	1	£13.12			
	2,000 mg powder for injection	1	£27.50			
6-mercaptopurine	50 mg tablet	25	£9.42	60mg/m²	£1.10	BNF [78]
Dexamethasone	2 mg tablet	50	£2.32	10mg/m²	£0.45	eMIT [110]

Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool.

For the CEM, blinatumomab was assumed to be dosed at 28 mcg per day, consistent with the dosing instructions in the label. However, not all patients in the E1910 trial completed the full course of blinatumomab and the consolidation chemotherapy treatment.[53] The drug acquisition and administration costs were therefore corrected by the observed proportion of patients starting each cycle of treatment in E1910, as shown in Table 36, to ensure the modelled costs match what is used in clinical practice. This observed treatment use already accounts for patients discontinuing due to relapse. The treatment costs were therefore modelled independently of RFS.

Additionally, in E1910, patients could receive various types of dose modifications, leading to a lower observed cumulative dose than 28 mcg per day, including:

- Dose held
- Dose delayed
- Dose escalated
- Dose missed
- Dose reduced

It is likely that these dose modifications may lead to a lower number of vials being used. Therefore, a scenario analysis has been provided that adjusts the blinatumomab treatment costs by the observed cumulative dose from E1910 (see Section B.3.10.3).[53] Although this adjustment may be more aligned with real-world use of blinatumomab dosing, it was not included in the base case because it is uncertain whether all these modifications would directly translate to lower drug acquisition costs without wastage.

Administration resource use

In line with the E1910 protocol, it was assumed that blinatumomab with SOC consolidation chemotherapy would be administered on an inpatient basis for 3 days during the first cycle and for the first 2 days of every subsequent cycle.[111] Following the inpatient stay, all remaining IV chemotherapy regimens were assumed to be administered on an outpatient basis. A summary of the administration resource use costs is provided in Table 34. It should be noted that as methotrexate, as part of SOC consolidation chemotherapy, was administered only during the inpatient period, its costs are already included in the inpatient costs.

Table 34: Inpatient and outpatient administration costs

Resource use	Cost	Source
Daily cost of hospitalisation	£577.45	SA24G, SA24H, SA24J[b]
Outpatient IV chemotherapy administration	£349.41	SB15Z[b]
Blinatumomab bag change[a]	£349.41	SB15Z[b]

Footnotes: [a]It is assumed that all bag changes occurred in an outpatient IV infusion centre. Patients receiving blinatumomab were assumed to receive a bag change at an outpatient infusion centre every 4 days. [b]Costs were inflated to 2022/2023 prices using the NHS Cost Inflation Index. NHSCII).[72, 81]
Source: NHS Reference Costs 2021/2022.[81]

The administration costs for blinatumomab also included pump acquisition, maintenance, and consumable costs. These costs were taken from TA589 and adjusted for inflation (assuming an original cost year of 2016/2017).[2] The modelled base case assumes the pump is costed on a prorated daily basis over the 5-year life span of the pump, which results in daily home infusion costs of £4.54 (Table 35). This daily home infusion cost was applied to patients receiving blinatumomab in the outpatient setting.

Table 35: Blinatumomab home infusion pump costs

Item	Cost (£)(Inflated to 2022/2023 Prices)	
	Total	Per day
Pump cost (5-year lifespan)	2,121.84	1.16
Annual maintenance costs	106.39	0.29
Daily consumables	3.09	3.09
Total	**2,094**	**4.54**

Total acquisition and administration costs

The total acquisition and administration costs of blinatumomab with SOC consolidation chemotherapy in the base case population are summarised in Table 36.

Table 36: Summary of acquisition and administration costs of blinatumomab with SOC consolidation chemotherapy

Cycle	Proportion starting treatment	Inpatient days	Outpatient blinatumomab bag change	Blinatumomab pump cost days	Outpatient IV	Outpatient IT	Total acquisition cost per treatment cycle	Total administration cost per treatment cycle
Cycle 1 – blinatumomab	[redacted]	3	6	25	0	Administered during inpatient period	[redacted]	[redacted]
Cycle 2 – blinatumomab	[redacted]	2	6	26	0		[redacted]	[redacted]
Consolidation Cycle 1	[redacted]	2	NA	NA	3		[redacted]	[redacted]
Consolidation Cycle 2	[redacted]	2	NA	NA	3		[redacted]	[redacted]
Consolidation Cycle 3	[redacted]	2	NA	NA	12		[redacted]	[redacted]
Consolidation Cycle 4 – blinatumomab	[redacted]	2	6	26	0		[redacted]	[redacted]
Consolidation Cycle 5	[redacted]	2	NA	NA	3		[redacted]	[redacted]
Consolidation Cycle 6 – blinatumomab	[redacted]	2	6	26	0		[redacted]	[redacted]
Total							[redacted]	[redacted]

Abbreviations: IT, intrathecal; IV, intravenous; NA, not applicable; SOC: standard of care.
Source: E1910 CSR. Amgen Data on File.[53]

Comparator: SOC consolidation chemotherapy

Drug acquisition resource use

The comparator considered in this CEM represents the SOC treatment, which is assumed to be the conventional consolidation chemotherapy for patients with MRD-negative disease based on the UKALL XII/ECOG 2993 protocol.[37] As outlined in Section B.3.2.3, UK expert clinicians confirmed during an advisory board that this aligns with the UKALL14 protocol used in typical UK clinical practice.[1, 24] The schedule and dosing of this regimen is displayed in Table 37. Patients receiving SOC consolidation chemotherapy were assumed to incur the same drug costs in Table 33, as they share the same treatment backbone therapy with the blinatumomab arm.

Table 37: Drug and dosing regimen for SOC consolidation chemotherapy arm

Cycle	Cycle length	Drug	Dose	Administration
Consolidation Cycle 1	28 days	Cytarabine	75 mg/m^2	IV on Days 1–5
		Etoposide	100 mg/m^2	IV on Days 1–5
		Methotrexate	12.5 mg	IT on Day 1
		Pegaspargase	2,000 IU/m^2, max dose of 3,750 IU	IV on Day 5
Consolidation Cycle 2	28 days	Cytarabine	75 mg/m^2	IV on Days 1–5
		Etoposide	100 mg/m^2	IV on Days 1–5
		Methotrexate	12.5 mg	IT on Day 1
Consolidation Cycle 3	42 days	Daunorubicin	25 mg/m^2	IV on Days 1, 8, 15, and 22
		Vincristine	1.4 mg/m^2, max dose of 2 mg	IV on Days 1, 8, 15, and 22
		Dexamethasone	10 mg/m^2, max dose of 20 mg	PO on Days 1–7, and 15–21
		Methotrexate	12.5 mg	IT on Day 2
		Cyclophosphamide	650 mg/m^2	IV on Day 29
		Cytarabine	75 mg/m^2	IV on Days 30–33, and 37–40
		6-mercaptopurine	60 mg/m^2	PO on Days 29–42
Consolidation Cycle 4	28 days	Cytarabine	75 mg/m^2	IV on Days 1–5
		Etoposide	100 mg/m^2	IV on Days 1–5
		Methotrexate	12.5 mg	IT on Day 1

Abbreviations: IT: intrathecal; IU: international units; IV: intravenous; PO: per oral; SOC: standard of care.

Administration resource use

Similar to blinatumomab, patients were assumed to require 3 days of inpatient stay for the first consolidation cycle, and 2 days at the start of each subsequent cycle. Thereafter, all chemotherapy regimens were administered on an outpatient basis. The cost of inpatient stays and the cost of outpatient IV administration aligned to blinatumomab (Table 34).[81] In further alignment with the intervention arm, the cost of IT administration for methotrexate was assumed to be zero as these costs are already included in the inpatient costs. The drug administration costs were weighted by the proportions starting treatment, detailed in Table 38.

Total acquisition and administration costs

The total acquisition and administration costs of SOC in the base case population are summarised in Table 38 and are derived from the unit costs presented in Table 33.

Table 38: Summary of acquisition and administration costs of SOC

Cycle	Proportion starting treatment	Inpatient days	IV (Outpatient)	Total acquisition cost per treatment cycle	Total administration cost per treatment cycle
Consolidation Cycle 1	[redacted]	3	2	[redacted]	[redacted]
Consolidation Cycle 2	[redacted]	2	3	[redacted]	[redacted]
Consolidation Cycle 3	[redacted]	2	12	[redacted]	[redacted]
Consolidation Cycle 4	[redacted]	2	2	[redacted]	[redacted]
Total	–	–	–	[redacted]	[redacted]

Abbreviations: IV: intravenous; SOC: standard of care.
Source: E1910 CSR. Amgen Data on File.[53]

AlloSCT costs

Patients who were randomised to the blinatumomab arm in the E1910 trial could receive alloSCT after two cycles of blinatumomab, while those randomised to the SOC arm could receive alloSCT at any time point during consolidation chemotherapy.[49] Intent to transplant was a stratification factor in E1910 and therefore the proportion of patients receiving alloSCT was well-balanced across the treatment arms. In total, [redacted] and [redacted] patients in the SOC consolidation chemotherapy plus blinatumomab arm and the SOC consolidation chemotherapy arm, respectively, received alloSCT pre-relapse in the base case population (this includes patients who received alloSCT on- and off-protocol, which captures patients receiving alloSCT even if they discontinued their on-protocol treatment).[49] Clinical expert feedback indicated the rate of alloSCT observed in E1910 may be higher than UK clinical practice, but agreed that it was most appropriate to ensure that the treatments used to determine efficacy in the model (i.e. trial data) correspond directly with the treatments for which costs are calculated.[93]

The cost of pre-relapse alloSCT was applied as a one-off cost at the start of the model. The cost of alloSCT was estimated in three parts: stem cell harvesting, cost of alloSCT procedure, and the cost of follow-up (Table 39). The cost of stem cell harvesting and the alloSCT procedure were based on NHS Reference Costs 2021/2022 and inflated to 2022/2023 costs.[81]

Table 39: AlloSCT cost

Component	Cost	Source
Stem cell harvesting	£5,824	NHS reference costs 2021/22 – Weighted average of elective inpatient bone marrow harvest (SA18Z) and peripheral blood stem cell harvest (SA34Z)[81] inflated to 2022/2023 costs using NHSCII[72]
AlloSCT procedure	£42,791	NHS reference costs 2021/22 - Weighted average of elective inpatient Bone Marrow Transplant, Allogeneic Graft (SA20A-SA23A) and Peripheral Blood Stem Cell Transplant (SA38A-SA40A) for 19 years and over[81] inflated to 2022/2023 costs using NHSCII[72]
AlloSCT follow-up, up to 24 months	£48,542	NHS Blood and Transplant 2014 (Table 40) inflated to 2022/2023 costs using NHSCII[72]
Total	£97,157	

Abbreviations: AlloSCT: allogeneic stem cell transplant.

The cost of follow-up was based on NHS Blood and Transplant costs in 2014, inflated to 2022/2023 values (Table 40).

Table 40: AlloSCT follow-up cost breakdown

Component	Cost (2012–2013)	Proportion alive	Inflated cost 2022–2023
Follow-up (up to 6 months)	£28,390	90%	£48,542
Follow-up (6 to 12 months)	£19,502	48%	
Follow-up (12 to 24 months)	£14,073	31%	

Abbreviations: AlloSCT: allogeneic stem cell transplant.

Therefore, the total cost of HSCT was estimated to be £97,157, resulting in an alloSCT cost of £21,685 in the blinatumomab plus SOC consolidation chemotherapy arm and £24,289 in the SOC consolidation chemotherapy arm.

Maintenance therapy costs

Upon completion of consolidation therapy, patients in both treatment arms were assumed to go on to receive maintenance therapy for up to 2.5 years or until relapse. Maintenance chemotherapy used in the CEM reflected the E1910 trial protocol and is comprised of the following:[111]

- 6-mercaptopurine: 75 mg/m^2 per oral (PO) daily
- Methotrexate: 20 mg/m^2 PO weekly
- Vincristine: 1.4 mg/m^2 IV on Day 1 every 3 months, with a max dose of 2 mg

- Prednisolone: 60 mg/m^2 PO on Days 1–5, every 3 months
- Methotrexate: 12.5 mg IT on Day 1 every 3 months

All drug costs were sourced from either BNF or the eMIT database (Table 41). The method of moments was also applied to determine the dose of all BSA or weight-based drugs.

Table 41: Unit cost of drug used in maintenance chemotherapy

Drug		Pack size	Unit cost	Dose	Cost per dose	Source
6-mercaptopurine	50 mg tablet	25	£9.42	75.0 mg/m²	£1.32	BNF[78]
Methotrexate (oral)	2.5 mg tablet	100	£3.18	20.0 mg/m²	£0.52	eMIT[110]
Methotrexate (IT)	50 mg/2 ml vial	5	£14.72	12.5 mg	£2.94	eMIT[110]
Vincristine	2 mg/2 ml vial	5	£12.09	1.4 mg/m²	£2.42	eMIT[110]
Prednisolone	1 mg tablet	28	£0.28	60 mg/m²	£0.96	eMIT[110]
	5 mg tablet	28	£0.41			eMIT[110]
	25 mg tablet	56	£11.76			eMIT[110]

Abbreviations: IT: intrathecal.

Maintenance chemotherapy was assumed to be administered exclusively in the outpatient setting. The cost of IT administration for methotrexate was estimated to be the same as for IV chemotherapy administration, based on SB15Z (i.e. delivery of subsequent elements of a chemotherapy cycle in the outpatient setting). Administration costs for oral medications were assumed to be zero. The total drug and administration costs for maintenance treatment were then applied as an average weekly cost in the CEM, as shown in Table 42.

Table 42: Summary of average weekly drug and administration costs for maintenance therapy

Cycle	Admin Route	Administration	Average weekly drug costs	Average weekly admin costs
Mercaptopurine	Oral	Daily	£9.23	£0.00
Methotrexate (Oral)	Oral	Weekly	£0.52	£0.00
Vincristine sulphate	IV subsequent (Outpatient)	Day 1, every 3 months	£0.19	£25.03
Prednisolone	Oral	Days 1 - 5, every 3 months	£0.37	£0.00
Methotrexate (IT)	IT (chemotherapy into CNS)	Day 1, every 3 months	£0.23	£25.03
Total			£10.53	£50.05

Abbreviations: CNS: central nervous system; IT: intrathecal; IV: intravenous.

Subsequent treatment costs

Upon relapse, patients were eligible to receive subsequent treatment with either blinatumomab, inotuzumab ozogamicin, chemotherapy, CAR-T, or alloSCT. The proportion of patients receiving these therapies was based on clinician feedback from a UK advisory board (Table 43).[1] While CAR-T therapy (including tisagenlecleucel and brexucabtagene autoleucel) is listed an option for second-line treatment, it was assumed that no patients receive these CAR-T therapies in the model. This is because:

- Brexucabtagene autoleucel is currently provided through the Cancer Drugs Fund (CDF) only and therefore does not represent a relevant subsequent therapy to consider (TA893).[50]
- Tisagenlecleucel was recently recommended for patients aged 25 years and under, whereas the mean starting age for this model is around [redacted] years of age, based on the E1910 trial, which enrolled only patients who were 30–70 years old (see Section B.3.3.1), so a negligible number of modelled patients were anticipated to be eligible for it (TA975).[112]

All subsequent treatment costs were applied as a one-off cost to patients who relapsed at each model cycle. After five years, patients were considered clinically cured and therefore no longer at risk of relapse. Thus, patients remaining relapse-free after five years would not incur any subsequent treatment costs.

Table 43: Proportion of post-relapse patients receiving subsequent treatment

Subsequent treatment	Blinatumomab (%)	SOC consolidation chemotherapy
Blinatumomab	[redacted]	[redacted]
Inotuzumab ozogamicin	[redacted]	[redacted]
Salvage chemotherapy (FLAG-IDA)	[redacted]	[redacted]
CAR-T	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]

Abbreviations: CAR-T: chimeric antigen receptor T-cell; FLAG-IDA: fludarabine, cytarabine, idarubicin, and filgrastim; SOC: standard of care.
Source: Amgen. Data on File. Amgen UK Advisory Board Meeting Report.[1]

Blinatumomab as subsequent therapy

The dosing regimen of blinatumomab as a second line treatment follows the dosing in the TOWER trial, in which blinatumomab was given as monotherapy at a dose of 9 mcg/day on days 1–7 of the first cycle, followed a dose of 28 mcg/day for the remaining days of the first cycle and for all subsequent cycles.[109] The proportion of patients who received blinatumomab was assumed to be the average of the percentages of patients starting and completing each cycle of blinatumomab from TOWER, for up to nine cycles (Table 44). In TOWER, the mean number of cycles of blinatumomab was [redacted] and median number of cycles of blinatumomab was 2, which UK clinical experts agreed was in line with clinical practice where patients typically receive between two to three cycles of blinatumomab in the relapse/refractory setting.[1]

Table 44: Proportion of patients starting, completing, and receiving each cycle of blinatumomab as a subsequent treatment

Cycle	Patients starting cycle (%)	Patients completing cycle (%)	Patients receiving blinatumomab in model (%)
Cycle 1	98.52%	73.06%	[redacted]
Cycle 2	55.72%	50.18%	[redacted]
Cycle 3	31.73%	28.04%	[redacted]
Cycle 4	22.14%	20.30%	[redacted]
Cycle 5	14.76%	13.28%	[redacted]
Cycle 6	9.96%	9.59%	[redacted]
Cycle 7	6.27%	5.90%	[redacted]
Cycle 8	2.21%	1.85%	[redacted]
Cycle 9	1.48%	1.48%	[redacted]

The administration of blinatumomab as a subsequent treatment is assumed to be similar to frontline, with an initial inpatient period, followed by outpatient administration comprised of pump costs and outpatient bag changes. For blinatumomab as a subsequent therapy, patients were assumed to require ten inpatient administration days for the first cycle, two inpatient days for the second cycle, and all outpatient administration for cycles three to nine. The resulting total cost of second line blinatumomab is shown in Table 45.

Table 45: Total cost of second line blinatumomab

Cycle	Total acquisition cost[a]	Total administration cost
Cycle 1	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]
Total[b]	[redacted]	[redacted]

Footnotes: [a]Applied as a one-off; [b]Takes into account the proportion of patients who received blinatumomab in Table 44.

Inotuzumab ozogamicin as subsequent therapy

The unit cost of inotuzumab is £8,048.00 per 1 mg vial. In addition, TA541 reported the average course of treatment, using method of moments, required 9.49 vials.[92] In the absence of more granular publicly available treatment use data, this was multiplied by the cost per vial to calculate the total treatment costs, which amounted to £76,375.52.

In line with the ERG-preferred approach from TA541[92], inotuzumab was assumed to be administered inpatient for the first 9.5 days of Cycle 1, and the cost was the weighted average for elected inpatient stays for ALL (SA24G, SA24H, SA24J) at £577.45 from NHS Reference Cost 2021/2022 (inflated to 2022/2023 costs).[81] Inotuzumab was then modelled to be administered on an outpatient basis for the remainder of Cycle 1, and for Cycles 2 and 3, costing £349.41 per IV administration based on NHS Reference Cost Outpatient SB15Z, inflated to 2022/2023 costs (Table 46).

Table 46: Inotuzumab administration costs

Cycle	Inpatient days	Outpatient IV	Total costs
Cycle 1	9.5	1	£5,835
Cycle 2	0	3	£1,048
Cycle 3	0	3	£1,048
Total			£7,932

Abbreviations: IV: intravenous.

Salvage chemotherapy (FLAG-IDA) as subsequent therapy

The dosing of FLAG-IDA comprised of the following:

- Fludarabine: 30 mg/m^2 for 5 consecutive days per 28-day cycle for up to four cycles
- Cytarabine: 2 g/m^2 for 5 consecutive days per 28-day cycle for up to four cycles
- Filgrastim: 0.005 mg/kg for a maximum of 14 days
- Idarubicin: 8 mg/m^2 for 3 days per 28-day cycle

The acquisition costs of the different drugs are retrieved from eMIT, BNF, and Monthly Index of Medical Specialties when appropriate (Table 47). A maximum of four cycles was applied in line with UK clinical practice.

Table 47: Unit cost of drugs used in FLAG-IDA

Drug		Pack size	Unit cost	Dose	Cost per administration	Source
Fludarabine	25 mg/2 ml vial	1	£83.86	30 mg/m²	£158.30	eMIT[110]
Cytarabine	20 mg/ml vial	5	£4.19	2000 mg/m²	£27.14	eMIT[110]
	100 mg/ml vial	1	£7.72			
	100 mg/ml vial	1	£8.50			
	100 mg/ml vial	5	£2.75			
Idarubicin	1 mg/ml vial	1	£87.36	8.00 mg/m²	£323.82	MIMS[113, 114]
	1 mg/ml vial	1	£174.72			

Drug		Pack size	Unit cost	Dose	Cost per administration	Source
Filgrastim	0.30 mg/ml vial	5	£175.68	0.005 mg/kg	£86.52	BNF[78]
	0.60 mg/ml vial	7	£189.33			
	0.60 mg/ml vial	1	£175.67			
	0.96 mg/ml vial	5	£166.46			
	0.96 mg/ml vial	7	£189.88			
	0.96 mg/ml vial	5	£189.12			
	0.96 mg/ml vial	1	£175.13			

Abbreviations: BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool; FLAG-IDA: fludarabine, cytarabine, idarubicin, and filgrastim; MIMS: Monthly Index of Medical Specialties.

The proportion of patients who received FLAG-IDA was based on the exposure data of the SOC cohort in the TOWER trial up to a total of four cycles (Table 48).

Table 48: Proportion of patients receiving each cycle of FLAG-IDA as a subsequent treatment

Cycle	Patients receiving FLAG-IDA in model (%)
Cycle 1	[redacted]
Cycle 2	[redacted]
Cycle 3	[redacted]
Cycle 4	[redacted]

Abbreviations: FLAG-IDA: fludarabine, cytarabine, idarubicin, and filgrastim.
Source: Amgen Data on File.

In line with TA893 and TA450, FLAG-IDA was assumed to be administered in an inpatient setting for an average of 16.8 days. The cost of the each inpatient day aligned with those used for blinatumomab and inotuzumab ozogamicin (£577.45).[81] This resulted in a total administration cost of FLAG-IDA as a subsequent treatment of £10,280. The total cost per course of therapy was estimated to be £13,576.

Post-relapse alloSCT

In addition to the aforementioned subsequent treatment options, patients who had relapsed and were eligible, may also receive alloSCT. In the blinatumomab alternating with consolidation chemotherapy treatment arm, [redacted] experienced a relapse event over the course of the E1910 trial. Of these patients, [redacted] received alloSCT after they relapsed. In the SOC alone treatment arm, [redacted] relapsed during the E1910 trial time horizon. Of these patients, [redacted] went on to receive alloSCT. As patients may receive any of the subsequent therapies from Table 43 as a bridge to alloSCT, alloSCT costs were calculated in addition to the

subsequent therapy costs outlined in the previous sections. The costs incurred as a result of post-relapse alloSCT were assumed to be the same as the pre-relapse alloSCT (Table 39).

B.3.5.2 Health-state unit costs and resource use

All health-state unit costs and resource use are considered in the costs for each treatment arm as presented above.

B.3.5.3 Adverse reaction unit costs and resource use

The CEM included all AEs of Grade 3 and above that occurred in ≥5% of patients in either treatment arm in E1910 (see Section B.3.3.5). The cost of treating the AEs was first calculated by multiplying the frequency at which each AE (Table 30) occurred with the unit cost of that AE, and thereafter applied as one-off costs at the start of the model. Unit costs were sourced from NHS Reference Costs and Personal Social Services Research Unit (PSSRU) when appropriate and were inflated to 2022/2023 using NHSCII.[72] The resulting unit costs are shown in Table 49.

Table 49: Cost per event of AEs included in the model

Adverse event	Cost per event	Source
Alanine aminotransferase increased	£808.79	NHS reference costs 2021/22 - Non-elective Short Stay Liver Failure Disorders without Interventions, with CC Score 0-4 (GC01F) [81]
Anaemia	£646.20	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Iron Deficiency Anaemia (SA04G-SA04L) [81]
Aphasia	£661.85	NHS reference costs 2021/22 - Rehabilitation for Other Neurological Disorders (VC12Z) [81]
Aspartate aminotransferase increased	£808.79	NHS reference costs 2021/22 - Non-elective Short Stay Liver Failure Disorders without Interventions, with CC Score 0-4 (GC01F) [81]
Cytokine release syndrome	£9,865.09	NHS reference costs 2021/22 - Non-elective Short Stay Liver Failure Disorders without Interventions, with CC Score 0-4 (GC01F) [81]
Device related infection	£3,337.28	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Infections or Other Complications of Procedures (WH07E-WH07G) [81]
Diarrhoea	£609.11	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Non-Malignant Gastrointestinal Tract Disorders (FD10J-FD10M) [81]
Fatigue	£646.20	Assumed to be the same as anemia
Febrile neutropenia	£580.93	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Other Haematological or Splenic Disorders (SA08G-SA08J) [81]
Headache	£472.14	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Headache, Migraine or Cerebrospinal Fluid Leak (AA31C-AA31E) [81]

Adverse event	Cost per event	Source
Hyperglycaemia	£613.47	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Diabetes with Hyperglycaemic Disorders (KB02G-KB02K) [81]
Hypertension	£454.45	NHS reference costs 2021/22 - Hypertension (EB04Z) [81]
Hypertriglyceridemia	£56.00	PSSRU 2022, cost assumed to be 1 GP visit
Hypotension	£454.45	Cost assumed to be same as hypertension
Lymphocyte count decreased	£580.93	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Other Haematological or Splenic Disorders (SA08G-SA08J) [81]
Nausea	£609.11	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Non-Malignant Gastrointestinal Tract Disorders (FD10J-FD10M) [81]
Neutrophil count decreased	£580.93	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Other Haematological or Splenic Disorders (SA08G-SA08J) [81]
Platelet count decreased	£748.20	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Thrombocytopenia (SA12G-SA12K) [81]
Sepsis	£782.91	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Sepsis with Multiple Interventions (WJ06A-WJ06C), Sepsis with Single Intervention (WJ06D-WJ06F), and Sepsis without Interventions (WJ06-WJ06J) [81]
White blood cell count decreased	£580.93	NHS reference costs 2021/22 - Weighted average of Non-elective Short Stay Other Haematological or Splenic Disorders (SA08G-SA08J) [81]

Abbreviations: AE: adverse event: NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

In addition to the grade ≥3 AEs, costs associated with CRS were included in the CEM despite [redacted] of patients in the blinatumomab arm experienced it in the E1910 trial, because it is an AE listed in the label boxed warning for blinatumomab and is associated with substantial economic burden.[49] The cost of CRS was calculated with an assumption that CRS requires a mean duration of 4.3 days in the intensive care unit (ICU) in line with TA893.[50] The daily cost of an ICU visits is presented in Table 50, this resulted in total CRS costs of £9,865.[81]

Table 50: CRS management costs

Resource use	Cost	Source
Daily ICU cost	£2,294	XC01Z–XC07Z
Total costs: £9,865 (based on mean duration of 4.3 days in ICU)		

Abbreviations: CRS: cytokine release syndrome. ICU: intensive care unit.
Source: NHS Reference Costs 2021/2022, inflated to 2022/2023 prices.[81]

B.3.5.4 Miscellaneous unit costs and resource use

Dosing assumptions (wastage)

In the modelled base case, drug wastage is assumed for drugs administered intravenously, meaning that a full vial would be used when opened, without vial sharing. This applies for all injection-based treatments used in the CEM in the base case.

Terminal care costs

All patients who die in the model prior to the five-year cure timepoint were assumed to incur a one-time terminal care cost applied at the time of death. Given patients who survive beyond this cure timepoint are considered long-term survivors, it was assumed that these patients would not incur the costs of terminal care, as described in NICE TA554[83]

The cost of terminal care was based on a weighted average of NHS Reference Costs 2021–2022 SA24G–SA24J, inflated to 2022/2023 costs, resulting in an average terminal care cost of £10,953.

B.3.6 *Severity*

The severity modifier tool developed by the Sheffield Centre for Health and Related Research (SCHARR) was used to calculate the absolute and proportional severity modifiers.[115] The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider et al. (2022).[116] The total life expectancy for the modelled population was calculated using population mortality data from the Office for National Statistics (ONS) for 2017–2019. The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava et al. (2022) through the NICE DSU.

The baseline characteristics for the modelled population were informed by the E1910 trial, as detailed in Table 51 below, and the total QALYs for the population of patients receiving SOC in UK clinical practice was informed by the results of the base case probabilistic economic analysis, where SOC was associated with [redacted] QALYs.

As shown in Table 52, the results of the severity modifier calculations demonstrate that blinatumomab is not eligible for a severity modifier when compared to SOC.

Table 51: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Percentage male	49.6%	Section B.3.3.1
Starting age (years)	50.05	

Abbreviations: QALY: quality-adjusted life year.

Table 52: QALY shortfall analysis results

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
[redacted]	[redacted]	[redacted]	[redacted]	1

Abbreviations: AS: absolute shortfall; PS: proportional shortfall; QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year; SOC: standard of care.

B.3.7 *Uncertainty*

B-cell precursor ALL is a rare disease, and therefore is inherently associated with greater uncertainty than more prevalent diseases.[20] Nonetheless, the multinational Phase 3 RCT E1910 study represents the highest quality of evidence for a single study evaluating clinical efficacy of blinatumomab in this indication, and its relatively large sample size for the MRD-negative population (N=224) is particularly notable given the rarity of the disease. Furthermore, the study was statistically powered to detect differences in survival among MRD-negative patients, the specific population of interest. As such, while there are unavoidable uncertainties associated with rare indications, these uncertainties are sufficiently mitigated by the evidence package presented for this submission.

B.3.8 *Summary of base-case analysis inputs and assumptions*

B.3.8.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 53.

Table 53: Summary of variables applied in the CEM

Variable	Input	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Model settings			
Discount rate (costs and benefits)	3.5%	N/A	B.3.2.2
Time horizon, years	50		
Patient characteristics			
Mean age, years	50.1	0.77 (Normal)	B.3.3.1

Male, %	49.6%	0.03 (Beta)	
Mean weight, kg	86.6	1.47 (Normal)	
BSA	2.0	0.02 (Normal)	
Clinical inputs			
OS (blinatumomab+SOC consolidation chemotherapy)	Weibull MCM	Implemented by covariance matrix	B.3.3.4
RFS (blinatumomab+SOC consolidation chemotherapy)	Log-normal MCM	Implemented by covariance matrix	
OS (SOC consolidation chemotherapy)	Weibull MCM	Implemented by covariance matrix	
RFS (SOC consolidation chemotherapy)	Log-normal MCM	Implemented by covariance matrix	
Adverse events, incidence	*Various*	Implemented by covariance matrix	
SMR	1.09	0.22 (Gamma)	
Utility inputs			
Relapse free			B.3.4.4
Blinatumomab (off-treatment)	0.850	0.17 (Beta)	
Blinatumomab on-treatment decrement	-0.01	0.00 (Beta)	
SOC consolidation chemotherapy	0.850	0.17 (Beta)	
Post-relapse	0.692	0.14 (Beta)	
Post-alloSCT decrement	−0.57	0.11 (Beta)	
Death within ≤ 6 months	−0.129	0.03 (Beta)	
Adverse event disutility			
Alanine aminotransferase increased	0.00	0 (Beta)	B.3.4.4
Anaemia	0.12	0.02 (Beta)	
Aphasia	0.00	0 (Beta)	
Aspartate aminotransferase increased	0.00	0 (Beta)	
Cytokine release syndrome	0.23	0.05 (Beta)	
Device related infection	0.20	0.04 (Beta)	
Diarrhoea	0.05	0.01 (Beta)	
Fatigue	0.12	0.02 (Beta)	
Febrile neutropenia	0.09	0.02 (Beta)	
Headache	0.03	0.01 (Beta)	

Hyperglycaemia	0.06	0.01 (Beta)	
Hypertension	0.07	0.01 (Beta)	
Hypertriglyceridemia	0.00	0 (Beta)	
Hypotension	0.07	0.01 (Beta)	
Lymphocyte count decreased	0.07	0.01 (Beta)	
Nausea	0.05	0.01 (Beta)	
Neutrophil count decreased	0.00	0 (Beta)	
Platelet count decreased	0.05	0.01 (Beta)	
Sepsis	0.20	0.04 (Beta)	
White blood cell count decreased	0.05	0.01 (Beta)	
Adverse event durations			
Alanine aminotransferase increased	20.00	4.00 (Gamma)	B.3.4.4
Anaemia	14.90	2.98 (Gamma)	
Aphasia	0.00	0 (Gamma)	
Aspartate aminotransferase increased	20.00	4.00 (Gamma)	
Cytokine release syndrome	4.30	0.86 (Gamma)	
Device related infection	15.10	3.02 (Gamma)	
Diarrhoea	7.00	1.40 (Gamma)	
Fatigue	7.00	1.40 (Gamma)	
Febrile neutropenia	6.20	1.24 (Gamma)	
Headache	2.00	0.40 (Gamma)	
Hyperglycaemia	7.50	1.5 (Gamma)	
Hypertension	4.00	0.8 (Gamma)	
Hypertriglyceridemia	0.00	0 (Gamma)	
Hypotension	2.30	0.46 (Gamma)	
Lymphocyte count decreased	19.00	3.8 (Gamma)	
Nausea	7.00	1.4 (Gamma)	
Neutrophil count decreased	9.80	1.96 (Gamma)	
Platelet count decreased	11.90	2.38 (Gamma)	
Sepsis	15.10	3.02 (Gamma)	
White blood cell count decreased	16.90	3.38 (Gamma)	
Drug administration			
Cost per administration: Inpatient days	£577.45	107.91 (Gamma)	B.3.5.1
Cost per administration: Outpatient bag change	£349.41	65.29 (Gamma)	
Cost per administration: Pump costs	£127.37	23.8 (Gamma)	
Cost per administration: IV (Outpatient)	£349.41	65.29 (Gamma)	

Cost per administration: IT (chemotherapy into CNS) (Outpatient)	£349.41	65.29 (Gamma)	
Cost per administration: Oral	£0.00	0 (Gamma)	
Frequency of bag change	4	0.8 (Gamma)	
Pump costs			
Pump acquisition cost	[redacted]	359 (Gamma)	B.3.5.1
Pump life expectancy (years)	[redacted]	1 (Gamma)	
Pump maintenance costs, annual	[redacted]	18 (Gamma)	
Pump daily supply costs	[redacted]	0.52 (Gamma)	
Stem cell transplant costs			
Cost per administration: Stem cell harvesting cost	£5,823.97	1088.29 (Gamma)	B.3.5.1
Cost per administration: alloSCT procedure	£42,791	7995.99 (Gamma)	
Cost per administration: alloSCT follow-up cost	£48,542	7854.92 (Gamma)	
Other admin costs			
Cost per administration: ICU	£2,294.21	428.7 (Gamma)	B.3.5.1
Treatment use			
Proportion of patients receiving Cycle 1 - Blinatumomab	[redacted]	Calculated (see model), varied using Beta distribution	B.3.5.1
Proportion of patients receiving Cycle 2 - Blinatumomab	[redacted]		
Proportion of patients receiving Consolidation Cycle 1	[redacted]		
Proportion of patients receiving Consolidation Cycle 2	[redacted]		
Proportion of patients receiving Consolidation Cycle 3	[redacted]		
Proportion of patients receiving Consolidation Cycle 4 - Blinatumomab	[redacted]		
Proportion of patients receiving Consolidation Cycle 5	[redacted]		
Proportion of patients receiving Consolidation Cycle 6 - Blinatumomab	[redacted]		
Proportion of patients receiving Consolidation Cycle 1	[redacted]		
Proportion of patients receiving Consolidation Cycle 2	[redacted]		
Proportion of patients receiving Consolidation Cycle 3	[redacted]		
Proportion of patients receiving Consolidation Cycle 4	[redacted]		

AlloSCT distribution			
Relapse-free alloSCT distribution: (Blinatumomab)	[redacted]	[redacted]	B.3.5.1
Relapse-free alloSCT distribution: (SOC Chemotherapy)	[redacted]	[redacted]	
2L therapy distribution			
2L treatment distribution: Blinatumomab (Blinatumomab)	[redacted]	[redacted]	B.3.5.1
2L treatment distribution: Inotuzumab ozogamicin (Blinatumomab)	[redacted]	[redacted]	
2L treatment distribution: CAR-T (Blinatumomab)	[redacted]	[redacted]	
2L treatment distribution: FLAG-IDA (Blinatumomab)	[redacted]	[redacted]	
2L treatment distribution: No active treatment (Blinatumomab)	[redacted]	[redacted]	
2L treatment distribution: Blinatumomab (SOC Chemotherapy)	[redacted]	[redacted]	
2L treatment distribution: Inotuzumab ozogamicin (SOC Chemotherapy)	[redacted]	[redacted]	
2L treatment distribution: CAR-T (SOC Chemotherapy)	[redacted]	[redacted]	
2L treatment distribution: FLAG-IDA (SOC Chemotherapy)	[redacted]	[redacted]	
2L treatment distribution: No active treatment (SOC Chemotherapy)	[redacted]	[redacted]	
2L (Post-relapse) alloSCT distribution			
Blinatumomab	[redacted]	[redacted]	B.3.5.1
SOC chemotherapy	[redacted]	[redacted]	
Adverse event costs			
Alanine aminotransferase increased	£808.79	151.13 (Gamma)	B.3.4.3
Anaemia	£646.20	120.75 (Gamma)	
Aphasia	£661.85	123.68 (Gamma)	
Aspartate aminotransferase increased	£808.79	151.13 (Gamma)	
Cytokine release syndrome	£9,865.09	1843.42 (Gamma)	
Device related infection	£3,337.28	623.62 (Gamma)	

Diarrhoea	£609.11	113.82 (Gamma)	
Fatigue	£646.20	120.75 (Gamma)	
Febrile neutropenia	£580.93	108.55 (Gamma)	
Headache	£472.14	88.23 (Gamma)	
Hyperglycaemia	£613.47	114.64 (Gamma)	
Hypertension	£454.45	84.92 (Gamma)	
Hypertriglyceridemia	£56.00	11.2 (Gamma)	
Hypotension	£454.45	84.92 (Gamma)	
Lymphocyte count decreased	£580.93	108.55 (Gamma)	
Nausea	£609.11	113.82 (Gamma)	
Neutrophil count decreased	£580.93	108.55 (Gamma)	
Platelet count decreased	£748.20	139.81 (Gamma)	
Sepsis	£782.91	146.3 (Gamma)	
White blood cell count decreased	£580.93	108.55 (Gamma)	
End-of-life cost			
End-of-life costs	£10,952.83	2046.68 (Gamma)	B.3.5.4

Abbreviations: AE: adverse event; ALL: acute lymphoblastic leukaemia; alloSCT: allogeneic SCT; BSA: body surface area; ICU: intensive care unit; MRD: minimal residual disease; OS: overall survival; RFS: relapse-free survival; SCT: stem cell transplant; SOC: standard of care; SMR: standardised mortality ratio.

B.3.8.2 Assumptions

The key assumptions adopted in the base case of the CEM are presented in Table 54.

Table 54: Key model assumptions for the base case cost-effectiveness analysis

Assumption in the base case	Justification	Addressed in scenario analysis?
Extrapolations of OS and RFS were based on mixture cure models	In the MRD-negative population, a plateau in the KM curves of RFS and OS of blinatumomab plus SOC chemotherapy and SOC alone emerges from 4 years and 6 years onwards, respectively. This suggests that a proportion of patients may no longer be at risk of relapse or death due to ALL, and therefore may be considered cured. Additionally, the survival extrapolations were performed using data from E1910 and were validated using the insights of clinical experts.	Yes – standard parametric models are explored (log-normal for RFS and OS). Please see Section B.3.3.2 for more details.
To prevent the RFS and OS curves from converging, RFS risk is modelled to be equal to or higher than the OS risk at all times.	Modelling approaches in which the extrapolated RFS and OS curves converge are not clinically appropriate and indicate an unrealistic lack of post-relapse survival. This was observed particularly in the SOC consolidation chemotherapy arm, where the KM curves begin to converge at 3 years. To adjust for this, the RFS risk was modelled to be equal to or higher than the OS risk at all times. This adjustment provides a clinically realistic prediction of post-relapse survival without favouring either treatment arm.	No other methods for addressing the RFS and OS convergence were identified.
An SMR of 1.09 was assumed for the cured patients	The cost-effectiveness model uses a SMR of 1.09 based on clinical validation that this represents a suitable SMR for the MRD-negative population in the E1910 trial. Higher SMRs used in previous NICE TAs (3.00 – 4.00) were validated with the UK clinical experts who confirmed them to be too high for frontline ALL patients who are MRD-negative, given their better prognosis (versus MRD-positive and R/R patients) and the low transplant rates in this population.[90, 93]	No, as there are no other published data available to inform SMR in frontline ALL.
The distribution of subsequent therapies was not collected in the clinical trial (with the exception of alloSCT). The distribution of novel regimens were assumed to be split equally between both arms	The distribution of subsequent therapy regimens (with the exception of alloSCT) was not collected in the clinical trial. As such, the choice and distribution of novel therapies was informed by clinical experts. Furthermore, the share of patients receiving novel therapies (blinatumomab or inotuzumab) was assumed to be equal in both treatment arms to minimise the potential cost or survival bias. Post-relapse alloSCT rates were captured in the E1910 trial, which informed the model.	No, as the distribution of subsequent treatments was directly informed by expert clinicians at an advisory board.[1]
Quality of life of the cured population returns to that of	General population utility has been applied to patients remaining relapse-free starting at 5 years, based on the assumption of clinical cure, as validated by UK clinicians. The general population utility	No, as the 5-year clinical cure timepoint

Assumption in the base case	Justification	Addressed in scenario analysis?
the age- and gender-matched general population values after 5 years	was previously assumed for the long-term survivors in published cost-effectiveness evaluations and NICE submissions.[117-119]	is based on clinical expert opinion.
After 5 years, patients do not incur any ALL-related costs	Aligned with clinicians assumption of five-year cure point, it was assumed that patients would not incur any further ALL-related costs, i.e. subsequent therapy and terminal care costs. This is in line with past NICE appraisals, that included a cure assumption, such as TA554.[79]	No, as the 5-year clinical cure timepoint is based on clinical expert opinion.

Abbreviations: alloSCT: allogeneic stem cell transplant; ALL: acute lymphoblastic leukaemia; KM: Kaplan Meier; MRD: minimal residual disease; NICE: National Institute for Health and Care Excellence; OS: overall survival; RFS: relapse-free survival; SMR: standardised mortality ratio; SOC: standard of care; TA: technology appraisal.

B.3.9 *Base-case results*

A summary of the base case analysis for adults with Ph-negative, MRD-negative, B-cell precursor ALL are presented below. The clinical outcomes and disaggregated base case cost-effectiveness results and QALYs are presented in Appendix J.

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The base case probabilistic and deterministic cost-effectiveness results for blinatumomab with SOC consolidation chemotherapy versus SOC consolidation chemotherapy are presented in Table 55 and Table 56, respectively. As discussed in Section B.3.6, no severity modifier on the QALY has been considered in any presented cost-effectiveness results.

The results illustrate that blinatumomab with SOC consolidation chemotherapy is associated with greater QALYs and life years gained (LYG) than SOC consolidation chemotherapy alone, reflecting the high levels of efficacy of blinatumomab with SOC consolidation chemotherapy in MRD-negative patients. The total QALYs for patients receiving blinatumomab with SOC consolidation chemotherapy are estimated to be [redacted] compared with [redacted] for patients treated with SOC consolidation chemotherapy. The total costs for patients receiving blinatumomab with SOC consolidation chemotherapy are estimated to be [redacted] compared with [redacted] for patients treated with SOC consolidation chemotherapy.

In the probabilistic base case, this resulted in a pairwise incremental cost-effectiveness ratio (ICER) for blinatumomab with SOC consolidation chemotherapy of £32,311 per QALY gained versus SOC consolidation chemotherapy alone. These analyses were performed with a PAS for blinatumomab; all other modelled treatments were at list price.

Table 55: Probabilistic base-case results (with blinatumomab PAS)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs	Incremental Costs	ICER (£/QALY)	NHB at £30,000/QALY WTP threshold
SOC consolidation chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab + SOC consolidation chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,311	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 56: Deterministic base-case results (with blinatumomab PAS)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs	Incremental Costs	ICER (£/QALY)	NHB at £30,000/QALY WTP threshold
SOC consolidation chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Blinatumomab + SOC consolidation chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,643	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

B.3.10 *Exploring uncertainty*

B.3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to estimate the probability for blinatumomab to be cost-effective compared to SOC consolidation chemotherapy, based on different willingness-to-pay (WTP) thresholds. A Monte-Carlo simulation with 1,000 iterations was conducted to ensure convergence of model results as shown in Figure 23. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarised in Section B.3.8.1.

Whenever available, the SE of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the SE for each cost parameter was assumed to be equal to 20% of the mean value.

The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for blinatumomab with SOC consolidation chemotherapy versus SOC consolidation chemotherapy alone are presented in Figure 24 and Figure 25, respectively. Assuming a willingness-to-pay threshold of £30,000, blinatumomab has a 39.7% probability of being cost-effective versus SOC consolidation chemotherapy.

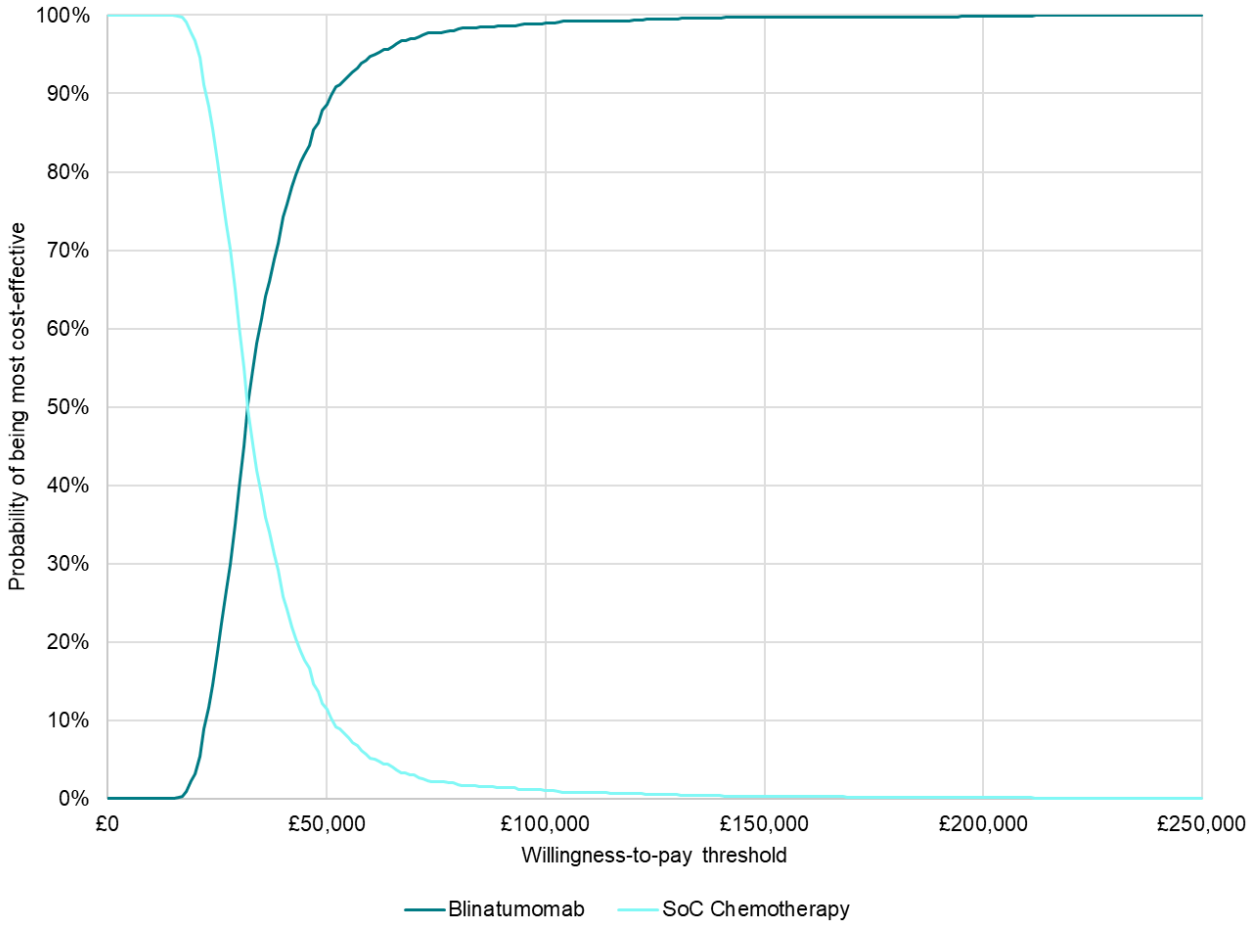
Figure 23: ICER convergence plot

Abbreviations: ICER: incremental cost-effectiveness ratio.

Figure 24: Cost-effectiveness scatter plot for blinatumomab with SOC consolidation chemotherapy versus SOC consolidation chemotherapy alone (PAS price)

Abbreviations: PAS: patient access scheme ; QALY: quality adjusted life year; SOC : standard of care; WTP: willingness to pay threshold.

Figure 25: Cost-effectiveness acceptability curve for blinatumomab with SOC consolidation chemotherapy versus SOC consolidation chemotherapy alone (PAS price)



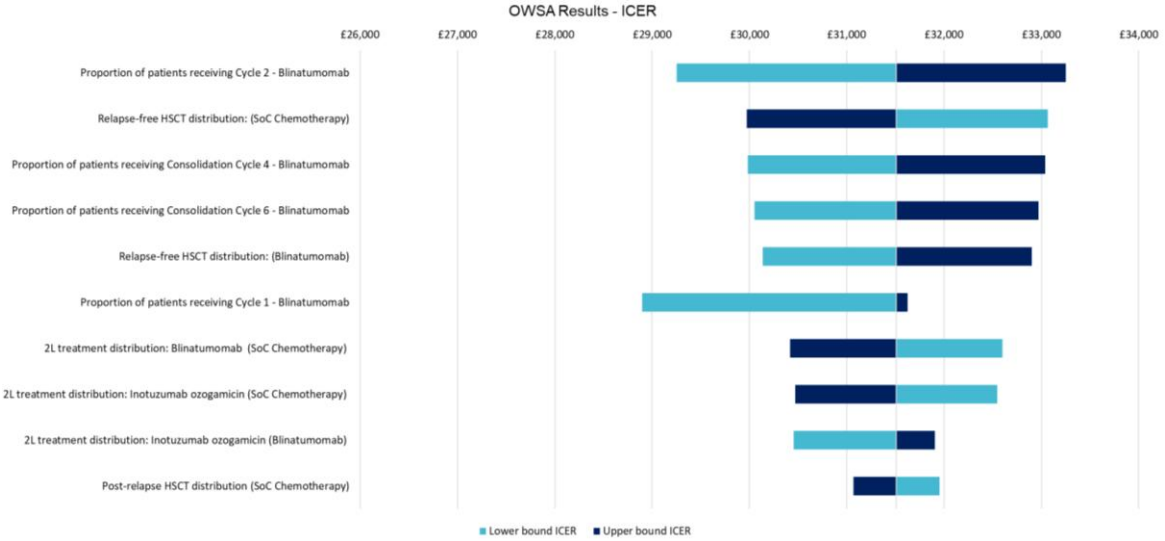
Abbreviations: PAS: patient access scheme ; SOC : standard of care.

B.3.10.2 Deterministic sensitivity analysis

To account for uncertainty around the input parameters used in the base case analysis, a deterministic sensitivity analysis (DSA) was conducted. Each parameter was varied by ±20% of its mean value.

The tornado diagram for blinatumomab with SOC consolidation chemotherapy versus SOC consolidation chemotherapy alone is presented in Figure 26; each of the top 10 most influential parameters and its resulting impact was ranked from the highest to lowest. The proportion of patients receiving blinatumomab medication in Cycles 2 and 4, and the proportion of patients receiving alloSCT in the relapse-free health state in the SOC consolidation chemotherapy arm were the three most influential variables on the CEM results.

Figure 26: DSA tornado plot for blinatumomab with SOC consolidation chemotherapy versus SOC consolidation chemotherapy (blinatumomab PAS price)



Abbreviations: 2L: second-line; HSCT: Hematopoietic stem cell transplantation; ICER: incremental cost-effectiveness ratio.

B.3.10.3 Scenario analysis

Scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the CEM. A list of the scenarios and the rationale for their inclusion is presented in Table 57. A summary of the scenario analysis results for blinatumomab versus blinatumomab with SOC consolidation chemotherapy are presented in Table 58. All scenario analyses were conducted probabilistically.

The changes in ICER compared to the base case for all scenarios were generally minor. The choice of MCM had little impact on the results and the model was modestly sensitive to the discount rate. Further, implementation of standard parametric models yielded a lower ICER for blinatumomab, indicating that the base case is conservative. Overall, this demonstrates that the base case results are associated with minimal uncertainty.

Table 57: List of scenarios

#	Scenario	Rationale
1	Use of 1.5% discounting for all costs and health effects	To explore the impact of differing discount rates per year for costs and health effects, rather than the 3.5% used in the base case.
2	Use of 5% discounting for all costs and health effects	
3	Using standard parametric modelling, RFS (Log-normal), OS (Log-normal)	Survival is modelled using parametric models, instead of the MCMs used in the base case.
4	Adjustment of the blinatumomab dose by the observed dose per treatment cycle from E1910	In E1910, there were several potential reasons why patients could receive a dose different to that detailed in the license (as discussed in Section B.3.5.1). While the base case takes into consideration the proportion of patients starting each cycle, it does not account for patients who discontinue treatment mid-cycle, or have a missed or reduced dose. Instead, the base case assumes that patients who continue treatment all

		receive a full vial per day of blinatumomab (i.e. no vial sharing). This scenario adjusts the modelled dose to that of the observed dose per treatment cycle in the E1910 study, and may therefore more accurately reflect real-world usage of blinatumomab.
5	Use of an alternative RFS distribution (Exponential MCM)	The CEM includes various extrapolation options for RFS and OS. The best fitting OS and RFS options were selected for the modelled base case. This scenario explores the impact of using alternative survival curves.
6	Use of an alternative OS distribution (Log-logistic MCM)	
7	Use of an alternative OS distribution (Gamma MCM)	
8	Use of an alternative RFS distribution (Log-logistic MCM)	

Abbreviations: ALL: Acute lymphoblastic leukaemia; PSM: parametric survival model; MCM: mixture cure model; MRD: minimal residual disease; RFS: relapse-free survival; OS: overall survival.

Table 58: Scenario analysis results for blinatumomab versus relevant comparators

Scenario		Blinatumomab vs blinatumomab + SOC consolidation chemotherapy		
		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base case				
1	Use 1.5% discounting for all costs and health effects	[redacted]	[redacted]	£23,683
2	Use 5% discounting for all costs and health effects	[redacted]	[redacted]	£40,381
3	Using standard parametric models to model survival. RFS (Log-normal), OS (Log-normal)	[redacted]	[redacted]	£25,734
4	Adjust the Blin dose by the observed dose per treatment cycle, from E1910	[redacted]	[redacted]	£28,561
5	Using an alternative RFS distribution (Exponential MCM)	[redacted]	[redacted]	£32,957
6	Using an alternative RFS distribution (Log-logistic MCM)	[redacted]	[redacted]	£32,783
7	Using an alternative OS distribution (Gamma MCM)	[redacted]	[redacted]	£32,075
8	Using an alternative OS distribution (Log-logistic MCM)	[redacted]	[redacted]	£32,173

Abbreviations: HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; N/A: not applicable; OS: overall survival; RFS: relapse-free survival.

B.3.10.4 Summary of sensitivity analysis results

The probabilistic and deterministic base case results were in close alignment, indicating that the CEM is robust to parameter uncertainty. Similarly, the DSA results identified a small number of key influential parameters including the proportion of patients receiving alloSCT in the SOC consolidation chemotherapy arm and the proportion of patients receiving blinatumomab medication in cycles 2 and 4, but overall the CEM largely showed robustness to uncertainty in the majority of parameters. Scenario analyses were conducted to address sources of uncertainty in the CEM. The changes in ICER compared to the base case were generally minor, demonstrating that the base case results are associated with minimal uncertainty.

B.3.11 *Subgroup analysis*

No subgroup analyses were conducted.

B.3.12 *Benefits not captured in the QALY calculation*

As highlighted in Section B.1.3, B-cell precursor ALL is a serious, life-threatening illness associated with a poor prognosis and a considerable burden.[22] Hence there remains an unmet need for a more effective treatment in B-cell ALL that can improve survival, as well as avoiding and reducing relapse in MRD-negative patients. The clinical evidence base from E1910 demonstrates that blinatumomab added to SOC consolidation chemotherapy represents a potential paradigm shift in how patients with Ph-negative MRD-negative precursor B-cell ALL are managed in routine clinical practice. Further, if recommended, blinatumomab will represent the *only* targeted therapy for frontline MRD-negative patients in the consolidation phase in the UK. Indirect costs are not captured in the model, therefore the wider indirect benefits of blinatumomab plus SOC consolidation chemotherapy to patients, caregivers and society are not captured in this analysis. The totality of the clinical evidence base demonstrates that blinatumomab added to SOC consolidation chemotherapy has a favourable benefit-risk profile and represents a potential paradigm shift in how patients with newly diagnosed Ph- BCP-ALL that is MRD-negative are managed in routine clinical practice, offering the very real potential for a curative therapy. Additionally, this sense of hope that blinatumomab plus SOC consolidation chemotherapy may offer to prospective patients and families is not captured in this cost-effectiveness analysis.

B.3.12.1 Validation of cost-effectiveness analysis

Internal validity

Quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development. These procedures included verification of all input data with original sources and programming validation. Any discrepancies were discussed, and the model input data was updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code.

External validity

To ensure that the cost-effectiveness analysis was consistent with clinical expectations and rationale, key model assumptions were externally validated. The CEM was reviewed by clinical experts (haematologists) in December 2023 and May 2024.[93] Furthermore, Amgen conducted an advisory board in October 2023. Conclusions from both meetings were that:

- The health states were appropriate.
- The cure assumption was validated for both treatment arms; the cured patients have a quality of life and mortality similar to those of general population.
- The MCM models provide reasonable predictions of long-term mortality.
- The treatment pathway presented in the CEM was generally in line with UK clinical practice.

B.3.13 *Interpretation and conclusions of economic evidence*

In order to assess the potential cost-effectiveness of blinatumomab versus SOC consolidation chemotherapy in adults patients with Ph-negative, MRD-negative B-cell precursor ALL in the UK, a *de novo* cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England.

The model primarily used data from the E1910 trial, which demonstrate that blinatumomab has a superior OS and RFS profile when added to frontline SOC consolidation chemotherapy compared to SOC consolidation chemotherapy alone. In the pre-specified OS (primary endpoint) and RFS (secondary endpoint) analyses in MRD-negative patients, blinatumomab with SOC chemotherapy led to a statistically and clinically significant reduction in death (OS: HR 0.44; 95% CI 0.25, 0.76; log-rank test TD: p=0.001) and relapse or death (RFS: HR 0.53; 95% CI 0.32, 0.88; log-rank test TD: p=0.006), relative to SOC consolidation chemotherapy alone.

These clinically meaningful efficacy results were reflected in the base case probabilistic economic analysis, where blinatumomab with SOC chemotherapy was associated with a substantially increased [redacted] LYGs and [redacted] QALYs when compared to SOC consolidation chemotherapy alone. These results underscore the potential for blinatumomab to improve both the quality and duration of life for patients with CD19-positive Ph-negative precursor B-cell ALL that is MRD-negative who do not currently have access to a targeted treatment in the frontline consolidation phase that is able to deepen responses, prevent relapse and prolong survival.

In the probabilistic base case analysis, the ICER for blinatumomab with SOC consolidation chemotherapy versus SOC consolidation chemotherapy was found to be £32,311 per QALY gained. The PSA found the probability of blinatumomab being cost cost-effective to be [redacted] and at a WTP threshold of £30,000 per QALY. The DSA results identified a small number of key influential parameters including the proportion of patients receiving blinatumomab medication in Cycles 2 and 4, and the proportion of patients receiving alloSCT in SOC consolidation chemotherapy arm. This is to be expected given the high acquisition costs of blinatumomab but these costs are partially offset by savings in subsequent therapy costs due to avoidance of relapse. Overall, the CEM was largely robust to uncertainty in the majority of parameters. Scenario analyses were also conducted to address sources of uncertainty in the CEM. Furthermore, the changes in ICER compared to the base case were generally minor, demonstrating that the base case results are associated with minimal uncertainty.

Blinatumomab plus SOC consolidation chemotherapy has the potential to be cost-effective, and is an innovative and generally well-tolerated therapy, with demonstrable efficacy in preventing relapse and prolonging survival in patients with Ph-negative CD19+ B-ALL that is MRD-negative. Blinatumomab plus SOC consolidation chemotherapy represents a potentially curative treatment for patients with this rare and deadly cancer and therefore would represent a paradigm shift in care if recommended for the treatment of frontline adult patients with Ph-negative CD19+ B-ALL in the consolidation phase.

B.3.13.1 Strengths

The analysis was conducted from an NHS/Personal Social Services (PSS) perspective, and the model adopted a lifetime horizon (50 years) ensuring all costs and QALY gains are captured. The structure of the CEM was deemed appropriate for this decision problem; a PSM is a transparent,

intuitive approach which yields estimates of survival that correspond closely to survival observed during the study that are the basis for the evaluation.[120] The E1910 study was a multinational phase 3 RCT that represents the highest quality of evidence for evaluating clinical efficacy. The survival data from the study are mature, with a median follow-up time of 4.5 years, and the PSM structure allows for the direct use of the RFS and OS data from this trial. In addition, a PSM approach has been used in prior economic analyses of treatments for oncology therapies including haematologic malignancies, as well as in a previous NICE submission for blinatumomab for the treatment of Ph-negative precursor B-cell ALL (TA450).[2, 54, 120] Furthermore, clinical experts validated that the model structure and health states were appropriate for this cost effectiveness analyses.[2, 54, 120] They also were in agreement with the cure assumption, noting that the MCM models provide reasonable predictions of long-term mortality.[2, 54, 120] Moreover, the baseline characteristics inputted to the CEM were reflective of UK clinical practice, as confirmed by clinical experts during an advisory board conducted by Amgen in October 2023.[1]

B.3.13.2 Limitations

HRQoL data were not collected in Study E1910. However, utility values were leveraged from TA589.[5, 6] Thus utility values from the BLAST and TOWER trials were used to inform pre-relapse and post-relapse health-state utility values for the modelled population. As the BLAST trial included patients with newly diagnosed Ph-negative CD19-positive B-ALL, utilities for the MRD-responders (i.e. patients who went from MRD-positive to MRD-negative status) are appropriate for modelling utilities for the pre-relapse health state in the E1910 trial, and do not present a significant source of uncertainty. Likewise, the no prior salvage subgroup of the TOWER trial included patients with previously treated Ph-negative CD19-positive B-ALL, and therefore provides a good source for modelling patients following relapse, as was done in the TA589. Furthermore, the suitability of these utility values were confirmed by UK clinical experts to represent the expected quality of life for the modelled population.[93]

Similarly, while data on subsequent treatments were not systematically collected in E1910, the proportion of patients receiving each therapy was sought through an advisory board with UK clinical experts.[84] In addition, data on alloSCT, the most influential subsequent treatment on OS, was collected in E1910 and these alloSCT rates are used in the model. Furthermore, at 4 years onwards, 77% of patients in the blinatumomab plus SOC chemotherapy arm remained relapse-free. This indicates that the strong survival benefit of blinatumomab plus SOC chemotherapy is driven by avoiding relapse and potentially curing patients, and not by receipt of subsequent therapies. Therefore, this limitation is not anticipated to greatly impact the economic results.

B.3.13.3 Conclusion

B-cell precursor ALL is a serious, life-threatening illness associated with a poor prognosis and a considerable burden on patients.[22] For adult patients with Ph-negative, MRD-negative, precursor B-cell ALL, blinatumomab in combination with SOC consolidation chemotherapy has demonstrated to be an efficacious treatment at improving survival and delaying and avoiding relapse for this patient population compared to SOC consolidation chemotherapy alone. In addition, the adverse events observed were consistent with blinatumomab's well-characterised and generally manageable safety profile. As such, if recommended, blinatumomab in combination with SOC consolidation chemotherapy would address the high unmet need in this patient population and could represent a potential paradigm shift in how patients with Ph-

negative MRD-negative precursor B-cell ALL are managed in routine clinical practice in the UK. Furthermore, as no new RFS events were observed from 4 years onwards in the blinatumomab plus SOC chemotherapy arm, this could represent a potential curative therapy for patients. Additionally, the results of the economic analyses presented in this submission demonstrate that blinatumomab in combination with SOC consolidation chemotherapy has potential to be a cost-effective use of NHS resources for these patients.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

Company evidence submission

July 2024

File name	Version	Contains confidential information	Date
ID6405_Blinatumomab in Ph-negative MRD-negative ALL_SIP_NoCON	V1.0	No	26th July 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: blinatumomab

Brand name: Blincyto®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

The population blinatumomab is intended to treat are adult patients (18 years and above) with **precursor B-cell acute lymphoblastic leukaemia (ALL)** that is:

- **CD19-positive** (this is a surface marker expressed on the leukaemia cells) *and*
- **Philadelphia chromosome (Ph)-negative** (this refers to the absence of a genetic abnormality called the Philadelphia chromosome) *and*
- **Without measurable residual disease (MRD) i.e. MRD-negative** (this refers to a very low level of leukaemia cells (below a certain threshold) in the body that can only be detected using very sensitive tests) *and*
- In the frontline **consolidation chemotherapy** phase of their treatment (this refers to a phase of treatment aimed at removing further cancer cells after the initial [induction] treatment has successfully reduced the number of leukaemia cells and led to remission).

Please see **Section 2a** for more information on what this means and how this condition affects people who have it.

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (Section 4b). Cross-references to other sections or documents are highlighted in orange.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **Medicines and Healthcare products Regulatory Agency (MHRA)** has granted **marketing authorisation** for blinatumomab for the following patient groups:[1, 2]

- As monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.
- As monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- As monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.
- As monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-cell precursor ALL as part of the consolidation therapy

A **license extension** that covers the population of interest for this submission is currently pending approval from the MHRA. More information on this can be found in Document B in Section B.1.1.

1d) Disclosures:

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Amgen collaborates with a range of stakeholders with an interest in ALL. In particular, this includes grants and sponsorships with patient groups to support improvements in health and care for individuals with ALL. Where this includes any Transfer of Value this is

declared and available at: https://www.amgen.co.uk/about/partnerships-and-support/disclosures.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact:

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Blinatumomab is intended to treat adult patients with Ph-negative, MRD-negative, precursor B-cell ALL in the consolidation chemotherapy phase of their frontline treatment

What is B-cell ALL?

B-cell ALL is a type of leukaemia (**cancer** of the blood) in which a particular type of **white blood cell** called a "**B-cell lymphocyte**" grows and multiplies rapidly out of control.[3, 4] ALL has various types and subgroups, which doctors define by looking at the features of the leukaemia cells.

The disease usually has an abrupt onset and progresses quickly. Therefore, it needs to be diagnosed and treated very soon after the disease is identified.[4] Anyone can develop ALL, but it is most commonly seen in children and young people, especially children aged 4 and under.[4, 5] B-cell ALL is a life-threatening condition and the patient's outcome can depend on the specific subtype of ALL they have as well as their age and general health and fitness.[4] In general, younger people tend to have more favourable outcomes long-term (referred to as a better **prognosis**) compared with older patients.[6]

What is Ph-negative precursor B-cell ALL?

ALL can be divided into subgroups. Precursor B-cell ALL is the most common subtype; in fact, around 3 out of 4 (75%) of people with ALL have this type.[5] This is a condition in which there are too many of a specific type of immature immune cell in the blood called a "precursor B-cell".[7] If these cells do *not* have a specific genetic abnormality, called a Philadelphia chromosome, then the patient is said to have "Ph-negative" precursor B-cell ALL.[8] Patients who are Ph-negative generally have a better outlook compared to those with the Philadelphia chromosome. The Philadelphia chromosome is seen in approximately one in four (25%) of adults patients with B-cell ALL.[9]

What does minimal residual disease (MRD)-negative mean?

When ALL is under control (has improved or is no longer detectable in the blood/bone marrow), this is called disease **remission.** The term 'relapsed' refers to disease that returns or worsens following a period of remission. MRD tests investigate the presence of detectable cancer cells in the bone marrow or blood at a level above or below a certain threshold when the patient is in remission. MRD testing can help doctors determine if their

patients are at a higher risk of the leukaemia returning (relapsing), and whether further treatment to clear the residual cells is needed.[10]

A positive MRD test result means that the number of cancer cells found to remain in the body is above a certain threshold and these patients with levels above the MRD threshold are referred to as “MRD-positive”. Patients who have “MRD-negative” disease have no detected leukaemia cells or have a very small number of leukaemia cells that fall below the threshold of these sensitive tests.[10] The importance of MRD testing is that compared with MRD-negative patients, patients with MRD-positive disease have a higher risk of disease relapse and a worse prognosis. However, at any level of MRD (i.e. MRD-negative or MRD-positive), there is a chance of leukaemia coming back and potentially causing an eventual relapse.

What does it mean to be in the consolidation phase of chemotherapy treatment?

The chemotherapy that is used at the beginning of a patient’s leukaemia treatment, is referred to as remission induction or more commonly “**induction” chemotherapy.** The aim of induction chemotherapy is to reduce the number of leukaemia cells to a level that the patient is deemed to be in remission. However, even when the patient is in remission, there may still be a very small amount of cancer cells left in the body that could cause the cancer to come back. Therefore, the aim of consolidation chemotherapy, which comes after induction therapy, is to eradicate any cancer cells that are remaining in the body after the initial induction phase and reduce the risk of the disease returning.[11] Please see **Section 2c** for more details on the phases of ALL treatment.

What are the signs and symptoms of B-cell ALL?

The main symptoms include:[4]

- Feeling tired or weak
- Bleeding or bruising easily or for no reason
- Looking more pale than usual
- Getting ill a lot or taking longer than usual to recover from illnesses
- A high temperature
- Swollen glands (usually in the neck, armpits and groin)
- Pain in the bones or joints
- Loss of appetite or losing weight without trying
- Shortness of breath
- A swollen tummy

How many people have Ph-negative, MRD-negative, precursor B-cell ALL in the UK?

Ph-negative, MRD-negative, precursor B-cell ALL is a rare disease, with approximately 100 new adult cases reported every year in the UK.

Survival of patients with ALL in the UK

While there are approximately 800 new cases of ALL each year in the UK, around 250 people die from the disease each year.[12]

Age affects how well leukaemia responds to treatment, with older people tending to have worse prognosis.[6] The outlook for ALL also depends on other factors such as:[6]

- The specific type of white blood cell the leukaemia affects (B- or T-cells)
- If the patient has a high number of white blood cells at diagnosis
- The **genetic mutations** that are found in the cancer cells, such as the Philadelphia chromosome as well as others

The outlook is also affected by the patient's response to treatment, how long it takes for a patient to enter remission and whether they have MRD above the threshold level in remission.[6]

What is the personal (quality of life) and societal cost of ALL?

Personal cost

The diagnosis of ALL can be a very stressful and worrying time.[13] Furthermore, the financial impact of cancer for patients is well documented in the "Cancer's Hidden Price Tag" report commissioned by UK cancer charity Macmillan. This report found that approximately four in five patients are, on average, £570 a month worse off as a result of a cancer diagnosis.[14] Those in work at the time of diagnosis experience the highest financial burden.[14] These types of financial issues are also experienced by patients with ALL specifically, as they often need to stop employment, either permanently or temporarily, as a result of their disease.[15]

Economic cost

The economic cost of ALL is considered to be high as it requires a lot of **healthcare resource use** (e.g. time in hospital, medication, and medical equipment). This cost is expected to be even higher for patients who relapse. Therefore, treatments that prevent relapse would be expected to help to reduce these healthcare resource costs.[16]

Societal cost

ALL is also associated with a wider societal cost. This is because, understandably, working people with ALL may need to miss work and/or be less productive at work due to their disease. For example, Leukaemia Care (UK) reported, of the patients who were working or studying prior to their ALL diagnosis, seven in ten (70%) experienced a decrease in their productivity.[17]

Family and Caregivers

Patients with ALL are often unwell and frequently require support from family and friends. ALL is a life-threatening condition and it can be an overwhelming diagnosis. It is difficult to be a carer sharing all the fears, thoughts and emotions, but also having to deal with the practicalities of life, and feeling helpless and out of control.[18, 19]

2b) Diagnosis of the condition (in relation to the medicine being evaluated):

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is ALL diagnosed?

A patient may experience some of the symptoms mentioned in **Section 2a** and schedule an appointment with their doctor or attend the A&E department. At this initial appointment, the **healthcare professional** would typically ask some questions about the patient's health and may conduct a simple physical examination and blood tests.[20] If the results show signs of ALL, the doctor would then refer the patient urgently to a specialist.[20]

The specialist the patient is referred to is called a **haematologist**, who will work closely with a multidisciplinary team. They would repeat the blood tests conducted previously as well as perform some additional tests such as:[21]

- A **bone marrow sampling test** (called a bone marrow aspirate) to look for the presence of leukaemia cancer cells in the bone marrow
- Tests on the leukaemia cells to see which type they are and which **proteins** they have on their surface, such as CD19
- A **lumbar puncture** (the sampling of the fluid around the spinal region called the lumbar spine to look for the presence of leukaemia cancer cells in the cerebrospinal fluid from around the spinal cord)
- Scans such as chest **X-ray**, **CT scan** or **MRI scan** to help determine the extent of the disease
- Tests to check for infection
- Tests to look at markers on the surface of cells and tissues in order to match the patient with a suitable transplant donor. These are called **tissue typing tests**

A haematologist will use the results of these tests to determine what type of ALL the patient has and assess the prognosis, so they can then work with the patient to decide on the best treatment plan. Through these tests, it is possible to determine whether a patient has Ph-negative CD19-positive B-cell precursor ALL and are MRD-negative, which is the specific patient population of interest in this submission.

2c) Current treatment options:

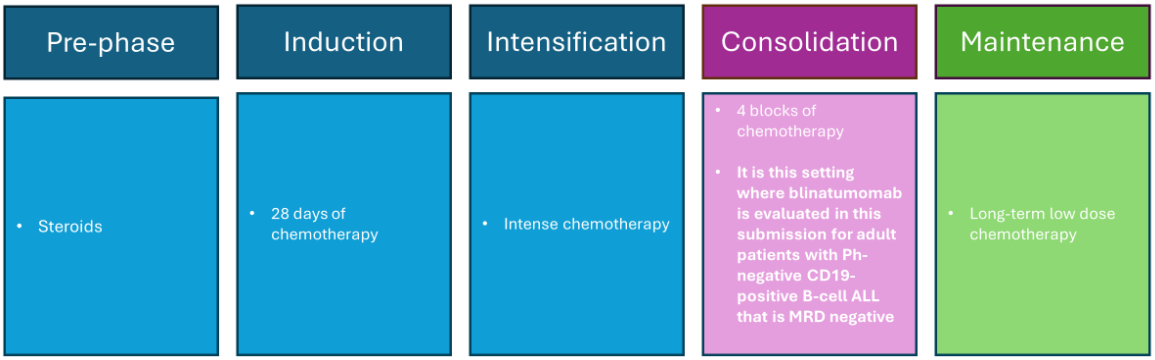
The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for patients with newly diagnosed Ph-negative precursor B-cell ALL and who are MRD-negative?

Chemotherapy refers to a type of treatment that uses powerful chemicals to target and kill fast-growing cells in the body. Chemotherapy is often used to treat cancers, since cancer cells grow and multiply more quickly than most normal cells within the body. However, some normal cells in the body that also multiply quickly (such as hair and skin cells) are also affected by chemotherapy. Therefore, chemotherapy is referred to as a **systemic** (and non-specific) **cancer treatment** and often leads to patients experiencing a range of side effects.[22] It also tends to involve several treatment sessions, typically spread over a several months.[23]

The current treatment for patients with newly diagnosed Ph-negative precursor B-cell ALL and who are MRD-negative in the UK follows a protocol called UKALL14. This divides treatment into five main phases:



Currently, chemotherapy represents the bulk and mainstay of the treatment for this disease, but depending on the subtype of ALL and the stage of the disease the patient might also receive a different treatment. This could include a **targeted cancer treatment**, or a procedure to replace unhealthy blood cells with healthy stem cells (known as a **stem cell transplant)**.[24] Targeted treatments refer to treatments that specifically attack cancer cells without harming most healthy cells. The type of treatment used depends on the phases of treatment:[25]

- Steroid **pre-phase**: The aim of the steroid pre-phase is to eliminate as many of the leukaemia cells as possible. During this time, some important genetic tests are carried out to determine the next steps of treatment.

- **Induction**: where patients receive several chemotherapy medicines with the aim of having no or very low levels of leukaemia remaining (attaining "complete remission")

- **Intensification then consolidation**: where patients receive more intensive treatment in order to eradicate any leukaemia cells that might still be present and to prevent the return of cancer (i.e. prevent future "relapse").

- **Maintenance**: where patients receive long-term **low-dose chemotherapy** with the aim of maintaining remission and preventing cancer regrowth

In this submission, blinatumomab is intended to be used in adult patients with Ph-negative B-cell precursor ALL that is MRD-negative in the frontline *consolidation* phase. In this phase, patients are usually treated with similar chemotherapies to what they received in the induction phase.

A significant proportion of adult patients with Ph-negative B-cell precursor ALL that is MRD-negative in the frontline *consolidation* phase go on to relapse and do not survive beyond 5 years.[26] Therefore, there is an unmet need for an effective and targeted treatment for patients with this condition in the consolidation phase that can reduce the chance of relapse after initial therapy. Currently, there are no "targeted" cancer treatments specifically used for the treatment of Ph-negative, precursor B-cell ALL that is MRD-negative in the frontline consolidation phase. This is the setting in this submission where blinatumomab is being discussed (see **Section 3** below for details on blinatumomab as a treatment).

A reason not to give blinatumomab, referred to as a contraindication, is if the patient is breastfeeding or if they have an allergic reaction or "sensitivity" to the components that make up blinatumomab. This represents a very small proportion of patients who present with B-cell ALL.

2d) Patient-based evidence (PBE) about living with the condition:

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Amgen have collected patient-based evidence through the **health-related quality of life (HRQoL)** measures in the TOWER and BLAST blinatumomab registrational clinical trials, which investigated blinatumomab in relapsed disease or disease that does not respond to initial treatment (termed refractory disease), as well as in patients with MRD-positive

disease, respectively. Please see **Section 3f** for more information on quality of life impact of blinatumomab.

This current section summarises some of the key considerations from published literature about the impacts of ALL on patients.

ALL from the patient perspective

A high symptom burden, poor prognosis, treatment side effects, and prolonged periods of hospitalisation can affect patients' physical, social, and emotional well-being.[27, 28] Most patients report experiencing pain (64%), difficulty moving around (62%), and difficulty performing daily activities such as cooking and cleaning (65%) as a direct result of their condition. Further, almost half (48%) report having problems taking care of themselves.[17]

Furthermore, an ALL diagnosis can have a huge impact on patients and their families. It can cause feelings of disbelief, denial, anger, fear, blame, guilt, isolation, and depression.[17] In fact, around 60% of patients with ALL report feeling depressed or anxious more often since their diagnosis.[17]

Lastly, it is important to note that relapse represents one of the most difficult parts of the patient journey. Patients who experience relapse are more likely to report feeling constantly depressed or anxious compared with patients that do not experience relapse (18% vs 4%).[17] Therefore, treatments that help to reduce the risk of relapse could help to relieve this emotional burden.

Patient-based evidence from Leukaemia Matters

To understand the impact of living with ALL on patients further, Amgen provide some patient testimonials collected by Leukaemia Matters, a patient-focused magazine about the experience of living with leukaemia, from their Spring Edition 2024.

Adult patient 1 describes the impact of his diagnosis on him:[29]

"I knew leukaemia was a type of cancer, but not much more than that. In fact, I had always thought it was something that affected younger people. I wasn't ready for it at all. I made some calls to let my girlfriend, family and ex-wife know what was happening. I was in shock. It was the thought of telling my daughters that upset me the most."

Adult patient 2 details the impact of the symptoms he experienced:[29]

"I was having night sweats and found myself frequently out of breath. I was bruising easily, was suffering with bleeding gums and nosebleeds, and seemed to be constantly picking up infections. Eventually, after almost passing out while climbing the stairs, I went to see my GP. He suggested I had blood tests. And as soon as he had my test results back, he came round to my house and insisted I get myself straight to hospital. It was a traumatic time."

Adult patient 3 recounts the impact of treatment on her:[29]

"The following two months [of treatment] were gruelling. Constant rounds of chemotherapy left me physically and emotionally drained. The side effects were merciless – hair loss, excruciating mouth sores, constant nausea, and debilitating fatigue. The other aspect I remember with horror was when one of my teeth became infected while still struggling with neutropenia [low white blood cells in the blood]. I developed neutropenic sepsis which nearly took my life."

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

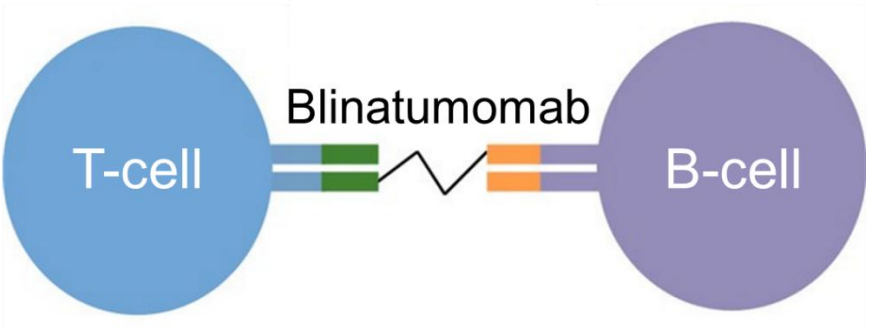
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Blinatumomab belongs to a group of medicines called **antineoplastic agents** which target cancer cells.[1, 3] This particular type of targeted therapy is a **bispecific T-cell engager (BiTE),** which falls under the category of **immunotherapy** and specifically targets diseased leukaemic cells.[30, 31]

In people with ALL, white blood cells called B-cells grow rapidly out of control.[1, 3] Blinatumomab works by targeting a certain protein on the leukaemia cells surface so the **immune system** can recognise them.[31] The protein on the leukaemia cells is called CD19.[31] By doing so, blinatumomab brings the cancer cells (leukaemic B-cells) and the healthy immune system (T-cells) close together, as shown in **Figure 1**. This allows the immune system cells to then attack and kill the leukaemia cells, hence this is referred to as "immunotherapy".[1, 31]

Figure 1: How blinatumomab works



If it were to be approved for use, blinatumomab would represent the *first* targeted treatment available in the UK for the treatment of adult patients with Ph-negative, MRD-negative, B-cell precursor ALL in the frontline consolidation phase. Therefore, it could fulfil the unmet need for an effective and targeted treatment in this population that has the potential to avoid and/or reduce the rate of relapse in adult patients with Ph-negative MRD-negative B-cell precursor ALL and maintain disease remission for longer than the

currently used standard of care, which is consolidation chemotherapy alone (see **Section 3e** for more details).

3b) Combinations with other medicines:

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Yes.

Blinatumomab would be given in the frontline consolidation phase of treatment alongside the existing chemotherapy treatment that is currently the standard treatment for adult patients with Ph-negative, MRD-negative precursor B-cell ALL. Patients would receive cycles of blinatumomab **interspersed** with cycles of consolidation chemotherapy, so they would receive both treatments as part of their course **but not at the same time.**

Note: Blinatumomab is a “monotherapy” which means at the time of administration, it is given on its own.

3c) Administration and dosing:

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is blinatumomab given?

Before treatment

Before starting blinatumomab the patient would have pre-treatment with steroids, termed “pre-phase”. One reason for this is to try to reduce the chances of a patient’s immune system over-responding to blinatumomab.[31]

During treatment

Blinatumomab is given through a drip into a vein, known as **intravenous infusion**. This is typically given via:[30, 31]

- A **central line** (a fine tube inserted under the skin of the chest wall and into a nearby vein)

- A **PICC line** (a fine tube inserted into a vein in the arm and up into a vein in the chest)

- An implantable port or **portacath** (a disc that is inserted under the skin on the chest wall or arm that has a tube that is threaded through a vein until it reaches the heart)

Treatment course

Blinatumomab is given in "cycles" of treatment.[31] This means that a patient receives blinatumomab followed by a rest period to allow their body to recover.[31] Each cycle takes 42 days (6 weeks). The patient would have a continuous drip (infusion) of blinatumomab for 28 days (4 weeks, days 1–28). This is followed by a break from treatment for 14 days (2 weeks, days 29–42).[30]

In the frontline consolidation phase, it is expected that the patient would receive up to four cycles of blinatumomab. However, the number of cycles a patient receives may depend on the treating doctor's preference and:[30, 31]

- How the cancer responds to the treatment

- Any side effects the patient experiences

In the NHS, cycles of blinatumomab would be interspersed with cycles of the consolidation chemotherapy treatment (see **Section 3b**).[32] As such, blinatumomab would be given in addition to the standard consolidation chemotherapy regimen, but not at the same time as other treatments. In the consolidation phase, it is expected that two cycles of blinatumomab will be given, followed by three cycles of chemotherapy, followed by one cycle of blinatumomab, followed by one cycle of chemotherapy and followed by one final cycle of blinatumomab. Therefore, in total in the consolidation phase, four cycles of blinatumomab will be given, interspersed with four cycles of chemotherapy.

Dosing

Blinatumomab treatment is given at a dose of 28 mcg/day for most patients. However, if patient weighs less than 45 kg, then a lower dose of 15 mcg/m^2/day is given instead.

After treatment

Adult patients receiving blinatumomab in the consolidation phase are recommended to begin treatment in hospital but return home with the drip after the first three days of the first cycle. It is recommended that patients would stay in hospital again in the first two days of the second cycle.[31] The infusion is typically given through a small portable pump connected to either their central line, PICC line or portacath.[31] Patients can carry the pump on a belt or in a bag.[31] The infusion duration can last up to 96 hours and at the end of the visit, the patient needs to return to a treatment centre/clinic to have the infusion bag changed and set up a new bag for the next infusion.

3d) Current clinical trials:

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
There is one main registrational **Phase III clinical trial** that provides evidence on the efficacy and safety of blinatumomab in treating adult patients with newly diagnosed Ph-negative precursor B-cell ALL that is MRD-negative and in the frontline consolidation phase. This trial is called the "E1910 study" (NCT02003222): • Location: This study was conducted at 77 centres in the United States, Canada, and Israel • Population: Adult patients with newly diagnosed Philadelphia negative precursor B cell ALL • Investigation group: 112 patients who were MRD negative with blinatumomab in addition to standard of care consolidation chemotherapy • Comparator: 112 patients who were MRD negative with standard of care consolidation chemotherapy alone • Inclusion criteria: Adult patients with newly diagnosed Philadelphia negative precursor B cell ALL • Exclusion criteria: patients with another active cancer or with ALL disease affecting the nervous system • Initiation date: 19th May 2014 (first patient randomised) • Completion date: The date of the main analysis was 23rd June 2023

3e) Efficacy:

Efficacy is the measure of how well a treatment works in treating a specific condition. In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.
The E1910 study measured how effective blinatumomab and consolidation chemotherapy was in adult patients with newly diagnosed Ph-negative, precursor B-cell ALL that is MRD-negative compared with patients who received consolidation chemotherapy alone. The main measure in which this was assessed was through measuring an outcome called **overall survival**. This measured how long a patient lived for after receiving either treatment in the E1910 trial, including the time during and after treatment. At four and a half years (when the data were collected), a significantly greater number of patients treated with blinatumomab and chemotherapy were alive compared to patients treated with chemotherapy alone. This demonstrates the benefit of blinatumomab, when used

alongside existing consolidation chemotherapy, in extending patients' lives compared with consolidation chemotherapy alone.

Another way in which the effectiveness of blinatumomab was determined was through measuring **relapse-free survival**. This measured how long a patient remained alive and without their disease relapsing after receiving either treatment in the E1910 trial, including the time during and after treatment. The results were similar to overall survival. At four and a half years (when the data were collected), a significantly greater number of patients treated with blinatumomab and chemotherapy were relapse-free compared to patients treated with chemotherapy alone. This demonstrates the benefit of blinatumomab, when used alongside existing consolidation chemotherapy, in better helping patients avoid relapse compared with consolidation chemotherapy alone.

In summary, adding blinatumomab to frontline consolidation chemotherapy keeps more adult patients with Ph-negative precursor B-cell ALL that is MRD-negative free from disease and in remission, and improves their chances of survival compared with treating patients with consolidation chemotherapy alone.[33]

3f) Quality of life impact of the medicine and patient preference information:

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The way in which blinatumomab affects HRQoL was not measured directly in the E1910 trial itself. However, there are HRQoL data for similar patient populations from previous trials, called the BLAST and TOWER trials:[34, 35]

- BLAST trial: a Phase II trial investigating the effectiveness of blinatumomab in treating patients with newly diagnosed Ph-negative B-cell precursor ALL that is MRD-*positive*. HRQoL data for MRD-responders (i.e. patients in remission whose leukaemic burden was reduced, going from MRD-positive to MRD-negative status) in the BLAST trial is expected to be similar to the quality of life of the MRD-negative patients in remission in the E1910 trial.

- TOWER trial: a Phase III trial investigating the effectiveness of blinatumomab compared with chemotherapy in patients with relapsed or refractory Ph-negative B-cell precursor ALL

In these trials, HRQoL was measured through **patient-reported outcomes** (questionnaires that patients complete themselves). These are standardised ways of measuring HRQoL in clinical trials. Similar questionnaires to measure patient-reported outcomes were used in the BLAST and TOWER trials, which means they can be compared to assess differences between patients in remission and in relapse, respectively.

The BLAST trial showed that patients treated with blinatumomab in complete remission maintain their HRQoL during and after treatment.[36] The TOWER trial showed that blinatumomab alone delayed the worsening of quality of life compared to chemotherapy alone in patients with relapsed disease.[37]

3g) Safety of the medicine and side effects:

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

What are the side effects of blinatumomab that the MHRA list?

Many treatments have side effects and the same treatment can produce different side effects in different people. The regulatory paperwork for blinatumomab, published by the MHRA, presents some very common side effects of blinatumomab when it is used in the conditions that it is *currently licensed to treat* (see **Section 1c**). The very common side effects are defined as those that occur in more than or equal to 1 in every 10 patients who receive blinatumomab, and include:[1]

- Infections from bacterial and viruses
- Low blood counts for red blood cells (anaemia), white blood cells and platelets (thrombocytopenia)
- Low white blood cells associated with a fever (febrile neutropenia)
- A disorder of the immune system (called cytokine release syndrome)
- Poor sleep (insomnia)
- Headache
- Tremor
- High heart rate (tachycardia)
- High and low blood pressure
- Cough
- Nausea and vomiting
- Diarrhoea and constipation

- Tummy (abdominal) pain
- Rash
- Back pain and pain in the leg or arm
- Fever or chills
- Swelling (oedema)
- Raised liver proteins, called enzymes
- Reactions at the site of infusion

What were the side effects of blinatumomab, alongside consolidation chemotherapy, that were recorded in the E1910 clinical trial?

Data on the side effects of blinatumomab, given alongside consolidation chemotherapy, when used to treat the specific condition of interest to this appraisal (adult patients with Ph-negative precursor B-cell ALL that is MRD-negative in frontline consolidation) were collected in the E1910 clinical trial. It is important to note that *no new side effects* were observed in patients treated with blinatumomab alongside consolidation chemotherapy as compared with those already known and described in the regulatory paperwork for blinatumomab (see above).

In clinical trials, side effects are **graded** on a scale from 1–5 depending on increasing severity (most clinical trials place a larger focus on grade 3 or higher events):[38]

- Grade 1–2: mild side effects that may interfere with doing some activities but are not dangerous
- Grade 3–4: serious side effects that interfere with patients' ability to do basic things. They may also require medical intervention
- Grade 5: side effects that result in death

In the E1910 clinical trial, all patients who received blinatumomab and consolidation chemotherapy experienced side effects related to their treatment. Many of these were serious side effects (grade 3 or higher) and some common side effects seen included a decrease in platelets and white or red blood cells, as well as headache. The side effects were generally manageable with appropriate monitoring and supportive care and less than 1 in every 10 patients stopped their treatment due to side effects. Only a very small number of Ph-negative MRD-negative adult patients treated with blinatumomab and consolidation chemotherapy experienced fatal side effects in the trial (less than 3 in every 100 patients). Patients treated with consolidation chemotherapy alone had similar side effects at a similar frequency to those treated with blinatumomab and consolidation chemotherapy. Therefore, the addition of blinatumomab did not appear to substantially change the number, type or severity of the side effects that patients experienced in E1910 trial when compared to patients receiving consolidation chemotherapy alone.

3h) Summary of key benefits of treatment for patients:

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The main benefits of blinatumomab to adult patients with Ph-negative precursor B-cell ALL that is MRD-negative in the consolidation chemotherapy phase of their treatment include:

- Blinatumomab, when used alongside frontline consolidation chemotherapy, **keeps more patients in remission and improves their survival** compared with consolidation chemotherapy alone. By reducing the number of patients who relapse and keeping more patients in long-term remission, blinatumomab will reduce the number of patients who require subsequent treatments for relapse.

- Blinatumomab would be the **first targeted treatment** specifically used for the treatment of Ph-negative B-cell precursor ALL that is MRD-negative and in the frontline consolidation phase. Therefore, it could **fulfil the unmet need** for an effective and targeted treatment in this population that “deepens” remissions and reduces the risk of disease relapse in MRD-negative patients.

- When blinatumomab is used alongside frontline consolidation chemotherapy, the **side effects** that patients experienced were as expected from previous studies when chemotherapy or blinatumomab were used alone. No new types of side effects were identified in the new trial and any side effects that were observed were consistent with those already known and described in the regulatory paperwork for blinatumomab.

3i) Summary of key disadvantages of treatment for patients:

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Blinatumomab alongside consolidation chemotherapy is generally well-tolerated and was shown in E1910 to be effective in extending patients’ lives compared to consolidation chemotherapy alone. However, some things that patients may want to consider before starting treatment include:

Effectiveness

Blinatumomab alongside consolidation chemotherapy does not work for all patients. This means that some patients will still relapse even with this treatment.

Side effects

All patients who received blinatumomab and consolidation chemotherapy in the E1910 trial experienced side effects related to their treatment. This is to be expected regardless of how effective blinatumomab and consolidation chemotherapy is for a particular patient. When blinatumomab is used alongside frontline consolidation chemotherapy, the side effects that patients experienced were as expected based on previous studies when chemotherapy or blinatumomab were used alone. Side effects associated with blinatumomab are generally manageable with appropriate monitoring and measures such as delaying treatment and/or providing additional medical support.

Administration

Blinatumomab is administered through a continuous intravenous infusion. This may be uncomfortable or inconvenient for patients and reduce their mobility, impacting their daily activities.[39] However, given that patients would already be receiving consolidation chemotherapy intravenously, it is not anticipated that receiving blinatumomab would lead to considerably more discomfort beyond that of consolidation chemotherapy alone. Whilst receiving blinatumomab, patients will need to attend hospital (as an outpatient) to have their infusion bags changed, which can cause some inconvenience to their daily activities.

3i) Value and economic considerations:

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators seek to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health and quality of life of patients is likely to improve if they take it. The pharmaceutical company that develops a medicine provides this information to healthcare administrators using a

health economic model. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of a new treatment (blinatumomab as part of consolidation chemotherapy) with the currently available standard of care (consolidation chemotherapy alone) in a theoretical modelled cohort of patients.

How the model reflects adult patients with Ph-negative MRD-negative precursor B-cell ALL in the frontline consolidation phase

The economic model was designed to reflect the key features of the condition (B-cell ALL) and current **clinical practice** in the UK. To do this, a "partitioned survival model" structure was chosen which uses the overall survival and relapse free survival data from the E1910 trial. The model was used to predict future survival of the theoretical modelled cohort of patients with Ph-negative, MRD-negative precursor B-cell ALL in frontline consolidation, comparing treatment with blinatumomab and consolidation chemotherapy versus consolidation chemotherapy alone.

The results of the E1910 trial were used to inform the economic model, as they represent the best available data assessing the efficacy and safety of blinatumomab, alongside consolidation chemotherapy, in this population who would be expected to receive blinatumomab in the UK if it were recommended as a new treatment option. The main results from the E1910 trial that were used in the model were overall survival (how long patients lived for) and relapse-free survival (how long patients lived for without relapsing). These were the main results used in the model because they were considered most relevant to what would be considered a successful outcome to patients when treating adult patients with Ph-negative, MRD-negative B-cell precursor ALL in frontline consolidation in clinical practice, i.e. a treatment's ability to prevent a patient from relapsing and dying.

The results of the E1910 have an average study follow-up duration of four and a half years, but the economic model needs to simulate the theoretical patient cohort for the rest of their lifetime, which is a longer period of time than the length of the trial itself. Therefore, the longer-term impact of blinatumomab was evaluated by **extrapolating** the overall survival and relapse free survival data from the E1910 trial using statistical methods.

Modelling how much blinatumomab, alongside consolidation chemotherapy, improves quality of life

As well as looking at how blinatumomab alongside consolidation chemotherapy extends the lives of adult patients with Ph-negative, MRD-negative, B-cell precursor ALL in frontline consolidation, the model took into consideration the quality of life experienced by patients with ALL. This was quantified using measures called "**utility values"**. Utility values are generally a number between 0, which represents death, and 1, which represents perfect health. These utility values are in turn used to calculate **quality-adjusted life years** (**QALYs**). QALYs are a health outcome measure that consider both the length and the quality of life provided by a treatment. One year spent in perfect health (i.e. a utility score of 1) represents one QALY. Side effects are also taken into account by lowering patients' utility values, and therefore QALYs as well.

As HRQoL was not measured in the E1910 trial, utility values were used from the BLAST and TOWER trials.[34, 35] These studies measured quality of life of patients with ALL in complete remission and in relapse/refractory settings, respectively. Please see **Section 3f** of this document, or **Section B.3.4** of **Document B** for further information.

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model for blinatumomab and consolidation chemotherapy versus consolidation chemotherapy alone. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine, as well as any other medicines the patients may receive subsequently
- The cost of starting treatment and the cost of monitoring the patients during their treatment
- The cost of managing side effects that happen during their treatment, and end-of-life costs associated with caring for patients in their last months prior to death

These costs are considered for the new treatment (blinatumomab with consolidation chemotherapy) and for the currently available treatment option (consolidation chemotherapy alone). Comparing these costs shows how the cost of treating patients would change if blinatumomab were recommended for use in the setting investigated in the E1910 study.

Uncertainty

There are various assumptions that were made in the model, which can result in uncertainty in the results. Information on these assumptions can be found in **Document B, Section B.3.9.2**. Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B, Section 3.8.**

Benefits of blinatumomab not captured in the economic analysis

Treatment with blinatumomab, alongside consolidation chemotherapy, offers lasting benefits and potential for cure in some adult patients with Ph-negative, MRD-negative, B-cell precursor ALL in the frontline consolidation phase. However, this economic analysis does not capture the sense of hope the availability of a new targeted frontline treatment that reduces the risk of relapse would give to the patients and their families.

Cost effectiveness results

Based on modelling inputs and assumptions and the proposed **commercial arrangements**, treatment with blinatumomab and consolidation chemotherapy was associated with higher health benefits (or QALYs) at a higher cost than consolidation chemotherapy alone.

Resulting costs and QALYs associated with each treatment, and the ratio between these values, indicates whether the treatments are cost-effective or not. This ratio is called an **incremental cost-effectiveness ratio** (**ICER**). The ICER for blinatumomab with consolidation chemotherapy versus consolidation chemotherapy alone was calculated to be £32,311 per QALY. This means the addition of blinatumomab to frontline consolidation chemotherapy is estimated to cost the NHS £32,311 per additional QALY gained. It should be noted that these results are based on assumptions made by the company and account for the proposed confidential discount for blinatumomab, but do not account for any

discounts available for treatments forming part of standard of care as these are confidential and therefore unknown.

3j) Innovation:

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Ph-negative B-cell precursor ALL that is MRD-negative in frontline consolidation is a serious, life-threatening disease which places a considerable burden on patients due to the high risk of disease relapse. The main treatment for B-cell ALL in the consolidation phase is chemotherapy, which works non-selectively on cells throughout the body and does not specifically target leukaemia cells. Therefore, there remains an unmet need for an effective, targeted treatment for patients with B-cell ALL in the consolidation phase that avoids and reduces the risk of disease relapse.

The E1910 study has shown that blinatumomab, given alongside consolidation chemotherapy, is an effective treatment at extending patients' lives and reducing the risk of relapse, when compared with consolidation chemotherapy alone. It also showed that patients treated with consolidation chemotherapy alone had side effects at a similar frequency to those treated with blinatumomab and consolidation chemotherapy. Therefore, if recommended, blinatumomab could improve the outcomes of adult patients with Ph-negative, MRD-negative, B-cell precursor ALL in frontline consolidation, as it reduces the risk of relapse and offers a higher chance of sustained remission and potential of a cure, compared current standard of care, for this life-threatening disease. Further, it would be the first targeted therapy available for MRD negative adult patients in the frontline consolidation setting in B-cell ALL.

3k) Equalities:

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

There are no equality issues that are anticipated for the use of blinatumomab in adult patients with Ph-negative, MRD-negative, B-cell precursor ALL in the frontline consolidation phase.

SECTION 4: Further information, glossary and references

4a) Further information:

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

- Further information on NICE and the role of patients:
- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf
- Cancer Research UK. What is acute lymphoblastic leukaemia (ALL)?: https://www.cancerresearchuk.org/about-cancer/acute-lymphoblastic-leukaemia-all/about
- MHRA. Package leaflet: Information for the patient. BLINCYTO 38.5 micrograms powder for concentrate and solution for solution for infusion blinatumomab: https://mhraproducts4853.blob.core.windows.net/docs/5bd7c2fb7ac2259d9a272ec754278ff721330493

- NHS. What is acute lymphoblastic leukaemia?: https://www.nhs.uk/conditions/acute-lymphoblastic-leukaemia/what-is-acute-lymphoblastic-leukaemia/

4b) Glossary of terms:

This glossary explains terms highlighted in **black** in this document. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Acute lymphoblastic leukaemia (ALL)	A type of cancer of the blood and bone marrow that affects white blood cells.
Antibodies	Protective proteins produced by the immune system in response to the presence of foreign substances (antigens). They recognise and bind to specific antigens to destroy them. Antibodies are a key component of the immune response and play a critical role in protecting the body against infections and diseases.
Antigen	A protein that may trigger an immune response when introduced into the body. The immune system recognises antigens and produces antibodies to destroy them.
Antineoplastic agents	Medicines used to treat cancer by inhibiting the growth and spread of cancer cells.
B-cell	A type of white blood cell that plays a crucial role in the immune system, particularly in the production of antibodies.
B-cell precursor ALL	A subtype of acute lymphoblastic leukaemia that originates from cancerous immature B-cells that proliferate out of control.
Bispecific T cell engager (BiTE)	A type of engineered antibody that can simultaneously bind to two different antigens. In this case, they bring immune cells (T-cells) and leukaemia cells into close proximity, allowing the immune system to recognise and kill leukaemia cells.
Bone marrow sampling test	Also called a bone marrow aspirate, it is a medical procedure where a sample of bone marrow is extracted to examine the nature of the blood cells.

Cancer	A disease caused by the uncontrolled growth of abnormal cells in a part of the body.
CD19-positive	CD19 is a protein found on the surface of B-cells (a type of white blood cell). Being CD-19 positive means that the cancerous B-cells have these CD19 proteins.
Central line	A fine tube placed into a large vein, typically in the neck, chest, or groin, used for long-term medicine administration.
Chromosome	Long, threadlike structures of densely packed DNA that are present in every cell. DNA is the genetic code at the heart of all cells. It controls everything the cell does.
Clinical practice	The day-to-day practice of medicine by health professionals (e.g., doctors, nurses, pharmacists), often based on evidence and guidelines to provide the best patient care.
Clinical trial	A research study that tests how well new medical approaches work in people, including new methods of screening, prevention, diagnosis, or treatment.
Commercial arrangement	A type of agreement between NICE and a pharmaceutical company. These arrangements are designed to facilitate patient access to new treatments and ensure cost-effectiveness for the NHS. Commercial arrangements can include pricing agreements, patient access schemes, or managed access agreements. These agreements help determine how new treatments will be made available within the NHS and ensure that they provide good value for money while allowing patients to benefit from innovative therapies.
Consolidation chemotherapy	Chemotherapy given after initial treatment (induction therapy) to kill any remaining cancer cells and prevent relapse.
CT scan	Also referred to as Computed Tomography. It is a diagnostic imaging procedure that uses a combination of X-rays and computer technology to produce cross-sectional images of the body.
Enzymes	Proteins that help speed up chemical reactions in the human body.

Extrapolation	The process of estimating unknown values by extending or projecting from known data.
Gene	An inherited part of a cell in a living thing that controls physical characteristics, growth and development.
Genetic mutation	A change in a gene, which can lead to variations in the function or expression of the gene.
Haematologist	A doctor who specialises in the diagnosis and treatment of blood disorders.
Healthcare professional	A person who provides health care treatment and/or advice based on formal training and experience (e.g., doctors, nurses and pharmacists).
Healthcare resource use	The consumption of medical services and supplies necessary for diagnosing, treating, and managing health conditions. It includes the utilisation of healthcare providers and facilities, medications, medical tests and procedures, therapies and rehabilitation, and home health care.
Health economic model	A mathematical model used to evaluate the economic aspects of health care interventions, including cost-effectiveness and value for money.
Health-related quality of life (HRQoL)	A measure of how well individuals can perform their usual daily activities and enjoy life, considering their health conditions.
Immune system	A complex network of cells, tissues, and organs that work together to defend the body against harmful invaders like bacteria and viruses.
Immunotherapy	A type of cancer treatment that helps the immune system fight cancer.
Induction chemotherapy	The first phase of chemotherapy treatment aimed at reducing the number of cancer cells as much as possible.
Intravenous infusion	A method of delivering medication or fluids directly into a vein over a period of time.

Licensing extension	An approval to use an existing medication for a new patient population.
Low-dose chemotherapy	When a smaller amount of chemotherapy is given in order to reduce side effects of chemotherapy while maintaining its effectiveness.
Lumbar puncture	A procedure also known as a “spinal tap” that involves inserting a needle into the lower spine to collect or inject fluid.
Lymphocytes	A type of white blood cell that is part of the immune system.
Medicines and Healthcare products Regulatory Agency (MHRA)	The UK government agency responsible for ensuring that medicines and medical devices work and are acceptably effective and well tolerated.
Measurable residual disease (MRD)-negative	Also known as minimal residual disease, the presence of a very low number of detectable cancer cells in the bone marrow or blood after treatment, indicating remission.
Measurable residual disease (MRD)-positive	The presence of detectable cancer cells in the bone marrow or blood after treatment. MRD-positive status indicates that a small number of cancer cells (above a specific threshold) remain in the body.
MRI scan	Also referred to as Magnetic Resonance Imaging. It is a diagnostic imaging technique that uses magnetic fields and radio waves to create detailed images of the organs and tissues within the body.
Overall survival	How long a patient lives after receiving treatment a clinical trial, including the time during and after treatment.
Partitioned survival model	A type of economic model commonly used to map the life of cancer patients. The model predicts the probability of patients staying in pre-specified states of health over a specific time period.
Patient-reported outcomes	Reports coming directly from patients about how they feel or function in relation to their health condition and treatment, without interpretation by healthcare professionals.

Phase II clinical trial	A clinical trial is designed to evaluate the benefits of a new treatment or drug in a larger group of patients than in Phase I trials. The main objectives are to determine the optimal dose, further evaluate safety, and begin to assess the effectiveness of the new treatment compared to standard treatments or a placebo.
Phase III clinical trial	A clinical trial to build on Phase II findings to confirm the benefits of a new treatment compared with standard or existing treatments. The primary goals are to provide a definitive assessment of the treatment's effectiveness and safety, and to collect information that will allow the treatment to be used safely and effectively in the general population once it is approved.
Philadelphia chromosome (Ph)-negative	Refers to leukaemia cells that do not have the Philadelphia chromosome, a specific genetic abnormality.
PICC line	A fine tube that is put into a vein in the arm and goes up into a vein in the chest that is used for long-term medicine delivery.
Platelets	Blood cells that help with blood clotting to stop bleeding.
Portacath	A small medical appliance inserted under the skin on the chest or arm that has a tube that is threaded through a vein until it reaches the heart. It is used to give intravenous medications.
Precursor B-cell	An immature B-cell present in bone marrow.
Prognosis	The expected long-term future outcome of a patient with a disease.
Protein	Large, complex molecules that play many critical roles in the body, including building tissues and organs and supporting immune function.
Quality-adjusted life years (QALYs)	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a

	quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Refractory disease	A disease that does not respond to treatment.
Relapsed disease	The return of disease after a period of improvement.
Relapse-free survival	How long a patient lives and does not relapse after receiving a treatment in a clinical trial, including the time during and after treatment.
Remission	When the signs and symptoms of the cancer are reduced or disappear.
Stem cell transplant	A procedure to replace the diseased cells of the bone marrow with healthy stem cells.
Steroid	A type of medicine which reduces inflammation.
Systemic cancer treatment	Treatment that reaches cells all over the body, not just at the original tumour site, by traveling through the bloodstream.
Targeted cancer medicine	Medications designed to target specific molecules involved in the growth and spread of cancer cells.
T-cells	A type of white blood cell that plays a central role in the immune response. They have specialised receptors on their surfaces that recognise specific antigens.
Tissue typing tests	Tests that assess antigens on the surface of a patient's cells and tissues to determine the compatibility of tissues for transplantation, ensuring a match between donor and recipient tissues.
Utility values	Measures used in health economics to represent the preference for a given health state, typically ranging from 0 (death) to 1 (perfect health).
White blood cell	Cells of the immune system involved in protecting the body against infections and foreign invaders.

X-ray	A diagnostic test that uses radiation to produce images of the structures inside the body, particularly bones.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

12/08/2024

File name	Version	Contains confidential information	Date
ID6405_Blinatumomab for ALL_EAGClarificationLetter_120824	V0.1	Yes	12/08/24

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Searches

A1. Company's submission (CS), Appendix D, page 6, and Appendix G, page 23. Please explain why the searches were limited to studies published from 2012 onwards.

The economic and clinical systematic literature reviews (SLRs) were limited to studies published from 2012 onwards, to keep the scope and timelines manageable, while focussing on the most relevant, recent evidence, without restricting the search by clinical or humanistic outcome terms. This means that any clinical or humanistic evidence was captured.

A2. CS, Appendix G, published cost-effectiveness studies, Table 15 (Embase), page 26, and Table 16 (MEDLINE), pages 28-29. Please provide the reference for the source of the cost-effectiveness search filter and the health-related quality of life (HRQoL) filter.

The economic SLR searches used three robust sets of Emtree/MeSH and free-text terms, covering:

1. Economic evaluation
2. Health state utility value (HSUV)
3. Cost/resource use evidence from Embase, Medline and Cochrane database

The searches covered in Table 15 and Table 16 of the CS Appendix G focussed on HSUV evidence. HRQoL evidence is covered in a separate Clinical and Humanistic SLR that used study type filters by SIGN and was ***not restricted by outcomes terms***, i.e. covers ***any*** clinical or

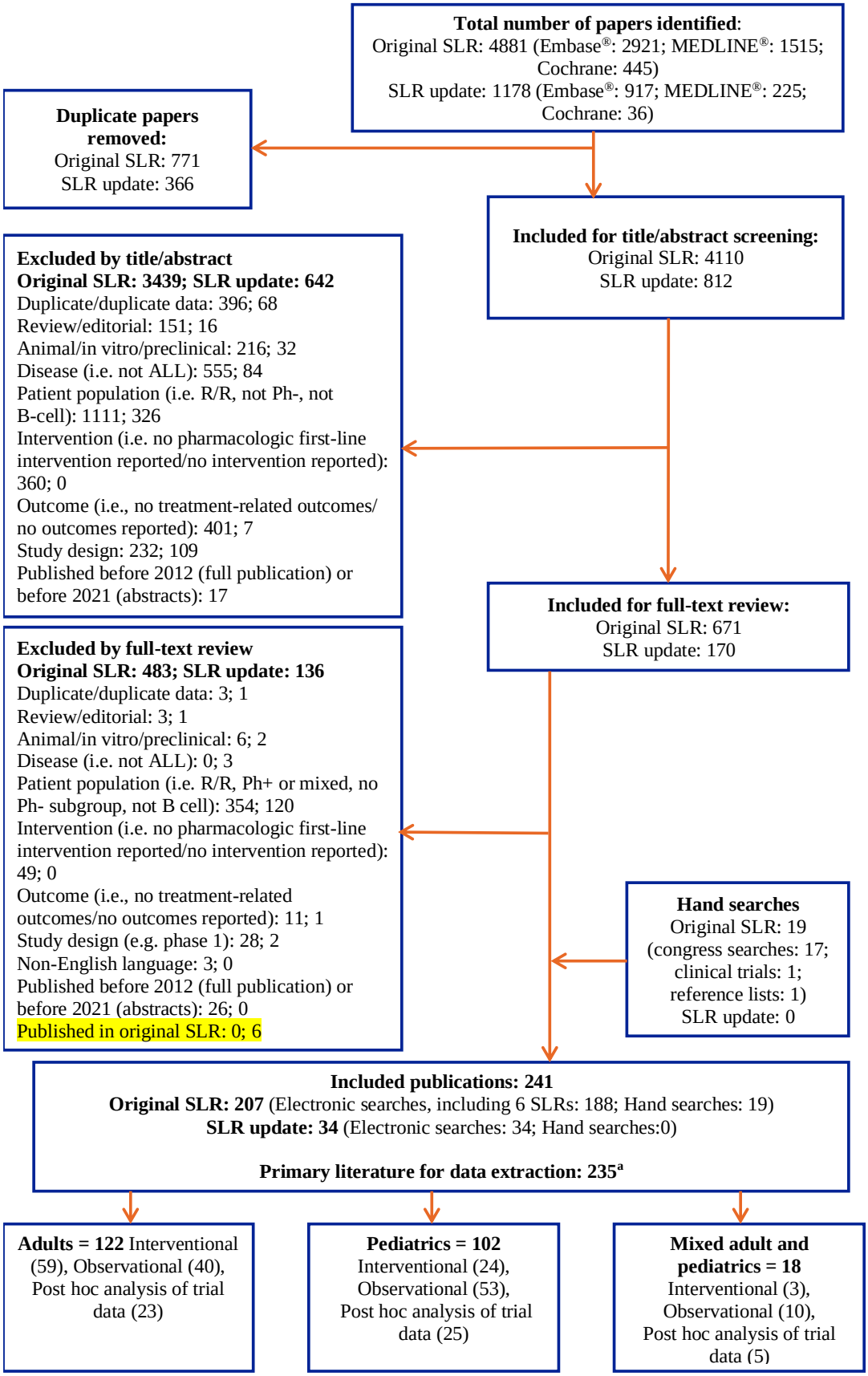
health related quality of life (HRQoL) evidence. The HSUV terms in Table 15 and Table 16 of the CS Appendix G are based on validated utilities filters by Arber et al. 2017 and these are also mentioned in the ISSG filter database.[1, 2]

The cost-effectiveness terms are adapted from several sources from the ISSG search filter resource for economic evaluation (such as Canadian Agency for Drugs Technologies In Health).[1] They cover a mixture of robust Emtree/MeSH and free-text terms for cost effectiveness analysis, cost minimisation analysis, cost benefit analysis, cost utility analysis, budget impact and cost consequence analysis. In addition, the separate set of cost/resource use terms covers broad cost and health economics terms (e.g. cost*.mp., budget*.mp., economics/ or Economics, Medical/).

A3. CS, Appendix D, Figure 1, page 19. The number of the excluded studies by full-text review for the update search (n=136) does not match the breakdown provided beneath it (n=130; duplicate/duplicate data: 1, review/editorial: 1, animal/*in vitro*/ preclinical: 2, disease: 3, patient population: 120, outcome: 1, study design: 2). Please clarify the reason for this difference and provide a corrected PRISMA diagram.

The Company apologise for this discrepancy and can confirm that the outstanding six studies were excluded because they were published before 2023 and thus were already captured in the original SLR. The corrected Preferred Reporting Items for Systematic reviews and Meta-Analyses diagram can be found below, wherein the missing studies have been highlighted in yellow.

Figure 1: Corrected PRISMA flow diagram



Footnotes: [a]Six publications reported results across multiple age categories: 2 publications reported data for paediatrics and for mixed adult and paediatrics; 3 publications reported data for adults and for paediatrics separately; and 1 publication reported data for adults, paediatrics and for mixed adult and paediatric populations. Studies including patients aged <18 years old were categorised as paediatric (studies were also included considering the median age range and proportion of patients <18, with a description of the included population e.g. "80% of patients were aged 1 to 15 years"), patients aged ≥18 (with a cut-off of ≥15 for studies that included a minority of adolescent patients) were categorised as adults, and studies including a broad age range were considered as mixed population studies.
Abbreviations: ALL: acute lymphoblastic leukaemia; Ph: Philadelphia chromosome; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR: systematic literature review

A4. PRIORITY. CS, Appendix D, page 21. The text states that *"Fourteen studies (35 publications) involving blinatumomab were identified, two were randomised controlled trials (RCTs; E1910 [Litzow et al.][6-8] and Golden Gate (Jabbour et al. 2022).[9]"* Please provide references for the remaining 12 studies.

The 12 studies referred to in CS, Appendix D can be found in Table 1. Please note that some studies were cited in several publications.

Table 1: SATs reporting blinatumomab as a treatment

Reference, Trial (name, NCT)	Study Design, RoB	Population	Intervention	Main efficacy outcomes
Standard of care (blinatumomab MRD+)				
NCT 01207388 BLAST study[3, 4]	Phase 2, SAT, Low to moderate	Adults with Ph-BCP-ALL in CR and MRD+ (> 10^{-3}) after 3 cycles of intensive therapy N=110 CR1, n=75[a]	Up to 4 cycles of blinatumomab monotherapy. ASCT after cycle 1 at discretion of treating physician (55 of CR1 patients received ASCT)	MRD response=60/75 (80%) Median OS=41.2 m (95% CI 23.5, not reached) Median OS by MRD response: OS in MRD responders N/R (95%CI 29.5 m - N/R) vs 10.6 m (95%CI 2.7 m - 39.7 m) in MRD non responder p=0.008 Median RFS 24.6m (95% 18.7-NR); RFS at 18 m 62% (95% CI 0.5-0.72). Median duration of response N/R (95% CI , N/R)
Investigational therapies				
NCT02877303 [5-11]	SAT, phase 2 Abstract only	ND Ph- B-ALL aged 14-59 years N=69 Median age 34 years 52% ⩾1 high-risk characteristics	Hyper-CVAD alternating with high-dose MTX-ara-C (four cycles) plus blinatumomab (4 cycles)+ anti-CD20 therapy (if CD20+) plus maintenance alternating between POMP (12 cycles) and blinatumomab (3 cycles). Inotuzumab (4 cycles) was added after patient 39	CR: 100% MRD-: 95% 3-year continuous remission duration: 83% 3-year OS: 87%. No difference between patients who underwent ASCT in CR1 vs those who did not (3-year OS 86% vs 88% respectively) 15-month OS with inotuzumab vs no inotuzumab: 100% vs 87%; p=0.06 4-year OS with blinatumomab: 82% (n=38) 4-year RFS with blinatumomab: 74% (n=38) High-risk cytogenetic subgroup analysis (e.g., low-hypoploidy or near triploidy, complex karyotype, IGH and KMT2A rearrangement) n=71 High-risk, 3-year OS: 89% Non-high-risk, 3-year OS: 82% HR 0.64 (reference non-high-risk)

ACTRN12617000084381 ALLG ALL8 study[12, 13]	SAT, phase 2, Low	ND Ph- B-ALL aged 40-65 years N=30 Median age 51.7 years 17% high risk cytogenetics	Hyper-CVAD like regimen alternating with blinatumomab for a total of 4 cycles. High-risk patients were recommended for HSCT, patients who were not high-risk received maintenance with POMP for 2 years	100% CR/CRi 70% MRD- after 2 cycles (83% at the end of 4 cycles) 24-m EFS 60.4%; median EFS 36.1 months 24-m OS 78.6%; median OS not reached
NCT02143414 SWOG 1318[14]	SAT, phase 2, Low	ND Ph- B-ALL aged ⩾ 65 years N=29 Median age 75 years 34% cytogenetic risk poor	Induction: 1-2 cycles of blinatumomab monotherapy until CR/CRi. Consolidation: 3 cycles of blinatumomab monotherapy, Maintenance: POMP for 18 months.	CR/CRi= 66% MRD-= 92% 3-year DFS: 37% (95% CI 17-57) 3-year OS: 37% (95% CI 20-55)
NCT03367299 GIMEMA LAL2317[15, 16]	SAT, phase 2, Abstract only	ND Ph- B-ALL aged 18-65 years N=146 Median age 41 years 48% Very high risk/ high risk	GIMEMA LAL 1913 chemotherapy + 2 blinatumomab cycles after early consolidation cycle 3 and late consolidation cycle 6, respectively Very high-risk patients were assigned early HSCT; High-risk and standard-risk with MRD + at week 10-22 were also allocated to late HSCT	Hematologic CR=90.4% MRD-= 73% after early consolidation; increase to 96% after first blinatumomab administration (p=0.018) 1-year OS: 83.8% 3-year OS: 71% (18-40 years: 76%; 40-55 years: 74%; >55 years: 49%) 1-year DFS: 71.6% 3-year DFS: 66% (18-40 years: 71%; 40-55 years: 62%; >55 years: 42%)
NCT03480438 GMALL Bold[17, 18]	SAT, phase 2, Abstract only	Newly diagnosed Ph-BCP-ALL, aged 56-76 years N=50 Median age 65 years	Induction: 1 cycle of dose-reduced chemotherapy (another cycle if not CR), followed by Blinatumomab cycle 1 Consolidation: alternating cycles of intermediate-dose MTX/PEG-asparaginase, intermediate-dose cytarabine and reinduction and 3 further cycles of blinatumomab Rituximab if CD20+ Maintenance: 6 mercaptopurine + methotrexate for 2 years	Hematologic CR: 76% after induction 1, 85% after blinatumomab cycle 1 Molecular response: 17% after induction 1, 69% after blinatumomab cycle 1 (n=34) 1-year DFS: 89% (n=34) 1-year OS: 82% 3-year OS: 65% 3-year EFS: 60%

NCT03541083[19]	SAT, phase 2, Abstract only	BCP-ALL, aged 18-70 years N=71 (45 Ph-) Patient characteristics for Ph- population not reported	HOVON 70 with reduced dose of anthracyclines, MTX, etoposide and PEG-ASP for patients > 40 years Blinatumomab was added for 14 days to prephase, 1 cycle (28 days) after consolidation 1 and 1 cycle after intensification 2 Rituximab if CD20+ HSCT was offered to intermediate/ high risk patients. Otherwise received maintenance	Ph- subgroup results: 2-year EFS: 53% SE±-9% 2-year OS: 68% SE±9%
NCT03709719 GRAALL-QUEST[20-22]	SAT, phase 2, Abstract only	High-risk ND Ph- BCP-ALL, in CR after induction and consolidation1 High-risk: KMT2 A rearrangement, IKZF1 intragenic deletion and post induction MRD >0.01% N=94 Median age 25 years (range 18-60) MRD + at enrollment 49%	GRAALL consolidation + blinatumomab (as part of consolidation and maintenance or as a bridge to HSCT): In HSCT candidates[a] blinatumomab was administered until HSCT. A minimum of 4 weeks was recommended. In non HSCT candidates, blinatumomab (5 cycles) was part of consolidation and maintenance: 2 cycles in consolidation 2 and 3 and at months 1, 3, and 5 of maintenance.	74% MRD – after first cycle of blinatumomab 18-m DFS 78.8% (95 CI % 66.9-86.8) 18-m OS 92.1% (95% CI 83.2-96.4%) <u>VHR patient subgroup</u>: 18-month DFS: 68.8% (95% CI 51.1-81.2) vs 90.6% in non VHR (95% CI 72.1-97.1) p=0.018 Comparison with control cohort GRAALL-Quest (n=94) vs control (n=104) DFS: HR 0.49 (95% CI 0.31, 0.78, p=0.002)
Blina CELL NCT04554485[23]	SAT, phase 2, Abstract only	ND Ph- B-ALL N=27 Median age: 41 years (range 19-65 years)	Induction: prephase+ 1 cycle of blinatumomab + high-dose chemotherapy (induction 2), followed by consolidation with GMALL 07/2003.	CR: 93% Molecular response at week 11: 80% With 18 months of median follow up, OS was 18.2 months and RFS 15.9 months.
NCT05557110[24]	SAT, phase 2	ND Ph- BCP-ALL N=25 Median (range): 42 years (15-53)	Induction: reduced intensity chemotherapy (idarubicin/vindesine/dexamethasone followed by 2 weeks of blinatumomab	CR/CRi: 21/21 (100%) at completion of induction and blinatumomab treatment Median EFS: Not reached

NCT01371630[25-32]	SAT, phase1- 2, Low	ND Ph- B-ALL, aged ⩾ 60 years N=80 Median age 68 years	Mini Hyper-CVAD + inotuzumab +/- blinatumomab. 49 patients received inotuzumab without blinatumomab while the remaining 31 patients received both	Overall cohort: Overall response 99% (CR 89%) MRD-: 94% Median OS: 45 m (95% CI 38.8-62.1) 2-year OS: 63.6% (95% CI 51.9-73.3) 5-year OS: 46% (95% CI 33.6-58) Median PFS: 40.9 m (95% CI 37-60.9) 2-Year PFS: 58.2% (95% CI 46.7-68.2) 5-Year PFS: 44% (31.2-54.3) The use of blinatumomab did not improve OS or PFS <u>Adverse cytogenetic and older age patient subgroups</u> (Jen 2023) 5-Year OS 60-69 years no adverse cytogenetics: 73% 60-69 years with adverse cytogenetics: 27% ⩾ 70 years no adverse cytogenetics: 39% ⩾ 70 years with adverse cytogenetics: 0%
ALLIANCE A041703 NCT03739814[33]	SAT, phase 2, Abstract only	ND CD22+, Ph- BCP-ALL, aged ⩾ 60 years, no candidates for HSCT N=33 Median age 71 years	Induction 1-2 cycles of inotuzumab followed by blinatumomab 3 cycles (if CR to inotuzumab); 5 cycles if no CR)	1-year OS: 84% (95% CI 72-98%) 1-year EFS: 75% (95% CI 61-92%) CR: 85% with inotuzumab; 97% with inotuzumab induction+ 1 cycle of blinatumomab.

Abbreviations: ALL: acute lymphoblastic leukaemia; ASCT: Allogeneic stem cell transplant; BCP: B-cell precursor; CI: confidence interval; CR: complete remission; CRI: complete remission with incomplete count recovery; DFS: disease-free survival; EFS: event-free survival; GMALL: German Multicenter Study Group for Adult Acute Lymphoblastic Leukaemia; HR: hazard ratio; hyper-CVAD: hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin (Adriamycin), and Dexamethasone; MRD: minimal residual disease; MTX: methotrexate; N/R; not reported; ND: newly diagnosed: OS: overall survival; PFS: progression-free survival; Ph: Philadelphia chromosome; POMP: prednisone, vincristine, 6-mercaptopurine, and methotrexate; RFS: relapse-free survival; RoB: risk of bias; SAT: single-arm trial; SE: standard error; VHR: very high risk.

Positioning of blinatumomab

A5. PRIORITY. CS, Section B.1.1, page 12, Table 1. The text in Table 1 states that the population under consideration in the CS is narrower than the anticipated licensed indication ([redacted] Please clarify how and why the population considered in the CS is narrower than the anticipated licence - which patients are not included?

The Company would like to clarify there was a typographical error in the license wording provided in Section B.1.1, page 11 of the CS. The marketing authorisation of blinatumomab is anticipated to be extended to include the population of [redacted].

The license extension will therefore [redacted] In contrast, as highlighted within the submission package, the population addressed in the CS is: adult patients with CD19-positive Ph-negative precursor B-cell ALL that is *MRD-negative* in frontline consolidation. As such, the population addressed in the CS is narrower than the anticipated license wording as it includes *MRD-negative patients* only. The use of blinatumomab in this indication for MRD-positive patients has already been appraised in TA589, and therefore MRD-positive patients are not considered in this submission.[34]

In addition, the population addressed in the CS is also narrower than the anticipated license wording because it is focusing on *frontline consolidation* only, whereas the anticipated license wording will not restrict to frontline consolidation.

When compared to the NICE final scope, which was 'People with Ph-chromosome-negative CD19- positive MRD-negative B-precursor ALL in frontline consolidation', the population addressed in the CS is narrower because it focuses on *adult patients* only.

The population addressed in the CS is in line with the available clinical evidence from the E1910 study that supports this submission, which aimed to compare overall survival (OS) in adult patients with Ph-negative B cell precursor ALL who are MRD-negative treated with blinatumomab and chemotherapy versus patients treated with frontline consolidation chemotherapy alone. The population addressed in this submission is therefore in line with the E1910 study and with the anticipated positioning of blinatumomab, in this context, in UK clinical practice.

Clinical effectiveness evidence

A6. PRIORITY. CS, Section B.2.2, page 23. The data cut-off for Study E1910 is June 2023. Are any further data cuts of this trial expected? If so, please provide further details.

The Company can confirm that the next data cut for Study E1910 will be at the time of the final analysis, after all patients have either discontinued the study or completed the study (i.e., completed long-term follow-up which is 10 years from start of the patient's induction treatment). The last patient's final visit for Study E1910 is anticipated in [redacted], so the final analysis would take place in [redacted].

A7. CS, Section B.2.3.1, page 26. The CS states that stratification factors included rituximab (yes/no) and minimal residual disease (MRD) status. Rituximab was included as an optional part of the treatment regimens in E1910. Please clarify what the rituximab variable relates to - is it prior use at the induction/intensification phases of the study? Please also confirm that MRD status was no longer a relevant stratification factor following the change in the design of Study E1910 (because all patients randomised and included in the analysis set presented in the CS were MRD-negative prior to receiving consolidation therapy).

Firstly, to clarify, as per the full E1910 study schema presented in CS Appendix M, Figure 4, rituximab was given as optional component at *both* the induction cycles and consolidation cycles. The stratification outlined in the protocol section 4.4 regarding rituximab use was "whether patient received or plans to receive rituximab". The stratification process and subsequent stratified analysis were conducted using the information entered by the study site at the time of randomisation. Importantly, once the randomisation was completed, the treatment assignment was finalised and could not be changed. Overall, within the full analysis set (FAS), 33 (29.5%) patients in the standard of care (SOC) consolidation chemotherapy plus blinatumomab (N=112) arm, and 36 (32.1%) patients in the SOC consolidation chemotherapy (N=112) arm received rituximab. As such, rituximab use was well-balanced between the arms.

Secondly, Amgen can confirm that the EAG's understanding is correct, MRD status was not a stratification factor in the final study design because all patients randomised and included in the analysis set presented in the CS were MRD-negative prior to receiving consolidation therapy.

A8. PRIORITY. Please provide plots of relapse-free survival (RFS) and overall survival (OS) (recentred such that time zero is the time of transplant) for the subset of MRD-negative patients who received allogeneic stem cell transplantation (alloSCT) in each treatment group at Step 3 in Study E1910. Please comment on any difference between the groups.

Overall Survival (OS)

The results of this post-hoc analysis for OS from Step 3 in the MRD-negative population who received pre-relapse alloSCT only are presented in Table 2 and the corresponding KM plot comparing the two treatment arms, recentred such that time zero is the time of transplant, is provided in Figure 2.

The un-stratified OS HR was [redacted] (95% confidence interval [CI]: [redacted]) for the blinatumomab plus SOC consolidation chemotherapy arm versus the SOC consolidation chemotherapy arm. While the un-stratified OS HR was not statistically significant (p-value: [redacted]), it could suggest a positive trend for OS observed for patients in the blinatumomab plus SOC consolidation chemotherapy arm.

Median OS was [redacted] in either treatment arm. The KM estimate of OS at five years was [redacted] (95% CI: [redacted]) in the blinatumomab plus SOC consolidation chemotherapy arm and [redacted] (95% CI: [redacted]) in the SOC consolidation chemotherapy arm.

These results demonstrate OS was similar between the blinatumomab plus SOC consolidation chemotherapy arm and the SOC consolidation chemotherapy arm once patients had received pre-relapse alloSCT. The favourable point estimate for the HR and separation of the KM curve suggests prior treatment with blinatumomab prior to receipt of pre-relapse alloSCT may be associated with a survival benefit, potentially due to the role of blinatumomab in eradicating remaining leukaemia cells pre-transplant and the prolonged residual effect of improved anti-neoplastic activity. However, these results should be interpreted with caution due to the small patient numbers included in this analysis, the wide confidence intervals and lack of statistical significance.

Table 2: OS from alloSCT for MRD-negative patients who received pre-relapse alloSCT (FAS)

	Blinatumomab + SOC consolidation chemotherapy ([redacted])	**SOC consolidation chemotherapy ([redacted])**
Number of events (death due to any cause), n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Completed study without event	[redacted]	[redacted]
Continued on study	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Time to event (KM) (yrs)[a]		
Median (95% CI)	[redacted]	[redacted]
KM estimate, % (95% CI)		
0.5 yrs	[redacted]	[redacted]
1 yrs	[redacted]	[redacted]
2 yrs	[redacted]	[redacted]
3 yrs	[redacted]	[redacted]
4 yrs	[redacted]	[redacted]

	Blinatumomab + SOC consolidation chemotherapy ([redacted])	SOC consolidation chemotherapy ([redacted])
5 yrs	[redacted]	[redacted]
6 yrs	[redacted]	[redacted]
7 yrs	[redacted]	[redacted]
Un-stratified HR[c] (95% CI)	[redacted]	
p-value	[redacted]	
Time to censoring (KM) for OS (yrs)[a,b]		
Median (95% CI)	[redacted]	[redacted]

Footnotes: [a] Years are calculated as days from allogeneic SCT date to event/censor date, divided by 365.25.
[b] Time to censoring measures follow-up time by reversing the status indicator for censored and events.
[c] The hazard ratio estimates are obtained from an un-stratified Cox regression model. A hazard ratio < 1.0 indicates a lower average death rate and a longer survival for subjects in the SOC consolidation chemotherapy + blinatumomab arm relative to subjects in the SOC consolidation chemotherapy arm.
Abbreviations: alloSCT: allogeneic stem cell transplant; CI: confidence interval; DCO: data cutoff; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; MRD: minimal residual disease; NE: not estimable; OS: overall survival; SOC: standard of care; yrs: years.
Source: Table 14-4.1.4. E1910 CSR. Amgen Data on File.[35]

Figure 2: KM for OS from alloSCT for MRD-negative patients who received pre-relapse alloSCT (FAS)

[redacted]

Footnotes: Censor indicated by vertical bar.
Abbreviations: alloSCT, allogeneic stem cell transplant; CI, confidence interval; DCO, data cutoff; FAS: full analysis set; KM, Kaplan-Meier; MRD, minimal residual disease; NE, not estimable; OS, overall survival; SOC, standard of care.
Source: Amgen Data on File.

Relapse Free Survival (RFS)

The results of this post-hoc analysis for RFS from Step 3 in the MRD-negative population who received pre-relapse alloSCT only are presented in Table 3 and the corresponding KM plot comparing the two treatment arms, recentred such that time zero is the time of transplant, is provided in Figure 3.

The un-stratified RFS HR was [redacted] (95% CI: [redacted]) for the blinatumomab plus SOC consolidation chemotherapy arm versus the SOC consolidation chemotherapy arm. As such, the post-hoc analysis of RFS for patients who received pre-relapse alloSCT showed similar results to OS; while the difference between arms was not statistically significant (p-value: [redacted]), it could suggest a positive trend for RFS observed for patients in the blinatumomab plus SOC consolidation chemotherapy arm

Median OS was [redacted] in either treatment arm. The KM estimate of OS at five years was [redacted] (95% CI: [redacted]) in the blinatumomab plus SOC consolidation chemotherapy arm and [redacted] (95% CI: [redacted]) in the SOC consolidation chemotherapy arm.

In line with the observed OS results, these results demonstrate RFS was broadly similar between the blinatumomab plus SOC consolidation chemotherapy arm and the SOC consolidation chemotherapy arm once patients had received pre-relapse alloSCT. The favourable point estimate for the HR and separation of the KM curve suggests prior treatment with blinatumomab prior to receipt of pre-relapse alloSCT may be associated with a survival benefit, however, these results should be interpreted with caution due to the small patient numbers included in this analysis, wide confidence intervals and a lack of statistical significance.

Table 3: RFS from alloSCT for MRD-negative patients who received pre-relapse alloSCT (FAS)

	Blinatumomab + SOC consolidation chemotherapy ([redacted])	**SOC consolidation chemotherapy ([redacted])**
Number of events, n (%)	[redacted]	[redacted]
Relapse	[redacted]	[redacted]
Death due to any cause	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Relapsed before start of RFS	[redacted]	[redacted]
Completed study without event	[redacted]	[redacted]
Continued on study	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Time to event (KM) (yrs)[a]		
Median (95% CI)	[redacted]	[redacted]
KM estimate, % (95% CI)		
0.5 yrs	[redacted]	[redacted]
1 yrs	[redacted]	[redacted]
2 yrs	[redacted]	[redacted]
3 yrs	[redacted]	[redacted]
4 yrs	[redacted]	[redacted]
5 yrs	[redacted]	[redacted]
6 yrs	[redacted]	[redacted]

	Blinatumomab + SOC consolidation chemotherapy ([redacted])	SOC consolidation chemotherapy ([redacted])
7 yrs	[redacted]	[redacted]
Un-stratified HR[c] (95% CI)	[redacted]	
p-value	[redacted]	
Time to censoring (KM) for OS (yrs)[a,b]		
Median (95% CI)	[redacted]	[redacted]

Footnotes: a Years are calculated as days from allogeneic SCT date to event/censor date, divided by 365.25.
b Time to censoring measures follow-up time by reversing the status indicator for censored and events.
c The hazard ratio estimates are obtained from an un-stratified Cox regression model. A hazard ratio < 1.0 indicates a lower average death rate and a longer survival for subjects in the SOC chemotherapy + blinatumomab arm relative to subjects in the SOC chemotherapy arm.
Abbreviations: alloSCT: allogeneic stem cell transplant; CI: confidence interval; DCO: data cutoff; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; MRD: minimal residual disease; NE: not estimable; OS: overall survival; SOC: standard of care; yrs: years.
Source: Table 14-4.2.4. E1910 CSR. Amgen Data on File.[35]

Figure 3: KM for RFS from alloSCT for MRD-negative patients who received pre-relapse alloSCT (FAS)

[redacted]

Footnotes: Censor indicated by vertical bar.
Abbreviations: alloSCT, allogeneic stem cell transplant; CI, confidence interval; DCO, data cutoff; FAS: full analysis set; KM, Kaplan-Meier; MRD, minimal residual disease; NE, not estimable; OS, overall survival; SOC, standard of care.
Source: Amgen Data on File.

A9. CS, Section B.2.6, page 39. Please clarify if the hazard ratio (HR) reported for the analysis which includes censoring for alloSCT is from a stratified Cox model (as per the primary analysis).

Yes, Amgen can confirm that the HR reported for the analysis which includes censoring for alloSCT is from a stratified Cox model (as per the primary analysis).

A10. CS, Section B.2.6, page 39. Were any data collected on MRD positivity following consolidation therapy as an outcome in Study E1910 (rather than full relapse)?

In Study E1910, MRD assessments were performed periodically during the course of treatment as per the study schema including at induction, intensification and early consolidation. However, the study protocol did not stipulate for MRD assessment following consolidation therapy in the maintenance phase.[36] As such, these data for MRD positivity in the maintenance phase are not available.

A11. CS, Section B.2.3.2, page 30, Table 5. The table describes a number of pre-planned subgroup analyses (gender, race, ethnicity and age). However, the CS does not present the results of these analyses. Please explain why these have not been presented for the target population. Please provide these analyses and comment on them. Please also clarify whether data on other prognostic factors or treatment effect modifiers were collected for use in subgroup analyses e.g., risk stratification or time from diagnosis to receipt of blinatumomab and provide results, if applicable.

The data for the pre-planned subgroup analyses (gender, race, ethnicity, age, CD20 status and rituximab use) for OS and RFS are presented in Table 4 and Table 5, respectively.

Overall, when considering the pre-planned subgroup analyses (i.e. gender, race, ethnicity and age) the groups were well balanced and the benefit observed for blinatumomab plus SOC consolidation chemotherapy, compared with SOC consolidation chemotherapy alone, in terms of OS and RFS did [redacted] across the different subgroups. Furthermore, within each subgroup, the HR directionally favoured blinatumomab plus SOC consolidation chemotherapy, indicating the treatment effect of blinatumomab plus SOC consolidation chemotherapy treatment is consistent within subgroups. The notable exception is patients over ≥65 years, where the HR directionally favours the SOC arm, however, this could be attributed to the extremely small patient numbers in this age category and therefore a limited number of events.

Subgroup analyses were also performed to investigate the effect of the randomisation strata: CD20 status, rituximab use and intent to transplant. These data are also presented in Table 4 and Table 5. As shown by the data, although [redacted] was observed, a positive trend was observed in all subgroups for OS and RFS for patients in the blinatumomab plus SOC consolidation chemotherapy arm. Nonetheless, these analyses should be interpreted with a degree of caution given that the trial was not powered in these subgroups. As such, these analyses are associated with greater uncertainty.

Data on other prognostic factors or treatment effect modifiers were not used in subgroup analyses in the E1910 study. The patients were MRD-negative after induction treatment and were in complete remission and were all randomised prior to consolidation approximately 3−4 months after initial diagnosis.

Overall, the analysis of most relevance to this appraisal remains the intent to treat (ITT) analysis, which provides evidence for the full population being considered in this appraisal and for which the E1910 trial was designed and powered.

Table 4:OS – Subgroup Analysis (FAS)

	Blinatumomab + SOC consolidation chemotherapy (N=112) events/patients (%)	SOC consolidation chemotherapy (N=112) events/patients (%)	HR (95% CI)[a]	p-value[b]
Sex				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	
Race				
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	
Asian	[redacted]	[redacted]	[redacted]	
Black or African American	[redacted]	[redacted]	[redacted]	
Native Hawaiian or Other Pacific	[redacted]	[redacted]	[redacted]	[redacted]
islander				
White	[redacted]	[redacted]	[redacted]	
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	
Ethnicity				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	
Age				
≥18 and <35 years	[redacted]	[redacted]	[redacted]	
≥35 and <55 years	[redacted]	[redacted]	[redacted]	
≥55 and <65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	
All patients	[redacted]	[redacted]	[redacted]	
CD20 status				

Positive	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Rituximab use				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Intent to receive allogenic SCT				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	

Footnotes: OS is calculated from time of Step 3 randomisation until death due to any cause. [a]The HR estimate for all patients was obtained from an un-stratified Cox regression model. [b]p-value is from the test of the interaction term in an un-stratified Cox regression model with terms for the subgroup and treatment group.
Abbreviations: FAS: full analysis set; HR: hazard ratio; OS: overall survival; SCT: stem cell transplant; SOC: standard of care.
Source: Table 14-4.3 E1910. Amgen Data on File.[37]

Table 5: RFS – Subgroup Analysis (FAS)

	Blinatumomab + SOC consolidation chemotherapy (N=112) events/patients (%)	SOC consolidation chemotherapy (N=112) events/patients (%)	HR (95% CI)[a]	p-value[b]
Sex				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	
Race				
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	
Asian	[redacted]	[redacted]	[redacted]	
Black or African American	[redacted]	[redacted]	[redacted]	
Native Hawaiian or Other Pacific islander	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	

Ethnic				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	
Age				
≥18 and <35 years	[redacted]	[redacted]	[redacted]	
≥35 and <55 years	[redacted]	[redacted]	[redacted]	
≥55 and <65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	
All patients	[redacted]	[redacted]	[redacted]	
CD20 status				
Positive	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Rituximab use				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Intent to receive allogenic SCT				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	

Footnotes: RFS is calculated from time of Step 3 randomisation until death due to any cause. [a]The HR estimate for all patients was obtained from an un-stratified Cox regression model. [b]p-value is from the test of the interaction term in an un-stratified Cox regression model with terms for the subgroup and treatment group.
Abbreviations: FAS: full analysis set; HR: hazard ratio; RFS: relapse-free survival; SCT: stem cell transplant; SOC: standard of care.
Source: Table 14-4.4 E1910. Amgen Data on File.[37]

A12. CS, Table 9, page 38. Please provide a narrative summary of the critical appraisal for Study E1910.

As shown in Table 9, Section B.2.5 Document B of the CS, the E1910 study, which investigated the efficacy and safety of chemotherapy with or without blinatumomab in treating Ph-negative B-cell precursor ALL in the frontline consolidation phase, was a robust trial.

While the open-label nature of the study meant that treatment allocations were not concealed, introducing potential bias, concealment would have been impractical due to the continuous infusion associated with blinatumomab and the requirement for close monitoring and management of adverse events of interest. Furthermore, randomisation was carried out

appropriately using a permuted blocks within strata algorithm stratified by multiple prognostic factors (i.e., MRD status, age, CD20 status, rituximab use, and intended SCTs) thereby mitigating this risk and minimising the potential for selection bias.

The baseline characteristics were well-balanced between the treatment groups in the E1910 Study, ensuring comparability at the study's outset. The baseline characteristics of the FAS were also generalisable to UK clinical practice, as confirmed by clinical experts during an advisory board conducted by Amgen in October 2023.[38] In addition, the primary outcome of the trial was OS; the gold-standard outcome in oncology. This endpoint is also objective and unlikely to be subject to bias.

Regarding drop-outs, in the MRD negative population, 224 patients were randomised equally into the two treatment arms; only one patient in the blinatumomab plus SOC consolidation chemotherapy arm failed to receive Step 3 treatment, and all patients in the SOC chemotherapy alone arm received their intended treatment. There were no unexpected imbalances between the groups, further supporting the validity of the trial. Moreover, the study measured and reported all pre-specified outcomes, minimising the risk of selective outcome reporting. Additionally, the primary analysis of OS was based on the ITT principle, including all randomised patients and appropriately accounting for missing data. All outcomes reported in the methods were described in the results, ensuring a comprehensive analysis approach. The study was sufficiently powered to detect differences in the primary endpoint and highly statistically significant differences were observed for the primary (OS) and secondary (RFS) endpoints. Furthermore, the study conducted a sensitivity analysis for OS from Step 3 censored at alloSCT. This removed the effect of alloSCT from the OS analysis and showed that the survival benefit of blinatumomab plus SOC consolidation chemotherapy was consistent with the primary OS analysis, regardless of whether patients received alloSCT.

A13. CS, Section 2.9, page 50. Data on adverse events (AEs) leading to dose reductions, interruptions, or treatment discontinuations are not provided in the CS. Please clarify and report if any patients had to reduce dose, interrupt or discontinue their treatments due to AEs.

The number (percentage) of patients who discontinued treatment with blinatumomab in the blinatumomab plus SOC consolidation chemotherapy arm, had treatment interruption, or had dose modifications (i.e. dose reductions) due to an adverse reaction (AR) in Study E1910 is provided in Table 6 below. As there were multiple different chemotherapy components within the SOC consolidation chemotherapy arm, wherein patients may have experienced multiple dose reductions, interruptions, or treatment discontinuations, it is not possible to concisely present the corresponding table for the SOC consolidation chemotherapy alone. Nonetheless, as demonstrated by Table 7, the use of blinatumomab did not have a meaningful impact on the amount of frontline consolidation chemotherapy received during consolidation or maintenance when compared to the standard of care chemotherapy alone arm.

The most common AEs that led to blinatumomab treatment changes cannot be provided for Study E1910 as Eastern Cooperative Oncology Group (ECOG) - American College of Radiology Imaging Network (ACRIN) did not capture all adverse event (AE) information, including action taken in response to AE, in this study. Additionally, since ECOG-ACRIN did not capture the specific AE onset date or AE end date for events occurring during consolidation treatment, temporal linking of an AE with a dosing change is not possible.

Table 6: Summary of treatment discontinuation (SAS)

	Blinatumomab + SOC consolidation chemotherapy ([redacted])
Any discontinuation/interruption/dose reduction of blinatumomab in consolidation	[redacted]
Leading to discontinuation of blinatumomab	[redacted]
Leading to interruption of blinatumomab	[redacted]
Leading to dose reduction of blinatumomab	[redacted]

Abbreviations: SAS: safety analysis set; SOC: standard of care.
Source: Amgen Data on File: AE analysis.[39]

Table 7: Relative dose intensity treatment exposure during Step 3 and Step 4 (SAS)[a]

	Blinatumomab + SOC consolidation chemotherapy ([redacted])	SOC consolidation chemotherapy ([redacted])
Blinatumomab		
n	[redacted]	[redacted]
Mean	[redacted]	
SD	[redacted]	
Median	[redacted]	
Q1, Q3	[redacted]	
Min, Max	[redacted]	
SOC chemotherapy during consolidation[b]		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
SOC chemotherapy during maintenance[b]		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Footnotes: [a]For each regimen, relative dose intensity (RDI) is calculated as (actual dose intensity/planned dose intensity); [b]Overall RDI is reported, the average of the regimen-specific RDI.
Abbreviations: SAS: safety analysis set; SOC: standard of care; SD: standard deviation.
Source: Table 14-5.16 E1910 CSR. Amgen Data on File.[39]

Section B: Clarification on cost-effectiveness data

Review of previous models

B1. CS, Section B.3.1, page 60. The CS briefly describes the company's systematic review of published economic models of frontline treatments for Ph- B-cell precursor ALL. Three economic evaluations were included in this review, but these studies are not described in the CS. Please clarify whether these studies were considered relevant to the decision problem, and if so, explain how they were used to inform the company's economic model of blinatumomab for the current appraisal.

The EAG are correct that the Nam et al. 2018, Delea et al. 2018 and Delea et al. 2020 studies were identified by the economic SLR. However, these studies were not used to inform the modelling approaches in this appraisal as they were not considered relevant to the decision problem. This is because they adopted an irrelevant perspective (US/Canadian payer perspective). As such, a *de novo* cost-effectiveness model (CEM), conducted from an NHS/Personal Social Services perspective, was developed instead to assess the decision problem for the CS.

B2. CS Appendix G.3, page 34. The CS states that the review of published economic evaluations *"included a total of 6 publications, corresponding to 5 studies for data extraction and reporting."* The text on page 35 of Appendix G.3 states that three of these studies were economic evaluations. What were the other three excluded publications? Please provide references for these studies.

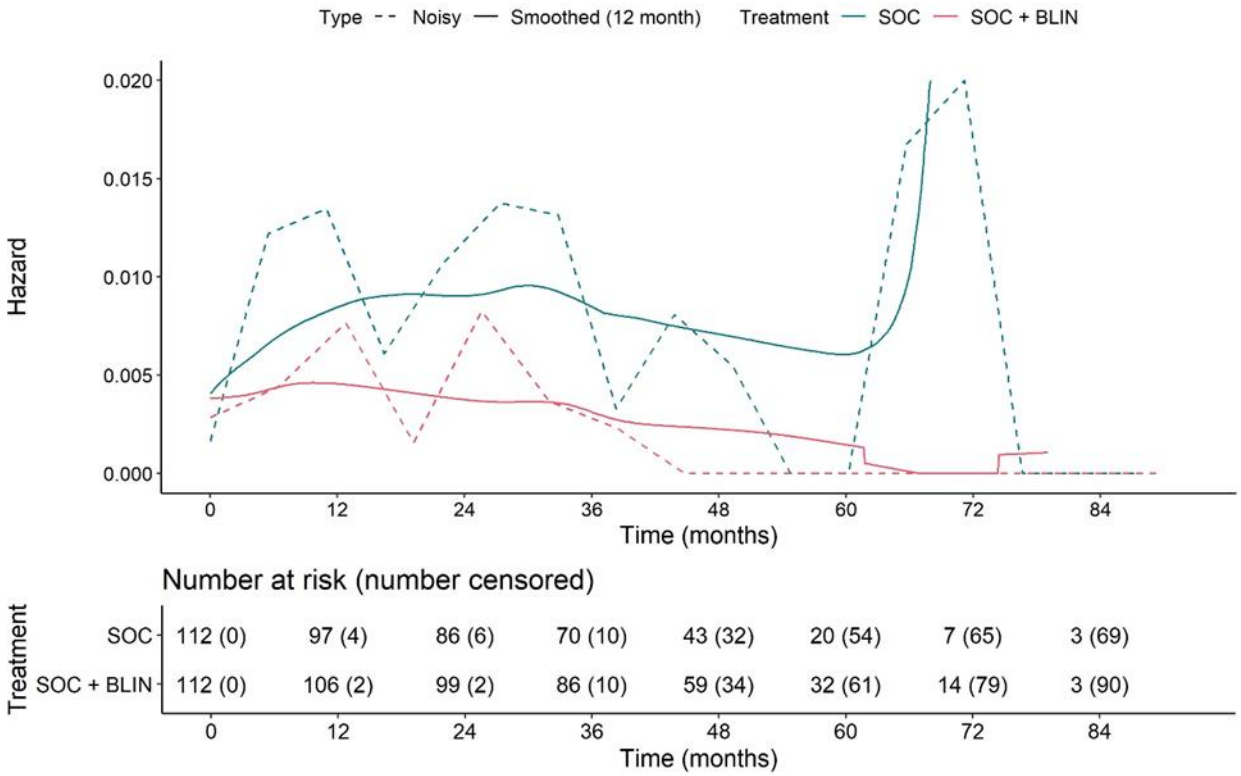
The Company would like to apologise for the confusion here and clarify that the statement in Appendix G.3, page 34 that "Overall, this SLR included a total of 6 publications, corresponding to 5 studies for data extraction and reporting" is referring to all three streams of the economic SLR (i.e. economic evaluations, HSUVs and direct costs).

Therefore, the economic SLR identified six publications overall (Nam et al. 2018, Delea et al. 2018, Delea et al. 2020, Gomez-De Leon et al. 2021, Gomez-De Leon et al. 2022, Sitthi-Amorn et al. 2016).[40-45] Three of which were publications reporting on economic evaluations,[40-42] one of which was a publication reporting on HSUVs,[42] and four of which were publications reporting direct costs.[42-45] Therefore, the remaining three publications, outlined above, were not excluded, they were included in the pool of publications, identified by the overall economic SLR, to be reporting on direct costs.

B3. PRIORITY. CS, Section B.3.3.3, pages 70-78. Please provide plots showing the empirical/unsmoothed and smoothed hazard functions for the data used in the analysis of RFS and OS. Please also plot the modelled hazards of each of the mixture-cure models (MCMs) on top of the empirical and smoothed hazard.

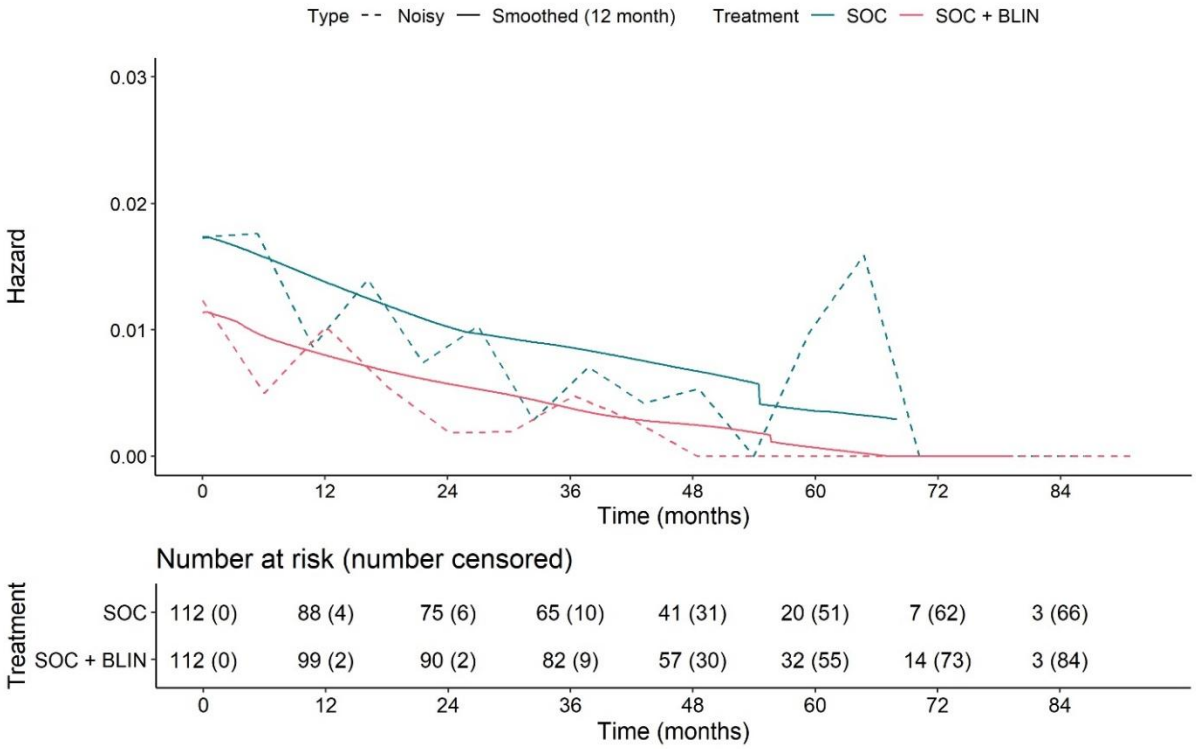
The mixture cure model (MCM) hazards (smooth and noisy) for OS and RFS are presented in Figure 4 and Figure 5. The individual hazard plots for different MCM models for OS and RFS with smooth and noisy overlay are presented in Figure 6−Figure 9.

Figure 4: Hazard plot: MCM OS, both treatment arms



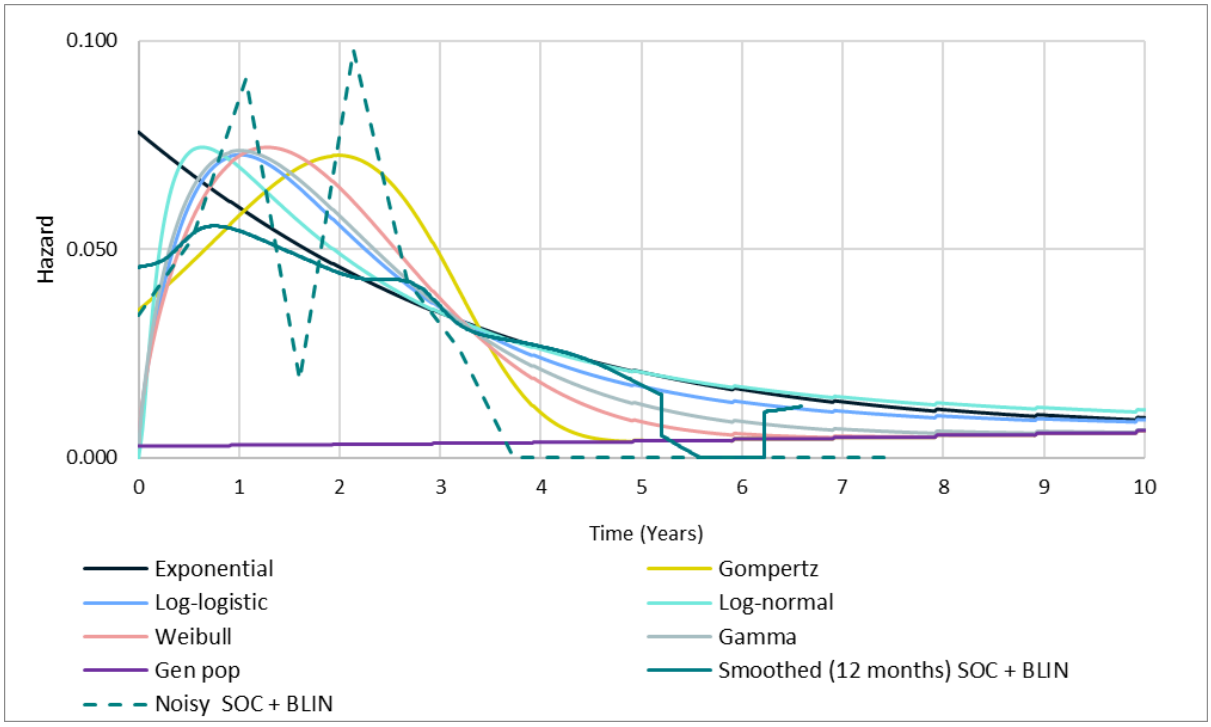
Abbreviations: BLIN: blinatumomab; MCM: mixture cure models; OS: overall survival; SOC: standard of care.

Figure 5: Hazard plot: MCM RFS, both treatment arms



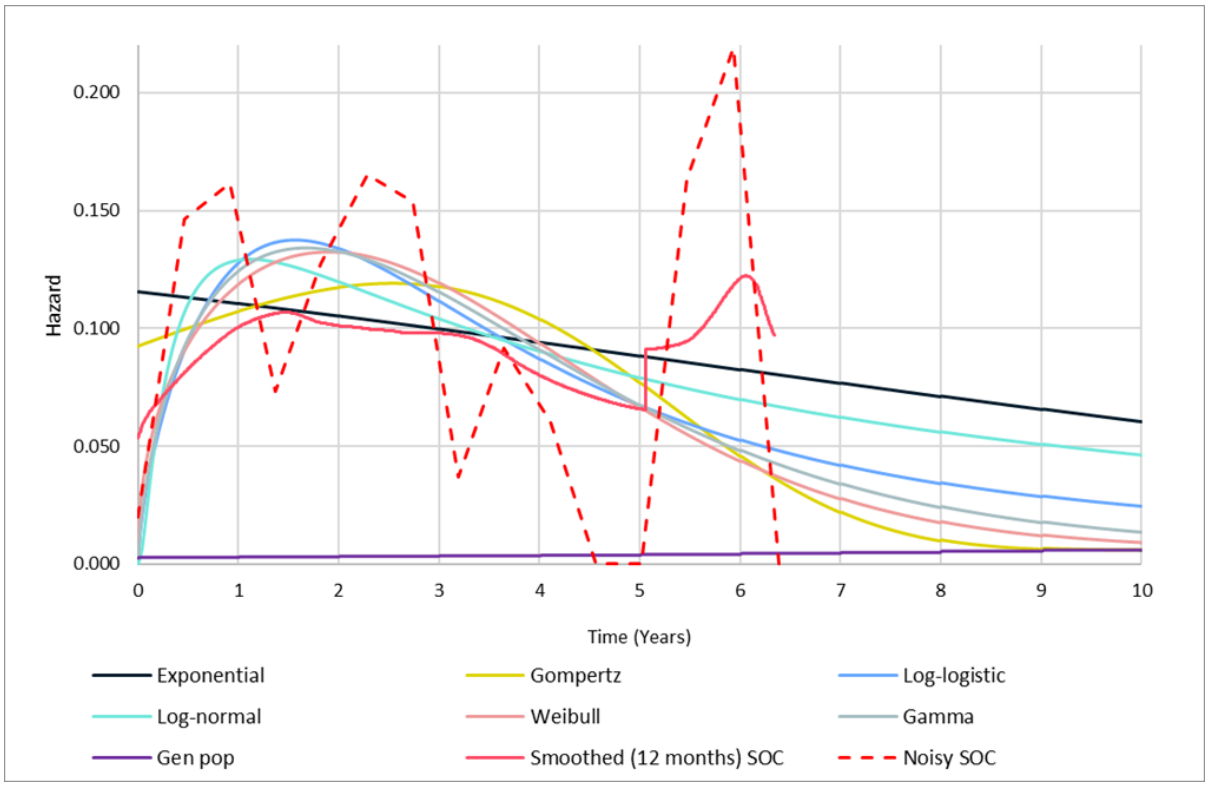
Abbreviations: BLIN: blinatumomab; MCM: mixture cure models; RFS: relapse-free survival; survival; SOC: tostandard of care.

Figure 6: Individual hazard plots: MCM OS, Blinatumomab + SOC consolidation chemotherapy



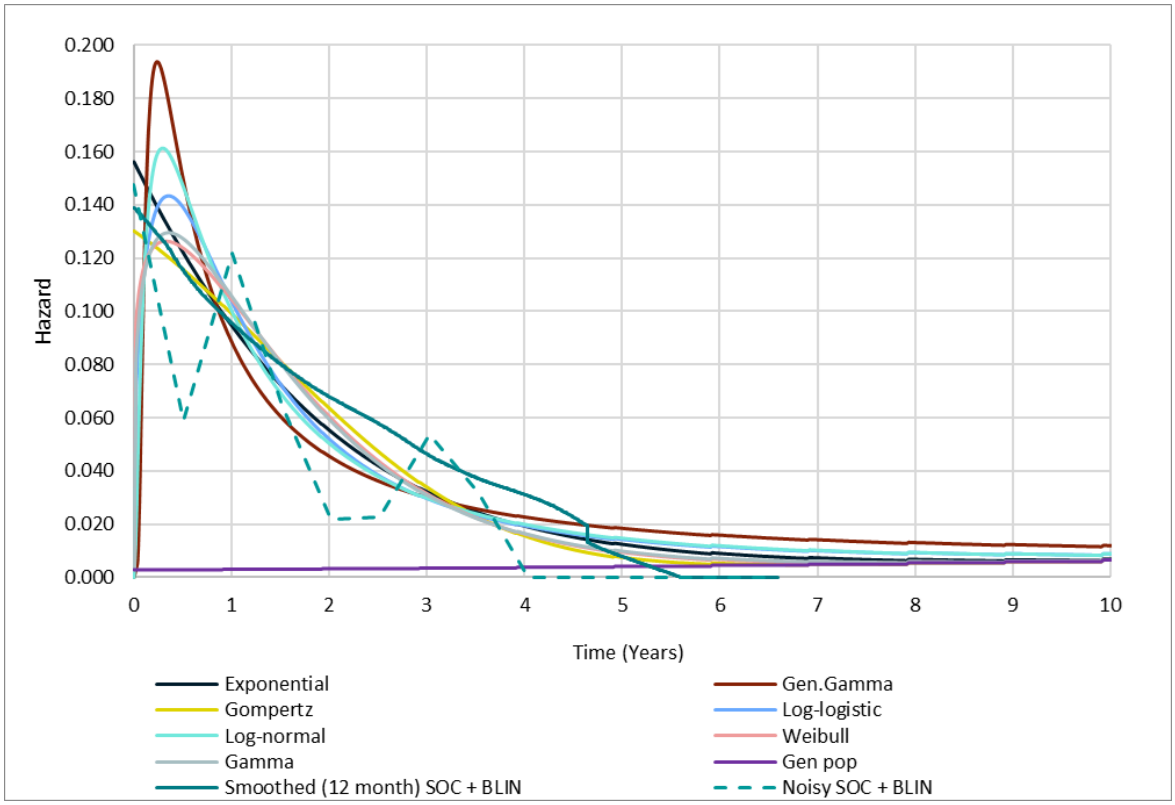
Abbreviations: BLIN: blinatumomab; MCM: mixture cure models; OS: overall survival; SOC: standard of care.

Figure 7: Individual hazard plots: MCM OS, SOC consolidation chemotherapy



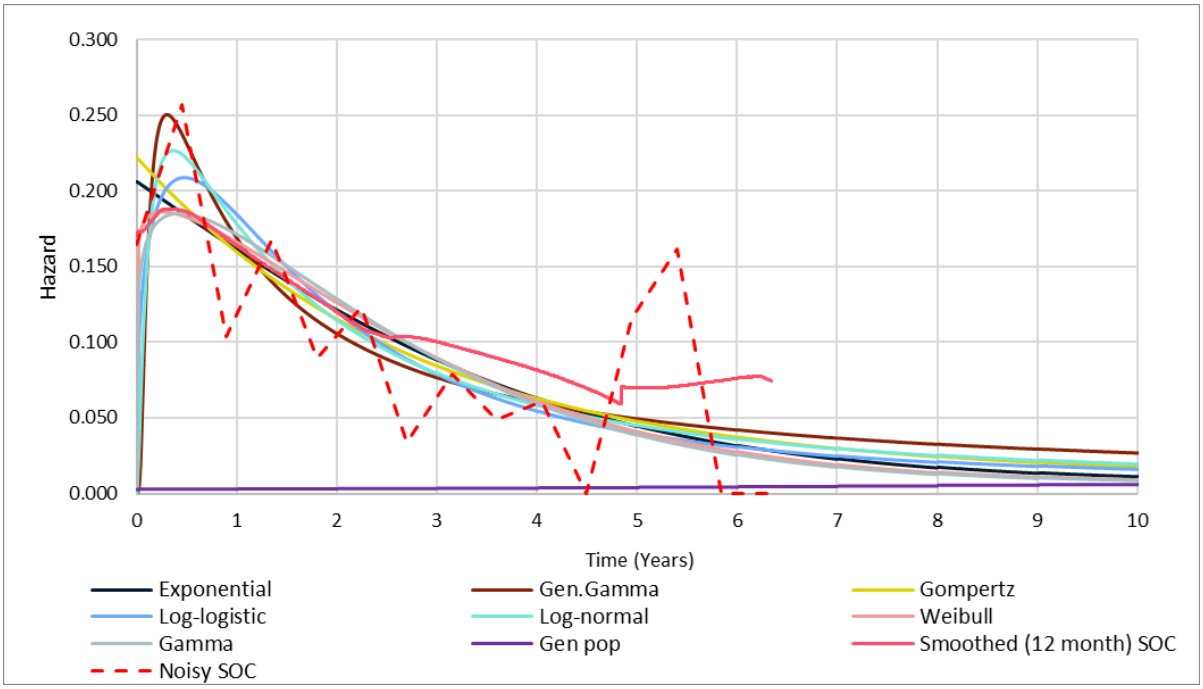
Abbreviations: BLIN: blinatumomab; MCM: mixture cure models; OS: overall survival; SOC: standard of care.

Figure 8: Individual hazard plots: MCM RFS, Blina + SoC



Abbreviations: BLIN: blinatumomab; MCM: mixture cure models; RFS: relapse-free survival; SOC: standard of care.

Figure 9: Individual hazard plots: MCM RFS, SoC



Abbreviations: BLIN: blinatumomab; MCM: mixture cure models; RFS: relapse-free survival; SOC: standard of care.

B4. PRIORITY. CS, Section B.3.3.3, pages 70-78. Please confirm that the data on RFS and OS used in the economic model do not include censoring for alloSCT.

The Company can confirm that the primary analysis data on RFS and OS used in the CEM does not include censoring for alloSCT.

B5. CS, Section B.3.3.3, Table 24, page 74, and Table 27, page 78. The model applies different cure fractions for RFS and OS in each treatment group. Please comment on the plausibility of this.

The RFS and OS curves were fitted independently to the RFS and OS data in the E1910 trial, and the corresponding cure fractions are reflective of slight differences in the proportions of patients experiencing long-term OS and RFS observed in the trial data. For example, following receipt of blinatumomab plus SOC, the probability of OS and RFS at 5 years was 82.4% and 77.0%, respectively. The trial data suggest that a small proportion of patients will subsequently relapse and receive curative treatment (for example, alloSCT or inotuzumab ozogamicin), following a relapse of their disease. This means that while most patients are cured in frontline, there is the possibility for relapsing patients to be cured by subsequent therapies, which is why the OS cure fraction should be slightly higher than the RFS cure fraction.

The chosen base case extrapolations reflect this observation, modelling the OS cure fraction to be slightly higher than the RFS cure fraction to reflect the potential for a small proportion of patients who relapse and subsequently receive curative treatments. This approach was validated by clinicians and is consistent with prior NICE TAs, where there is precedent for modelling different cure fractions for OS and RFS/event-free survival endpoints, reflecting the potential for some patients to receive curative treatment following relapse or progression on their initial line of treatment.[46-50]

B6. PRIORITY. CS, Section B.3.3.2, Figure 12, page 70 and executable model, worksheet "Executive Summary", cells C48:L78. The modelled RFS and OS projections for blinatumomab and standard of care (SoC) suggest that the proportion of patients in each group who are alive post-relapse increases between years 7 and 15. However, the data shown in Figure 12 of the CS suggest that the gap between RFS and OS in the SoC arm decreases and the gap between RFS and OS in the blinatumomab arm remains constant after around 3 years. Please comment on the plausibility of the modelled predictions.

As discussed in response to question B7 below, the Company accepts that the convergence of the SOC RFS and OS Kaplan-Meier curves is likely an artifact of the E1910 study design and is not clinically plausible. Therefore, the model includes an adjustment to correct for this, and OS and RFS curves that maximise this separation were selected. Although the proportion of patients who experience relapse during years 7 to 15 increases, it is likely to have a minimal impact on results. The base case long-term survival predictions were validated by UK clinical experts.[51]

Regarding the increasing proportion of patients in the post-relapse health state, it is important to note that this is only very minor - between Year 7 and Year 15, the health state occupancy of the post-relapse health state only increases by [redacted] and [redacted]% in the SOC consolidation chemotherapy and blinatumomab blinatumomab plus consolidation chemotherapy arms, respectively, as shown in Table 8. As such, any uncertainty around RFS for this population is unlikely to have any meaningful impact on the overall model results.

This was further demonstrated by the scenario analyses presented in Table 58, Section B.3.10.3 of the CS, which show that alternative RFS extrapolations have a minimal impact on the ICER. As such, this artifact of the E1910 study design should not be considered to represent a meaningful source of uncertainty in terms of decision making.

Table 8. OS and RFS for patients in the post-relapse health state

	SOC consolidation chemotherapy			Blinatumomab + SOC consolidation chemotherapy		
Year	OS	RFS (adjusted)	% of patients in the post-relapse health state	OS	RFS (adjusted)	% of patients in the post-relapse health state
5.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SOC: standard of care; OS: overall survival; RFS: relapse-free survival.

B7. PRIORITY. CS, Section B.3.3.2, Figure 12, page 70 and executable model, worksheet “Executive Summary”, cells C48:L78. The empirical Kaplan-Meier estimates suggest that RFS and OS for the SoC group nearly meet by around 6 years. However, the model predictions suggest a sustained gap between modelled RFS and OS for the SoC group. Please comment on the plausibility of this.

Per the E1910 trial protocol, patients are followed every three months for the first two years from study entry, every six months for the first two to five years from study entry, and every 12 months if the patients are six to 10 years from study entry.[36] Thus, while deaths were systematically captured throughout the study, some relapses may not have been captured during long-term follow-up and recorded only at the time of death. This does not appear to impact the blinatumomab plus SOC consolidation chemotherapy arm as there were no late relapses or deaths observed, however, in the SOC consolidation chemotherapy arm, RFS and OS KM curves do appear to start converge after approximately three years.

As previously detailed in response to QB5, clinicians would expect newly diagnosed ALL patients who relapse to be treated with salvage therapies prior to death. Given that these relapse patients still have the potential to be cured through innovative subsequent treatments (such as blinatumomab, inotuzumab ozogamicin and alloSCT) clinicians expressed that they would expect more RFS-OS KM curve separation rather than convergence.[51] They expressed that the separation between the RFS and OS KM curves in the blinatumomab plus SOC chemotherapy arm is more clinically plausible than the convergence in the SOC consolidation chemotherapy arm. Given that relapses in the SOC arm may have been lost to follow-up and only documented upon death, the SOC consolidation chemotherapy arm RFS curve appears to be an overestimation. This ultimately may have contributed to the convergence of the SOC consolidation chemotherapy RFS and OS KM curves observed.

Nonetheless, to mitigate any uncertainty relating to this and to ensure clinically plausible survival projections, the following constraints were implemented in the CEM (as discussed in section B.3.3.2 of the CS):

1. The log-normal mixture cure model for RFS and Weibull mixture cure model was selected for OS. This selection maximised the separation between the RFS and OS curves, ruling out survival extrapolations that caused the RFS and OS curves to converge early in the model time horizon (i.e., those distributions that underestimated OS relative to the overestimated RFS).

2. A constraint to the CEM that ensures that the hazard rate of an RFS event is always greater or equal to the hazard rate of an OS event, in each model cycle. As RFS includes both relapses and deaths, applying this constraint adjusts the overestimated RFS curve to be consistent with the OS curve on a per-cycle basis, providing more clinically realistic survival projections.

B8. PRIORITY. CS, Section B.3.3.3, page 70. The CS states that *"The goodness-of-fit statistics from the two arms of the same endpoint (i.e. OS or RFS) were added and subsequently ranked to determine which model had the best statistical fit."* Please provide separate Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for each MCM fitted to the RFS and OS data for each treatment group (i.e., not added together).

The AIC/BIC tables for individually fitted MCM models are presented in Table 9−Table 12.

Table 9: Goodness-of-fit statistics − Individually fitted MCM – OS − Blinatumomab + SOC consolidation chemotherapy

Model	AIC	AIC rank	BIC	BIC rank
Exponential	253.67	5	259.11	2
Generalized gamma	250.42	1	261.29	4
Gompertz	250.62	2	258.77	1
Log-logistic	253.96	6	262.12	6
Log-normal	255.14	7	263.30	7
Weibull	252.31	3	260.46	3
Gamma	253.17	4	261.33	5

Footnotes: Cells marked bold indicate the best fitting model.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MCM: mixture cure model; OS; overall survival; SOC: standard of care.

Table 10: Goodness-of-fit statistics − Individually fitted MCM – OS − SOC consolidation chemotherapy

Model	AIC	AIC rank	BIC	BIC rank
Exponential	464.91	5	470.35	1
Generalized gamma	465.23	6	476.10	7
Gompertz	465.54	7	473.69	6
Log-logistic	463.10	1	471.25	2
Log-normal	464.17	4	472.32	5
Weibull	463.43	3	471.59	4
Gamma	463.23	2	471.39	3

Footnotes: Cells marked bold indicate the best fitting model.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MCM: mixture cure model; OS; overall survival; SOC: standard of care.

Table 11: Goodness-of-fit statistics – Individually fitted MCM – RFS – Blinatumomab + SOC consolidation chemotherapy

Model	AIC	AIC rank	BIC	BIC rank
Exponential	306.9	1	312.3	1
Generalized gamma	309.5	7	320.4	7
Gompertz	308.4	5	316.6	5
Log-logistic	308.5	6	316.7	6
Log-normal	307.6	2	315.8	2

Weibull	308.4	4	316.5	4
Gamma	308.2	3	316.4	3

Footnotes: Cells marked bold indicate the best fitting model.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MCM: mixture cure model; RFS; relapse-free survival; SOC: standard of care.

Table 12: Goodness-of-fit statistics – Individually fitted MCM – RFS – SOC consolidation chemotherapy

Model	AIC	AIC rank	BIC	BIC rank
Exponential	478.0	2	483.4	1
Generalized gamma	478.3	4	489.2	7
Gompertz	479.7	6	487.9	5
Log-logistic	478.1	3	486.2	3
Log-normal	476.8	1	485.0	2
Weibull	479.8	7	488.0	6
Gamma	479.6	5	487.7	4

Footnotes: Cells marked bold indicate the best fitting model.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MCM: mixture cure model; RFS; relapse-free survival; SOC: standard of care.

B9. CS, Section B.3.3.3, page 76. With respect to modelling RFS, the CS states that *"the Gompertz MCM cure fraction was unstable"* when running the PSA. Please clarify what this means and explain the basis for judging that the cure fraction was unstable.

The survival function $S(t)$ for a Gompertz distribution with parameters $\lambda > 0, \theta \epsilon (-\infty, +\infty)$, is defined as:

$$e\{-\frac{\lambda}{\theta}\left(e^{\theta t}-1\right)\}$$

The application of this distribution in MCMs can be limited because when the shape parameter θ takes on values less than 0, this implies that the survival function never equals zero. In the MCM application, this suggests that all patients are cured and the model becomes a cure model without the need for a theta (cure fraction). Because of this flexibility, Gompertz MCMs can overestimate the uncertainty around the theta parameter, especially when there are a small number at risk towards the end of follow-up, since a broad range of theta values can still result in a good fit to the observed data. During the probabilistic sensitivity analysis (PSA), this variation in theta skews the curve from 0 to 100% because when theta is negative there is no longer any non-cured patients in the cure fraction. This appears to have happened to the Gompertz RFS MCM fit for SOC consolidation chemotherapy; since the probabilistic theta values during many PSA iterations result in implausible RFS curves, with virtually no patients experiencing any RFS events for SOC consolidation chemotherapy. Therefore, the Gompertz MCM was not selected as the base case.

B10. CS, Section B.3.3.4, page 79, Table 29. Standard (log-normal) parametric survival models for RFS and OS have been presented as scenario analyses. Please explain why these standard models were considered.

In line with NICE Decision Support Unit technical support document 14,[52] parametric survival models were also considered for extrapolating E1910 data. The recommended distributions were fitted to the RFS and OS data from E1910. Log-normal RFS and log-normal OS were selected as the base case curves for the standard parametric model scenario analysis based on clinical plausibility and statistical fit.

However, compared to MCMs, standard parametric distribution may be less accurate in predicting long-term survival in the presence of complex hazards due to clinical cure. Considering that the observed hazards for OS and RFS in the MRD-negative population indicate a general decreasing trajectory, standard parametric models were unlikely to be sufficiently flexible to model the observed hazards in the long term. Additionally, MCMs were validated by UK clinicians as having a better fit to the Kaplan-Meier curves and more realistic survival projections for this newly diagnosed MRD-negative population. Therefore, standard parametric models were not selected as the base case, and instead were presented as a scenario analysis.

B11. Executable model, worksheet "Life Tables", columns E and F. The model includes general population life tables for the UK. Please amend the model to use life tables for England.

The company has adhered to the EAG's request; an updated version of the CEM, including the updated life tables, has been provided alongside these responses. The deterministic incremental cost-effectiveness ratio (ICER) reduced by £121 (as shown in Table 14).

Health-related quality of life

B12. PRIORITY. CS, Section B.3.4.1, page 80. The model uses a utility value of 0.85 for patients who are relapse-free (off-blinatumomab). The source of this value is reported to be NICE TA589. However, the model used to inform this previous appraisal applied a utility value of 0.802 for this health state. Please clarify the source of the utility value of 0.85 applied in the current model of blinatumomab.

In TA589, the utility value of 0.802 for patients who are relapse-free (off-blinatumomab) was not used in the base case. Rather, 0.842 was used in the base case, representing patients with an MRD-response after 2 cycles of blinatumomab (see TA589 Committee Papers; pages 165, 167).[34]

As the CEM for this appraisal includes MRD-negative patients only, the same regression equation used in the BLAST CEM (TA589) was used here, however, the coefficient for MRD-response was applied *for all patients* (i.e. 100%), which lead to a relapse-free utility of 0.85.[34] The parameter estimates from the BLAST study are shown in Table 13, while the regression equation used to calculate the relapse-free utility of 0.85 is presented below.

Regression equation to calculate relapse-free utility of 0.85:

*Pre-relapse utility = intercept + baseline utility * mean utility value at baseline + off- vs on-treatment + MRD response vs no MRD response * % MRD-responders*

*= 0.353 + 0.543 * 0.809 + 0.010 + 0.047 * 1.0*

= 0.85

This pre-relapse utility value was validated with UK clinical experts, who confirmed that this utility value reasonably represents the quality of life of the modelled MRD-negative population.[51]

Table 13: Parameter estimates from regression on EQ-5D utility values in BLAST (pre-relapse)

Parameter	Value
Intercept	0.353
Baseline utility	0.543
Off- versus on-treatment	0.010
MRD response versus no MRD response	0.047
Death within ≤ 6 months versus death within > 6 months	-0.129
Mean utility value at baseline	0.809

Abbreviations: MRD: Minimal residual disease

B13. PRIORITY. CS, Section B.3.4.1, page 80. According to the CS, the model assumes that after 5 years, HRQoL for patients who are relapse-free returns to general population Euroqol 5-Dimensions (EQ-5D-3L) norms. Please comment on the plausibility of assuming no further HRQoL decrements beyond this time point. Is there any evidence to support this assumption? In addition, the EAG notes that the model actually applies general population utility values only to the relapse-free (cured) group, rather than all patients who are relapse-free. Was this an intentional assumption?

The use of the general population utility in the cured population was validated by clinical experts, who confirmed that the HRQoL of a frontline MRD-negative ALL patient who remained relapse-free after 5 years and who had not received a transplant will be comparable to the age-matched general population.[46, 53] As such, the experts agreed that this is a reasonable and clinically plausible assumption to incorporate into the CEM. Furthermore, assuming no HRQoL decrement beyond 5 years is in line with TA895,[54] where the Committee accepted that patients alive and event-free at 5 years would experience HRQoL equal to the general population, because they can be considered effectively cured. When discussing TA895 with the expert clinicians, they expressed that if there was any HRQoL decrement for the frontline MRD-negative ALL patients in the CEM, it would be trivial and profoundly less than that seen with extensive salvage therapies (i.e. TA895).

While the Company does not anticipate cured patients in the appraisal to have a HRQoL decrement, the impact of including a decrement was investigated as a conservative scenario analysis; in this scenario the utility for cured patients is set at 97.8% of the general population utility, and had minimal impact on the ICER.

Regarding the second part of QB13, the Company is in agreement with the EAG that this assumption should be applied to all patients who are relapse-free after 5 years. As such, for consistency, the CEM has been updated to apply the general population utility to all patients who have reached the cure point at 5 years, regardless of whether they belong to the cure fraction in the MCM or are non-cured but have remained relapse-free. The ICER did not change to the 5th decimal (see Table 14) since the utility for relapse-free patients was similar to that of the general population at a median age of 50 years (0.85 vs. 0.87, respectively).

B14. PRIORITY. CS, Section B.3.4.2, page 80. The model uses a post-relapse utility value from TA589. In this previous appraisal, the External Assessment Group (EAG) raised concerns that the post-relapse utility estimate of 0.692 was implausibly high. Please justify the inclusion of this estimate in the current model. Please also provide details about how this post-relapse utility value was estimated in NICE TA450.

As part of TA589, as post-relapse utility assessments were limited in the BLAST trial, utility values of patients who were receiving SoC salvage chemotherapy in the TOWER trial of blinatumomab versus chemotherapy in R/R B-cell ALL were therefore used instead to inform the post-relapse utility in TA589.

These utility values were mapped from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 to the EuroQol Five Dimensions (EQ-5D). Specifically, this analysis included patients in the BLAST trial whose disease had relapsed and were considered similar to patients in the TOWER trial who did not have prior salvage therapy and had relapsed disease. A logistic regression model was used to estimate the probability of this group of patients being in BLAST versus TOWER, and weights were generated for patients in TOWER to match to those in BLAST, thereby resulting in a mean EQ-5D of 0.692 for the PRS health state. This value was thus used in this economic analysis in TA589, and was considered to represent an appropriate proxy to inform the post-relapse health state utility in this appraisal, in the absence of other utility data.

The PRS utility of 0.692 was validated with UK clinical experts, who confirmed that this utility value reasonably represents the quality of life of the modelled PRS population. A similar post-relapse utility value of 0.69 was also used in TA541. However, in TA589, the EAG had concerns about the post-relapse utility of 0.692 being too high, and therefore ran exploratory analyses with lower utility values (0.50 and 0.25). As such, these scenarios have also been included as options in the CEM for this submission, which reduced the deterministic ICER by £155 and £356, respectively (as shown in Table 15) – in line with the conclusions of TA589, these scenarios had a minimal impact on the ICER, demonstrating that the choice of post-relapse utility value is not a key driver of the CEM results.

Costs

B15. PRIORITY. CS, Section B.3.5, page 82. The model does not include any health care resource use relating to regular clinic visits, follow-up, imaging or other tests used for monitoring in either treatment group for people who are relapse-free or in people who have relapsed disease. Please include these costs in the model. Please also include the costs associated with any additional monitoring requirements for blinatumomab, as indicated in the Summary of Product Characteristics (SmPC).

The Company has included these costs in line with the EAG's request.

HCRU was modelled to be health-state specific, but was modelled to be equal across both treatment arms. Beyond HCRU, blinatumomab is associated with additional hospitalisation, but this is already accounted for in the CEM as part of the administration costs. Similarly, the Summary of Product Characteristics (SmPC) states that blinatumomab is associated with an increased risk of cytokine release syndrome (CRS); however, there are no specific monitoring costs related to its monitoring or prevention. The cost of CRS management is already included as part of the adverse events. As such, modelling HCRU to be equal across both treatment arms is the most appropriate assumption.

The modelled HCRU rates were derived from TA589 (blinatumomab for ALL in remission with minimal residual disease activity), where they were collected via face-to-face interviews with UK clinical experts. TA589 values were then validated and refined by UK clinical experts, as part of these clarification questions.[34] The resulting HCRU rates were split between: 1st – 2nd year in relapse-free state, 3rd – 5th year in relapse-free state, and post-relapse state, and applied for patients from treatment discontinuation onwards.

In addition, as per clinician feedback, it was assumed that after 5 years in the relapse-free state, patients were considered clinically cured and did not require further ALL-related HCRU. An updated version of the CEM has been provided alongside these responses. The addition of HCRU costs as a scenario reduced the deterministic ICER by £291 (as shown in Table 15).

B16. CS, Section B.3.3.5, page 79. The economic model includes costs and HRQoL losses associated with Grade 3+ treatment-emergent adverse events (TEAEs) based on the frequencies observed in Study E1910. The Clinical Study Report (CSR) for Study E1910 states that these events were captured during the Step 3 treatment period or within 30 days of Step 3 treatment end. Please consider including the impact of AEs on costs and HRQoL associated with subsequent treatments for patients with relapsed disease.

While the Company accepts that subsequent treatments have the potential to have broader impact than currently modelled, due to the costs and disutilities of subsequent treatment AEs, these costs were excluded from the initial submission, because publicly available data for all inotuzumab AEs are limited and the expected impact of second line (2L) AEs on the modelled results is minor.

Nonetheless, in order to investigate the impact of 2L AEs, the updated CEM now includes a scenario with adverse events for 2L inotuzumab, blinatumomab, and FLAG-IDA. For this analysis, the blinatumomab, and FLAG-IDA AEs rates were sourced from the TOWER study,[55] and the AEs for inotuzumab from INO-VATE.[56] To provide a like-for-like comparison, only AEs reported in at least 5% of patients in either arm were included in the CEM, in line with how AEs were reported for blinatumomab and salvage chemotherapy (FLAG-IDA). AE costs and disutilities were either assumed equal to comparable AEs in the CEM, or sourced from NHS Reference costs when no comparable AE was available. The costs and disutilities for veno-occlusive liver disease was sourced directly from TA541, and inflated to 22/23 to £88,058.37. This resulted in an average AE cost of £1,253.07, £970.49, and £6,374.31, and an average disutility of −0.0033, −0.0045, and −0.0013 for 2L blinatumomab, FLAG-IDA, and inotuzumab respectively. Including these costs and disutilities as a scenario analysis reduces the ICER to by £51 (as shown in Table 15) showing that 2L AEs have minimal impact on the modelled results.

B17. Executable model, all worksheets containing unit costs. Please update all relevant unit costs using the current 2022/23 NHS Reference Costs (available from here - https://www.england.nhs.uk/publication/2022-23-national-cost-collection-data-publication/).

The request has been withdrawn by EAG, due to data issues with the 22/23 NHS Reference costs. However, the submitted CEM has inflated the 21/22 NHS Reference costs to 22/23, so the expected impact of using these older cost inputs is minor.

B18. CS, Section B.3.5.3, Table 49, page 96. Regarding the management costs of cytokine release syndrome (CRS), please provide the reason for not including the costs of tocilizumab (the models developed to inform TA893 and TA957 each included tocilizumab costs in addition to intensive care unit [ICU] costs).

TA893 and TA957 focus on CAR-T therapies, where the management of treatment-emergent CRS differs from that with blinatumomab.[48, 57] CAR-T therapies, which are cellular-based treatments, have a prolonged effect as the cells persist in the body for months. This sustained presence increases the necessity for tocilizumab to manage CRS. Blinatumomab, on the other hand, has a very short half-life. According to the SmPC (section 4.2), the primary treatment for CRS associated with blinatumomab is to stop the infusion.[58, 59] Consequently, blinatumomab is cleared from the patient's system relatively quickly, which is the mainstay of managing CRS in cases of blinatumomab treatment. The need for tocilizumab is not indicated in the blinatumomab SmPC, unlike with TA893 and TA957.[48, 57-59] Additionally, 3 clinical experts were consulted who confirmed that they have never used tocilizumab for the management of CRS associated with blinatumomab. The costs of tocilizumab were therefore not included in the CEM as part of CRS management

B19. PRIORITY. CS, Section B.3.5, page 92. The model includes the costs associated with acquisition and administration of one subsequent line of drug therapy for people who experience relapse. Please explain why the costs of further subsequent-line therapies are not included and consider including these in the model, if appropriate.

The decision to exclude third-line (3L+) and beyond treatment costs was based on several key considerations. Firstly, there is insufficient data available to accurately model the distribution of patients across 3L+ therapy options, as data on subsequent therapies was not systematically captured in the E1910 trial. Therefore, including these costs without reliable data would introduce significant uncertainty into the CEM. Additionally, this is a conservative assumption as 2nd relapse SOC consolidation chemotherapy arm patients would likely receive costly innovative immunotherapy, whereas blinatumomab arm patients would likely only receive chemotherapy, as they would have already exhausted immunotherapy options in prior lines.

For these reasons, the CEM focused on the cost of subsequent treatments in 2L, where the data is more reliable and the impact on outcomes is more significant.

B20. PRIORITY. CS, Section B.3.5.1, page 92, Table 43. The proportion of relapsed patients receiving inotuzumab ozogamicin as a subsequent-line therapy is [redacted]% in the blinatumomab plus SoC group and [redacted]% in the SoC group. Please justify these assumptions. The EAG also notes that several of the clinicians consulted by the company suggested that blinatumomab re-treatment would be given in some cases, but the model assumes that 0% of patients receive blinatumomab re-treatment. Please justify this assumption.

It has been assumed that patients would not receive re-treatment with blinatumomab after discussing the topic with clinical experts via pre-advisory board questionnaire and at the advisory board meeting.[38, 46] The consensus was that most clinicians would not retreat. However, one clinician said they would only re-treat with blinatumomab in very narrow circumstances, depending on the patient's previous response. Consequently, the only available subsequent treatments for the blinatumomab plus SOC consolidation chemotherapy arm are inotuzumab ozogamicin and salvage chemotherapy. Since inotuzumab ozogamicin is the only immunotherapy option the proportion of patients receiving subsequent inotuzumab ozogamicin is much higher in the blinatumomab plus SOC consolidation chemotherapy arm ([redacted]) than the SOC consolidation chemotherapy arm ([redacted]). Conversely, since both blinatumomab and inotuzumab ozogamicin are available as subsequent treatments in the SOC consolidation chemotherapy arm, there is a more even split between these two innovative immunotherapies.

Overall, the final subsequent treatment distributions used in the CEM were again assessed during clinical validation and deemed appropriate.

Discount rates

B21. CS, Section B.3.10.3, page 113. Please clarify why discount rates of 1.5% and 5% have been presented. Does the company intend to make a case in support of non-Reference Case discount rates in this appraisal?

The Company can confirm they do not intend to make a case in support of non-Reference Case discount rates in this appraisal. Discount rates of 1.5% and 5% have been presented in order to demonstrate the sensitivity of CEM results to alternative discount assumptions, as much of the quality-adjusted life year benefit of blinatumomab is realised far in the future.

Executable model

B22. Executable model, worksheets “Trace Blin" and “Trace SoC” (columns AU, BU:BW). When calculating the disutility and acquisition costs of subsequent treatments including post-relapse HSCT, the proportion of patients is based on RFS which counts both relapse and death as events. This may overestimate disutility and cost (because these should only be applied to those patients who do not die during the model cycle). Please adjust the analysis to account for the proportion of RFS events which were deaths.

The Company has addressed the EAG’s request; an option to adjust all 2L costs and disutilities based on the fatal progression rate for blinatumomab and SoC, as observed in E1910, has been added as a scenario to the updated CEM. The fatal progression rate was calculated by dividing the number of RFS death events by the total number of RFS events per arm, resulting in a rate of [redacted]) for blinatumomab plus SOC consolidation chemotherapy and [redacted] for SOC. This adjustment led to an increase of £563 in the deterministic ICER (as shown in Table 15).

This adjustment has not been included in the updated base case for several reasons. Firstly, it is important to note that these fatal progression rates may not accurately represent the true proportion of fatal events. The absolute number of deaths is nearly the same between the arms ([redacted] for blinatumomab plus SOC consolidation chemotherapy arm and [redacted] for SOC consolidation chemotherapy arm alone), where most deaths were caused by infections. However, the number of relapses is higher in the SOC consolidation chemotherapy arm, resulting in a higher total number of events and therefore, different proportions. Additionally, the accuracy of the fatal progression rates may have been influenced by the lower frequency of RFS measurements after three years, as discussed in Priority Question B7.

B23. Executable model, all worksheets relating to the survival analysis. The model applies standardised mortality ratio (SMR)-adjusted hazards to general life tables and applies these adjusted hazards to the cured subgroup in the MCMs. However, the model applies unadjusted hazards from the life table in the uncured subgroup (without an SMR), which is inconsistent. Please amend the model to include the SMR in both the cured and uncured subgroups of the MCMs.

The EAG’s request has been addressed in the updated CEM. The ICER was not changed to the 7th decimal (as shown in Table 14).

B24. Executable model, worksheet “Drug Costs”, cells K186:K190. The calculations in this cell range should have used “adm_array_costs_active” rather than “adm_array_costs” in order to include uplifting of unit costs to current prices. Please correct this error.

The Company apologises for this error, which has now been corrected in the updated CEM. The deterministic ICER reduced by £8 (as shown in Table 14).

B25. Executable model, sheet “Trace SoC”, Columns BK and BP. When calculating the acquisition and administration costs of maintenance therapy, the formula currently includes the array “*(1-INDEX('Drug Costs'!$F$36:$F$43,....)*” to account for those patients who discontinued consolidation therapy early. However, the values in the array “*'Drug Costs'!$F$36:$F$43”* represent the proportion of patients starting each treatment cycle in the blinatumomab plus SoC arm. Instead, the array should be “*'Drug Costs'!$F$44:$F$47”* to correctly account for those patients in the SoC group. Please correct this error.

The Company apologises for this error, which has now been corrected in the updated CEM. The deterministic ICER reduced by £8 (as shown in Table 14).

B26. Executable model, sheet “Parameters”, cells V48:V59. The approach used to estimate the proportion of people starting each cycle of blinatumomab or SoC is based on independent beta distributions. Within the blinatumomab group, the probabilistic samples frequently allow for a higher proportion of patients to receive blinatumomab in cycle 4 versus cycle 3 within an individual sample. Please comment on whether this is both intentional and plausible (i.e., in E1910, did any patients miss cycle 3 of blinatumomab but receive cycle 4 of blinatumomab?).

The Company is in agreement with the EAG that a higher proportion of patients receiving blinatumomab in Cycle 4 versus Cycle 3 lacks face validity. As such, the updated CEM has been corrected to ensure that the proportion of patients receiving treatment in any cycle can never be higher than the previous cycle. The deterministic ICER reduced by £3 (as shown in Table 14).

Section C: Additional analyses

C1. PRIORITY. Please provide an updated version of the executable model which includes functionality to address questions B11, B15, B16, B17, B19, B22, B23, B24, and B25. Please also include additional functionality to address other clarification questions not included in this list, as deemed appropriate by the company.

The updated CEM has been provided alongside these responses. The following errors were corrected and included in the updated base case:

- **B11**. Update life tables to England
- **B13**. General population utility applied to all patients who are relapse-free after 5 years
- **B23**. Apply SMR to per cycle correction of OS and RFS extrapolations
- **B24.** Correction for “Drug Costs”, cells K186:K190 (uplift admin costs to 22/23)
- **B25**. Correct the SoC maintenance calculations to SoC drug use %
- **B26**. Cap treatment use at treatment use of the previous cycle

The submitted deterministic base case ICER was £31,643. The updated deterministic base case ICER is £31,505. Assumptions updated in the base case, and associated incremental ICER are presented in Table 14.

All the other queries were explored via scenarios. The associated ICER impact of each scenario is presented in Table 15.

Appendix 1: Updated base case cost-effectiveness analysis

As detailed throughout the responses above, a number of assumptions have been updated in the base case economic analyses in response to the requests from the EAG. An overview of the updated assumptions is presented in Table 14.

Table 14: Assumptions updated in the base case, and associated incremental ICER (deterministic – blinatumomab PAS price)

Scenario	ICER (£/QALY)	Change from base case ICER (£/QALY)
Submitted base case	**£31,643**	–
B11. Update life tables to England	£31,522	−£121
B13. General population utility applied to all patients who are relapse-free after 5 years	£31,643	No change to the 5th decimal
B23. Apply SMR to per cycle correction of OS and RFS extrapolations	£31,643	No change to the 7th decimal
B24. Correction for “Drug Costs”, cells K186:K190 (uplift admin costs to 22/23)	£31,637	−£6
B25. Correct the SOC maintenance calculations to SOC drug use %	£31,635	−£8
B26. Cap treatment use at treatment use of the previous cycle	£31,640	−£3
Updated deterministic base case	**£31,505**	–

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; RFS: relapse-free survival; SMR: standardised mortality ratio; SOC: standard of care.

Appendix 2: Results of EAGs requested scenarios

As detailed throughout the responses above, a number of scenarios have been provided in response to the requests from the EAG. An overview of the scenarios and their impact on the ICEs are presented in Table 15.

Table 15: Scenarios explored and their associated ICER impact (deterministic – blinatumomab PAS price)

Scenario	ICER (£/QALY)	Change from updated ICER (£/QALY)
Updated base case ICER (after error corrections)	**£31,505**	-
B13. HRQoL decrement for cured population	£32,134	£629
B14. Lower post-relapse utility: 0.50 and 0.25	£31,350 £31,149	−£155 −£356
B15. Include HCRU up to 5 years	£31,214	−£291
B16. Include 2L Tx. AE costs and disutilities	£31,454	−£51
B22. Adjust 2L costs and disutilities for proportion of RFS events that are deaths (fatal rate)	£32,068	£563

Abbreviations: 2L: second-line; AE: adverse events; HCRU: Healthcare resource use; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; RFS: relapse-free survival; Tx: treatment.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Leukaemia Care** is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	As per our latest publicly available report, we have received support from the following companies: Amgen £5,000 support services Jazz £30,000 awareness and patient support Pfizer £10,000 core funding

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information was gathered through Leukaemia Care's patient survey 'Living with Leukaemia (2017), which included responses from XX ALL patients. We have also included some statistics from the 2022 survey conducted globally by the Acute Leukaemia, CML and CLL Advocate Networks. Some statistics were taken from an ALAN (Acute Leukaemia Advocates Network) report looking specifically at the quality of life of patients across the whole leukaemia pathway. We were unable to discuss directly with patients who have had experience of blinatumomab, although we did speak to other ALL patients for context.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. As of 2018 there are 791 new cases of acute lymphoblastic leukaemia in the UK each year. The highest incidence rates of ALL are in children aged 0-4, after which the risk of ALL drops gradually, but starts to increase again at age 50. Five-year survival outcomes vary greatly by age, from over 90% in the under 15s and falling gradually to approximately 58% in those aged 15-39. However, in the relapsed/refractory setting, survival is significantly reduced with approximately 10% of all patients surviving 5 years. This makes it important to avoid relapsed disease in order to improve survival. Symptoms do vary slightly depending on the age of the patient, but common symptoms include pain in the bones and joints, repeated infections, fatigue, fever and night sweats and unusual bruises or bleeding. Bone pain was identified as more common in children than in adults in our Living with Leukaemia survey, although it makes the top 6 for both children and adults. One ALL patient we spoke to who was 20 years old when she was diagnosed also reported severe headaches and neck pain, claiming that "*nothing would make the headaches go away*". Due to the rapidly progressing nature of the condition, 63% of adult patients had only experienced symptoms for less than a month before visiting their GP. ALL is similarly as rapidly progressing in children and young people. The NCIN/NCRAS 'Routes to Diagnosis' report shows that 64% of all ALL patients are diagnosed via emergency presentation (of which 42% were A&E, 27% emergency GP referral, 5% inpatient emergency and 26% outpatient emergency). This compares to a cancer average of 22% and is the highest of any cancer type in the report. The rapidly progressing nature of the condition means that 86% of ALL patients start treatment within a week of diagnosis. Recent less detailed figures for all leukaemia publish by NHS England show there has been no significant change in this emergency presentation rate since.

	Being diagnosed with ALL can also have a significant emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation, and depression. This can be particularly difficult for children and young adults. In our 2016 survey, two thirds of 16-24 years old reported feeling more depressed or anxious since diagnosis. Evidence indicates that having relapsed from initial treatment worsens a patient's quality of life further. Relapsed patients are more likely to feel isolated all of the time, and they are also the most likely group to experience anxiety (74% of those surveyed). Additionally, relapsed patients will have to experience the physical and emotional effects of sometimes gruelling treatment again. There are also practical impacts of an ALL diagnosis; with our 2016 survey showing that 58% of 16–24-year-olds experiencing pain as a direct result of their condition (37% occasionally, 16% regularly and 5% constantly). Additionally, 45% have difficulty moving around (sometimes 30%, often 10% and always 5%) and 60% have difficulty performing some of their daily routines, such as cooking or cleaning. Another 37% reported that they have problems taking care of themselves. The financial impact on a young person can also be significant. In our 2016 survey, 80% of 16-24-year-olds had to reduce their hours in education or employment with the majority having to stop completely (45%). This impact has likely worsened recently with the rising cost of living in the UK. Leukaemia Care's conducted research in 2023 for our #LeukaemiaLevy campaign, to understand more about the financial impact on patients in the 2023/24 cost of living crisis. We found that the number of patients reporting to have been affected financially since diagnosis has increased from 43% in 2017 to nearly 60% in 2023. On average, patients with acute leukaemia were more likely to experience both an increase in living costs and a decrease in their income compared with all leukaemia patients combined (75% vs. 54.5% respectively). The emotional impact does not affect the patient in isolation. A diagnosis of ALL can place huge emotional strain on families and friends, many of whom may be affected. As such, improvements in a patients' treatment and quality of life will also have a wider impact on the lives of their family and friends. Whether the patient is an adult or a child, many of our patients describe an increase in caring

	responsibilities that affect their emotional health, but also have a practical and financial impact as they must find time to dedicate to the person who has been diagnosed. An ALL patient we spoke to, who was 20 at diagnosis, said: *"The impact that my diagnosis had on my family was profound. Initially, shock was the overruling emotion felt by them in the first few weeks. We had to try and explain everything to my niece, who was just 6 at the time. It was so difficult for all of them to even begin to process what was happening. My mum had to stop working as a shop assistant so that she could support me when I was in the hospital and whilst I was at home in between treatments. She became my main carer. My dad is self-employed and had to continue working throughout my treatment to support us and to keep paying the bills. Even after working all day, he would still make the trip to the hospital every single day, rain or shine. It was really tough on all of us, but we got through it together."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	When we asked in our 2021 survey whether ALL patients thought existing treatments for this disease were sufficient, 100% of respondents said either no, or were not sure. Most of these respondents were adults, so are much less likely to have benefitted from recent advancements like CAR-T therapy (only made available on the NHS in 2024 for adults) and are also less likely to have been fit for transplant. CAR-T therapies are likely to only be appropriate for a subset of patients, as is transplant, so if we can improve the chemotherapy regimens available to ALL patients and avoid the most intensive therapies, this is highly likely to be welcomed by patients. Improving survival is the main feature people with ALL would like to see new treatments address. A majority of people who we surveyed indicated that they would be happy to have additional side effects to gain this treatment benefit, although this is likely to depend on the specific person, treatment regimen and side effects. The precise preferences for treatments and trade offs patients make is currently being researched by the Acute Leukaemia Advocates Network in collaboration with the Office for Health Economics, but is not available at the time of writing. A potential reason for adults with ALL to claim that current treatments available on the NHS are insufficient is that it can be challenging to cure these patients, due to concerns about surviving chemotherapy. Whilst this treatment is additional to standard of care, and so does not reduce side effects, it is possible that some of these patients may be more open to chemotherapy if an agent is shown to improve their chances of survival after initial treatment, given older adults are less likely to be able to withstand multiple treatment rounds due to relapse. Finally, there would also be support from many patients for additional therapy post-transplant or CAR-T therapy. Whilst these are both innovative treatments that have been transformational for many patients, the lengthy procedures, the practical implications such as travel from home and the physical side effects can mean the relapse after these treatments is even more devastating. Avoiding this where possible through maintenance therapy is a positive thing.

8. Is there an unmet need for patients with this condition?	Given relapsed and refractory ALL continues to have poor outcomes, it is essential that clincians have a range of frontline options suitable to the wide range of people who are affected by ALL. It will also benefit the NHS and wider society to reduce relapse in terms of the impact on the patients emotional wellbeing. Further treatment would be welcomed for this reason.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**As mentioned above, there a number of patients who are in need of more effective treatments to prevent relapse. Whilst blinatumomab is currently available to some patients, such as those who are MRD positive, if blinatumomab can provide a greater benefit by being given earlier, this would be welcome by patients, in spite of additional side effects.** **Blinatumomab has been in use in the NHS for some years and we understand that it can be given as an outpatient in many cases, something that can help many patients and their families have a higher quality of life.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Additional side effects are often a concern, particularly in older patients. However, this is often a very individual decision between clinician and patient. Many of those who responded to our survey were over the age of 65, and the majority still favoured additional survival in the face of additional side effects, so it is important we offer the best potential chance of increased survival and reduction in relapse.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	n/a

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• ALL continues to be a life threatening illness with a high chance of relapse. • The emotional and practical burden of ALL is also huge, with other treatments potentially adding to this burden. Therefore, maximising the efficacy of treatments first time would be preferable to patients. • Relapsed patients have been shown to have a significantly worse quality of life and report worse mental health than those in active treatment. • Blinatumomab given as maintenance, if effective, could prevent relapse from occurring. Even being MRD detectable is associated with a high chance of relapse, so giving blinatumomab at an earlier stage of treatment could help this. • Patients are keen to see treatments that improve survival and may consider this worth additional side effects.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Single Technology Appraisal

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

Clinical expert statement

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Part 1: Treating acute lymphoblastic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr.N.J.Morley
2. Name of organisation	Sheffield Teaching Hospitals NHS Foundation Trust
3. Job title or position	Haematology Consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acute lymphoblastic leukaemia? ☒ A specialist in the clinical evidence base for acute lymphoblastic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
8. What is the main aim of treatment for acute lymphoblastic leukaemia?	Cure with least possible long term side effects.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Complete remission (Measurable residual disease (MRD) negative).
10. In your view, is there an unmet need for patients and healthcare professionals in acute lymphoblastic leukaemia?	Yes.
11. How is acute lymphoblastic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Upfront management, 1. Standard induction chemotherapy as per UKALL14 trial with additional Rituximab. 2. Patients who are MRD positive after Induction chemotherapy should also receive Blinatumomab. 3. Patients in remission, who are fit enough and have a suitable donor should have a risk assessment for consideration of consolidation stem transplant in first remission. 4. Depending on the outcome of that risk assessment patients should then either receive, consolidation and maintenance chemotherapy or a stem cell transplant.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Yes. Blinatumomab is currently used at the same timepoint for MRD positive disease. Currently this is usually only given in allogeneic transplant centres. If approved consideration should be given to using this treatment in all centres that treat ALL.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	To introduce this technology centres would need training in administration, training in dealing with complications and suitable infusion pumps.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, definitely to all of these.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This is more difficult for healthcare facilities. This is better for patients as it can be given out of hospital and is well tolerated compared to chemotherapy.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients who receive this treatment should have a bone marrow aspirate to assess disease levels before and after the first round of treatment.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	Yes. In my experience patients who receive this treatment for MRD prior to stem cell transplant have a significant improvement in their condition meaning that

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	they start the transplant fit and active as opposed to those who have a transplant after chemotherapy are usually unwell and significantly debilitated.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The results are very impressive and result in a large step change improvement for the patient in terms of overall survival rates. **Introduction of this will save lives.**
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Generally and specifically compared to chemotherapy treatment this is very well tolerated.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, I believe the results to extrapolatable.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	I believe that real world experience supports the trial data.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Not that I am aware of.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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Part 1: Treating acute lymphoblastic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Bela Wrench
2. Name of organisation	Barts Health
3. Job title or position	Clinical/Academic Head of the National centre for adult ALL MRD, consultant haemato-oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acute lymphoblastic leukaemia? ☒ A specialist in the clinical evidence base for acute lymphoblastic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

8. What is the main aim of treatment for acute lymphoblastic leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	In fit patients suitable for intensive treatment, curative outcomes are the primary aim of therapy. For older patients, a tailored approach based on fitness/age is usually applied aimed at achieving remission, preventing disease progression while preserving QOL and limiting treatment toxicity and treatment burden.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Complete remission, defined by morphological evaluation of the BM accompanied by meaningful haematological recovery. In addition, absence of measurable residual disease as assessed by a validated assay.
10. In your view, is there an unmet need for patients and healthcare professionals in acute lymphoblastic leukaemia?	Survival outcomes in adults with ALL remain inadequate, despite intensified therapies and emerging application of novel agents. Disease relapse and toxicity from intensive allogeneic stem cell transplant are principle factors limiting survival. Although prospects for relapsed disease have improved in B lineage ALL with immunotherapies becoming available for this indication, response rates are variable and long-term remissions are uncertain even in the CAR-T setting. Moreover, at least 30% of patients with R/R B-ALL will not reach a CAR-T platform, due to disease progression or insufficient fitness. Therefore, measures to bolster the efficacy of front-line therapy to reduce occurence of disease relapse remains an important priority.
11. How is acute lymphoblastic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	National trial protcols (UKALL 14, UKALL 60+) represent the main standard treatment pathways for B-ALL outwith of a frontline clinical study. Monoclonal antibody treatments, Rituximab (UKALL14) and Blinatumomab for MRD positive indications are recent adaptations to therapy. Integrated risk stratification recognises biologically defined subgroups and MRD-positive disease as adverse risk features eligible for therapy intensification (usually allogeneic stem cell transplant) while non high risk disease is usually managed with chemotherapy based consolidation. NICE approval would extend the treatment pathway for the latter group of patients.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Blinatumomab is approved for routine clinical use under relapsed/refractory and MRD indications Pathways, resources and delivery models are already defined for the drug, however would need to scale in accordance with the increase in use within the extended indication. Considerations for a wider delivery model via local/ambulatory services (vs tertiary centres) to address the practical convenience of drug infusion which requires attendance every 3-4 days for pump changes
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The published 3-year plus median OS and RFS rates are clinically significant, QOL was not explored, it is an open question as to whether additional interventions that extend the total treatment length impinge on QOL and whether it outweighs by the survival enhancements and the potential avoidance of disease relapse and interventions ensuing from that.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The licensing study is limited to Ph-negative patients, however equivalent benefit would be expected in Ph-pos B-ALL.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	See response to 12. MRD is generally assessed after each cycle, therefore potential implications for additional MRD testing after blina treatment blocks. Guidance on the optimal implementation of MRD monitoring is being developed via the BCSH.to standardise practice

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A key consideration will be how MRD criteria are defined for UK implementation given trial qualifying MRD negative status was assessed by different technologies (flow cytometry) to those utilised in the UK. Further stratified definitions of "MRD negativity" will be warranted to ensure qualifying criteria are benchmarked to the current reporting framework in operation within the UK.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Survival gains are significant and would be consistent with a step change.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Toxicities are well documented and manageable.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The basic chemotherapy treatment schedule within the report is a good proxy to UK practice. Principal outcomes of RFS, OS and AE's are standard and adequately addressed.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. How do data on real-world experience compare with the trial data?	Difficult to judge since there are no approvals of similar treatment practice in the UK. Toxicity occurrences are within what would be expected for this drug.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	Inequitable access to standard of care (molecular) MRD monitoring in older patients and certain biological subgroups due to lack of an identifiable MRD marker. These patients should be eligible for alternative MRD assessment appraoches, e.g. flow based or other non Ig/TCR genomic targets to ensure their access to MRD indicated therapy is equitably addressed. These groups should have distinct consideration in any proposals for approved use. A further important consideration is the group of patients falling between the two proposed indications of Blina in the frontline – those MRD positive >0.01% (but <0.1%) have a high probable risk of relapse but will not be actionable for targeted therapy based on current and propsed drug approval definitions. This group of patients have essentially been orphaned not due to a clinical or biological rationale but from a structural standpoint due to the clinical trial design studies

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Survival linked improvements in Ph-negative ALL after Blina consolidation are clinically meaningful

MRD negativity treatment indications require additional consideration for UK practice

MRD defined indications for Blinatumomab should specifically assess for any structural omissions of patient cohorts

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no measurable residual disease or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Tuesday 7 January 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no measurable residual disease

Table 1 About you, Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia with no measurable residual disease, current treatments and equality

1. Your name	Ariana Ortiz
2. Are you (please tick all that apply)	☒ A patient with this condition? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with this condition? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Leukaemia Care
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with this condition? **If you are a carer (for someone with this condition) please share your experience of caring for them**	I have been battling leukaemia for more than half of my life. I was diagnosed with acute lymphoblastic leukaemia (ALL) at the age of 16 in 2010. Since then, I have undergone various treatments, procedures, and healthcare experiences, including chemotherapy, radiotherapy, stem cell transplantation, and targeted therapy.
7a. What do you think of the current treatments and care available for this condition on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Treatment options are limited for patients with haematological diseases, leaving them with few non-aggressive alternatives and a high likelihood of relapse. Most of these treatments require either prolonged hospital stays or outpatient care involving daily or frequent visits several times a week
8. If there are disadvantages for patients of current NHS treatments for this condition (for example, how they are given or taken, side effects of treatment, and any others) please describe these	During my hospital stay, while receiving aggressive chemotherapy, I faced several challenges. I contracted COVID, had an infection in my PICC line, a blood clot in the arm, and temporarily lost mobility in one of my legs after a lumbar puncture. The inability to walk or care for oneself during the inpatient stay is a significant blow to one's sense of autonomy and self-worth. This leads to frustration, feelings of vulnerability, and a profound dependency on hospital staff and others for basic needs. Additionally, the emotional impact of an extended hospital stay can be profound. The sense of isolation or separation from loved ones can lead to anxiety, depression, or a sense of loneliness. Upon discharge from the hospital, uncertainty about recovery and the likelihood of fully regaining previous levels of functioning can lead to diminished motivation and hesitation about facing a similar experience in the event of a relapse. Additionally, it often necessitates reliance on other healthcare services, such as physiotherapy, psychological support, or palliative care.

9a. If there are advantages of blinatumomab with chemotherapy over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does blinatumomab with chemotherapy help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Blinatumomab made a significant difference in my quality of life. My fatigue was no longer excessive, which allowed me to do basic activities on my own, such as taking a shower, cooking simple meals, and even selling things online. I could also decide what food to have at home, no longer depending on the hospital menu. Overall, I felt better physically my hair even started growing back, and the colour of my nails began to recover. Being able to receive treatment at home wasn't just beneficial for me, but also for my family, as they could return to their normal activities without needing to assist or visit me in the hospital, which had been time-consuming for them. On weekends, I could go for walks, have a picnic in the park with my family, and be present at birthdays and special events. Being able to access all of this while receiving treatment was a blessing. Even during my hospital visits, I could feel the joy the nurses shared when they saw my progress. It became an enjoyable ritual to visit the hospital for a few hours each week, where I could connect with the nurses or other patients.
10. If there are disadvantages of blinatumomab with chemotherapy over current treatments on the NHS please describe these. For example, are there any risks with blinatumomab with chemotherapy? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am aware that blinatumomab can cause side effects such as difficulty speaking or controlling movements, as well as issues with memory, thinking, or processing thoughts. However, knowing that these side effects are rare (occurring in 1-10% of cases), I would still prefer to undergo this treatment rather than aggressive chemotherapy as an inpatient.
11. Are there any groups of patients who might benefit more from blinatumomab with chemotherapy or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Being able to receive treatment at home, with fewer visits to the hospital, would have a profound effect on the mental and emotional health of most patients. It would provide a greater sense of comfort and flexibility, giving patients more control over their environment. The ability to rest in a familiar space, surrounded by loved ones, as opposed to the clinical and often impersonal setting of a hospital, offers significant psychological benefits. Financially, it would alleviate pressures as well. Family members would not need to take extended time off work to visit the patient, which would otherwise result in lost income. Additionally, for patients living far from the hospital, home treatment reduces travel costs and the need for frequent hospital visits, further lowering the financial burden.

12. Are there any potential equality issues that should be taken into account when considering this condition and blinatumomab with chemotherapy? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	To the best of my knowledge, no.
13. Are there any other issues that you would like the committee to consider?	Blinatumomab helped me recover enough to proceed to a successful bone marrow transplant. It not only controlled disease progression but also enhanced my physical and emotional strength.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Other aggressive treatments resulted in prolonged immobility, being confined to bed for weeks, leading to muscle weakness and loss of independence which caused severe emotional distress and feelings of dehumanisation.
- The intensity of conventional therapies creates emotional and physical exhaustion, contributing to a loss of hope and a diminished will to undergo similar experiences again in the event of a relapse.
- Intensive treatments left me debilitated after discharge, requiring considerable time to regain basic strength and mobility, and relying on additional services such as physiotherapy, psychology, and palliative care.
- Blinatumomab significantly reduced fatigue, enabling me to perform basic daily activities independently, such as showering, cooking, and engaging in simple tasks.
- The reduced intensity of side effects alleviated depression and isolation allowing me to participate in social events such as birthdays, picnics, and family gatherings, fostering emotional well-being and maintaining connections.

Thank you for your time.

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

External Assessment Group Report

Produced by	Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield
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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Paul Tappenden acted as the EAG lead. Ruth Wong critiqued the company's search strategy. Gamze Nalbant summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Sa Ren critiqued the statistical aspects of the submission. Paul Tappenden, Mon Mon Yee and Sunhong Kwon critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

About SCHARR

The Sheffield Centre for Health and Related Research (SCHARR) is part of the School of Medicine and Population Health at the University of Sheffield. SCHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research, and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The SCHARR Technology Assessment Group (SCHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of healthcare interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Care Excellence (NICE). SCHARR-TAG is part of a wider collaboration of a number of units from other regions including: Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, The University of Warwick; the BMJ Group, Kleijnen Systematic Reviews, Bristol Technology Assessment Group (Bristol TAG), University of Bristol and the Newcastle NIHR TAR Team, Newcastle University.

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
AlloSCT	Allogeneic stem cell transplantation
ALT	Alanine transaminase
AMCP	Academy of Managed Care Pharmacy
ASA	Additional sensitivity analysis
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate transaminase
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSA	Body surface area
CAR-T	Chimeric antigen receptor T cell
CC	Complication/comorbidity
CDC	Centers for Disease Control and Prevention
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMR	Cochrane Methodology Register
CMU	Commercial Medicines Unit
CNS	Central nervous system
CR	Complete remission
CRD	Centre for Reviews and Dissemination
CRi	Complete remission with incomplete blood count recovery
CRS	Cytokine release syndrome
CS	Company's submission
CSR	Clinical Study Report
CVAD	Cyclophosphamide, vincristine, doxorubicin and dexamethasone
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EHA	European Hematology Association
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item
ERG	Evidence Review Group
EQ-5D	Euroqol 5-Dimensions
ESMO	European Society for Medical Oncology
EUCTR	EU Clinical Trials Register
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLAG-IDA	Fludarabine, cytarabine, G-CSF and idarubicin
G-CSF	Granulocyte colony-stimulating factor

GEE	Generalised estimating equations
GLM	Generalised linear model
HCRU	Health care resource use
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IPD	Individual patient data
ISPOR	The Professional Society for Health Economics and Outcomes Research
IT	Intrathecal
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LYG	Life year gained
MCM	Mixture-cure model
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIH	National Institutes for Health
NOPHO	Nordic Society of Paediatric Haematology
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient Access Scheme
PCR	Polymerase chain reaction
Ph	Philadelphia-chromosome
PO	*Per os*
POMP	6-mercaptopurine, vincristine, methotrexate, and prednisone
PR	Post-relapse
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
Q-Q	Quantile-quantile
R/R	Relapsed/refractory
RCT	Randomised controlled trial
RF	Relapse-free
RFS	Relapse-free survival
SAS	Safety Analysis Set
SC	Subcutaneous
SIOP	Society for Pediatric Oncology
SITC	Society for Immunotherapy of Cancer
SLR	Systematic literature review
SMR	Standardised mortality ratio
SoC	Standard of care

TA	Technology Appraisal
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TLS	Tumour lysis syndrome
TRM	Transplant-related mortality
TSD	Technical Support Document
TTO	Time trade-off
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This report assesses blinatumomab given in combination with consolidation chemotherapy for the treatment of adult patients with CD19-positive Philadelphia-chromosome (Ph) negative precursor B-cell acute lymphoblastic leukaemia (ALL) that is minimal residual disease (MRD) negative at the start of the consolidation therapy phase. This executive summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 outlines the key model outcomes and the modelling assumptions that have the greatest effect of the ICER. Sections 1.3 to 1.5 summarise the decision problem and the evidence and explain the key issues in more detail. The results of the EAG's preferred analyses and additional sensitivity analyses are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues is detailed in the main EAG report.

All issues identified represent the EAG's view, not necessarily the opinion of the National Institute for Health and Care Excellence (NICE).

1.1. Overview of the EAG's key issues

The company's submission (CS) includes a systematic literature review (SLR) of randomised controlled trials (RCTs) of people with newly diagnosed Ph-negative B-cell ALL receiving any pharmacologic first-line therapy (irrespective of whether the therapy has received regulatory approval), including induction, consolidation, and maintenance treatment. The SLR identified one relevant RCT – Study E1910 – which evaluated blinatumomab plus standard of care (SoC) consolidation chemotherapy versus SoC consolidation therapy alone in adult patients with Ph-negative CD19-positive B-precursor ALL with no measurable residual disease. The company's economic model assesses the cost-effectiveness of blinatumomab plus SoC versus SoC in this same indication based on outcomes data reported in Study E1910. The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID6405	Summary of issue	Report sections
Issue 1	Exclusion of younger adult patients aged <30 years from Study E1910	Section 3.5
Issue 2	Differences in thresholds for minimal residual disease between Study E1910 and the BLAST study used to inform TA589	Section 3.5
Issue 3	Uncertainty surrounding long-term RFS and OS	Section 5.3.5

EAG - External Assessment Group; RFS - relapse-free survival; OS - overall survival; TA - Technology Appraisal

The EAG's preferred economic analysis includes only minor changes from the company's base case analysis. These amendments include: (i) the correction of errors and other minor issues; (ii) the adjustment of relapse-free survival (RFS) to account for fatal events; (iii) the inclusion of monitoring-related health care resource use (HCRU) costs and (iv) the inclusion of subsequent-line treatment/allogeneic stem cell transplantation (alloSCT) costs and QALY losses, regardless of when relapse occurs. None of the amendments included in the EAG's preferred analysis have a substantial impact on the ICER for blinatumomab plus SoC versus SoC.

1.2. Overview of the key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life (overall survival [OS]) and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with SoC alone, the company's model indicates that blinatumomab plus SoC impacts on QALYs by:

- Extending RFS, with a higher proportion of patients predicted to be cured versus SoC alone
- Extending OS, again with a higher proportion of patients predicted to be cured versus SoC alone
- Slightly reducing QALY losses associated with alloSCT and ALL-related death
- Slightly increasing QALY losses associated with adverse events (AEs).

The company's model suggests that blinatumomab plus SoC affects costs by:

- Increasing drug costs due to the use of blinatumomab as part of consolidation therapy
- Slightly reducing the costs of maintenance therapy
- Reducing the expected costs associated with alloSCT, subsequent-line drug therapy and ALL-related death
- Slightly increasing the expected costs of managing AEs associated with consolidation therapy.

The modelling assumptions that have the greatest effect on the ICER are:

- The choice of parametric survival functions for OS, and to a lesser degree, RFS. However, the EAG considers the company's selected parametric survival models to be generally reasonable. Based on the subset of OS models which: (a) were potentially plausible, (b) converged and (c) gave stable cure fractions (i.e., the Weibull, log-logistic and gamma mixture-cure models [MCMs]), the EAG's preferred ICER range is narrow (£29,013 to £32,144 per QALY gained).

1.3. The decision problem: Summary of the EAG's key issues

The decision problem addressed in the CS is generally in line with the final NICE scope. The marketing authorisation for blinatumomab currently includes an indication as monotherapy for the treatment of

adults with Ph-negative CD19 positive B-cell precursor ALL in first or second complete remission (CR) with MRD greater than or equal to 0.1% (1×10^{-3}). The population considered in the CS is expected to be fully covered by the anticipated extension to the marketing authorisation for blinatumomab, which will include all adult patients with CD19-positive Ph-negative B-cell precursor ALL in the consolidation phase, regardless of MRD status. The comparator included in the CS is SoC consolidation chemotherapy, which reflects the modified UKALLXII/E2993 regimen used in Study E1910. The EAG's clinical advisors agreed that this regimen is very similar to the UKALL14 protocol which is used in current NHS practice. The CS excludes alloSCT as a comparator on the basis that it is usually used in patients with high-risk features (e.g., adverse cytogenetics), subject to the availability of a suitable donor, and because alloSCT would be offered at the end of induction/intensification therapy (prior to consolidation therapy). The EAG's clinical advisors agreed that alloSCT is not a relevant comparator for blinatumomab and commented that blinatumomab would not displace alloSCT where alloSCT is clinically indicated. Outcomes addressed in the CS are partly consistent with the final NICE scope and include OS, RFS, and AEs. The CS argues that rate of alloSCT is not a relevant outcome, although the number of patients receiving alloSCT in each treatment arm in Study E1910 are reported in the CS (albeit not as an outcome). The company and the EAG agree that treatment response rate is not a suitable outcome in this population. Data on HRQoL were not collected in Study E1910.

The EAG's clinical advisors raised two concerns regarding any positive future NICE recommendation for the use of blinatumomab as treatment for adult patients with CD19-positive Ph-negative precursor B-cell acute ALL that is MRD-negative at the start of consolidation therapy. These concerns relate to the exclusion of younger adult patients from Study E1910 (Issue 1) and differences in thresholds for MRD between Study E1910 and the BLAST study which informed the NICE recommendation for blinatumomab for patients with MRD-positive ALL in TA589 (Issue 2).

Issue 1: Exclusion of younger adult patients aged <30 years from Study E1910

Report section	Section 3.5
Description of issue and why the EAG has identified it as important	The inclusion criteria for Study E1910 included a requirement for patients to be aged between 30 and 70 years at enrolment. The CS states that the existing marketing authorisation for blinatumomab is expected to be extended between October and November 2024 to include adult patients with CD19-positive Ph- negative B-cell precursor ALL in the consolidation phase (regardless of MRD status). This extended licenced population is anticipated to include a broader population of adults with ALL who are under the age of 30 years. However, Study E1910 does not provide evidence on the effectiveness or safety for this younger adult population. The ongoing Golden Gate study of blinatumomab for newly diagnosed adult patients with B-cell precursor ALL (Jabbour *et al.*) is restricted older adults aged 55 years and above (or 40 to <55 years for patients with severe, pre-defined comorbidities). The EAG's clinical advisors commented that the investigators of Study E1910 selected the lower cut-off of 30 years for practical reasons rather than because of any

	underlying biological rationale, and that they would expect blinatumomab to also be an effective therapy in younger adult patients who are under 30 years of age. They raised concerns that a positive NICE recommendation for blinatumomab restricted by an age cut-off of 30 years would unnecessarily lead to inequality of access to this technology for younger adult patients with ALL. In particular, such a restriction would affect those patients who are managed under an adult ALL protocol but who are below the Study E1910 age cut-off i.e., those aged >25 years and <30 years).
What alternative approach has the EAG suggested?	The EAG believes that the NICE Appraisal Committee should consider whether it is reasonable to extend the findings of Study E1910 to the broader adult population, including adults aged 18 to <30 years.
What is the expected effect on the cost-effectiveness estimates?	The clinical effectiveness and cost-effectiveness of blinatumomab in adults aged <30 years with CD19-positive Ph- negative B-cell precursor ALL which is MRD-negative is unknown. However, the EAG's clinical advisors commented that there is no *a priori* reason why the effect of blinatumomab would be different in younger adults.
What additional evidence or analyses might help to resolve this key issue?	No further evidence or analysis is available to resolve this issue.

Issue 2: Differences in thresholds for minimal residual disease between Study E1910 and the BLAST study used to inform TA589

Report section	Section 3.5
Description of issue and why the EAG has identified it as important	NICE TA589 recommends the use of blinatumomab as an option for treating Ph-negative CD19-positive B-precursor ALL in adults with MRD of at least 0.1% (1 x 10^{-3}). This recommendation was informed by evidence from the BLAST study. Study E1910 applied an MRD threshold of 0.01% (1 x 10^{-4}), whereas the BLAST study applied an MRD threshold of 0.1% (1 x 10^{-3}). The EAG's clinical advisors raised concerns that if NICE issues a positive recommendation for blinatumomab in the current appraisal indication based on the MRD threshold applied in Study E1910, this would leave a group of MRD-positive patients ineligible for treatment with blinatumomab, because although they have detectable MRD, it has not yet reached the threshold specified for treatment under the TA589 guidance recommendation (i.e., those patients with an MRD of between 0.01% and 0.1%). The EAG's clinical advisors stated that if this were to happen, they would expect to have to repeatedly monitor the patient's MRD whilst they wait for the patient's disease to progress. The EAG's clinical advisors highlighted that patients with an MRD of 0.01% have a markedly higher risk of relapse compared to those who are MRD-negative, but they also have a better chance of cure with blinatumomab compared with patients with an MRD of 0.1% who are currently eligible for blinatumomab under the TA589 recommendation. They also highlighted that relapse is rarely linear and that monitoring a patient's MRD in order to catch the disease rising is a high-risk strategy as the patient may progress from 0.01% to frank disease, thereby missing the opportunity for blinatumomab to have a good chance of achieving a second remission. As such, excluding patients who have an MRD of between 0.01% and 0.1% would put this group of patients in a very disadvantaged position.

What alternative approach has the EAG suggested?	The EAG believes that any future positive recommendation for blinatumomab in the MRD-negative ALL population should be carefully phrased to ensure that it does not leave a group of patients ineligible for treatment with blinatumomab with no biological basis for their exclusion.
What is the expected effect on the cost-effectiveness estimates?	Cost-effectiveness estimates for blinatumomab assessed in the MRD-negative population, based on an MRD threshold of less than 1×10^{-4} (0.01%) in Study E1910 are provided in Table 2 and Table 3. Cost-effectiveness estimates for blinatumomab assessed in an MRD-positive population, based on an MRD threshold of 10^{-3} (0.1%) in BLAST have previously been reported and deemed acceptable in TA589.
What additional evidence or analyses might help to resolve this key issue?	No further evidence or analysis is available to resolve this issue.

1.4. The clinical effectiveness evidence: Summary of the EAG's key issues

The CS presents data from the E1910 RCT of blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy alone in 224 adult patients with CD19-positive Ph-negative MRD-negative B-cell precursor ALL in the frontline consolidation phase. Initially, the trial randomised patients who were either MRD-positive or MRD-negative after induction therapy, with MRD status included as a stratification factor. In 2018, the trial protocol was amended such that all patients who were still MRD-positive after induction therapy were no longer randomised and were instead assigned to the blinatumomab plus SoC chemotherapy arm. The data presented in the CS and this EAG report relate only to patients who were MRD-negative after induction therapy (at Step 3, described below) in Study E1910.

The final trial design was as follows. Prior to randomisation to the blinatumomab and SoC groups, all patients received induction (Step 1) and intensification treatments (Step 2). Subsequently, remission status was assessed, and MRD status was determined centrally by six colour flow cytometry, with MRD negativity defined as $\leq 1 \times 10^{-4}$ (0.01%). MRD-negative patients were randomised to the blinatumomab and SoC groups for consolidation treatment (Step 3). Following completion of consolidation chemotherapy with or without blinatumomab, patients were given 2.5 years of POMP maintenance therapy (6-mercaptopurine, vincristine, methotrexate, and prednisone) timed from the start of the intensification cycle. Patients could proceed to alloSCT at the discretion of the treating physician, which was suggested to be done after the first two cycles of blinatumomab in the blinatumomab plus SoC chemotherapy arm or at any time following intensification chemotherapy in the SoC chemotherapy arm.

At the 23rd June 2023data cut-off (DCO), significant reductions in the risks of death (hazard ratio [HR] 0.44; 95% confidence interval [CI] 0.25, 0.76, p=0.001) and relapse or death (HR 0.53; 95% CI 0.32, 0.88, p=0.006) were reported for the blinatumomab group versus the SoC group. Median OS and median RFS were not reached in either treatment group. The most common Grade 3 or 4 treatment-

emergent adverse events (TEAEs) in the blinatumomab plus SoC consolidation chemotherapy group (vs SoC) were: neutrophil count decreased ([redacted]); platelet count decreased ([redacted]); white blood cell count decreased ([redacted]); lymphocyte count decreased ([redacted]); anaemia ([redacted]) and febrile neutropenia ([redacted]). TEAEs of special interest included cytokine release syndrome (CRS) ([redacted]) and neurologic events; most commonly headache ([redacted]), and tremor ([redacted]).

The EAG's clinical advisors considered Study E1910 to be representative of UK clinical practice to some extent, but they highlighted differences in terms of patient age and race.

1.5. The cost-effectiveness evidence: Summary of the EAG's key issues

The company's economic model assesses the cost-effectiveness of blinatumomab in combination with SoC consolidation chemotherapy versus SoC consolidation chemotherapy alone for the treatment of adults with Ph-negative CD19-positive MRD-negative B-precursor ALL over a lifetime horizon from the perspective of NHS and Personal Social Services (PSS). The model uses a partitioned survival model which includes three health states: (i) relapse-free, (ii) post-relapse and (iii) dead. Caregiver effects are not included. Health outcomes and costs are discounted at a rate of 3.5% per annum in the base case analysis. AlloSCT is not included as a comparator. No subgroup analyses are presented.

RFS and OS are modelled using MCMs fitted to the data from Study E1910. Pre-relapse and post-relapse alloSCT rates for both treatment groups are also based on this study. As Study E1910 did not include data collection on HRQoL, utility values for the relapse-free and post-relapse states were instead based on estimates used to inform the model in TA589 (based on the BLAST and TOWER studies of blinatumomab). Disutility values associated with alloSCT and AEs were based on previous NICE TAs, published literature and assumptions. The model assumes that the HRQoL of patients who remain relapse-free after 5 years rebounds to age-and sex-matched general population norms. The model includes costs associated with: (i) consolidation therapy; (ii) maintenance therapy; (iii) alloSCT (pre- and post-relapse); (iv) the management of AEs; (v) subsequent-line therapy and (vi) terminal care. Monitoring-related HCRU costs were not included in the original model, but were later included in an updated version of the model provided following the clarification round. Resource costs were based on Study E1910, published studies, previous NICE TAs, standard costing sources and assumptions. The model assumes that patients who remain alive after 5 years no longer incur any treatment-related costs, HCRU costs or terminal care costs, although the model predicts that a small proportion of patients will relapse beyond this time point in both treatment groups.

A Patient Access Scheme (PAS) is available for blinatumomab which takes the form of a simple price discount of [redacted]. All results presented in this EAG report include this PAS. The probabilistic version of

the company's original model suggests that the ICER for blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy is expected to be £32,539 per QALY gained (based on a re-run by the EAG). The deterministic ICER is slightly lower at £31,643 per QALY gained. Severity-related QALY weighting is not applicable (i.e., the decision modifier is 1.0). The company's updated model which was provided following the clarification round included some error corrections and additional functionality. This updated model suggests a probabilistic ICER of £31,361 per QALY gained and a deterministic ICER of £31,505 per QALY gained.

The EAG's critical appraisal identified several issues relating to the company's original model, including: the identification of model errors; limitations in the model structure and assumptions; uncertainty around the long-term RFS and OS predictions; the inclusion of a clinically implausible utility value for the post-relapse state and several concerns regarding costs. However, most of these issues do not have a marked impact on the ICER for blinatumomab. The EAG believes that only one of these issues should be considered as being key – this relates to uncertainty surrounding long-term RFS and OS outcomes for patients treated with blinatumomab plus SoC or SoC alone (Issue 3). This issue is discussed below.

Issue 3: Uncertainty surrounding long-term RFS and OS

Report section	Section 5.3.5 (critical appraisal point 3)
Description of issue and why the EAG has identified it as important	The company's economic model includes the use of MCMs for RFS and OS. The company selected the log-normal MCM for RFS and the Weibull MCM for OS. Owing to the limited sample size and relatively short follow-up for both end points in Study E1910 (median = 4.5 years), there is uncertainty around the long-term RFS and OS projections. There is also some uncertainty around the magnitude of the standardised mortality ratio (SMR) applied to patients in both the cured and uncured subgroups of the MCMs. In addition, other approaches are available for representing cure within economic models which have not been included in the analyses presented by the company (e.g., applying structural assumptions of a cure at a given time point). The company's scenario analyses include consideration of only a limited set of alternative RFS and OS survival models.
What alternative approach has the EAG suggested?	The EAG believes that the company's survival analysis methods are generally appropriate and the EAG does not disagree with the MCMs selected for inclusion in the company's base case analysis. In addition, the EAG's clinical advisors supported the use of a low SMR in this MRD-negative population because these patients are unlikely to undergo alloSCT. As such, the EAG's preferred analysis retains the same survival model choices and SMR as the company's base case analysis. However, the EAG has conducted additional sensitivity analyses to explore the potential impacts of: (a) selecting all other alternative fitted MCMs for RFS and OS; (b) using the observed Kaplan-Meier survival functions for RFS and OS followed by structural cure assumptions at 5 years and 7.5 years in both treatment groups, and (c) applying higher SMRs compared with the company's base case.
What is the expected effect on the cost-effectiveness estimates?	The EAG's sensitivity analyses around alternative MCMs (ASA1a-j) suggest ICERs ranging from £22,643 to £32,144 per QALY gained. However, the EAG's clinical advisors did not consider the exponential MCM or log-normal MCMs for the SoC group to be clinically plausible. When these OS models are ruled out, the remaining RFS and OS MCMs lead to a narrow range of ICERs (from £29,013 to £32,144 per QALY gained).

	The EAG's analysis which uses the observed Kaplan-Meier RFS and OS followed by a fixed cure time point of 5 years results in an ICER of £38,834 per QALY gained (ASA2a). The equivalent analysis using a fixed cure time point of 7.5 years results in an ICER of £27,375 per QALY gained (ASA2b). It should be noted that applying a 5-year cure time point excludes some observed late RFS and OS events in the SoC group of Study E1910 and therefore biases against blinatumomab. In addition, both of these analyses are flawed in that they necessarily assume that all patients who remain alive at these time points are cured (including those who have previously relapsed) and they assume that no deaths occur during the periods in which the observed Kaplan-Meier estimates are flat. The EAG does not prefer these analyses over the use of MCMs in this case. The EAG's analyses of alternative SMRs of 2.0 and 3.0 lead to higher ICERs of £34,908 and £38,845 per QALY gained, respectively (ASAs 3a-b). However, these analyses are exploratory only and the EAG believes that these SMRs are likely to be overestimates for this population.
What additional evidence or analyses might help to resolve this key issue?	The EAG believes that taken together, the range of sensitivity analyses undertaken in the CS, the company's clarification response and the EAG's exploratory analyses are comprehensive in demonstrating the impact of alternative survival models on the ICER. The EAG does not believe that further economic analyses are required.

1.6. Summary of the EAG's preferred model results

The results of the EAG's preferred analyses are summarised in Table 2. Results are presented separately using the probabilistic and deterministic versions of the models. The results of the EAG's additional sensitivity analyses (ASAs) are presented in Table 3.

Modelling errors identified by the EAG are described in Section 5.3.5. For further details of the exploratory and sensitivity analyses undertaken by the EAG, see Section 5.5.

Table 2: EAG's preferred model results, blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy, including blinatumomab PAS

Option	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated base case, deterministic	[redacted]	[redacted]	[redacted]	**£31,505**
EA1: Correction of remaining model errors and other minor issues	[redacted]	[redacted]	[redacted]	£31,485
EA2: Adjustment of RFS for fatal events	[redacted]	[redacted]	[redacted]	£32,047
EA3: Inclusion of HCRU costs with no 5-year cap for post-relapse state	[redacted]	[redacted]	[redacted]	£31,165
EA4: No 5-year cap for subsequent-line treatment/alloSCT costs and QALY losses	[redacted]	[redacted]	[redacted]	£30,317
EA5a: EAG-preferred analysis (EA1-4 combined), deterministic	[redacted]	[redacted]	[redacted]	**£30,815**
EA5b: EAG-preferred analysis (EA1-4 combined), probabilistic	[redacted]	[redacted]	[redacted]	**£31,214**

** Undiscounted*

EAG - External Assessment Group; SoC - standard of care; EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; RFS - relapse-free survival; HCRU - health care resource use; alloSCT - allogenic stem cell transplant; PAS - Patient Access Scheme

Table 3: EAG's additional sensitivity analysis results, blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy, including blinatumomab PAS

Option	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA5a: EAG-preferred analysis (EA1-4 combined), deterministic (RFS = log-normal MCM, OS = Weibull MCM)	[redacted]	[redacted]	[redacted]	**£30,815**
ASA1a: RFS = exponential MCM, OS = Weibull MCM	[redacted]	[redacted]	[redacted]	**£32,144**
ASA1b: RFS = Weibull MCM, OS = Weibull MCM	[redacted]	[redacted]	[redacted]	**£32,097**
ASA1c: RFS = Gompertz MCM, OS = Weibull MCM	[redacted]	[redacted]	[redacted]	**£29,652**
ASA1d: RFS = log-logistic MCM, OS = Weibull MCM	[redacted]	[redacted]	[redacted]	**£31,333**
ASA1e: RFS = gamma MCM, OS = Weibull MCM	[redacted]	[redacted]	[redacted]	**£32,138**
ASA1f: RFS = log-normal MCM, OS = exponential MCM	[redacted]	[redacted]	[redacted]	**£22,643**
ASA1g: RFS = log-normal MCM OS = Gompertz MCM	[redacted]	[redacted]	[redacted]	**£31,220**
ASA1h: RFS = log-normal MCM, OS = log-normal MCM	[redacted]	[redacted]	[redacted]	**£25,088**
ASA1i: RFS = log-normal MCM, OS = log-logistic MCM	[redacted]	[redacted]	[redacted]	**£29,013**
ASA1j: RFS = log-normal MCM, OS = gamma MCM	[redacted]	[redacted]	[redacted]	**£30,128**
ASA2a: RFS and OS based on Kaplan-Meier function with cure time point at 5 years	[redacted]	[redacted]	[redacted]	**£38,834**
ASA2b: RFS and OS based on Kaplan-Meier function with cure time point at 7.5 years	[redacted]	[redacted]	[redacted]	**£27,375**
ASA3a: SMR=2.0	[redacted]	[redacted]	[redacted]	**£34,908**
ASA3b: SMR=3.0	[redacted]	[redacted]	[redacted]	**£38,845**

ASA4a: Post-relapse utility value = 0.50	[redacted]	[redacted]	[redacted]	**£30,663**
ASA4b: Post-relapse utility value = 0.25	[redacted]	[redacted]	[redacted]	**£30,466**
ASA5: Inclusion of second-line treatment AEs costs and disutilities	[redacted]	[redacted]	[redacted]	**£30,693**
ASA6: Pre-relapse alloSCT proportion = 0%	[redacted]	[redacted]	[redacted]	**£31,641**
ASA7: Adjustment for fatal RFS events excluded	[redacted]	[redacted]	[redacted]	**£29,996**
ASA8: HCRU costs applied from start of consolidation	[redacted]	[redacted]	[redacted]	**£31,228**
ASA9: Relapse-free utility applied indefinitely (no rebound to general population utility)	[redacted]	[redacted]	[redacted]	**£31,430**

** Undiscounted*

EAG - External Assessment Group; SoC - standard of care; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; EA - exploratory analysis; ASA - additional sensitivity analysis; RFS - relapse-free survival; OS - overall survival; MCM - mixture-cure model; HCRU - health care resource use; SMR - standardised mortality ratio; AE - adverse events; alloSCT - allogenic stem cell transplantation; PAS - Patient Access Scheme

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease (Section 2.1) and the company's overview of the current treatment pathway and their intended positioning of blinatumomab in the frontline consolidation therapy setting (Section 2.2), as described in the company's submission (CS).[1] For completeness, additional information has been included by the External Assessment Group (EAG).

2.1. Company's description of the underlying health problem

Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia which affects the blood and bone marrow. ALL is characterised by the excess production of immature lymphocyte precursor cells, called lymphoblasts or blasts cells, in the bone marrow.[2] Lymphocytes are white blood cells that are vital for the body's immune system. The proliferation of lymphoblasts in patients with ALL inhibits normal blood cell production and function and can lead to the spread and infiltration of lymphoblasts to other organs in the body, including the lymph nodes, liver, spleen, and central nervous system (CNS). ALL accounts for approximately 20% of all leukaemias in adults. Symptoms of ALL commonly include "B symptoms" (including fever, weight loss and night sweats), easy bleeding or bruising, fatigue, dyspnoea and infection.[3] ALL is an aggressive disease which can progress rapidly and if left untreated, can lead to death within weeks or months.

ALL can be classified into three groups: (i) precursor-B-cell ALL; (ii) mature B-cell ALL and (iii) T-cell ALL.[4] B-cell ALL is substantially more common than T-cell ALL, and accounts for approximately 75% of the adult ALL population.[3] Precursor-B-cell ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22 and CD79a expression. An estimated 20-30% of adult patients with B-ALL have a specific chromosomal abnormality known as the 'Philadelphia chromosome' (Ph) which is detected by molecular or genetic testing. The target population for the current appraisal relates to adult patients with Ph-negative precursor B-cell CD19-positive ALL without the presence of minimal residual disease (MRD) following induction/intensification therapy. This represents a subset of the broader population of people with newly diagnosed ALL.

According to data published by Cancer Research UK, there were an estimated 649 new cases of ALL (all subtypes and all ages) per year in England during the period 2017-2019.[5] The age-standardised incidence rate of ALL in England is estimated at 1.1 cases per 100,000 population. ALL is more common in men than women, accounting for 59% and 41% of all cases, respectively. The disease is most common in children, with a peak age of incidence of ALL in children under the age of 5 years. Approximately one-third of all cases of ALL are in adults aged over 30 years of age.[5] Data from Cancer Research UK indicate that there were 214 deaths due to ALL (all subtypes and all ages) per year during the period 2017-2019.[5]

Current estimates from the Haematological Malignancy Research Network (HMRN) suggest that the 5-year net survival estimate for people with B-cell ALL is 66.6% (95% confidence interval [CI] 61.8% to 71.5%). Survival is strongly influenced by patient age at diagnosis, with 5-year survival estimates amongst patients aged <15 years, 15-39 years and ≥40 years of 91%, 57% and 28%, respectively.[6]

The CS[1] highlights that B-cell ALL results in a considerable burden on patient health-related quality of life (HRQoL) as a consequence of symptoms related to the disease as well as toxicity resulting from some of the available treatments. However, the CS comments that there is a lack of relevant HRQoL evidence available with which to quantify these impacts. The CS refers to a Swedish study[7] in which 225 people with ALL completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30). This study found that people with ALL have lower global health status, lower physical and psychological function and higher symptom burden compared with the adult general population. The CS also refers to a UK general population time-trade-off (TTO) valuation study[8] which reported higher utility values for health states relating to complete remission (CR) and CR with partial haematological recovery (utility values ranging from 0.75 to 0.86) compared with health states related to aplastic bone marrow, partial remission and progressive disease (utility values ranging from 0.30 to 0.59).

The CS[1] states that the aim of treatment is to induce and maintain complete haematological response and to restore normalisation of bone marrow function to <5% blasts in the bone marrow by standard microscopy, with no circulating blasts outside the bone marrow and normal blood counts for neutrophils, platelets and haemoglobin.[9] However, some patients who achieve CR may still have MRD, which relates to the presence of blast cells which cannot be detected by standard microscopy, but which are detectable using more sensitive molecular techniques such as polymerase chain reaction (PCR) and flow cytometry. The presence of MRD is a poor prognostic factor for patients whose disease is in haematological CR – the EAG's clinical advisors stated that the presence of MRD is likely to be the most important prognostic factor for poor rates of survival. There also remains a risk of relapse for people with MRD-negative ALL. The relevant population under consideration in the current appraisal relates to patients who have MRD-negative ALL.

2.2. Critique of company's overview of current service provision

2.2.1. *Current treatment pathway for adult patients with newly diagnosed Ph-negative CD-19 positive MRD-negative B-cell precursor ALL*

The current standard of care for newly diagnosed adult patients with Ph-negative B-cell precursor ALL in the UK follows the UKALL14 protocol.[10] The treatment approach for patients with Ph-negative ALL is summarised below based on the description provided in the CS[1] and the UKALL14 trial protocol.[10]

- **Pre-phase:** Steroids (dexamethasone) are given for 5-7 days with the intention of reducing the patient's blast count and to reduce the risk of complications, e.g., tumour lysis syndrome (TLS) and cytokine release syndrome (CRS).
- **Induction therapy (Phases 1 and 2):** Treatment aims to clear as many leukaemia cells as possible and to induce bone marrow remission (<5% blasts). Intensive chemotherapy is given for 8 weeks to induce CR. During Phase 1 (Weeks 1-4), treatment includes daunorubicin, vincristine, dexamethasone, and peg-asparaginase. Rituximab may also be given during Phase 1 once per week for 4 weeks. During Phase 2 (Weeks 5-8), treatment includes cyclophosphamide, cytarabine, and mercaptopurine. Intrathecal methotrexate is given throughout both Phases 1 and 2.
- **Intensification therapy:** Treatment is primarily given to reduce the risk of CNS relapse. Drugs used at the intensification stage include high-dose methotrexate and peg-asparaginase given for a period of 4 weeks. Patients with Ph-negative MRD-negative B-cell precursor ALL who achieve a haematological CR after induction but who have high-risk features (e.g., adverse cytogenetics) may be considered for allogeneic stem cell transplantation (alloSCT) if a suitable donor is available. Transplantation can also be done prior to intensification if the patient is going to receive a myeloablative conditioned transplant.
- **Consolidation therapy:** Treatment aims to consolidate the initial response achieved through induction/intensification chemotherapy and to eradicate any remaining leukaemia cells. Treatment is given over 4 cycles and includes the same drugs given in Phases 1 and 2 of the induction therapy stage described above, as well as some additional drugs. The EAG's clinical advisors commented that many centres have now dropped cycle 4 of consolidation therapy.
- **Maintenance therapy:** Treatment aims to prevent the cancer from coming back and to maintain long-term remission. Drugs used include vincristine, prednisolone, mercaptopurine and methotrexate for 2 full years following the completion of consolidation therapy.

The main evidence for blinatumomab in the current appraisal is Study E1910.[11] This study compared blinatumomab plus standard of care (SoC) consolidation chemotherapy versus SoC consolidation chemotherapy without blinatumomab. The consolidation chemotherapy backbone within this study was based on the modified UKALLXII/E2993 regimen.[12] The clinical advisors consulted by the company stated that the UKALLXII/E2993 regimen used in the trial is very similar to the UKALL14 adult frontline protocol with respect to the composition of agents and blocks of treatments.[13] The EAG's clinical advisors agreed that the UKALLXII/E2993 regimen is very similar to the UKALL14 protocol used in the UK.

2.2.2. *Treatments for relapsed and refractory B-cell ALL*

The CS[1] states that around 50% of patients with newly diagnosed ALL will relapse following standard frontline therapy. Treatment options for patients with relapsed or refractory (R/R) B-cell precursor ALL

include chemotherapy, blinatumomab, inotuzumab ozogamicin, or chimeric antigen receptor T cell (CAR-T) therapy using tisagenlecleucel (for people aged 25 years and under) or brexucabtagene autoleucel (for people aged 26 years and over). Some patients may also be eligible for alloSCT following chemotherapy or targeted therapy. The EAG's clinical advisors commented that chemotherapy is now rarely used for treating first relapse, as randomised controlled trials (RCTs) have demonstrated that blinatumomab and inotuzumab ozogamicin have superior efficacy. The CS highlights that brexucabtagene autoleucel is currently only available via the Cancer Drugs Fund (CDF).

2.2.3. *NICE recommendations for treatments for people with Ph-negative R/R ALL*

A summary of current NICE recommendations for patients with Ph-negative B-cell precursor ALL is provided in Table 4.

Table 4: Previous NICE recommendations for patients with Ph-negative ALL

NICE TA	NICE recommendation
Newly diagnosed ALL	
TA408 (2016)[14]	Pegaspargase, as part of antineoplastic combination therapy, is recommended as an option for treating ALL in children, young people and adults only when they have untreated newly diagnosed disease.
TA589 (2019)[15]	Blinatumomab is recommended as an option for treating Ph-negative CD19-positive B-precursor ALL in adults with MRD of at least 0.1%, only if: • the disease is in first CR and • the company provides blinatumomab according to the commercial arrangement.
Relapsed/refractory ALL	
TA450 (2017)[16]	Blinatumomab is recommended within its marketing authorisation as an option for treating Ph-negative R/R precursor B-cell ALL in adults, only if the company provides it with the discount agreed in the PAS.
TA541 (2018)[17]	Inotuzumab ozogamicin is recommended, within its marketing authorisation, as an option for treating R/R CD22-positive B-cell precursor ALL in adults. People with R/R Ph-positive disease should have had at least 1 TKI.
TA893 (2023)[18]	Brexucabtagene autoleucel is recommended for use within the CDF as an option for treating R/R B-cell ALL in people 26 years and over. It is recommended only if the conditions in the managed access agreement for brexucabtagene autoleucel are followed.
TA975 (2024)[19]	Tisagenlecleucel is recommended, within its marketing authorisation, as an option for people 25 years and under for treating B-cell ALL that is: • relapsed after a transplant, or • relapsed for a second or later time, or • refractory. It is only recommended if the company provides it according to the commercial arrangement.

NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; ALL - acute lymphoblastic leukaemia; Ph - Philadelphia chromosome; MRD - minimal residual disease; CR - complete remission; R/R - relapsed or refractory; PAS - Patient Access Scheme; TKI - tyrosine kinase inhibitor; CDF - Cancer Drugs Fund

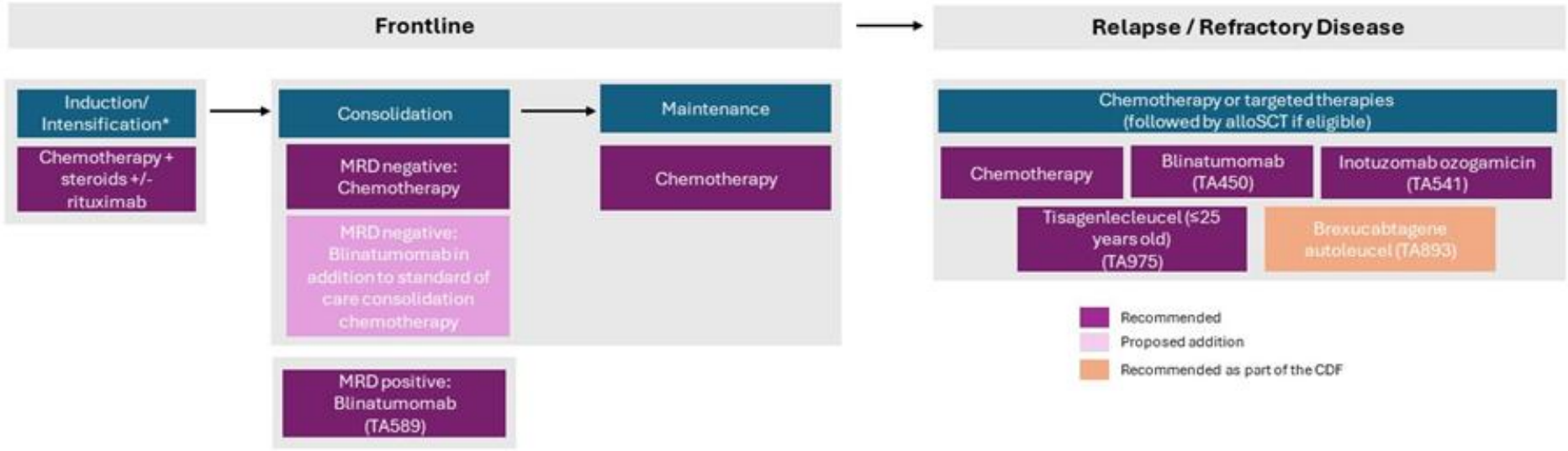
2.2.4. *Company's proposed positioning of blinatumomab*

The company's proposed positioning of blinatumomab is shown in Figure 1. The target population relates to patients with Ph-negative CD-19 positive MRD-negative B-cell precursor ALL following induction and intensification therapy. AlloSCT is unlikely to be indicated in this population. The company's proposed positioning for blinatumomab is as part of frontline consolidation therapy, whereby additional cycles of blinatumomab are added to the current consolidation chemotherapy protocol.

2.2.5. *Additional comments from the EAG clinical advisors*

The EAG's clinical advisors were generally satisfied with the company's description of the disease, the treatment pathway and the proposed positioning of blinatumomab as part of consolidation therapy, as reported in the CS.[1] They clarified that being over 40 years (rather than 65 years as described in the CS) and having MRD-positive status post-induction therapy are poor prognostic factors. They further clarified that most centres no longer use consolidation cycle 4 as part of SoC chemotherapy. The clinical advisors also raised one point of inaccuracy in the CS. The CS states that: *"MRD-negative status is generally defined as the presence of a small number leukaemic cells in the bone marrow during remission, although thresholds used to define MRD-negativity in previous clinical studies have varied."* The EAG's clinical advisors stated that an MRD-negative test result means that there is no detectable disease and highlighted that patients do not have MRD-negative status because this categorisation relates to the time at which the test is done and only applies until the next test is done. They also clarified that the threshold used to define MRD negativity depends on the sensitivity and quantitative range of the test and that there are well-defined criteria for reporting MRD negativity, rather than criteria which are defined per trial.

Figure 1: Company's proposed positioning of blinatumomab (reproduced from CS, Figure 3)



**If eligible (e.g., adverse cytogenetics), patients may proceed to alloSCT after intensification and before the consolidation phase*
AlloSCT - allogenic stem cell transplant; CDF - Cancer Drugs Fund; MRD - minimal residual disease; TA - Technology Appraisal
NICE TA589;[15] Cancer Research UK;[10] E1910 CSR;[11] NICE TA975;[19] NICE TA450;[16] NICE TA541;[17] NICE TA893[18]

3. CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[20] and addressed in the CS is presented in Table 5. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 5: The decision problem (reproduced with minor changes from CS, Table 1)

	Final scope issued by NICE[20]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	EAG comments
Population	People with Ph-negative CD19-positive MRD-negative B-precursor ALL in frontline consolidation.	Adult patients with CD19-positive Ph-negative precursor B-cell ALL that is MRD-negative at the start of the consolidation phase.	The population of focus is narrower than the NICE final scope and the anticipated full licence as it focuses on adults only. This is in line with the available clinical evidence base for blinatumomab in this indication and with the anticipated positioning of blinatumomab in UK clinical practice.	The population addressed in the CS[1] is consistent with the evidence from Study E1910[11] and those patients with MRD-negative disease who would be covered by the anticipated extension to the marketing authorisation for blinatumomab. Study E1910 enrolled adult patients who were aged 30-70 years. The EAG's clinical advisors stated that they would expect blinatumomab to also be an effective therapy in younger adults aged under 30 years. Study E1910 defined MRD status based on a threshold of 1 x 10^{-4} (0.01%).
Intervention	Blinatumomab with chemotherapy	Blinatumomab plus SoC consolidation chemotherapy	N/a – in line with NICE final scope.	In line with the final NICE scope.[20]
Comparator(s)	Established clinical management without blinatumomab with chemotherapy, which may include chemotherapy (with or without corticosteroids) and stem cell transplant	SoC consolidation chemotherapy	The NICE final scope includes stem cell transplant as part of established clinical management. However, UK clinicians stated that in practice, for patients with Ph- MRD-negative B-ALL, alloSCT is reserved only for high-risk patients (e.g., those with adverse cytogenetics). Further, if eligible and a suitable donor is available, alloSCT is received at the end of the induction/intensification phase, prior to the consolidation phase. As such, should blinatumomab (plus SoC consolidation chemotherapy) be made available in the frontline consolidation phase, it would not displace alloSCT. Therefore, alloSCT is not considered a comparator in this submission.	The CS[1] includes SoC consolidation chemotherapy as the sole comparator. The EAG's clinical advisors agreed that alloSCT is not a relevant comparator because it would typically be used in people with high-risk disease following the induction/intensification stage (prior to receiving consolidation therapy), subject a suitable donor being available. They also agreed that blinatumomab would not displace alloSCT.

	Final scope issued by NICE[20]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	EAG comments
Outcomes	The outcome measures to be considered include: • OS • PFS (including RFS and EFS) • Treatment response rate (including MRD, haematologic responses and complete remission) • Rate of stem cell transplant • AEs of treatment • HRQoL.	The outcome measures to be considered include: • OS • RFS • AEs of treatment	Treatment response rate is not considered in this appraisal as it does not represent an appropriate outcome measure. 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 also does not represent an appropriate outcome measure for consideration. This is because in UK clinical practice in the target population (patients with Ph- MRD-negative B-ALL), alloSCT is reserved for those with high-risk features (e.g., adverse cytogenetics) who are eligible for transplant and for whom a suitable donor is available, and it would be received at the end of induction/ intensification treatment (i.e., prior to the consolidation phase). Furthermore, in the E1910 trial, intent to transplant was a stratification factor during randomisation. The proportion of patients who received alloSCT was low and well-balanced between treatment arms, so treatment with blinatumomab did not influence whether a patient received alloSCT. HRQoL was not collected in the E1910 trial, therefore utility values in this submission are aligned with TA589.[15]	The CS[1] reports on RFS, OS and AEs. These are relevant endpoints for frontline consolidation therapy for ALL. Whilst not listed as an outcome in Table 1 of the CS, the CS also reports on the number/proportion of patients who received alloSCT in each arm of Study E1910.[11] The EAG agrees that treatment response is not relevant because all patients in the relevant trial population were required to be MRD-negative at Step 3 in Study E1910.[11] HRQoL data were not collected in Study E1910.

CS - company's submission; NICE - National Institute for Health and Care Excellence; MRD - minimal residual disease; Ph - Philadelphia chromosome; OS - overall survival; PFS - progression-free survival; RFS - relapse-free survival; EFS - event-free survival; ALL - acute lymphoblastic leukaemia; SoC - standard of care; alloSCT - allogeneic stem cell transplant; HRQoL - health-related quality of life; TA - Technology Appraisal; EAG - External Assessment Group; N/a - not applicable

3.1. Population

The final NICE scope[20] states that the relevant population for this appraisal relates to people with Ph-negative CD19-positive MRD-negative B-precursor ALL in frontline consolidation. The population considered within the CS[1] relates to adult patients with Ph-negative CD19-positive precursor B-cell ALL that is MRD-negative at the start of the consolidation phase. This is narrower than the population listed in the final NICE scope[20] in that it is restricted to adult patients. It is also narrower than the anticipated licensed indication for blinatumomab which is expected to be extended to adult patients with CD19-positive Philadelphia (Ph)-chromosome negative B-cell precursor ALL in the consolidation phase (regardless of MRD status). The company's clarification response[21] (question A5) explains that the decision problem addressed in the CS focuses on the start of consolidation therapy, whereas the anticipated extension to the wording of the marketing authorisation will not restrict the use of blinatumomab to the start of consolidation therapy.

The population considered in the CS[1] is in line with the evidence base for blinatumomab, as Study E1910[11] enrolled adult patients aged 30-70 years. The EAG's clinical advisors commented that the investigators of Study E1910 selected the lower cut-off of 30 years of age due to practical reasons relating to the US health care insurance system rather than because of any underlying biological rationale, and stated that they would expect blinatumomab to also be an effective therapy in younger adult patients who are under 30 years of age. The clinical experts consulted by the company also stated that they would expect blinatumomab to be effective in adults under the age of 30 years. The CS does not report on any clinical or economic subgroup analyses.

3.2. Intervention

The intervention described in the CS[1] is consistent with the final NICE scope.[20] The intervention under consideration is blinatumomab (Blincyto®) given alongside SoC consolidation chemotherapy. According to the Summary of Product Characteristics (SmPC),[22] blinatumomab is a bispecific T-cell engager molecule that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. Blinatumomab activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B-cells. Blinatumomab mediates the formation of a cytolytic synapse between the T-cell and the tumour cell, releasing proteolytic enzymes to kill both proliferating and resting target cells.[22]

Blinatumomab does not yet have a full European Medicines Agency (EMA) or Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for use as consolidation therapy for adults with CD19-positive Ph-negative MRD-negative B-cell precursor ALL. The CS[1] states that it is anticipated that the current licence for blinatumomab will be extended for this population

between October and November 2024. Blinatumomab currently has a marketing authorisation for four indications:[22]

(i) As monotherapy for the treatment of adults with CD19 positive relapsed or refractory (R/R) B-cell precursor ALL. Patients with Ph-positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

(ii) As monotherapy for the treatment of adults with Ph-negative CD19 positive B-cell precursor ALL in first or second CR with MRD greater than or equal to 0.1%.

(iii) As monotherapy for the treatment of paediatric patients aged 1 year or older with Ph-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.

(iv) As monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Ph-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy.[22]

Within the adult Ph-negative CD19-positive MRD-negative B-cell precursor ALL target population, blinatumomab is administered by continuous intravenous (IV) infusion at a dose of 15µg daily for patients with a body weight of <45kg (up to a maximum daily dose of 28µg), or 28µg daily for patients with a body weight of ≥45kg. Treatment is administered using an infusion pump over a period of up to 96 hours. In the consolidation therapy setting, blinatumomab is given for a period of 28 days followed by a 14-day treatment-free interval. In the consolidation setting in Study E1910,[11] blinatumomab was given alongside SoC consolidation chemotherapy (see Section 3.3), with treatment cycles alternating between blinatumomab and chemotherapy. The treatment schedule adopted in Study E1910[11] is shown in Section 4.2.1 (Figure 2). The EAG's clinical advisors anticipated that a similar approach involving alternative between cycles of blinatumomab and chemotherapy would also be used in clinical practice.

The SmPC for blinatumomab[22] states that consideration to discontinue blinatumomab temporarily or permanently as appropriate should be made in the case of the following severe (Grade 3) or life-threatening (Grade 4) toxicities: CRS, TLS, neurological toxicity, elevated liver enzymes and any other clinically relevant toxicities.

The list price per pack containing one vial of blinatumomab is £2,017. A confidential Patient Access Scheme (PAS) discount is available for blinatumomab which takes the form of a simple price discount of [redacted]. The price per vial of blinatumomab including the PAS is [redacted].

The EAG's clinical advisors commented that the SoC consolidation chemotherapy backbone used in Study E1910[11] is very similar to the UKALL14 protocol which is used for the vast majority adult ALL cases in England. They also stated that they did not anticipate difficulties in including additional cycles of blinatumomab within the current UKALL14 consolidation chemotherapy protocol, but they noted that cycle 4 of the UKALL protocol is no longer used by most centres. The clinical advisors also stated that the MRD threshold used in Study E1910 (1×10^{-4}) was reasonable and that any positive MRD measurement (i.e., detectable disease at any threshold) should be classed as MRD-positive disease.

3.3. Comparators

The final NICE scope[20] describes the comparator for the appraisal as *"established clinical management without blinatumomab, which may include chemotherapy (with or without corticosteroids) and stem cell transplant."* The CS[1] includes a single comparator – consolidation chemotherapy – and is therefore narrower than the final NICE scope.

Within Study E1910,[11] consolidation therapy was given over four treatment cycles according to the modified UKALLXII/E2993 regimen[12] (including cytarabine, daunorubicin, cyclophosphamide, etoposide, methotrexate, peg-asparaginase, vincristine, 6-mercaptopurine and rituximab [optional]). Further details of this regimen are provided in Section 4.2.1. As noted in Section 3.2, the clinical advisors consulted by the EAG and the company stated that this regimen is very similar to the UKALL14 protocol.[10]

The CS[1] argues that alloSCT is not a relevant comparator as it is usually used in patients with high-risk features (e.g., adverse cytogenetics), subject to the availability of a suitable donor, and that alloSCT would be offered at the end of induction/intensification therapy (prior to consolidation therapy). The clinical advisors consulted by the company and the EAG agreed that alloSCT is not a relevant comparator for blinatumomab in MRD-negative patients undergoing consolidation therapy and that blinatumomab would not displace alloSCT.

3.4. Outcomes

The following outcomes are listed in the final NICE scope:[20]

- Overall survival (OS)
- Progression-free survival (PFS) (including relapse-free survival [RFS] and event-free survival [EFS])
- Treatment response rate (including MRD, haematologic responses and complete remission)
- Rate of stem cell transplant
- Adverse events (AEs) of treatment
- Health-related quality of life (HRQoL).

The CS[1] reports on a subset of these outcomes – OS, RFS and AEs. The CS explains that treatment response is not a relevant outcome because patients in Study E1910[11] were required to be MRD-negative at the end of treatment induction and intensification. The CS also states that the rate of alloSCT is not an appropriate outcome measure for the reasons detailed in Section 3.3. However, the CS does report on the number of MRD-negative patients who went on to receive alloSCT in each arm of Study E1910. This proportion was similar between the two treatment groups (proportion receiving alloSCT: blinatumomab plus SoC consolidation chemotherapy N=[redacted]; SoC consolidation chemotherapy N=[redacted]. The EAG's clinical advisors commented that in clinical practice they would expect very few (if any) MRD-negative patients to undergo alloSCT prior to relapse due to concerns about the risk of treatment-related mortality (TRM).

3.5. Other relevant factors

Section B.1.4 of the CS[1] states that it is not expected that this appraisal will exclude people protected by equality legislation, nor will it lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. The CS also states that it is not expected that the appraisal will lead to recommendations that have any adverse impact on people with disability or disabilities.

As noted in Section 3.1, the EAG's clinical advisors noted that Study E1910[11] applied inclusion criteria which required patients to be aged between 30 and 70 years at enrolment, but commented that they would expect blinatumomab to also be an effective therapy in younger adult patients who are under 30 years of age. They raised concerns that a positive NICE recommendation for blinatumomab restricted by an age cut-off of 30 years would lead to inequality of access to this technology for younger adult patients with ALL (in particular, for those patients who are managed under a UK adult ALL approach, but who are younger than the age cut-off in Study E1910 (i.e., patients aged >25 and <30 years).

The EAG's clinical advisors also highlighted that NICE TA589[15] recommends the use of blinatumomab as an option for treating Ph- -negative CD19-positive B-precursor ALL in adults with an MRD of at least 0.1% (1×10^{-3}). Study E1910[11] applied an MRD threshold of 0.01% (1×10^{-4}). The EAG's clinical advisors raised concerns that if NICE issues a positive recommendation for blinatumomab in the current appraisal indication based on the MRD threshold applied in Study E1910, this would leave a group of MRD-positive patients ineligible for treatment with blinatumomab because although they have detectable MRD, it has not yet reached the threshold specified for treatment under the TA589 recommendation (i.e., those patients with MRD of between 0.01% and 0.1%). The EAG's clinical advisors stated that if this were to happen, they would expect to have to repeatedly monitor the patient's MRD whilst they wait for the patient's disease to further progress. The EAG's clinical advisors commented that patients with an MRD of 0.01% have a markedly higher risk of relapse compared to

those who are MRD-negative, but they also have a better chance of cure with blinatumomab compared with patients with an MRD of 0.1% who are currently eligible for blinatumomab under the TA589 recommendation. They also highlighted that relapse is rarely linear and that monitoring a patient's MRD in order to catch the disease rising is a high-risk strategy as the patient may progress from 0.01% to frank disease, thereby missing the opportunity for blinatumomab to have a good chance of achieving a second remission. As such, excluding patients who have an MRD of between 0.01% and 0.1% would put this group of patients in a very disadvantaged position.

4. CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[1] is comprised of:

- A systematic literature review (SLR)
- A summary of the design and results of the E1910 trial of blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy.[11]

This chapter summarises and critiques the company's review methods and clinical effectiveness data. Full details of the company's SLR are presented in Section B.2 of the CS[1] and in CS Appendices D, E and F.[23]

4.1. Critique of the methods of review

4.1.1. *Searches*

The company undertook an SLR to identify all clinical effectiveness and safety studies of blinatumomab or comparator treatments for people with Ph-negative B-cell ALL.

The company searched several electronic bibliographic databases in July 2023 and undertook an update search in April 2024 (CS Appendix D.1[23]). Bibliographic databases searched included: MEDLINE (all segments, via Ovid); EMBASE (via Ovid); the Cochrane Database of Systematic Reviews (CDSR) (via Ovid); the Database of Abstracts of Reviews of Effects (DARE) (via Ovid); the Cochrane Central Register of Controlled Trials (CENTRAL) (via Ovid); the Cochrane Methodology Register (CMR) (via Ovid); the NHS Economic Evaluation Database (NHS EED) (via Ovid); the Health Technology Assessment (HTA) database (via Ovid), and the ACP Journal Club (via Ovid). The company also hand searched bibliographies of potentially relevant studies to identify other studies for inclusion. In addition, the company searched several clinical trials registries including: the clinicaltrials.gov registry, the National Cancer Institute (NCI) Clinical Trial Database, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the National Institutes for Health (NIH) Clinical Center Trials database, and the European Union Clinical Trials Register (EUCTR) for ongoing or completed or unpublished trials. Searches were limited to studies published in English from 2012 onwards. Following a request for clarification by the EAG (see clarification response,[21] question A1), the company explained that the 2012 date limit was applied with the intention of keeping the scope and timelines of the SLR manageable, whilst focussing on the most relevant, recent evidence.

The company also searched several key conference abstract websites in the last four years (2021-2024). These included: the American Society of Clinical Oncology (ASCO); the American Society of Haematology (ASH); the European Society for Blood and Marrow Transplantation (EBMT); the European Hematology Association (EHA); the European Society for Medical Oncology (ESMO); the

Nordic Society of Paediatric Haematology (NOPHO); the Asian Society for Pediatric Oncology (SIOP); and the Society for Immunotherapy of Cancer (SITC). The search terms applied are reported in CS Appendix D.1.1.[23]

The company also hand searched treatment guidelines in eleven countries, the National Comprehensive Cancer Network (NCCN) and NICE. Several government bodies and other report repositories were also searched including: the Centre for Reviews and Dissemination (CRD); the Food and Drug Administration (FDA); the EMA; the Centers for Disease Control and Prevention (CDC); WHO and the Academy of Managed Care Pharmacy (AMCP).

The reported terms used in the company database and supplementary searches are transparent and fully reported, although the EAG notes that the number of records retrieved from the individual sources which were hand searched could have also been reported. Overall, the EAG considered that the company's search was comprehensive and that there are no apparent errors in the search strategies. The EAG considers that the company's decision to restrict searches to studies published since 2012 is unlikely to have resulted in relevant evidence for the current appraisal being missed.

4.1.2. *Inclusion criteria for the SLR*

The inclusion criteria for the company's SLR are described in CS Appendix D.1.2[23] (Table 9, pages 15-16). The SLR was broad and included RCTs undertaken in people with newly diagnosed Ph-negative B-cell ALL receiving any pharmacologic first-line therapy (irrespective of whether the therapy has received regulatory approval), including induction, consolidation, and maintenance treatment, published from the year 2012 onwards. The specified inclusion and exclusion criteria were generally appropriate and generally reflect the decision problem for the current appraisal.

4.1.3. *Critique of study selection, data extraction and quality assessment*

Two reviewers screened all citations and full-text articles (CS Appendix D.1.2,[23] page 15). Extracted data were checked by a second reviewer and any discrepancies were resolved through discussion or through the intervention of a third reviewer (CS Appendix D.1.2, page 16). Study quality for the included RCT (Study E1910[11]) was assessed using the York CRD quality assessment checklist[24] using a double-blind approach. The EAG considers these methods to be appropriate.

4.1.4. *Overall EAG view on the company's review methods*

Overall, the EAG considers that the company's review methods were appropriate.

4.1.5. *Results of the company's SLR*

The company's clinical SLR identified a total of 241 publications, of which 35 publications (covering 14 studies) assessed blinatumomab and were deemed to be relevant to the submission (CS,[1] Section B.2.2). Of these, two studies were RCTs: Study E1910 (Litzow *et al.*)[25-27] and Golden Gate (Jabbour *et al.*).[28] However, the Jabbour *et al.* publication only reported results of the single-arm, safety run-in phase of the trial and results for the Phase III RCT part of the study have not yet been published (the primary analysis is expected to be available in [redacted]). The remaining 12 studies were single-arm studies.[29-57] Therefore, the SLR identified only one relevant comparative study: Study E1910.[11] This RCT compared blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation therapy alone.

4.2. Characteristics of Study E1910

4.2.1. *Study design: E1910 RCT*

Study E1910[11] is an international, multicentre, randomised, open-label, SoC controlled, Phase III trial in 224 patients with Ph-negative CD19-positive B-precursor ALL with no measurable residual disease. The study compared the efficacy and safety of blinatumomab plus SoC consolidation chemotherapy (hereafter referred to as the 'blinatumomab' group) versus SoC consolidation chemotherapy alone (hereafter referred to as the 'SoC' group) in patients who had received induction and intensification treatment. The study was conducted at 77 centres in the United States (US), Canada, and Israel. The design of Study E1910 is summarised in Table 6.

Study E1910[11] was originally designed to evaluate the effectiveness and safety of blinatumomab plus SoC consolidation therapy in patients with either MRD-positive or MRD-negative disease, with MRD status included as a stratification factor for randomisation. In 2018, the US Food and Drug Administration (FDA) granted an accelerated approval of blinatumomab in MRD-positive ALL. Subsequently, a protocol amendment was implemented whereby all patients who were still MRD-positive after induction therapy were no longer randomised and were instead assigned to the blinatumomab arm. The description of the trial and the outcomes data presented in this EAG report relate only to the MRD-negative population at Step 3 in the trial.

The study procedures under the final design of Study E1910[11] (following the 2018 protocol amendment) were as follows. Prior to randomisation to the blinatumomab and SoC groups, all patients received induction treatment (Step 1) and intensification treatment (Step 2). In the induction step, patients received two cycles of induction chemotherapy, with the addition of peg-asparaginase for patients <55 years of age, and the addition of rituximab for CD20-positive patients. Patients in haematologic CR / complete remission with incomplete blood count recovery (CRi) continued to the study and received one cycle of intensification chemotherapy of high-dose methotrexate for CNS prophylaxis, with the

addition of peg-asparaginase for patients <55 years of age. Subsequently, remission status was assessed, and MRD status was determined centrally by six colour flow cytometry, with MRD negativity defined as ≤1 x 10^{-4} (0.01%). MRD-negative patients were then randomised to the blinatumomab and SoC groups for consolidation treatment (Step 3). Following completion of consolidation chemotherapy with or without blinatumomab, patients were given 2.5 years of POMP maintenance therapy (6-mercaptopurine, vincristine, methotrexate, and prednisone) timed from the start of the intensification cycle. The treatment schedule applied in Study E1910 is outlined in Figure 2.

Table 6: Summary of Study E1910 design (adapted from CS, Table 4)

Study	E1910 (NCT02003222)
Settings and location	Multinational (US, Canada, and Israel)
Study design	Phase III, open-label RCT
Population*	- Patients with a new diagnosis of B-cell precursor ALL based upon bone marrow or peripheral blood immunophenotyping aged ≥30 years and ≤70 years - ECOG PS of 0 to 2 at randomisation - Maintained peripheral blood evidence of a remission - CR or CRi, and resolved any serious infections or medical complications related to therapy
Randomisation stratified by	- MRD status† - Age (<55 years vs ≥55 years) - CD20 status (positive vs negative) - Rituximab use (yes vs no) - Intent to receive alloSCT (yes vs no)
Intervention(s)	Blinatumomab (28mcg/day) + SoC consolidation chemotherapy
Comparator(s)	SoC consolidation chemotherapy alone
Relevant reported outcomes listed in the final NICE scope[20]	- OS - RFS - AEs
All other reported outcomes	- OS and RFS censored at alloSCT (sensitivity analyses)
Pre-planned subgroups‡	- Gender (Female vs. Male) - Race - Ethnicity - Age (≥18- and <35 years, ≥35 and <55 years, ≥55 and <65 years, ≥65 years) - CD20 status - Rituximab use (yes vs no) - Intent to transplant (yes vs no)

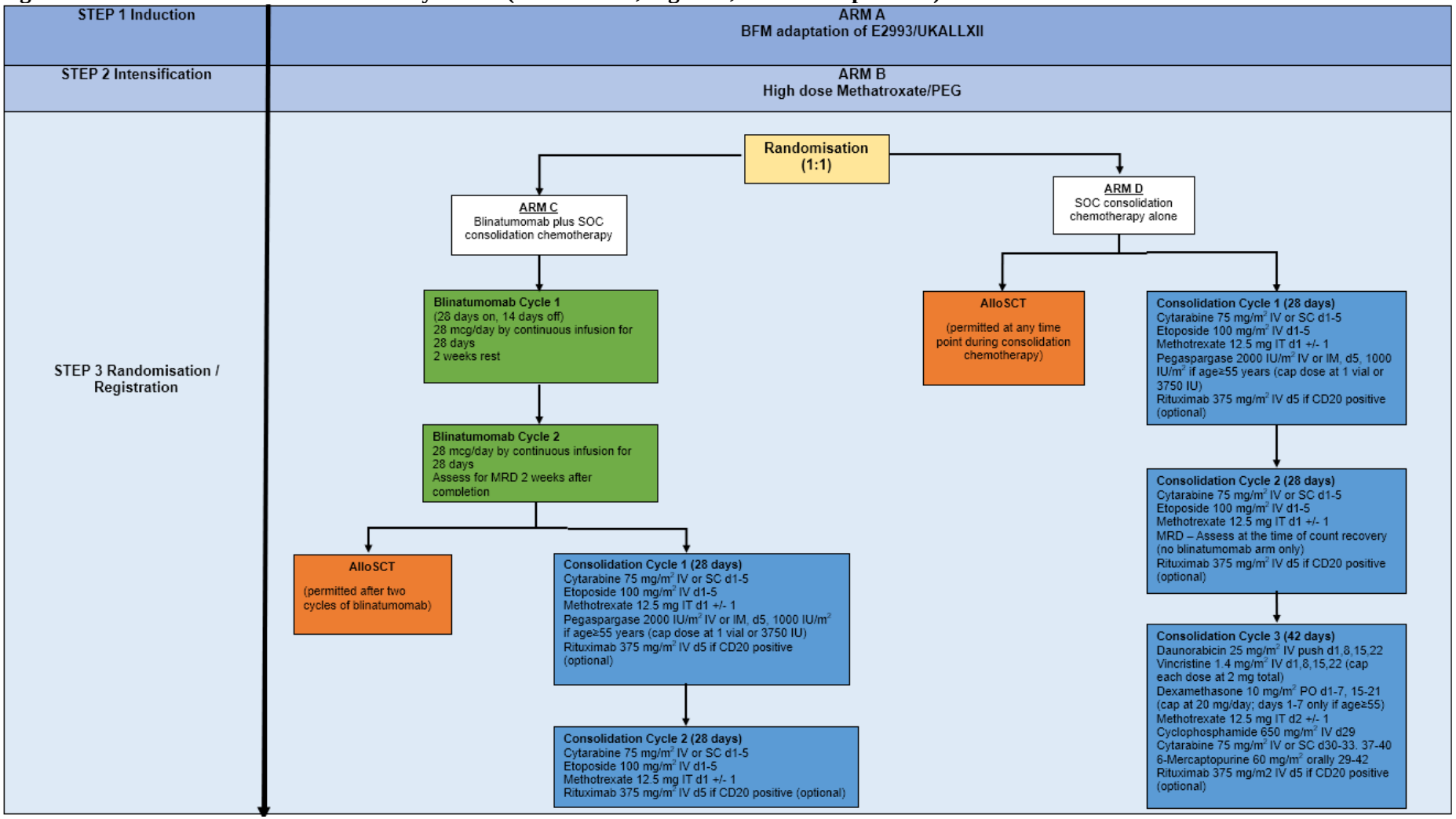
AE - adverse event; ALL - acute lymphoblastic leukaemia; alloSCT - allogeneic stem cell transplant; CR - complete remission; CRi - complete remission with incomplete blood count recovery; ECOG - Eastern Cooperative Oncology Group; MRD - minimal residual disease; OS - overall survival; PS - performance status; RCT - randomised controlled trial; RFS - relapse-free survival; SoC - standard of care

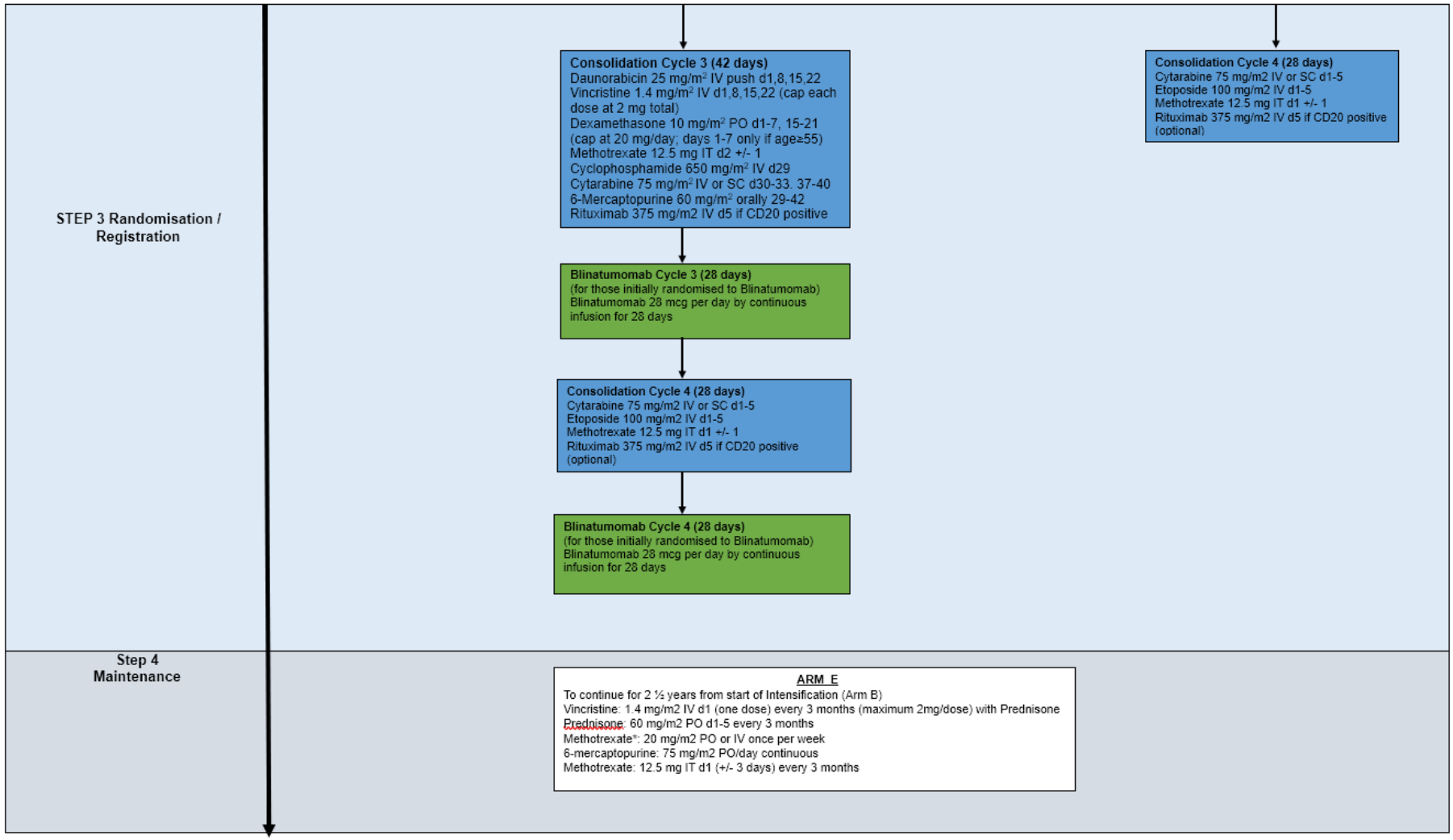
** CD19-positivity was not mandated for eligibility given its high incidence at B-cell ALL diagnosis*

†MRD status was removed as a stratification factor following the 2018 protocol amendment (see clarification response,[21] question A7)

‡The results of pre-planned subgroup analysis were reported in the CSR[11] but not the CS.[1] These were later provided in the company's clarification response.[21]

Figure 2: Treatment schedule in Study E1910 (based on CS, Figure 4, and E1910 protocol)





Footnotes: Patients could proceed to alloSCT at the discretion of the treating physician, which was suggested to be done after the first 2 cycles of blinatumomab in the blinatumomab plus SoC chemotherapy arm or at any time following intensification chemotherapy in the SoC chemotherapy arm.
AlloSCT - allogeneic stem cell transplant; BFM - Berlin-Frankfurt-Münster; CD - cluster of differentiation; chemo - chemotherapy; FDA - Food and Drug Administration; MRD - minimal residual disease; PEG - peg-asparaginase; Source: E1910 CSR[11]

4.2.2. *Population in Study E1910*

Patients enrolled in Study E1910[11] were individuals aged ≥30 years and ≤70 years who had: a new diagnosis of B-cell precursor ALL based upon bone marrow or peripheral blood immunophenotyping; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 at randomisation; maintained peripheral blood evidence of a remission, had a CR or CRi, and must have had any serious infections or medical complications related to therapy resolved. The inclusion criteria for Study E1910 are narrower than the population specified in the final NICE scope[20] as the study was restricted to adults only (aged ≥30 years and ≤70 years). The EAG's clinical advisors stated that they would expect blinatumomab to also be an effective treatment in younger adult patients who are under 30 years of age. Study eligibility criteria are presented in Table 7.

Table 7: Inclusion and exclusion criteria in Study E1910 (reproduced from CS, Table 5)

Inclusion criteria[a]	Exclusion criteria
Step 1 (Induction): • Patients ≥30 years and ≤70 years of age • New diagnosis of B-cell precursor ALL was based upon bone marrow or peripheral blood immunophenotyping • Patients with an ECOG performance status 0–3 were eligible for the induction phase of this study. **Step 2 (Intensification):** • Patients with an ECOG performance status of 0–2 were eligible for post-induction therapy. • These patients must have had achieved CR or CRi, must have been CNS-negative for leukaemia, and must have had resolved any serious infections or significant medical complications related to induction. **Step 3 (Randomisation):** • ECOG performance status of 0–2. • Patients must have maintained peripheral blood evidence of a remission, must have a CR or CRi, and must have resolved any serious infections or medical complications related to therapy.	**Step 1 (Induction):** • Patients with Philadelphia chromosome-positive/PH1-positive ALL, Burkitt leukaemia/lymphoma, or mature B-cell leukaemia were not eligible. • Patients must not have had an antecedent haematologic disorder, history of recent myocardial infarction, or uncontrolled heart failure. • Patients with pre-existing significant CNS pathology or uncontrollable seizure disorders were not eligible.

Footnotes: [a] CD19-positivity was not mandated for eligibility given its high incidence at B-cell ALL diagnosis
ALL - acute lymphoblastic leukaemia; CNS - central nervous system; CR - complete remission; CRi - complete remission with incomplete blood count recovery; ECOG - Eastern Cooperative Oncology Group
Source: E1910 CSR[11]

4.2.3. *Intervention in Study E1910*

Patients were randomised 1:1 to receive blinatumomab plus SoC consolidation chemotherapy or SoC consolidation chemotherapy alone. In total, 112 patients were randomised to blinatumomab and 112 to SoC. Patients in the blinatumomab group received 28mcg daily by continuous infusion (28-day cycle) interspersed with SoC consolidation chemotherapy for a total of 8 cycles (2 cycles blinatumomab, 3 cycles SoC consolidation chemotherapy, 1 cycle blinatumomab, 1 cycle SoC consolidation chemotherapy, 1 cycle blinatumomab; see Figure 2). Randomisation was stratified by: MRD status; age (<55 years vs ≥55 years); CD20 status (positive vs negative); rituximab use (yes vs no) and intent to receive alloSCT (yes vs no). MRD was removed as a stratification factor following the 2018 protocol amendment (see clarification response,[21] question A7).

4.2.4. *Comparator in Study E1910*

The comparator in Study E1910[11] was SoC consolidation therapy given over a total of 4 cycles according to the modified UKALLXII/E2993 regimen[12] (shown previously in Figure 2). As noted in Section 3.2, the clinical advisors consulted by the EAG and the company stated that this regimen is very similar to the UKALL14 protocol.[10] AlloSCT was not included as a comparator in Study E1910. As noted in Section 3.3, the EAG's clinical advisors agreed that alloSCT is not a relevant comparator, as it would be typically reserved for use in patients with high-risk disease, subject to the availability of a suitable donor, after the induction/intensification stage (before consolidation therapy).

4.2.5. *Outcomes in Study E1910*

Outcomes in Study E1910[11] included OS, RFS, response rates, AEs, and incidence of anti-blinatumomab antibody formation. The final NICE scope[20] also listed treatment response, rate of stem cell transplant and HRQoL as outcomes of interest, but these were not reported in the CS.[1] Treatment response was not deemed as an appropriate outcome measure by the company as the target population for this appraisal are patients who are already in CR and who are MRD-negative at the end of induction/intensification (prior to consolidation). In addition, the CS[1] does not report rate of stem cell transplantation as an outcome because it was not deemed a suitable outcome measure and because Study E1910[11] indicates that blinatumomab did not affect the likelihood of receiving alloSCT (although the CS does report the number of people who received alloSCT within the study). HRQoL data were not collected in Study E1910.

4.2.6. *Study quality: E1910*

The company's quality assessment of Study E1910[11] is presented in Section B.2.5 of the CS,[1] and a narrative summary of this assessment is provided in the company's clarification response[21] (question A12). The company's clarification response reports the study to be of high methodological quality in terms of: randomisation; baseline comparability of groups; no unexpected imbalances in drop-outs; no

selective outcome reporting and use of intention-to-treat (ITT) analysis. The EAG largely agrees with the company's quality assessment. However, the EAG notes the following points regarding study design:

(a) There were some imbalances in the number of patients in some age categories between the groups (blinatumomab vs SoC: ≥ 55 and < 65 years; 33% vs 27.7%, ≥ 65 years; 8% vs 14.3%).
(b) There were some imbalances in dropouts between the groups (blinatumomab vs SoC: disease progression/relapse; 6.3% vs 12.5%, AEs; [redacted] vs [redacted], and patient withdrawal; 4.5% vs 8%).
(c) The study was open-label (unblinded and not concealed) which may potentially introduce bias.

The first two of these factors may have impacted on OS.

4.2.7. *Analysis populations and data cut-offs in Study E1910*

The efficacy and safety of blinatumomab compared with SoC is based on the primary analysis data cut-off (DCO) of Study E1910 of the 23rd June 2023.[1] Median follow-up was 4.5 years in both trial arms. The company's clarification response[21] (question A6) states that the next data-cut for Study E1910 will be at the time of the final analysis, after all patients have either discontinued or completed the study (i.e., completed long-term follow-up which is 10 years from start of the patient's induction treatment). The last patient's final visit for Study E1910 is anticipated in [redacted], and the final analysis is expected to be available in [redacted].

The analysis populations were as follows:

- Efficacy analyses were based on the Full Analysis Set (FAS), which included all randomised patients who were assessed as MRD-negative centrally after induction and intensification chemotherapy (N=224).
- Safety analyses were based on the Safety Analysis Set (SAS), which included all randomised patients who received at least one dose of protocol-specific treatments (N=[redacted]).

4.2.8. *Participant flow in Study E1910*

Participant flow at the June 2023 DCO is shown in Figure 3 and Table 8. In total, 224 patients were randomised: 112 to the blinatumomab group ([redacted]) and 112 to the SoC group. At the DCO, 117 patients (52.2%) had completed treatment per-protocol (73 [65.2%] patients in the blinatumomab group and 64 [57.1%] patients in the SoC group). Thirty-eight (33.9%) patients in the blinatumomab group and 48 (42.9%) patients in the SoC group discontinued treatment, and [redacted] patients in the blinatumomab and [redacted] patients in the SoC group received alloSCT. The most common reason for treatment discontinuation in the SoC group was disease progression/relapse [redacted], whereas the most common reason for discontinuation in the blinatumomab group was AEs [redacted].

Figure 3: Patient disposition in E1910 trial (reproduced from CS, Figure 5)

MRD - minimal residual disease; SoC - standard of care

Table 8: Subject disposition in Study E1910 (adapted from CSR, Table 14-1.2)

	Blinatumomab plus SoC chemotherapy (N=112) n (%)	**SoC chemotherapy (N=112) n (%)**
Protocol treatment accounting		
Subjects who never started treatment	[redacted]	[redacted]
Subjects who completed treatment per protocol	73 (65.2)	64 (57.1)
Subjects who discontinued treatment	38 (33.9)	48 (42.9)
Disease progression relapse during active treatment	7 (6.3)	14 (12.5)
Adverse event/side effects/complications	[redacted]	[redacted]
Death on study	[redacted]	[redacted]
Cause of death		
Cardio-cerebrovascular event	2 (1.8)	0 (0.0)
Infection	4 (3.6)	2 (1.8)
Due to this disease	0 (0.0)	1 (0.9)
Treatment related	0 (0.0)	0 (0.0)
Subject withdrawal/refusal after beginning protocol therapy	5 (4.5)	9 (8)
Alternative therapy	2 (1.8)	3 (2.7)
Subject off-treatment for other complicating disease	3 (2.7)	2 (1.8)
Other	3 (2.7)	12 (10.7)
Subjects receiving off-protocol blinatumomab	0 (0.0)	22 (19.6)
Subjects receiving allogeneic SCT	28 (25.0)	33 (29.5)
On-protocol	22 (19.6)	22 (19.6)
Off-protocol	6 (5.4)	12 (10.7)
Subjects receiving non-protocol therapy for ALL		
Chemotherapy	1 (0.9)	3 (2.7)
Hormonal therapy	0 (0.0)	1 (0.9)
Immunotherapy	0 (0.0)	1 (0.9)
High dose chemotherapy/stem cell transplant (autologous or allogeneic)	0 (0.0)	3 (2.7)
Surgery	1 (0.9)	0 (0.0)
Study completion accounting		
Subjects ongoing on study	88 (78.6)	64 (57.1)
Subjects who completed study	0 (0.0)	0 (0.0)
Subjects who discontinued study	24 (21.4)	48 (42.9)
Subjects refusal for follow-up or withdrawal of consent	4 (3.6)	6 (5.4)
Lost to follow-up	1 (0.9)	2 (1.8)
Death	19 (17.0)	40 (35.7)

N = Number of subjects in the analysis set. n = Number of subjects with observed data.
SoC - standard of care; CSR - Clinical Study Report; ALL - acute lymphoblastic leukaemia. SCT - stem cell transplant.
First subject enrolled: 07JUN2014 Last subject enrolled: 18OCT2019
Step 3 subjects who complete treatment per protocol are subjects who complete all planned Step 3 treatment (i.e., all planned blinatumomab cycles, consolidation cycles or allogeneic transplant) and all maintenance cycles, when planned.
Subjects receiving allogeneic SCT: The subcategories within each category are mutually exclusive. Subjects are included within each subcategory.

4.2.9. *Baseline characteristics in E1910*

Baseline patient characteristics in Study E1910[11] are shown in Table 9. The EAG's clinical advisors considered that the patient characteristics in Study E1910 were reasonably well-balanced between the groups, and to some extent, representative of patients in clinical practice in the UK, except for patient age and race. In both groups, the majority of patients were from the US (blinatumomab 92.0% vs SoC 88.4%) and the mean age was approximately 50 years. The blinatumomab group had a lower proportion of patients aged ≥18 and <35 years (11.6% vs 15.2%) and ≥65 years (8.0% vs 14.3%) than the SoC group.

The blinatumomab and SoC groups had similar proportions of patients in each ECOG PS category and had similar proportions of male patients (49.1% vs 50.0%), patients with CD20-positive status at enrolment (40.2% vs 41.4%) and patients with three prior lines of therapy (rituximab use; 29.5% vs 32.1%, prior surgery; 3.6% vs 5.4%, and/or prior radiation therapy; 1.8% vs 3.6%). The EAG notes that CD20 status at enrolment and rituximab use data were not collected for around 36% of patients in both treatment arms. No subgroup analyses were presented in the CS;[1] however, subgroup analyses were subsequently provided as part of the company's clarification response[21] (question A11).

Table 9: Baseline characteristics in Study E1910 (reproduced from CS, Tables 6 and 7)

Characteristics	Blinatumomab + SoC consolidation chemotherapy (N=112)	SoC consolidation chemotherapy (N=112)
Sex, n (%)		
Male	55 (49.1)	56 (50.0)
Female	57 (50.9)	56 (50.0)
Race, n (%)		
American Indian or Alaska Native	2 (1.8)	1 (0.9)
Asian	3 (2.7)	2 (1.8)
Black or African American	9 (8.0)	4 (3.6)
Native Hawaiian or Other Pacific Islander	1 (0.9)	0 (0.0)
White	87 (77.7)	89 (79.5)
Not Reported	5 (4.5)	6 (5.4)
Unknown	5 (4.5)	10 (8.9)
Age at enrolment, years		
Mean	50.1	50.0
SD	11.0	11.9
Median	51.5	50.0
Q1, Q3	41.0, 59.0	40.0, 60.5
Min, Max	30, 69	30, 70
Age group, n (%)		
<55 years	66 (58.9)	65 (58.0)
⩾55 years	46 (41.1)	47 (42.0)
Unknown	0 (0.0)	0 (0.0)

Characteristics	Blinatumomab + SoC consolidation chemotherapy (N=112)	SoC consolidation chemotherapy (N=112)
Age group, n (%)		
⩾18 and <35 years	13 (11.6)	17 (15.2)
⩾35 and <55 years	53 (47.3)	48 (42.9)
⩾55 and < 65 years	37 (33.0)	31 (27.7)
⩾65 years	9 (8.0)	16 (14.3)
Country of residence, n (%)		
Canada	7 (6.3)	7 (6.3)
Israel	2 (1.8)	6 (5.4)
United States	103 (92.0)	99 (88.4)
ECOG performance status, n (%)		
0	39 (34.8)	40 (35.7)
1	67 (59.8)	69 (61.6)
2	6 (5.4)	3 (2.7)
CD20 status at enrolment, n (%)		
Positive	45 (40.2)	46 (41.4)
Negative	26 (23.2)	26 (23.2)
Not collected	41 (36.6)	40 (35.7)
Rituximab use, n (%)		
Yes	33 (29.5)	36 (32.1)
No	38 (33.9)	36 (32.1)
Not collected	41 (36.6)	40 (35.7)
Prior surgery,[a] n (%)		
Yes	4 (3.6)	6 (5.4)
No	108 (96.4)	106 (94.6)
Prior radiation therapy, n (%)		
Yes	2 (1.8)	4 (3.6)
No	110 (98.2)	108 (96.4)
Intent to receive alloSCT, n (%)		
Yes	36 (32.1)	35 (31.3)
No	76 (67.9)	77 (68.8)

Footnotes: [a] Prior surgery refers to prior cancer treatment with therapeutic intent.
alloSCT - allogeneic stem cell transplant; CD - cluster of differentiation; ECOG - Eastern Cooperative Oncology Group; FAS - Full Analysis Set; MRD - minimal residual disease; SD - standard deviation; Q - quartile; SoC - standard of care
Source: Table 14-2.1, Table 14-2.5, 14.2.6, and 14-2.7 E1910 CSR[11]

4.3. Effectiveness of blinatumomab

This section summarises the effectiveness data for blinatumomab from Study E1910.[11] The primary efficacy endpoint was OS. Secondary efficacy endpoints included: RFS; OS and RFS for patients who proceeded to alloSCT after treatment with or without blinatumomab; AEs and incidence of anti-blinatumomab antibody formation (CS,[1] Section B.2.3.2, Table 5).

4.3.1. *OS in Study E1910*

The primary end point in Study E1910[11] was OS. OS was defined as the time from randomisation until death due to any cause. The analysis was conducted on the FAS. OS outcomes in Study E1910 are

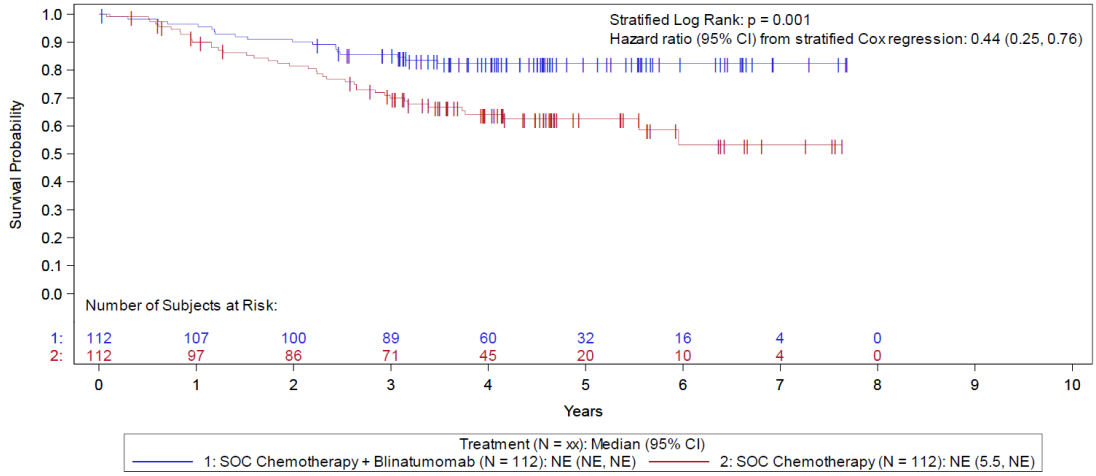
presented in Table 10 and Figure 4. The median follow-up time for OS was 4.5 years in both treatment groups. Median OS was not reached and was not evaluable in either treatment group at the June 2023 DCO. The 5-year Kaplan-Meier OS rate was 82.4% (95% CI: 73.7%, 88.4%) in the blinatumomab group and 62.5% (95% CI: 52.0%, 71.3%) in the SoC group. The trial reported a statistically significant improvement in OS for blinatumomab compared with SoC: HR 0.44, 95% CI 0.25, 0.76, *p*=0.001, indicating a 56% reduction in the hazard rate for death in the blinatumomab group versus the SoC group.

Table 10: OS for MRD-negative patients in Study E1910, FAS (reproduced from CS, Table 10)

	Blinatumomab + SoC consolidation chemotherapy (N=112)	**SoC consolidation chemotherapy (N=112)**
Number of events (deaths), n (%)	19 (17.0)	40 (35.7)
Censored, n (%)	93 (83.0)	72 (64.3)
Completed study without event	0 (0.0)	0 (0.0)
Continued on study	88 (78.6)	64 (57.1)
Discontinued study	5 (4.5)	8 (7.1)
Consent withdrawn	4 (3.6)	6 (5.4)
Lost to follow-up	1 (0.9)	2 (1.8)
Treatment difference (stratified log-rank test)[a,b]		
Normal score	3.02	
p-value	0.001	
Time to event (KM) (yrs)[c]		
Median (95% CI)	NE (NE, NE)	NE (5.5, NE)
KM estimate, % (95% CI)		
0.5 yrs	98.2 (93.0, 99.5)	99.1 (93.8, 99.9)
1 yr	96.4 (90.7, 98.6)	90.0 (82.6, 94.3)
2 yrs	90.1 (82.8, 94.4)	81.5 (72.8, 87.6)
3 yrs	85.5 (77.5, 90.9)	70.0 (60.3, 77.7)
4 yrs	82.4 (73.7, 88.4)	64.1 (53.9, 72.7)
5 yrs	82.4 (73.7, 88.4)	62.5 (52.0, 71.3)
6 yrs	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)
7 yrs	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)
Stratified HR[a,d] (95% CI)	0.44 (0.25, 0.76)	
Time to censoring (KM) for OS (yrs)[c, e]		
Median (95% CI)	4.5 (4.1, 4.6)	4.5 (4.0, 4.6)

Footnotes: [a] Stratification factors: age (<55 years vs. ≥55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive alloSCT (yes vs. no). [b] 1-sided stratified log-rank test p-value is provided. [c] Years are calculated as days from randomisation date to event/censor date, divided by 365.25. [d] Time to censoring measures follow-up time by reversing the status indicator for censored and events. [e] The HR estimates are obtained from a stratified Cox regression model. An HR <1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab + SoC consolidation chemotherapy arm relative to patients in the SoC consolidation chemotherapy arm.
CI - confidence interval; FAS - Full Analysis Set; HR - hazard ratio: MRD - minimal residual disease; OS - overall survival; SoC - standard of care; KM - Kaplan-Meier; yr - year
Source: Table 14-4.1.1. E1910 CSR[11]

Figure 4: Kaplan-Meier plot of OS for MRD-negative patients in Study E1910, FAS (reproduced from CS, Figure 6)



Footnotes: Censor indicated by vertical bar.
CI - confidence interval; FAS - Full Analysis Set; MRD - minimal residual disease; NE - non evaluable; OS - overall survival; SoC - standard of care
Source: Figure 10-1. E1910 CSR[11]

4.3.2. *RFS in Study E1910*

The key secondary efficacy endpoint was RFS, which was defined as the time from randomisation until relapse or death due to any cause (whichever occurred first). RFS outcomes from Study E1910[11] are presented in Table 11 and Figure 5. At the June 2023 DCO, the median follow-up time for RFS was 4.5 years in both treatment groups. Median RFS was not reached and was not evaluable in either treatment group. The 5-year Kaplan-Meier RFS rate was 77.0% (95% CI: 67.8%, 83.8%) in the blinatumomab group and 60.5% (95% CI: 50.1%, 69.4%) in the SoC group. The trial reported a statistically significant improvement in RFS for blinatumomab compared with SoC (HR 0.53, 95% CI 0.32, 0.88), indicating a 47% reduction in the hazard rate for relapse or death in the blinatumomab group versus the SoC group.

Section B.3.3.2 of the CS[1] highlights that as per the E1910 trial protocol,[58] patients were followed every three months during the first two years of the study, then every six months over the next three years, then every twelve months over the next five years. As such, disease assessment was not systematically captured during long-term follow-up, and only the patients' alive/death status was systematically captured during this period. The CS states that as a consequence, at later time points, the recorded time of relapse may not reflect the time of relapse in full and may therefore have been recorded at the same time as a death event. Any bias arising from this data collection issue is likely to have a greater impact on the SoC arm due to the higher number of RFS and OS events after three years.

Table 11: RFS for MRD-negative patients in Study E1910, FAS (reproduced from CS, Table 11)

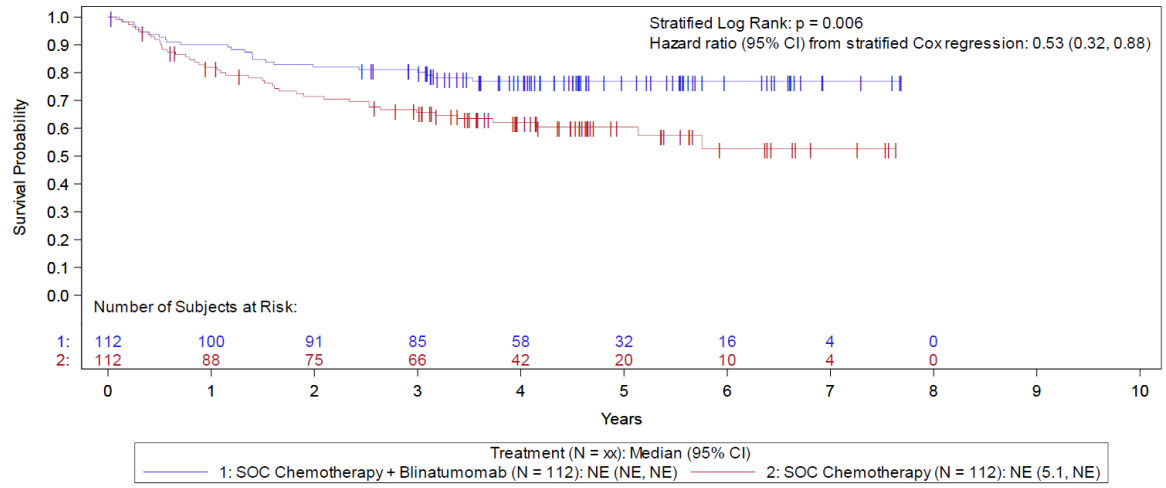
	Blinatumomab + SoC consolidation chemotherapy (N=112)	**SoC consolidation chemotherapy (N=112)**
Number of events, n (%)	25 (22.3)	43 (38.4)
Relapse	15 (13.4)	32 (28.6)
Death due to any cause	10 (8.9)	11 (9.8)
Censored, n (%)	87 (77.7)	69 (61.6)
Completed study without event	0 (0.0)	0 (0.0)
Continued on study	84 (75.0)	61 (54.5)
Discontinued study	3 (2.7)	8 (7.1)
Consent withdrawn	3 (2.7)	6 (5.4)
Lost to follow-up	0 (0.0)	2 (1.8)
Treatment difference (stratified log-rank test)[a,b]		
Normal score	2.51	
p-value	0.006	
Time to event (KM) (yrs)[c]		
Median (95% CI)	NE (NE, NE)	NE (5.1, NE)
KM estimate (yrs), % (95% CI)		
0.5	92.8 (86.1, 96.3)	91.9 (85.1, 95.7)
1	90.1 (82.8, 94.4)	81.9 (73.4, 87.9)
2	82.0 (73.5, 88.0)	71.5 (61.9, 79.0)
3	81.1 (72.5, 87.2)	65.7 (55.9, 73.8)
4	77.0 (67.8, 83.8)	62.1 (52.0, 70.7)
5	77.0 (67.8, 83.8)	60.5 (50.1, 69.4)
6	77.0 (67.8, 83.8)	52.7 (38.5, 65.0)
7	77.0 (67.8, 83.8)	52.7 (38.5, 65.0)
Stratified hazard HR[a,d] (95% CI)	0.53 (0.32, 0.88)	
Time to censoring (KM) for RFS (yrs)[a,e]		
Median (95% CI)	4.5 (4.1, 4.7)	4.5 (4.0, 4.6)

Footnotes: [a] Stratification factors: age (<55 years vs. ≥55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive alloSCT (yes vs. no). [b] 1-sided stratified log-rank test p-value is provided. [c] Years are calculated as days from randomisation date to event/censor date, divided by 365.25. [d] Time to censoring measures follow-up time by reversing the status indicator for censored and events. [e] The HR estimates are obtained from a stratified Cox regression model. An HR <1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab + SoC consolidation chemotherapy arm relative to patients in the SoC consolidation chemotherapy arm.

CI - confidence interval; FAS - Full Analysis Set; HR - hazard ratio; KM - Kaplan-Meier; MRD - minimal residual disease; RFS - relapse-free survival; SoC - standard of care; yr - year

Source: Table 14-4.2.1 E1910 CSR[11]

Figure 5: Kaplan-Meier plot of RFS for MRD-negative patients in Study E1910, FAS (reproduced from CS, Figure 7)



Footnotes: Censor indicated by vertical bar.
CI - confidence interval; FAS - Full Analysis Set; MRD - minimal residual disease; NE - non evaluable; RFS - relapse-free survival; SoC - standard of care
Source: Figure 10-2. E1910 CSR[11]

4.3.3. *Sensitivity analysis: OS censored at alloSCT*

Section B.2.6.3 of the CS[1] reports the results of a sensitivity analysis of OS whereby patients who received alloSCT were censored at the time of transplant. OS outcomes for this sensitivity analysis are presented Table 12 and Figure 6. The results of the analysis favoured the blinatumomab group, with a *** reduction in the risk of death compared to the SoC group (stratified HR: [redacted]; 95% CI: [redacted]) (CS,[1] Section B.2.6.3, pages 43-46). As per the primary analysis of OS, median OS was [redacted] in either treatment group. The CS concludes that the OS benefit of blinatumomab was consistent with the primary analysis, regardless of whether patients received alloSCT.

Table 12: OS censored at alloSCT for MRD-negative patients, FAS (reproduced from CS, Table 12)

	Blinatumomab + SoC consolidation chemotherapy (N=112)	SoC consolidation chemotherapy (N=112)
Number of events (death due to any cause), n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Completed study without event	[redacted]	[redacted]
Continued on study	[redacted]	[redacted]
Received alloSCT	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Time to event (KM) (yrs)[a]		
Median (95% CI)	[redacted]	[redacted]
Treatment difference (stratified log-rank test)[b]		
Normal score	[redacted]	
p-value	[redacted]	
KM estimate, % (95% CI)		
0.5 yrs	[redacted]	[redacted]
1 yrs	[redacted]	[redacted]
2 yrs	[redacted]	[redacted]
3 yrs	[redacted]	[redacted]
4 yrs	[redacted]	[redacted]
5 yrs	[redacted]	[redacted]
6 yrs	[redacted]	[redacted]
7 yrs	[redacted]	[redacted]
Stratified HR[c,d] (95% CI)	[redacted]	
Time to censoring (KM) for OS (yrs)[a,d]		
Median (95% CI)	[redacted]	[redacted]

Footnotes: [a] Years are calculated as days from randomisation date to event/censor date, divided by 365.25.
[b] 1-sided stratified log-rank test p-value is provided. The HR estimates are obtained from a stratified Cox regression model. An HR < 1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab plus SoC consolidation chemotherapy arm relative to patients in the SoC consolidation chemotherapy arm.
[c] Stratification factors: age (< 55 years vs. ≥ 55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive alloSCT (yes vs. no).
[d] Time to censoring, measured by reversing the status indicator for censored and events.
OS - overall survival; alloSCT - allogeneic stem cell transplant; MRD - minimal residual disease; SoC - standard of care; KM - Kaplan-Meier; CI - confidence interval; HR - hazard ratio; FAS - Full Analysis Set; NE - not estimable; yr - year
Source: Table 14-4.1.4. E1910 CSR[11]

Figure 6: Kaplan-Meier plot of OS censored at alloSCT for MRD-negative patients, FAS (reproduced from CS, Figure 8)

Footnotes: Censor indicated by vertical bar.
OS - overall survival; alloSCT - allogeneic stem cell transplant; MRD - minimal residual disease; FAS - Full Analysis Set; CI - confidence interval; SoC - standard of care
Source: Figure 14-4.1.3. E1910 CSR[11]

4.3.4. *Sensitivity analysis: RFS censored at alloSCT*

Section B.2.6.4 of the CS[1] reports the results of a sensitivity analysis of RFS whereby patients who received alloSCT were censored at the time of transplant. RFS outcomes for this sensitivity analysis are presented in Table 13 and Figure 7. Again, the results of the analysis favoured the blinatumomab group, with a [redacted] reduction in the risk of relapse or death compared to the SoC group (stratified HR: [redacted]; 95% CI: [redacted]). Median RFS was [redacted] in the SoC group and was [redacted] in the blinatumomab group. The CS concludes that the RFS benefit of blinatumomab was robust, regardless of whether patients received alloSCT.

Table 13: RFS censored for alloSCT for MRD-negative patients, FAS (reproduced from CS, Table 13)

	Blinatumomab + SoC consolidation chemotherapy (N=112)	SoC consolidation chemotherapy (N=112)
Number of events, n (%)	[redacted]	[redacted]
Relapse	[redacted]	[redacted]
Death due to any cause	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Relapsed before start of RFS assessment	[redacted]	[redacted]
Completed study without event	[redacted]	[redacted]
Continued on study	[redacted]	[redacted]
Received alloSCT	[redacted]	[redacted]
Discontinued study	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Time to event (KM) (yrs)[a]		
Median (95% CI)	[redacted]	[redacted]
Treatment difference (stratified log-rank test)[b]		
Normal score	[redacted]	
p-value	[redacted]	
KM estimate, % (95% CI)		
0.5 yrs	[redacted]	[redacted]
1 yrs	[redacted]	[redacted]
2 yrs	[redacted]	[redacted]
3 yrs	[redacted]	[redacted]
4 yrs	[redacted]	[redacted]
5 yrs	[redacted]	[redacted]
6 yrs	[redacted]	[redacted]
7 yrs	[redacted]	[redacted]
Stratified HR[c,d] (95% CI)	[redacted]	
Time to censoring (KM) for RFS (yrs)[a,d]		
Median (95% CI)	[redacted]	[redacted]

Footnotes: [a] Years are calculated as days from randomisation date to event/censor date, divided by 365.25.
[b] 1-sided stratified log-rank test p-value is provided. The HR estimates are obtained from a stratified Cox regression model. An HR < 1.0 indicates a lower average death rate and a longer survival for patients in the blinatumomab plus SoC. consolidation chemotherapy arm relative to patients in the SoC consolidation chemotherapy arm
[c] Stratification factors: age (< 55 years vs. ≥ 55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), intent to receive allogeneic SCT (yes vs. no).
[d] Time to censoring, measured by reversing the status indicator for censored and events.

RFS - relapse-free survival; MRD - minimal residual disease; alloSCT - allogeneic stem cell transplant; FAS - Full Analysis Set; CI - confidence interval; HR - hazard ratio; KM - Kaplan-Meier; NE - not estimable; SoC - standard of care; yr - year
Source: Table 14-4.2.4. E1910 CSR[11]

Figure 7: Kaplan-Meier plot of OS censored at alloSCT for MRD-negative patients (reproduced from CS, Figure 9)

Footnotes: Censor indicated by vertical bar
OS - overall survival; MRD - minimal residual disease; alloSCT - allogeneic stem cell transplant; SoC - standard of care; CI - confidence interval
Source: Figure 14-4.2.3. E1910 CSR.[11]

4.3.5. *Additional sensitivity analysis: RFS and OS in people receiving pre-relapse alloSCT (FAS)*

As part of the clarification process[21] (question A8), the EAG requested that the company provide plots of RFS and OS, with time recentred at the time of receipt of transplant, for the subset of MRD-negative patients who received alloSCT in each treatment group at Step 3 in Study E1910.[11] For brevity, these analyses have not been reproduced here, but they can be found in the company's clarification response (question A8, Figures 2 and 3 and Tables 2 and 3). These plots suggest a positive trend for both RFS and OS for patients in the blinatumomab group over the SoC group. For both end points, the HR favoured blinatumomab but was not statistically significant (p>0.05). The company's clarification response states that: *"the favourable point estimate for the HR and separation of the KM curve suggests prior treatment with blinatumomab prior to receipt of pre-relapse alloSCT may be associated with a survival benefit."* However, the company's response also states that these results should be interpreted with caution due to the small sample size, the wide CIs and the lack of statistical significance.

4.3.6. *Subgroup analysis*

The results of subgroup analyses in Study E1910[11] were not provided in the CS,[1] but were later provided as part of the company's clarification response[21] (question A11). Pre-planned subgroups included: gender; race; ethnicity; age; CD20 status; rituximab use (yes vs no), and intent to transplant (yes vs no). Subgroup analyses on other prognostic factors or effect modifiers were not included in Study E1910.[11]

The results of the subgroup analyses for OS and RFS are presented in Table 14 and Table 15, respectively. Outcomes were generally consistent across subgroups, with a positive trend favouring the

blinatumomab group over the SoC group for most subgroups. For patients aged over ≥65 years, the HRs for RFS and OS favour the SoC arm. However, these findings should be interpreted with caution due to the small number of patients included in the subgroup.

Table 14: Subgroup analysis, OS, FAS (reproduced from company's clarification response, question A11)

	Blinatumomab + SoC consolidation chemotherapy (N=112) events/patients (%)	SoC consolidation chemotherapy (N=112) events/patients (%)	HR (95% CI)[a]	*p*-value[b]
Sex				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	
Race				
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	
Asian	[redacted]	[redacted]	[redacted]	
Black or African American	[redacted]	[redacted]	[redacted]	
Native Hawaiian or Other Pacific islander	[redacted]	[redacted]	[redacted]	
White	[redacted]	[redacted]	[redacted]	
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	
Ethnicity				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	
Age				
≥18 and <35 years	[redacted]	[redacted]	[redacted]	
≥35 and <55 years	[redacted]	[redacted]	[redacted]	
≥55 and <65 years	[redacted]	[redacted]	[redacted]	
≥65 years	[redacted]	[redacted]	[redacted]	
All patients	[redacted]	[redacted]	[redacted]	
CD20 status				
Positive	[redacted]	[redacted]	[redacted]	[redacted]

Negative	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Rituximab use				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Intent to receive allogenic SCT				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	

Footnotes: OS is calculated from time of Step 3 randomisation until death due to any cause. [a]The HR estimate for all patients was obtained from an un-stratified Cox regression model. [b]p-value is from the test of the interaction term in an un-stratified Cox regression model with terms for the subgroup and treatment group.
FAS - Full Analysis Set; HR - hazard ratio; OS - overall survival; SCT - stem cell transplant; SoC - standard of care
Source: Table 14-4.3 E1910. E1910 CSR.[11]

Table 15: Subgroup analysis, RFS, FAS (reproduced from company's clarification response, question A8)

	Blinatumomab + SoC consolidation chemotherapy (N=112) events/patients (%)	**SoC consolidation chemotherapy (N=112) events/patients (%)**	**HR (95% CI)[a]**	***p*-value[b]**
Sex				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	
Race				
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	
Asian	[redacted]	[redacted]	[redacted]	
Black or African American	[redacted]	[redacted]	[redacted]	
Native Hawaiian or Other Pacific islander	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	
Ethnic				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	
Not Reported	[redacted]	[redacted]	[redacted]	

Age				
≥18 and <35 years	[redacted]	[redacted]	[redacted]	
≥35 and <55 years	[redacted]	[redacted]	[redacted]	
≥55 and <65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	
All patients	[redacted]	[redacted]	[redacted]	
CD20 status				
Positive	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Rituximab use				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	
Not collected	[redacted]	[redacted]	[redacted]	
Intent to receive allogenic SCT				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	

Footnotes: RFS is calculated from time of Step 3 randomisation until death due to any cause. [a]The HR estimate for all patients was obtained from an un-stratified Cox regression model. [b]p-value is from the test of the interaction term in an un-stratified Cox regression model with terms for the subgroup and treatment group.
FAS - Full Analysis Set; HR - hazard ratio; RFS - relapse-free survival; SCT - stem cell transplant; SoC - standard of care
Table 14-4.4 E1910. E1910 CSR.[11]

Health-related quality of life

HRQoL data were not collected in Study E1910.[11]

4.4. Safety of blinatumomab

4.4.1. *Studies providing safety data on blinatumomab*

Section B.2.9 of the CS[1] presents safety data from Study E1910[11] based on the SAS population. The SAS population included all patients in the FAS who received at least one dose of protocol-specified therapies. The SAS population included [redacted] of [redacted] patients randomised to blinatumomab ([redacted]) and all patients randomised to SoC (i.e., a total of [redacted] of 224 randomised patients).

4.4.2. *Summary of safety data in Study E1910*

A summary of safety data is provided in Table 16, including additional information provided in the company's clarification response[21] (question A13).

The overall frequencies of treatment-emergent adverse events (TEAEs) (any grade) and Grade ≥3 TEAEs were similar for the blinatumomab and SoC groups ([redacted] and [redacted], respectively). The frequency of Grade ≥4 TEAEs was slightly higher for SoC than blinatumomab group ([redacted]). There were [redacted] fatal TEAEs in the blinatumomab group and [redacted] in the SoC group.

Data on AEs leading to dose reductions, interruptions, or treatment discontinuations for patients in the blinatumomab group were provided in the company's clarification response[21] (question A13). The company's response states that it was not possible to concisely report these data for the SoC group as multiple different chemotherapy components would lead to varying dose reductions, interruptions, or treatment discontinuations. In total, [redacted] patients discontinued blinatumomab plus SoC consolidation therapy due to AEs and [redacted] patients discontinued SoC treatment due to AEs.

Table 16: Summary of TEAEs in E1910, SAS (reproduced from CS, Tables 14 and 15)

	Blinatumomab + SoC consolidation chemotherapy ( )	**SoC consolidation chemotherapy ( )**	**Overall ( )**
All Step 3 TEAE, n (%)			
Expedited events*			
Grade ⩾3			
Grade ⩾4			
Fatal			
System organ class PT, n (%)			
Number of patients reporting Step 3 TEAEs			
Blood and lymphatic system disorders			
Anaemia			
Gastrointestinal disorders			
Vomiting			
Diarrhoea			
Investigations			
Neutrophil count decreased			
Platelet count decreased			
White blood cell count decreased			
Lymphocyte count decreased			
Nervous system disorders			
Headache			

PT - preferred term; SAS - Safety Analysis Set; SoC - standard of care; TEAE - treatment-emergent adverse event
Source: Table 14-6.6.1 and Table 14-6.6.2. E1910 CSR[11]
** The Study E1910 protocol states that in addition to routine reporting, certain AEs must be reported in an expedited manner via the Cancer Therapy Evaluation Program Adverse Events Reporting System (CTEP-AERS) for timelier monitoring of patient safety and care.*

4.4.3. *Fatal AEs*

Fatal AEs were reported for : of sepsis and of intracranial haemorrhage. In the SoC group, fatal AEs were reported for (sepsis) (see Table 16).

4.4.4. *AEs by type*

Table 16 summarises TEAEs by system organ class and preferred term (PT) (in ≥30% of patients) observed in Study E1910.[11] The most common TEAEs (≥30%) in the blinatumomab group (vs SoC) were: neutrophil count decreased ([redacted]); platelet count decreased ([redacted]); anaemia ([redacted]); white blood cell count decreased ([redacted]); headache ([redacted]); lymphocyte count decreased ([redacted]); vomiting ([redacted]) and diarrhoea ([redacted]). The grading (severity) of these AEs was not specified in the CS.[1]

4.4.5. *Grade 3 and 4 AEs*

Table 17 summarises Grade ≥3 TEAEs reported for ≥5% of patients in either treatment group in Study E1910.[11] The most frequent Grade ≥3 TEAEs in the blinatumomab group (vs SoC) were: neutrophil count decreased ([redacted]); platelet count decreased ([redacted]); white blood cell count decreased ([redacted]); lymphocyte count decreased ([redacted]); anaemia ([redacted]) and febrile neutropenia ([redacted]). Grade ≥3 aphasia and psychiatric disorders were considerably increased ([redacted] vs [redacted] and [redacted] vs [redacted], respectively) and sepsis was slightly higher ([redacted]) in the blinatumomab group than the SoC group.

Table 17: Grade ≥3 TEAEs by system organ class and preferred term reported in ≥5% of patients within any treatment category, SAS (reproduced from CS, Table 16)

System organ class preferred term, n (%)	**Blinatumomab + SoC consolidation chemotherapy ([redacted])**	**SoC consolidation chemotherapy ([redacted])**	**Overall ([redacted])**
Number of patients reporting grade 3 and above Step 3 TEAEs	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]

System organ class preferred term, n (%)	Blinatumomab + SoC consolidation chemotherapy ( )	SoC consolidation chemotherapy ( )	Overall ( )
Platelet count decreased			
White blood cell count decreased			
Lymphocyte count decreased			
Alanine aminotransferase increased			
Aspartate aminotransferase increased			
Metabolism and nutrition disorders			
Hyperglycaemia			
Hypertriglyceridaemia			
Musculoskeletal and connective tissue disorders			
Nervous system disorders			
Headache			
Syncope			
Aphasia			
Psychiatric disorders			
Respiratory, thoracic and mediastinal disorders			
Vascular disorders			
Hypertension			
Hypotension			

PT - preferred term; SAS - Safety Analysis Set; SoC - standard of care; TEAE - treatment-emergent adverse event
Source: Table 14-6.6.4. E1910 CSR[11]

4.4.6. *AEs of special interest*

TEAEs of special interest are shown in Table 18. The number of TEAEs of special interest was significantly higher in the blinatumomab group than the SoC group ( ). CRS occurred in of patients in the blinatumomab group, of which patients experienced a Grade ≥3 event. .

Neurologic events were more commonly reported in the blinatumomab group than the SoC group ( ). The number of patients experiencing Grade ≥3 neurologic events was also higher in the blinatumomab group than the SoC group ( ). The most frequently reported neurologic events (in ≥10% of patients) in the blinatumomab group were headache ( ), and tremor ( ).

Table 18: TEAEs of interest by event of interest category and preferred terms, SAS (reproduced from CS, Table 17)

Event of interest category, preferred terms, n (%)	Blinatumomab + SoC consolidation chemotherapy ([redacted])	SoC consolidation chemotherapy ([redacted])	Overall ([redacted])
Number of patients reporting Step 3 treatment-emergent adverse EOI (on protocol)	[redacted]	[redacted]	[redacted]
Cytokine release syndrome (Narrow)	[redacted]	[redacted]	[redacted]
Cytokine release syndrome	[redacted]	[redacted]	[redacted]
Medication errors (Broad)	[redacted]	[redacted]	[redacted]
Device malfunction	[redacted]	[redacted]	[redacted]
Neurologic events (Narrow)	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]
Ataxia	[redacted]	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]	[redacted]
Disturbance in attention	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]
Depressed level of consciousness	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]	[redacted]
Hypoesthesia	[redacted]	[redacted]	[redacted]
Mental status changes	[redacted]	[redacted]	[redacted]
Neurotoxicity	[redacted]	[redacted]	[redacted]
Memory impairment	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]	[redacted]
Seizure	[redacted]	[redacted]	[redacted]
Tinnitus	[redacted]	[redacted]	[redacted]

Event of interest category, preferred terms, n (%)	Blinatumomab + SoC consolidation chemotherapy ([redacted])	SoC consolidation chemotherapy ([redacted])	Overall ([redacted])
Agitation	[redacted]	[redacted]	[redacted]
Amnesia	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]
Failure to thrive	[redacted]	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]	[redacted]
Lethargy	[redacted]	[redacted]	[redacted]
Oral dysaesthesia	[redacted]	[redacted]	[redacted]
Sleep apnoea syndrome	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]
Trismus	[redacted]	[redacted]	[redacted]

EOI - event of interest; SAS - Safety Analysis Set; SoC - standard of care: TEAE - treatment-emergent adverse event
Source: Table 14-6.6.8 E1910 CSR[11]

4.4.7. *Anti-blinatumomab antibody assays*

All enrolled patients who received at least one dose of blinatumomab on-protocol were included in the analysis; patients who received blinatumomab off-protocol were excluded. [redacted] patients who provided informed consent for the testing of blinatumomab immunogenicity were included in the blinatumomab immunogenicity analysis. No patients developed anti-blinatumomab antibodies.

4.5. Ongoing studies

In addition to Study E1910,[11] there is one ongoing Phase III RCT which is assessing the comparative efficacy of blinatumomab alternating with low-intensity chemotherapy versus SoC for older adults with Ph-negative precursor B-cell ALL (Golden Gate - NCT04994717).[28] The CS[1] states that no results are currently available from this study; the results of the primary analysis are anticipated to become available in [redacted]. The EAG's clinical advisors were also unaware of any other trials in this area.

4.6. Meta-analysis

Meta-analysis was not conducted as only one relevant RCT (Study E1910[11]) was identified for inclusion in the company's SLR. The EAG agrees that meta-analysis is not required.

4.7. Indirect comparison and/or mixed treatment comparison

The CS[1] states that no indirect or mixed treatment comparison was conducted since only one study (Study E1910[11]) was identified in the SLR as being relevant to the submission, and this study included the only comparator of interest (SoC consolidation chemotherapy).

4.8. Additional work on clinical effectiveness undertaken by the EAG

The EAG did not undertake additional analyses of the clinical effectiveness data.

4.9. Conclusions of the clinical effectiveness section

Methods of systematic review: The EAG considers the company's systematic review methods to be of a good standard.

Clinical evidence: The CS[1] presents data from the E1910 RCT[11] of blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy alone in 224 adult patients with CD19-positive Ph-negative MRD-negative B-cell precursor ALL. The population addressed in the CS is in line with the available clinical evidence from Study E1910, but it is narrower than the final NICE scope[20] because the trial included adult patients aged ≥30 years only. The CS states that the existing marketing authorisation for blinatumomab is expected to be extended to include a broader population of adults with ALL (an age cut-off is not specified). The EAG's clinical advisors considered Study E1910 to be some extent representative of UK clinical practice but noted differences in terms of age and race. However, they considered the outcomes that were seen in Study E1910 would be expected to be seen in UK clinical practice. They also stated that they would expect blinatumomab to also be an effective treatment in younger adult patients who are under 30 years of age.

At the June 2023 DCO, significant reductions in the hazards of death (OS: HR 0.44%; 95% CI 0.25, 0.76, *p*=0.001) and relapse or death (RFS: HR 0.53%; 95% CI 0.32, 0.88, *p*=0.006) were observed in the blinatumomab group compared to the SoC group. Median OS and RFS were not reached in either treatment group. HRQoL data were not collected in the Study E1910. The most common Grade 3 or 4 TEAEs in the blinatumomab group were: neutrophil count decreased ([redacted]); platelet count decreased ([redacted]); white blood cell count decreased ([redacted]); lymphocyte count decreased ([redacted]); anaemia ([redacted]) and febrile neutropenia ([redacted]). TEAEs of special interest included CRS ([redacted]) and neurologic events; most commonly headache ([redacted]), and tremor ([redacted]) in the blinatumomab vs SoC groups, respectively.

5. COST EFFECTIVENESS

5.1. Critique of the company's review of existing economic analyses

5.1.1. *Summary and critique of the company's searches*

The company undertook an SLR of: (i) published cost-effectiveness studies of patients with Ph-negative B-cell ALL; (ii) HRQoL studies and (iii) cost and resource use studies (described in CS Appendices G, H and I, respectively).[23] The company undertook a three-in-one search to identify evidence for all three study types. The company performed an initial SLR in September 2023, followed by an update review in April 2024.

The company searched all relevant electronic bibliographic databases in September 2023. These included: MEDLINE (all segments, via Ovid), EMBASE (via Ovid), CDSR (via Ovid), DARE (via Ovid), the Cochrane Central Register of Controlled Trials (via Ovid), CENTRAL (via Ovid), the NHS Economic Evaluation Database (NHS EED) (via Ovid), HTA (via Ovid), the ACP Journal Club (via Ovid), and EconLit (via Ovid). In April 2024, the company also searched several key conference abstract websites since 2018, including: ASCO; ASH: EBMT; EHA; ESMO; The Professional Society for Health Economics and Outcomes Research (ISPOR); NOPHO; SIOP and SITC. In addition, the company hand searched treatment guidelines in eleven countries, the NCCN and NICE, as well as government bodies and other relevant reports relating to burden of disease.

The EAG considers company's searches to be appropriate. The EAG notes that the free-text search terms applied in the economics search filter could have been broadened by searching for "cost*", "pharmacoeconomic*" and "economic*" alone, rather than applying a proximity operator, although the impact on finding relevant studies may be inconsequential. The EAG considers the company's searches for HRQoL and cost and resource use studies to be comprehensive and free from errors. The company's searches are fully reported, and the EAG believes that relevant economic studies are unlikely to have been missed.

5.1.2. *Summary and critique of the company's review of existing economic evaluations*

The inclusion criteria for the company's review of existing economic evaluations are reported in Table 18 of CS Appendix G.[23] Studies were eligible for inclusion in the review if the population included in the analysis related to patients with newly diagnosed Ph-negative B-cell ALL and if the intervention and comparators included pharmacologic first-line therapy including induction, consolidation and maintenance treatment. The inclusion criteria state that any study type was includable, including economic models and evaluations. SLRs, meta-analyses and indirect treatment comparisons (ITCs) were also listed as includable study types, although the reasons for including ITCs are unclear. Relevant outcomes included medical costs (direct/indirect), resource use, incremental cost-effectiveness ratios (ICERs), budget impact estimates and health state utility values. Full texts published from 2012 onwards

and conference abstracts published from 2018 onwards were eligible for inclusion. General reviews, editorials, letters, case series, case reports and animal and *in vitro* studies were excluded, as were studies not published in the English language.

The company's original search identified 1,010 studies and the SLR update identified a further 723 studies. Of these 1,733 studies, a total of six publications met the review inclusion criteria. Three of the included studies were economic evaluations.[59-61] The company's clarification response[21] (question B2) explains that the remaining three studies[62-64] were not included because they reported only costs or utility values. The characteristics of the three included economic evaluations are summarised in Table 19.

Only one of the three included economic evaluations was reported in full text format (Nam *et al.*[59]); the other two studies[60, 61] were published as abstracts and the reporting of the methods used was limited. Nam *et al.*[59] was undertaken in a Canadian setting, whilst the other two studies[60, 61] were US-based. All three studies adopted a health care payer perspective. Two of the analyses adopted a lifetime horizon, whilst the third study did not report the time horizon used. The populations included in all three studies related to adults with Ph-negative B-cell ALL. The two US studies[60, 61] reflected patients who were MRD-positive in CR; information about MRD status is not reported in Nam *et al*.[59] Interventions and comparators included rituximab, blinatumomab and SoC chemotherapy. All three studies were model-based analyses. The modelling approaches adopted differed between the studies: Nam *et al.*[59] used a state transition approach; Delea *et al.*[60] used a partitioned survival model, and Delea *et al.*[61] used both partitioned survival and state transition modelling approaches. Two of the studies explicitly mentioned how cure was modelled: Nam *et al.*[59] assumed a fixed time point for cure for patients who remained event-free at 60 months, whereas Delea *et al.*[60] used mixture-cure models (MCMs) to estimate OS. It is unclear whether the other study by Delea *et al.*[61] included the possibility of cure, and if so, how this was reflected in the modelling analyses.

The CS[1] explains that these three studies[59-61] were included in the review of published economic evaluations, but does not provide any further information about their design or whether or how they were used to inform the current model of blinatumomab for patients with Ph-negative B-cell ALL which is MRD-negative. In response to a request for clarification by the EAG[21] (question B1), the company stated that these three existing economic evaluation studies were not considered relevant to the decision problem for the current appraisal because they adopted an irrelevant perspective (US/Canadian payer) and so a *de novo* model was developed instead. The EAG notes that because none of the included studies relate to the population under consideration in the current appraisal, their relevance is limited.

Table 19: Summary of economic evaluations included in the company's review

Study	Publication type	Setting	Perspective	Time horizon	Population	Intervention / comparators	Analysis type	Model type	Cure assumptions
Nam *et al.* (2018)[59]	Full text	Canada	Payer	Lifetime (60 years)	Adults with Ph-negative, CD20+, B-cell ALL	SoC (Hyper-CVAD or DFCI) +/- rituximab	Cost-utility analysis	State transition model	Cure time point of 60 months in EFS state
Delea *et al.* (2018)[60]	Abstract	US	Payer	Lifetime (50 years)	Adults with Ph-negative, B-cell ALL, MRD-positive in CR	Blinatumomab vs SoC maintenance chemotherapy	Cost-utility analysis	Partitioned survival model	Mixture-cure models used for OS (but not RFS)
Delea *et al.* (2020)[61]	Abstract	US	Payer	Not reported	Adults with Ph-negative, B-cell ALL, MRD-positive in CR	Blinatumomab vs SoC chemotherapy	Cost-utility analysis	Partitioned survival and Markov cohort model	Not reported

SoC - standard of care; DFCI - Dana-Farber Cancer Institute; hyper-CVAD - hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; Ph - Philadelphia chromosome; MRD - minimal residual disease; ALL - acute lymphoblastic leukaemia; RFS - relapse-free survival; EFS - event-free survival; OS - overall survival

5.2. Summary of the company's original submitted economic analysis

5.2.1. *Scope of the company's economic analyses*

As part of their submission to NICE,[1] the company submitted an executable health economic model programmed in Microsoft Excel.® The scope of the company's economic analysis is summarised in Table 20. Following the clarification round, the company submitted an updated version of the model which included the correction of several minor errors; this updated model and its results are summarised separately in Section 5.4.

Table 20: Scope of the company's economic analysis

Population	Adult patients with CD19-positive, Ph-negative, precursor B-cell ALL that is MRD-negative at the start of the consolidation phase (after induction and intensification chemotherapy)
Time horizon	50 years (lifetime)
Intervention	Blinatumomab plus SoC consolidation chemotherapy
Comparator	SoC consolidation chemotherapy alone
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2022/23

Ph - Philadelphia-chromosome; ALL - acute lymphoblastic leukaemia; MRD - minimal residual disease; SoC - standard of care; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

The company's economic model assesses the incremental cost-effectiveness of blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy alone for the treatment of adult patients with CD19-positive Ph-negative precursor B-cell ALL that is MRD-negative at the start of the consolidation phase (after induction and intensification chemotherapy). Cost-effectiveness is assessed in terms of the incremental cost per quality-adjusted life year (QALY) gained from the perspective of NHS and Personal Social Services (PSS) over a 50-year (lifetime) horizon.

Population

The company's economic analysis is intended to reflect the population of adult patients with CD19-positive Ph-negative precursor B-cell ALL that is MRD-negative at the start of the consolidation phase (after induction and intensification chemotherapy). Patient characteristics are based on patients who were assessed as being MRD-negative centrally after induction and intensification therapy (at Step 3) in Study E1910.[11] At model entry, patients are assumed to be 50.1 years of age and 50.4% are assumed to be female. The patient population is expected to be fully covered by the anticipated marketing authorisation for blinatumomab for B-cell ALL which is expected to be extended between October and November 2024 to include adult patients with CD19-positive Ph-chromosome negative B-cell precursor ALL in the frontline consolidation phase, regardless of MRD status.[1]

Intervention

The intervention included in the company's economic analysis is blinatumomab in combination with SoC consolidation chemotherapy. This is in line with the final NICE scope.[20]

The treatment schedule for the intervention group is based on the design of Study E1910[11] and involves two consecutive cycles of blinatumomab administered as a continuous intravenous (IV) infusion at a dose of 28μg/day for 28 days, followed by a 14-day infusion-free interval in each cycle, followed by three consecutive cycles of consolidation chemotherapy, followed by alternating cycles of blinatumomab and standard consolidation chemotherapy for a further 3 cycles. In total, patients assigned to Arm C received 4 cycles of blinatumomab and 4 cycles of consolidation chemotherapy. The consolidation chemotherapy regimen included in the economic analysis follows the modified UKALLXII/ECOG E2993 protocol followed in Study E1910.[12] As noted in Section 2.2, clinical experts consulted by the company suggested that this regimen is very similar to the UKALL14 protocol.[10, 13] The EAG's clinical advisors agreed with this view.

Comparator

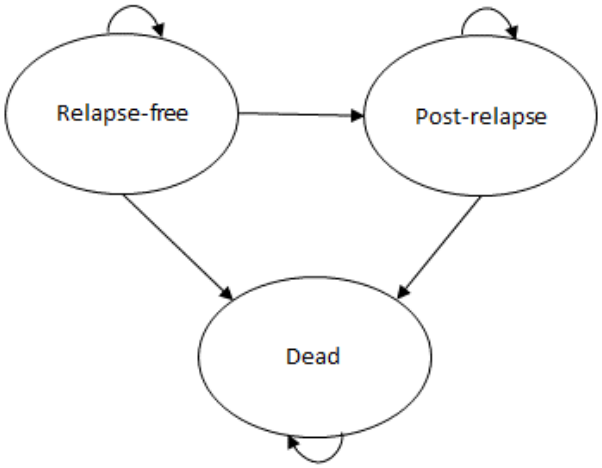
The company's economic analysis includes a single comparator: SoC consolidation chemotherapy. As with the intervention group, SoC consolidation chemotherapy is based on the modified UKALL XII/ECOG E2993 protocol.[12] Patients received 4 cycles of consolidation chemotherapy. Details of the drugs and dosing schedules are described in Section 2.2.

AlloSCT is not included as a comparator in the company's economic model. However, alloSCT is included as part of the pathway in both treatment groups and may be given before and/or after relapse. The CS[1] states that the UK clinical advisors that they consulted stated that alloSCT is typically reserved for high-risk patients (e.g., those with adverse cytogenetics), subject to the availability of a suitable donor, and that it is used prior to the consolidation phase.[13] Therefore, alloSCT would not be displaced by the availability of blinatumomab. The EAG's clinical advisors agreed with this view. As such, the EAG is satisfied that alloSCT should not be considered as a relevant comparator within this appraisal.

5.2.2. *Model structure and logic*

The company's economic model adopts a partitioned survival approach, including three mutually exclusive health states: (i) relapse-free; (ii) post-relapse and (iii) dead (see Figure 8).

Figure 8: Company's model structure



The model logic operates as follows. Patients enter the model in the relapse-free state and are treated with either blinatumomab plus SoC consolidation chemotherapy or SoC consolidation chemotherapy alone. At any time *t*, health state occupancy is determined by the cumulative probabilities of RFS and OS, whereby: the probability of being alive and relapse-free is given by the cumulative probability of RFS; the probability of being alive following relapse is estimated by the cumulative probability of OS minus the cumulative probability of RFS, and the probability of being dead is calculated as one minus the cumulative probability of OS. The company's base case model does not include half-cycle correction, although the functionality to apply half-cycle correction is available in the executable model settings. A proportion of patients are assumed to receive alloSCT in the relapse-free and post-relapse states. The probability of receiving alloSCT differs between the treatment groups and between the health states and is informed by Study E1910.[11] Following the consolidation therapy phase, patients who remain relapse-free are assumed to go on to receive maintenance chemotherapy (up to a maximum treatment time of 2.5 years from the start of consolidation therapy). All patients who relapse after consolidation or maintenance chemotherapy within the first 5 years of the model time horizon are assumed to receive subsequent-line therapy for relapsed disease.

The cumulative probabilities of RFS and OS for patients receiving either blinatumomab plus SoC consolidation chemotherapy or SoC consolidation chemotherapy alone are modelled using MCMs fitted to time-to-event data on RFS and OS from Study E1910[11] (DCO June 2023). The economic model includes two structural constraints: (i) the per-cycle risk of death in the modelled ALL population cannot be lower than that of the standardised mortality ratio (SMR)-uplifted age-and sex-matched general population (based on Office for National Statistics [ONS] general population life tables[65]), and (ii) the cumulative probability of RFS cannot be higher than the cumulative probability of OS at any timepoint. The EAG notes that the first of these constraints is subject to a minor error as it is only applied to the cured group of the MCM, rather than both the cured and uncured groups (see Section 5.3.5).

HRQoL is assumed to be determined primarily by the presence or absence of relapse and the modelled cure assumptions. As HRQoL data were not collected in Study E1910,[11] the utility value for the relapse-free state is based on Euroqol 5-Dimensions (EQ-5D) data for MRD-responders in the BLAST study[29] (blinatumomab for adults with Ph-negative MRD-positive B-ALL in CR) whilst the utility value for post-relapse state is informed by mapped EQ-5D data for the SoC salvage chemotherapy group from the TOWER study[66] (blinatumomab versus chemotherapy for adults with R/R Ph-negative B-ALL). These utility values align with the values used in TA589[15] (blinatumomab for treating ALL in remission with MRD activity). The model assumes that patients who remain relapse-free after 5 years are no longer at risk of ALL-related disutility and therefore age-and sex-matched general population utilities are applied beyond this time point. Utility values are adjusted for increasing age. The model also includes QALY losses for patients who experience Grade ≥3 TEAEs during consolidation therapy, for patients who undergo alloSCT, for patients who are currently receiving blinatumomab consolidation therapy in a given model cycle, and for patients who are within 6 months of death. QALY losses resulting from short-term AEs are applied in the first 1-week model cycle. QALY losses associated with alloSCT are applied as one-off decrements in the first weekly model cycle for patients undergoing alloSCT prior to relapse and to all new patients undergoing alloSCT after relapse within the first 5 years of model entry. QALY losses for patients who are close to death are applied in every model cycle during the first 5 years of the time horizon.

The company's model includes costs associated with: (i) consolidation therapy; (ii) maintenance therapy; (iii) alloSCT (pre- and post-relapse); (iv) the management of AEs; (v) subsequent-line therapy and (vi) terminal care. The model includes an assumption that patients who remain relapse-free after 5 years no longer incur any treatment-related costs or terminal care costs (although the model predicts that some relapses still occur after this time point). The model does not include any additional drug treatments after second relapse. In addition, the model does not include any health care resource use (HCRU) relating to regular clinic visits or tests for monitoring in either treatment group.

The incremental health gains, costs and cost-effectiveness of blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy alone are estimated over a 50-year time horizon using a weekly cycle duration. No economic subgroup analyses are presented in the CS.[1]

5.2.3. *Key assumptions employed in the company's model*

The company's economic model employs the following key assumptions:

- The modelled population is 50.1 years of age at model entry, and 50.4% of patients are female.
- SoC consolidation chemotherapy is the only comparator for blinatumomab plus SoC consolidation chemotherapy. AlloSCT is included as part of the treatment pathway but is not included as a comparator.

- RFS and OS are modelled using log-normal MCMs and Weibull MCMs, respectively, which have been fitted to data from each arm in Study E1910.[11]
- Modelled RFS and OS probabilities are structurally unrelated to the receipt of alloSCT, either before or after relapse.
- The model includes two structural constraints: (i) the per-cycle risk of death in the target population cannot be lower than that of the SMR-uplifted age-and sex-matched general population, and (ii) the cumulative probability of RFS cannot be higher than that of OS at any timepoint. Given the use of partitioned survival approach, the risks of relapse and death are structurally unrelated.
- HRQoL is determined primarily by the presence or absence of disease relapse and modelled cure assumptions. The same utility values are applied in each treatment group. The utility value for the relapse-free state is higher than the utility value for the post-relapse state. Utility values are adjusted for increasing age. Patients who remain relapse-free beyond 5 years and who are cured (according to the MCM) have an equivalent level of HRQoL as the age-and sex-matched general population.
- Further QALY losses are included for patients who are receiving blinatumomab in a given model cycle, for patients who undergo alloSCT, for patients who experience Grade ≥3 TEAEs and for patients who are within 6 months of death (applied to patients who die within 5 years of model entry).
- The model includes costs associated with Grade ≥3 TEAEs during the consolidation therapy phase. AEs related to subsequent-line therapies for R/R ALL are not included.
- Patients who relapse are assumed to receive one subsequent line of active drug therapy (fludarabine, cytarabine, G-CSF and idarubicin [FLAG-IDA], inotuzumab ozogamicin or blinatumomab). Amongst patients in the blinatumomab plus SoC group who relapse, [redacted] receive inotuzumab ozogamicin and [redacted] receive salvage chemotherapy using FLAG-IDA as subsequent therapy. Amongst patients in the SoC consolidation chemotherapy group who relapse, [redacted] receive blinatumomab, [redacted] receive inotuzumab ozogamicin and [redacted] receive FLAG-IDA as subsequent therapy. Retreatment with blinatumomab is not included in the model.
- Only patients who relapse within the first 5 years incur subsequent-line therapy costs including post-relapse alloSCT costs, and only those who die within the first 5 years incur terminal care costs.

5.2.4. *Evidence used to inform the company's model parameters*

Table 21 summarises the evidence sources used to inform the model parameter values. The evidence sources and the derivation of the parameter values are described in detail in the subsequent sections.

Table 21: Summary of evidence used to inform the company's base case model

Parameter group	Source
Patient charcteristics (age, BSA, weight)	Study E1910[11]
RFS, blinatumomab+SoC	Log-normal MCM fitted to RFS data for blinatumomab+SoC arm of Study E1910[11]
RFS, SoC	Log-normal MCM fitted to RFS data for SoC arm of Study E1910[11]
OS, blinatumomab+SoC	Weibull MCM fitted to OS data for blinatumomab+SoC arm of Study E1910[11]
OS, SoC	Weibull MCM fitted to OS data for SoC arm of Study E1910[11]
General population mortality risk	General population life tables for the UK, 2017-2019[65]
SMR for ALL	Assumed to be 1.09, based on Maurer *et al.*[67]
AE frequency	Grade ≥3 TEAEs from Study E1910[11]
Probability of receiving alloSCT pre-/post-relapse	Based on data from Study E1910[11]
Health state utility values	Relapse-free utility value based on EQ-5D estimates for MRD-responders based on data from the BLAST study.[29] Post-relapse utility value based on EORTC QLQ C30 data mapped to the EQ-5D, with matching between patients in TOWER[66] and BLAST.[29] Post-alloSCT utility value taken from Sung *et al.*[68] Terminal care disutility taken from BLAST.[29]
AE disutility values	Literature, previous NICE TAs and assumptions[69-77]
General population utility	Hernández Alava *et al.*[78]
Consolidation therapy drug acquisition costs	Treatment schedule and proportion starting each cycle of therapy based on Study E1910.[11] Drug prices taken from eMIT[79] and BNF.[80] PAS provided by the company.[1] Wastage assumptions based on patient BSA/weight in Study E1910[11]
Drug administration costs (consolidation, maintenance and subsequent therapy)	NHS Reference Costs 2021/22[81]
Maintenance therapy acquisition costs	Treatment schedule based on Study E1910.[11] Drug prices taken from eMIT[79] and BNF.[80]
AlloSCT cost	Costs of stem cell harvesting and alloSCT procedure taken from NHS Reference Costs 2021/22.[81] Follow-up costs taken from UK Stem Cell Strategy Oversight Committee report.[82]
AE management costs	NHS Reference Costs 2021/22[81] and Jones *et al.*[83]
Subsequent-line therapy use and costs	Usage of therapies informed by clinical input.[84] No. of cycles of blinatumomab and inotuzumab ozogamicin informed by TOWER,[85] and TA541.[17] FLAG-IDA inpatient duration informed by TA893[18] and TA450.[16] Unit costs taken from NHS Reference Costs 2021/22,[81] eMIT,[79] BNF[80] and MIMS.[86]
Terminal care costs	NHS Reference Costs 2021/22[81]

BSA - body surface area; RFS - relapse-free survival; OS - overall survvial; SoC - standard of care; alloSCT - allogeneic stem cell transplant; AE - adverse event; TEAE - treatment-emergent adverse event; MCM - mixture-cure model; NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; FLAG-IDA - fludarabine, cytarabine, idarubicin and G-CSF; PAS - Patient Access Scheme; eMIT - electronic Market Information Tool; BNF - British National Formulary; MIMS - Monthly Index of Medical Specialities

Patient characteristics

Patient characteristics are based on the population of patients who were assessed as being MRD-negative at randomisation at Step 3 in Study E1910 (N=224).[11] At model entry, patients are assumed to have a mean age of 50.1 years and 50.4% of patients are assumed to be female. These characteristics

are used to estimate general population mortality risks and to adjust health state utility values for increasing age. Body surface area (BSA) and body weight are assumed to be 2.0m^2 and 86.6kg, respectively; these parameters are used to estimate treatment dosages and associated costs.

Time-to-event inputs - RFS and OS

The company fitted MCMs to the available data on OS and RFS data from Study E1910.[11] The data used in the analysis do not include censoring for alloSCT (see clarification response,[21] question B4). Model fitting was conducted for the blinatumomab plus SoC and SoC groups separately. MCMs assume that the population consists of two discrete patient groups: (i) a cured group that will not relapse or die from the disease, and (ii) an uncured group that follows a standard parametric survival trajectory.[87] The proportion of patients who are cured is determined by the cure fraction, which is estimated through the model fitting procedure. The company also fitted standard parametric survival models to the RFS and OS data from Study E1910, including exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma distributions. These standard survival analyses are not presented in CS,[1] although the survivor functions for the standard log-normal distribution are considered in the company's scenario analyses (see Section 5.2.6).

The CS[1] states that the company's model selection process included: (i) consideration of the clinical plausibility of the survival model predictions, (ii) visual inspection of the fitted survival models against the observed Kaplan-Meier survival functions and hazard plots, (iii) examination of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics based on summed values for both treatment groups for each end point and (iv) the use of the same distribution across both arms for the same end point.

The company held a clinical validation meeting in December 2023[88] with the intention of obtaining clinical guidance on the survival inputs. Two clinical experts attended the meeting via a teleconference. The experts commented that blinatumomab-treated patients appeared to be cured after three years based on the data presented from Study E1910.[11] During the meeting, the experts were also asked if the estimates from the Gompertz MCM aligned with their long-term expectations of RFS. The experts agreed with using similar analyses for RFS in both treatment groups and commented that there is little significant variation between different models of RFS. The clinical experts agreed with the use of the Gompertz MCM for OS.

Subsequently, the company held a second validation meeting with one expert in May 2024[88] to obtain clinical input on the selection of an alternative MCM, as the previously selected Gompertz MCM generated an unstable cure fraction in the probabilistic sensitivity analysis (PSA). For RFS, the clinical expert was shown the extrapolated curves and estimated cure fractions from the previously selected Gompertz MCM and the newly selected log-normal MCM, followed by the extrapolated curves and

predicted probabilities of RFS at 5, 10, 15, 20 and 30 years for the exponential, gamma, Gompertz and log-normal MCMs. The clinical expert supported the use of the log-normal MCM and stated that the long-term extrapolation in the SoC group may be optimistic. For OS, the clinical expert was shown the extrapolated survival model predictions and estimated cure fractions from the previously selected Gompertz MCM and the newly selected Weibull MCM, followed by the extrapolated curves and predicted probabilities of OS at 5, 10, 15, 20 and 30 years for the gamma, Gompertz, log-logistic and Weibull MCMs. The clinical expert supported the use of the Weibull MCM and commented that the long-term extrapolation in the SoC group may be optimistic.

RFS

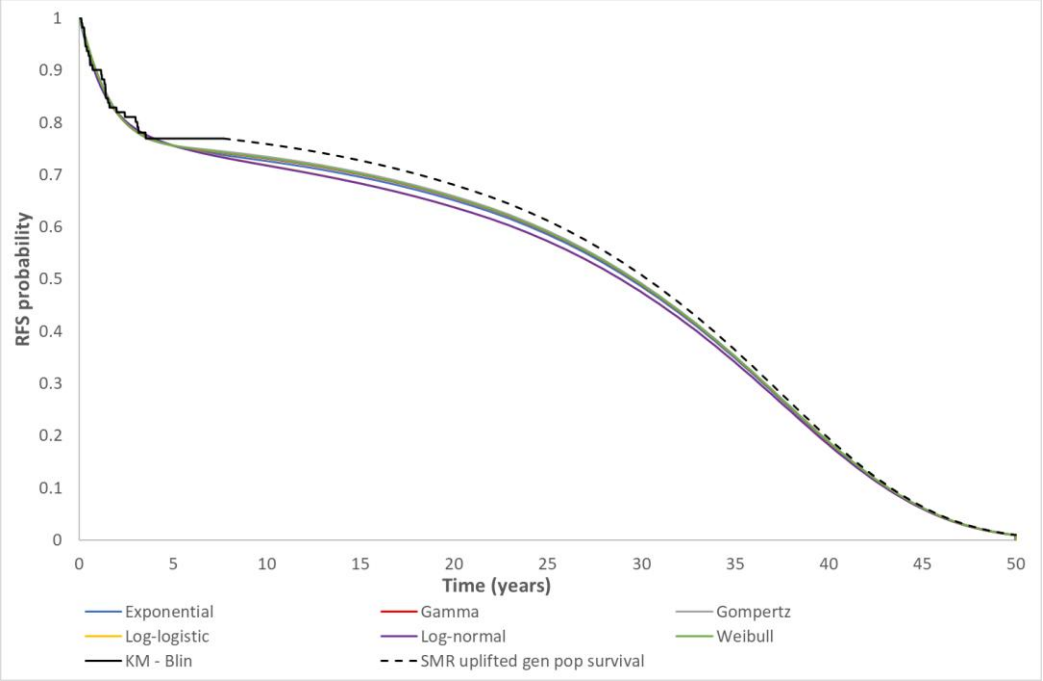
RFS was estimated separately for the blinatumomab plus SoC and SoC groups using individual patient data (IPD) from Study E1910.[11] The AIC and BIC values from the fitted MCMs for each treatment group are shown in Table 22. Comparisons of observed and predicted RFS using MCMs for the blinatumomab plus SoC and SoC groups are presented in Figure 9 and Figure 10, respectively. Empirical hazard plots and hazard plots from the fitted MCMs are presented for the blinatumomab plus SoC and SoC groups in Figure 11 and Figure 12, respectively. Estimated cure fractions from the MCMs are presented in Table 23.

Table 22: AIC and BIC statistics for MCMs of RFS

MCM	Blinatumomab plus SoC		SoC	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	306.9 (1)	312.3 (1)	478.0 (2)	483.4 (1)
Generalised gamma	309.5 (7)	320.4 (7)	478.3 (4)	489.2 (7)
Gompertz	308.4 (5)	316.6 (5)	479.7 (6)	487.9 (5)
Log-logistic	308.5 (6)	316.7 (6)	478.1 (3)	486.2 (3)
Log-normal	**307.6 (2)**	**315.8 (2)**	**476.8 (1)**	**485.0 (2)**
Weibull	308.4 (4)	316.5 (4)	479.8 (7)	488.0 (6)
Gamma	308.2 (3)	316.4 (3)	479.6 (5)	487.7 (4)

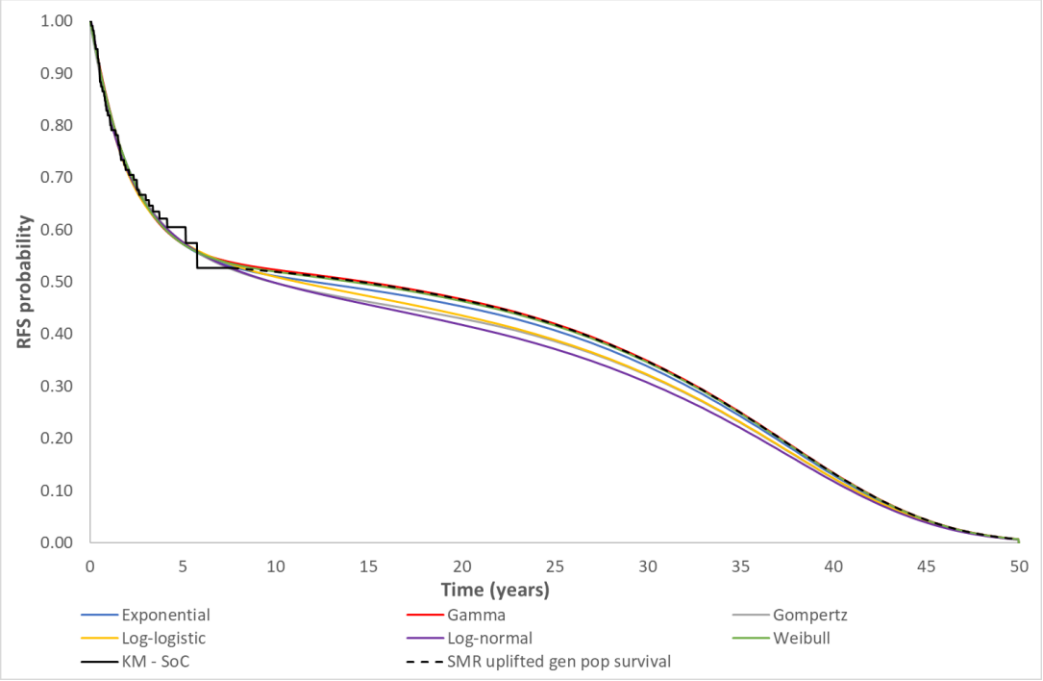
MCM - mixture-cure model; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; RFS - relapse-free survival; SoC - standard of care
Company's selected base case model highlighted in bold
AIC and BIC statistics for individual treatment groups provided in clarification response,[21] question B8.

Figure 9: Observed and MCM-predicted RFS, blinatumomab plus SoC (drawn by the EAG)



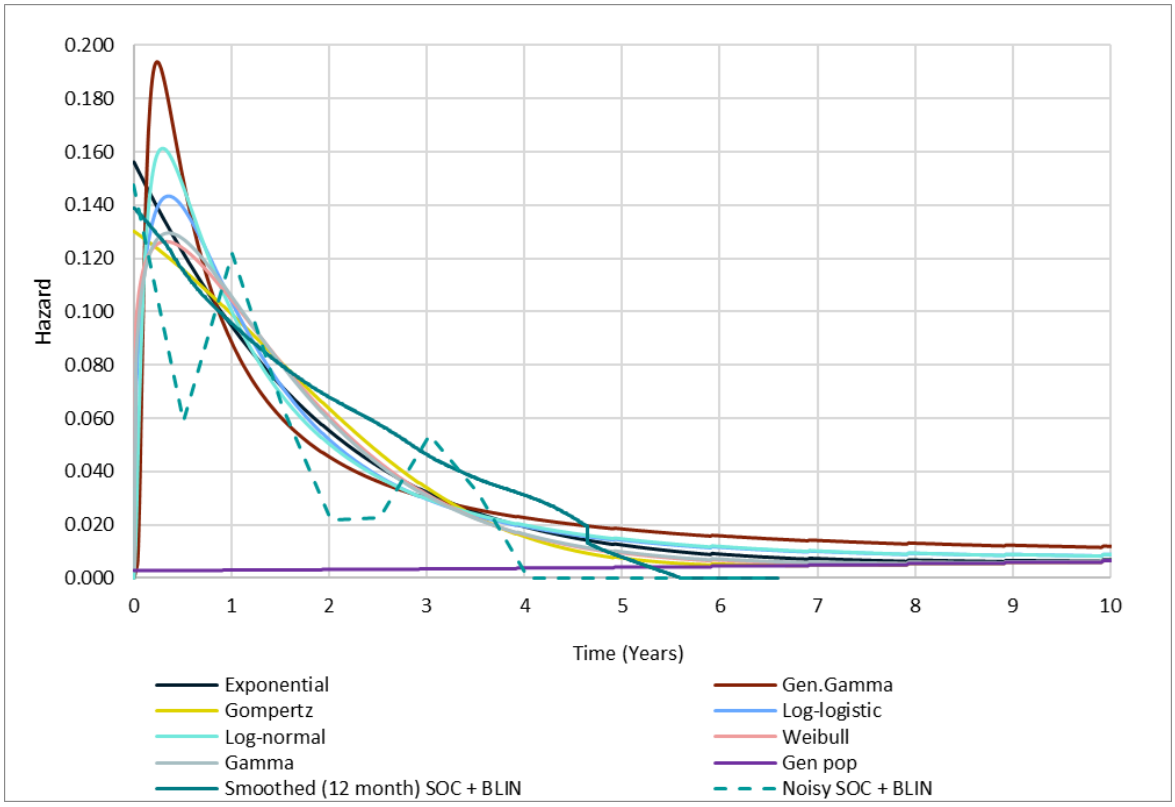
RFS - relapse-free survival; SoC - standard of care

Figure 10: Observed and MCM-predicted RFS, SoC (drawn by the EAG)



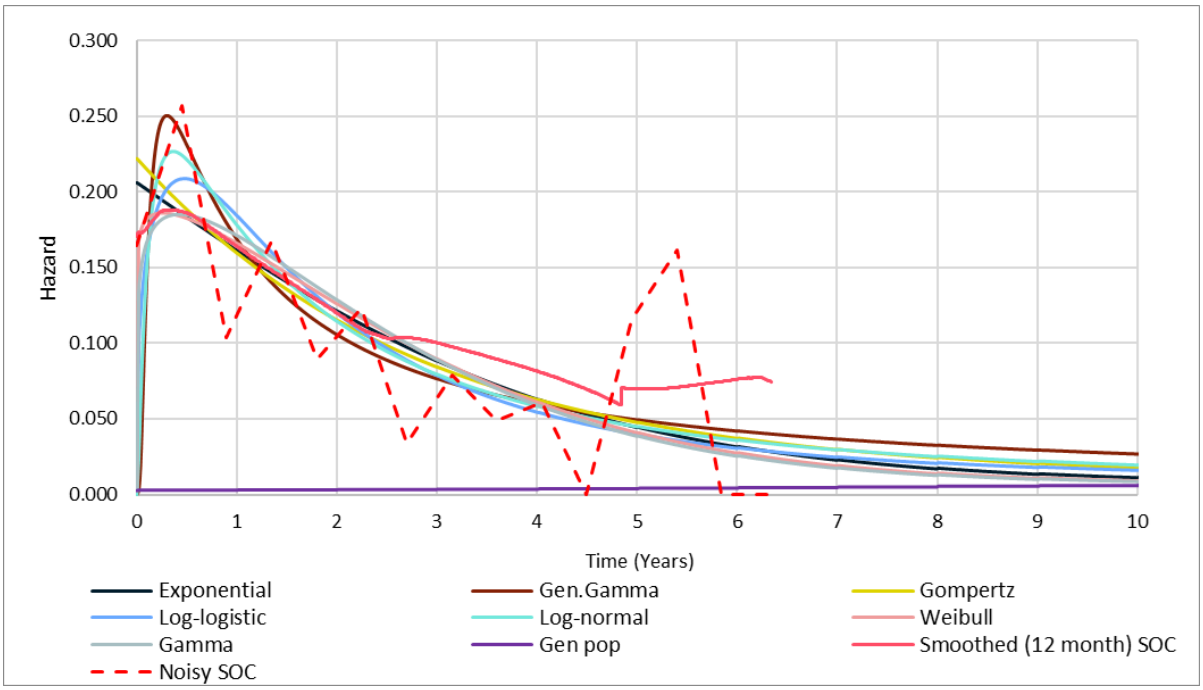
RFS - relapse-free survival; SoC - standard of care

Figure 11: Empirical and modelled hazard plots from MCMs for RFS, blinatumomab plus SoC (reproduced from clarification response, Figure 8)



RFS - relapse-free survival; SoC - standard of care

Figure 12: Empirical and modelled hazard plots from MCMs for RFS, SoC (reproduced from clarification response, Figure 9)



RFS - relapse-free survival; SoC - standard of care

Table 23: Estimated cure fractions for MCMs of RFS

MCM	Blinatumomab plus SoC	SoC
Exponential	0.759	0.528
Weibull	0.765	0.540
Gompertz	0.768	0.425
Gamma	0.764	0.544
Log-normal	**0.740**	**0.465**
Log-logistic	0.737	0.486

RFS - relapse-free survival; SoC - standard of care
Company base case model highlighted in bold

The generalised gamma MCM was excluded as it appeared to over-fit the RFS data, provided low cure fractions, and did not converge for OS. The Gompertz MCM was excluded because it resulted in unstable cure fraction estimates. All of the remaining MCMs resulted in a similar statistical fit and visual fit for both treatment groups, with each model underestimating the tail of the Kaplan-Meier survival function in the blinatumomab plus SoC group and overestimating the tail of the Kaplan-Meier survival function in the SoC group. The CS[1] states that the exponential, log-normal and log-logistic MCMs had the best statistical fit based on the sum of the AIC/BIC values across the treatment groups. The company selected the log-normal MCM to model RFS in the base case analysis because it overestimates the tail of the Kaplan-Meier function in the SoC group to a lesser degree than the other MCMs. Across the range of fitted MCMs, the cure fractions ranged from 0.74 to 0.77 in the blinatumomab plus SoC group and from 0.43 to 0.54 in the SoC group. The differences in the estimated cure fractions for RFS across the alternative MCMs are fairly small, particularly in the blinatumomab plus SoC group. The company's selected log-normal MCM suggests a cure fraction of 0.74 for blinatumomab plus SoC and 0.47 for SoC; this is the second-most pessimistic MCM in terms of cure fractions in both treatment groups.

Following a request for clarification from the EAG[21] (question B8), the company provided separate AIC/BIC values for each treatment group (shown previously in Table 22). The EAG notes that within the blinatumomab plus SoC group, the exponential MCM was the best-fitting model based on both AIC and BIC, followed by the log-normal, gamma, Weibull, Gompertz, log-logistic and generalised gamma MCMs. Differences in AIC were less than 3 points across all models; BIC values were also generally similar across all models, although the BIC for the generalised gamma MCM was noticeably higher than the other MCMs. In the SoC group, the log-normal MCM was the best-fitting model based on AIC and the exponential MCM was the best-fitting model based on BIC, followed by the log-logistic, generalised gamma, gamma, Gompertz and Weibull MCMs. The AIC and BIC values were generally similar across all models, although again the BIC for the generalised gamma MCM was higher.

Overall survival

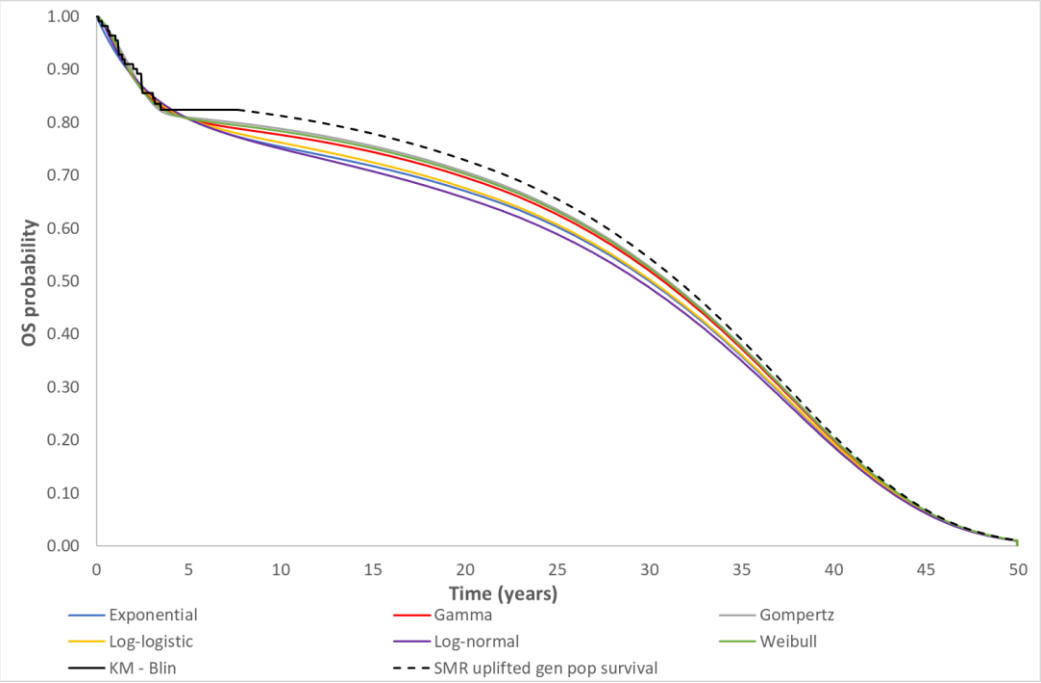
OS was estimated separately for the blinatumomab plus SoC and SoC groups using IPD from Study E1910.[11] The AIC and BIC values from the fitted MCMs are shown in Table 24. Comparisons of observed and predicted OS using MCMs for the blinatumomab plus SoC and SoC groups are presented in Figure 13 and Figure 14, respectively. Empirical hazard plots and hazard plots from the fitted MCMs are presented for the blinatumomab plus SoC and SoC groups separately in Figure 15 and Figure 16, respectively. Estimated cure fractions from the MCMs are presented in Table 25.

Table 24: AIC and BIC statistics for MCMs of OS

MCM	Blinatumomab plus SoC		SoC	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	253.67 (5)	259.11 (2)	464.91 (5)	470.35 (1)
Generalised gamma	250.42 (1)	261.29 (4)	465.23 (6)	476.10 (7)
Gompertz	250.62 (2)	258.77 (1)	465.54 (7)	473.69 (6)
Log-logistic	253.96 (6)	262.12 (6)	463.10 (1)	471.25 (2)
Log-normal	255.14 (7)	263.30 (7)	464.17 (4)	472.32 (5)
Weibull	**252.31 (3)**	**260.46 (3)**	**463.43 (3)**	**471.59 (4)**
Gamma	253.17 (4)	261.33 (5)	463.23 (2)	471.39 (3)

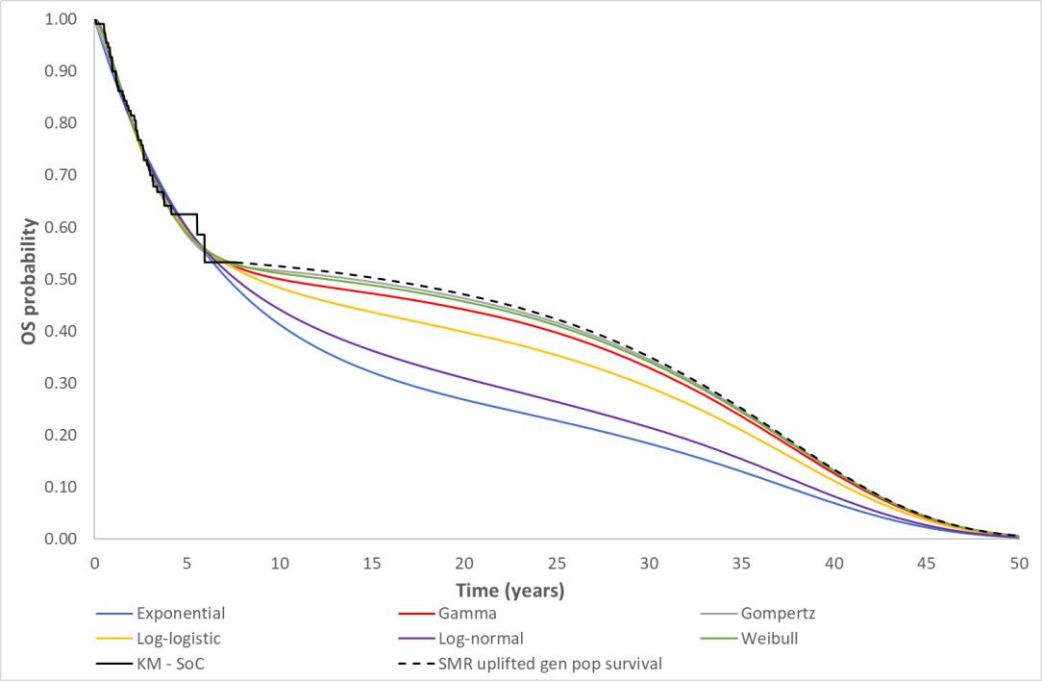
MCM - mixture-cure model; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; OS - overall survival; SoC - standard of care
Company's selected base case model highlighted in bold
AIC and BIC statistics for individual treatment groups provided in clarification response,[21] question B8

Figure 13: Observed and MCM-predicted OS, blinatumomab plus SoC (drawn by the EAG)



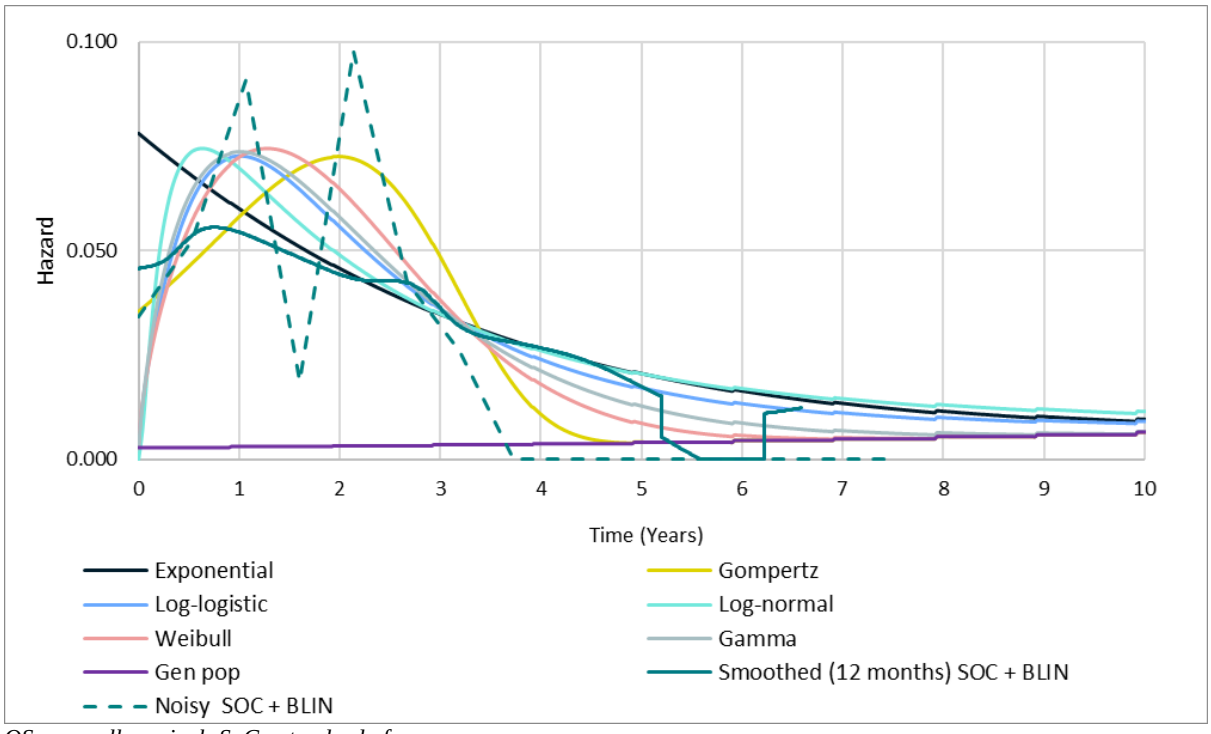
OS - overall survival; SoC - standard of care

Figure 14: Observed and MCM-predicted OS, SoC (drawn by the EAG)



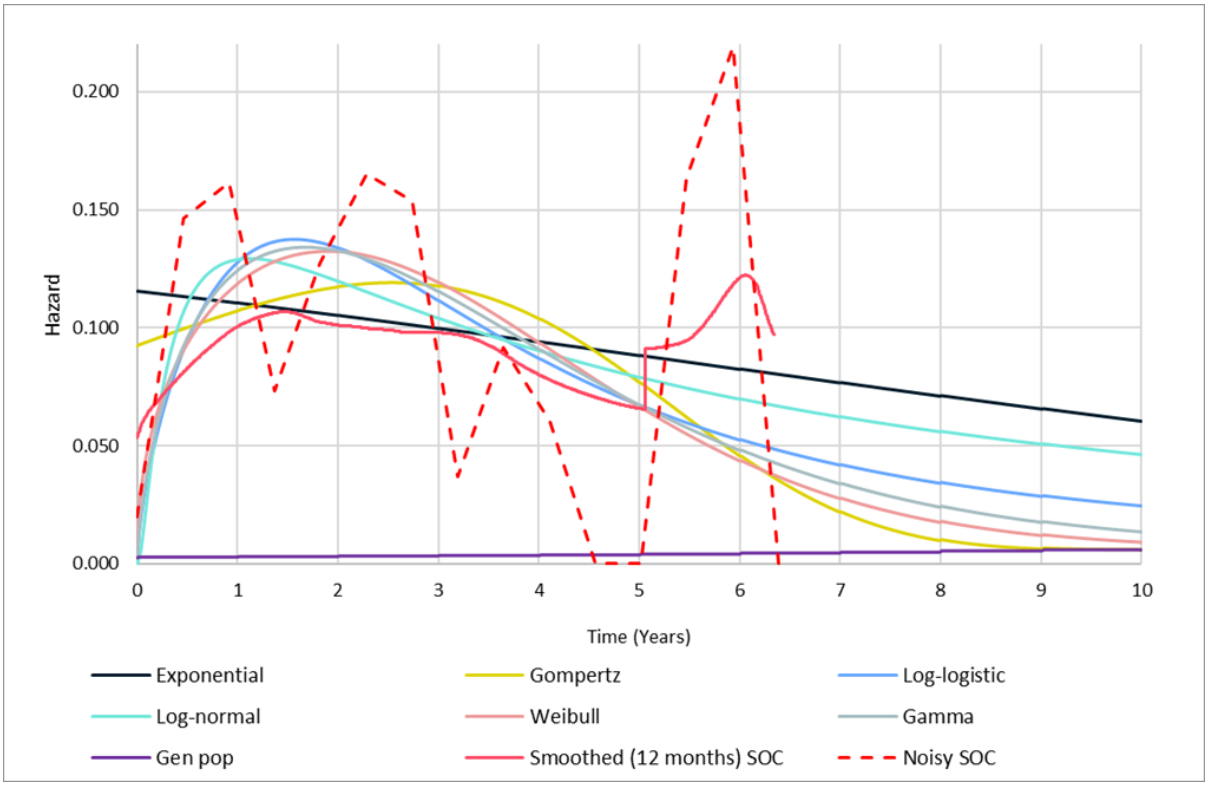
OS - overall survival; SoC - standard of care

Figure 15: Empirical and modelled hazard plots from MCMs for OS, blinatumomab plus SoC (reproduced from clarification response, Figure 6)



OS - overall survival; SoC - standard of care

Figure 16: Empirical and modelled hazard plots from MCMs for OS, SoC (reproduced from clarification response, Figure 7)



OS - overall survival; SoC - standard of care

Table 25: Estimated cure fractions for OS from MCMs

MCM	Blinatumomab plus SoC	SoC
Exponential	0.781	0.278
Weibull	**0.819**	**0.533**
Gompertz	0.823	0.540
Gamma	0.811	0.515
Log-normal	0.756	0.257
Log-logistic	0.783	0.439

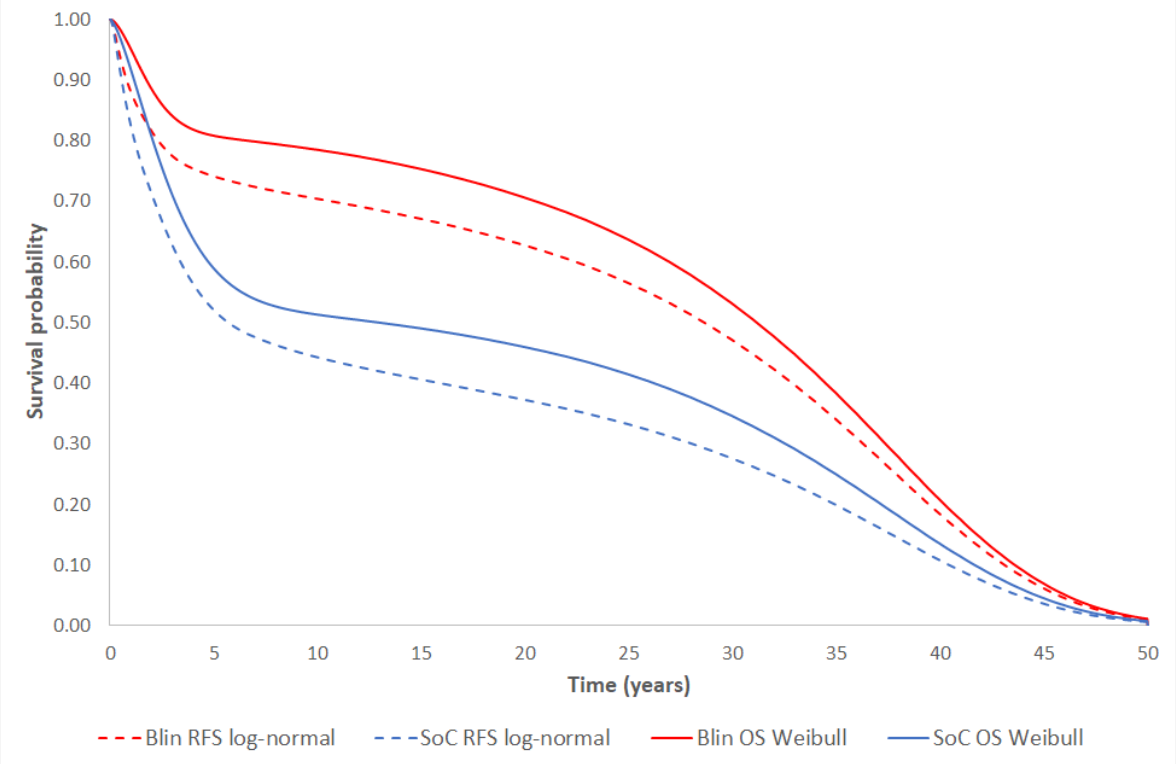
OS - overall survival; SoC - standard of care
Company base case model highlighted in bold

The EAG notes that the company used summed AIC/BIC values across the treatment groups to inform model selection. On this basis, the Weibull MCM was the best-fitting model based on AIC. The CS[1] states that the exponential, log-logistic and log-normal MCMs underestimate long-term survival and the Weibull, Gompertz and gamma MCMs provide plausible extrapolations. As noted above, the Weibull MCM was selected for inclusion the company's base case analysis as it provided stable cure fractions whereas the Gompertz MCM did not. The generalised gamma MCM was excluded as it did not converge for OS. The MCMs suggested cure fractions ranging from 0.76 to 0.82 in the blinatumomab plus SoC group and from 0.26 to 0.54 in the SoC group. The company's selected Weibull MCM suggests a cure fraction of 0.82 for blinatumomab plus SoC and 0.53 for SoC; these are the second highest cure fractions across both treatment groups.

The company's clarification response[21] (question B8) included AIC/BIC values for models fitted to the OS data for each treatment group separately (previously shown in Table 24). When the generalised gamma MCM is not considered, for blinatumomab plus SoC, the Gompertz MCM was the best-fitting model based on AIC and BIC, followed by the Weibull, gamma, exponential, log-logistic and log-normal MCMs based on AIC values, with differences in AIC and BIC of less than 5 points across all models. For SoC, the log-logistic MCM was the best-fitting model based on AIC, followed by the gamma, Weibull, log-normal, exponential, and Gompertz MCMs with differences in AIC less than 3 points across all models excluding the generalised gamma. When based on BIC, the exponential MCM was the best-fitting model, and all other models except the generalised gamma MCM are similar.

The company's selected MCMs for RFS (log-normal) and OS (Weibull) are shown in Figure 17.

Figure 17: Company's selected base case RFS and OS models* (drawn by the EAG)



** This plot has been generated using the revised version of the company's model provided as part of the clarification response. RFS and OS include uplifted mortality risks using an SMR of 1.09 for cured and uncured patients*

Probability of receiving alloSCT

The probability of undergoing alloSCT in the relapse-free and post-relapse states of the model was derived from the MRD-negative population in Study E1910 (including patients who underwent alloSCT either on- or off-protocol).[11] [redacted] of patients in the blinatumomab plus SoC group and [redacted] of patients in the SoC group are assumed to receive alloSCT prior to relapse. [redacted] of patients who relapse following blinatumomab plus SoC and [redacted] of patients who relapse following SoC are assumed to undergo alloSCT.

Health-related quality of life

Health state utility values (relapse-free and post-relapse health states)

Study E1910[11] did not collect data on HRQoL. The company's SLR of HRQoL studies (CS Appendix H[23]) identified one model-based economic evaluation which reported utility values for Ph-negative B-cell ALL health states (Nam *et al.*[59]); however, this study was not mentioned in the CS[1] and the utility values applied in this study were not included in the company's economic model. Instead, the utility values for the relapse-free and post-relapse states of the model were based on the same sources used in TA589.[15] EQ-5D-3L estimates for the UK general population reported by Hernández Alava *et al.*[89] were used to adjust utility values for age; this same source was also used to inform the utility values for patients who remain relapse-free and who are assumed to be cured after 5 years.

The utility values applied in the relapse-free and post-relapse health states of the model used to inform TA589[15] were based on EQ-5D data from two studies: the BLAST study[66] (blinatumomab for adults with Ph-negative MRD-positive B-ALL in CR) and the TOWER study[85] (blinatumomab versus chemotherapy for adults with R/R Ph-negative B-ALL). The utility value for the relapse-free state was based on estimates obtained from a generalised linear model/generalised estimating equations (GLM/GEE) model fitted to EQ-5D data from BLAST. The GLM/GEE model was also used to estimate the disutility associated with being within 6 months of death. The utility value applied in the post-relapse state was based data from the TOWER study; data obtained using the EORTC QLQ-C30 collected in TOWER were mapped to the EQ-5D and matched with relapsed patients in BLAST.

The health state utility values used in the company's model are summarised in Table 26. The utility values for the relapse-free state (on or off-treatment) were calculated from the BLAST GLM/GEE model coefficients.[66] The model applies the coefficient for MRD-response to all patients in the relapse-free state (because they are MRD-negative). Hence, the utility value for the SoC group and the blinatumomab plus SoC group (off-treatment) was calculated as the sum of the mean baseline utility (0.802) plus the coefficient for MRD response (+0.0474). A disutility of -0.0105 was applied for patients who are receiving blinatumomab treatment in a given model cycle (utility = 0.840). The utility value for the post-relapse state was estimated to be 0.692 based on TOWER.[85] These health utility values are applied to the time spent in each health state to estimate QALYs gained. The disutility associated with being within 6 months of death is applied as a QALY loss to patients when they enter the dead state. As noted in Section 5.2.2, the model applies general population EQ-5D-3L values to patients who remain relapse-free and who are assumed to be cured after 5-years and no further QALY loss is applied to new deaths after this time point.

Table 26: Summary of health state utility values applied in the company's model

Health state	TA589[15]	Values used in current model		
		Blinatumomab plus SoC	SoC	Source
Relapse-free	Mean relapse-free utility, off-treatment, no MRD response: 0.802 Parameter estimates from the regression on EQ-5D utility values. • MRD response versus no MRD response: 0.047 • On- versus off-treatment: −0.011	On-treatment: 0.840 Off-treatment: 0.850	0.850	Calculated based on values reported in TA589[15]
Post-relapse	0.692	0.692		TA589[15]
Death	−0.129	−0.129		TA589[15]

TA - Technology Appraisal; SoC - standard of care; CR1 - first haematological complete remission; EQ-5D - Euroqol 5-Dimensions; MRD - minimal residual disease

Disutility related to alloSCT

The disutility associated with alloSCT was based on a previous modelling analysis reported by Sung *et al*.[68] This study reported a disutility value associated with bone marrow transplantation of -0.57 based on Visual Analogue Scale (VAS) estimates provided by 12 expert physicians in Toronto, Canada. The company's model applies this disutility for a period of one year. This disutility value and assumed duration have been used in previous NICE appraisals of ALL therapies.[18, 19, 90] Within the company's current model, the impact of alloSCT received prior to relapse on patient HRQoL is applied as a once-only QALY loss in the first model cycle. The QALY loss is also applied to all new patients experiencing an RFS event and undergoing post-relapse alloSCT in each cycle up to the end of year 5. The proportion of patients who are assumed to undergo alloSCT before and after relapse in each treatment group are summarised in Table 27.

Table 27: Proportion of patients experiencing alloSCT

Health state	Blinatumomab plus SoC	SoC	Source
Relapse-free	[redacted]	[redacted]	Study E1910[11]
Post-relapse occurring in first 5 years	[redacted]	[redacted]	

SoC - standard of care

QALY losses due to AEs

The company's model includes QALY losses associated with AEs in both treatment groups. The model includes Grade ≥3 TEAEs that occurred in ≥5% of patients in either trial arm from Study E1910,[11] as well as Grade ≥3 CRS in the blinatumomab plus SoC group, despite [redacted] of patients in the blinatumomab plus SoC arm of Study E1910 experiencing this AE.

Disutility values were used to estimate the reduction in HRQoL for the duration of the AEs. The model incorporates expected QALY losses associated with AEs by multiplying the disutility for each AE by its respective duration and the proportion of patients who experienced each AE in the trial. Aphasia, increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), decreased neutrophil count and hypertriglyceridemia are assumed to have no impact on patient HRQoL. The resulting expected values were then summed across all AEs to determine a once-only QALY loss which is applied in the first model cycle (blinatumomab plus SoC = [redacted] QALYs lost; SoC = [redacted] QALYs lost). AE frequencies, utility decrements and their corresponding durations and sources, are presented in Table 28.

Table 28: Utility decrements associated with AEs included in the model

AE	Probability of Grade ≥3 AE		Utility value (SE)	Duration, days	Source of disutility
	Blin+SoC	SoC			
ALT increased	[redacted]	[redacted]	-	20.0	Assumed no disutility for abnormal lab tests
Anaemia	[redacted]	[redacted]	-0.120 (0.020)	14.9	Swinburn *et al.*[69]
Aphasia	[redacted]	[redacted]	-	-	Assumption
AST increased	[redacted]	[redacted]	-	20.0	Assumed no disutility for abnormal lab tests
CRS	[redacted]	[redacted]	-0.230 (0.023)	4.3	Howell *et al.*[70]
Device-related infection	[redacted]	[redacted]	-0.200 (0.040)	15.1	Assumed same as sepsis
Diarrhoea	[redacted]	[redacted]	-0.050 (0.005)	7.0	Nafees *et al.*[71]
Fatigue	[redacted]	[redacted]	-0.115 (0.012)	7.0	Lloyd *et al.*[72]
Febrile neutropenia	[redacted]	[redacted]	-0.090 (0.020)	6.2	Nafees *et al.*[71]
Headache	[redacted]	[redacted]	-0.027 (0.003)	2.0	Sullivan *et al.*[73]
Hyperglycaemia	[redacted]	[redacted]	-0.062 (0.010)	7.5	Sullivan *et al.*[73]
Hypertension	[redacted]	[redacted]	-0.070 (0.010)	4.0	Assumed same as hypotension
Hypertriglyceridemia	[redacted]	[redacted]	-	-	Assumed no disutility for abnormal lab tests
Hypotension	[redacted]	[redacted]	-0.070 (0.010)	2.3	TA783[75]
Lymphocyte count decreased	[redacted]	[redacted]	-0.070 (0.010)	19.0	TA783[75]
Nausea	[redacted]	[redacted]	-0.050 (0.010)	7.0	Assumed same as diarrhoea
Neutrophil count decreased	[redacted]	[redacted]	-	9.8	TA520[76]
Platelet count decreased	[redacted]	[redacted]	-0.050 (0.010)	11.9	TA653[77]
Sepsis	[redacted]	[redacted]	-0.200 (0.040)	15.1	Tolley *et al.*[74]

AE	Probability of Grade ≥3 AE		Utility value (SE)	Duration, days	Source of disutility
	Blin+SoC	SoC			
WBC decreased	[redacted]	[redacted]	-0.050 (0.010)	16.9	TA520[76]

AE - adverse event; SE - standard error; blin - blinatumomab; SoC - standard of care; ALT - alanine aminotransferase; AST - aspartate aminotransferase; CRS - cytokine release syndrome WBC - white blood cell count; TA - technology appraisal; SE - standard error

Resource use and costs

Overview of resource costs included in the company's model

The company's economic model includes costs associated with: (i) consolidation therapy; (ii) maintenance therapy; (iii) alloSCT (pre- and post-relapse); (iv) the management of AEs; (v) subsequent-line therapy and (vi) terminal care. A summary of the costs applied in the company's model is shown in Table 29. The sources of individual cost components applied in the model are described in the subsequent sections.

Table 29: Summary of costs applied in the company's model

Cost component	Blinatumomab plus SoC	SoC
Blinatumomab drug acquisition (total expected cost*)	[redacted]	-
Blinatumomab administration (total expected cost*)	[redacted]	-
Consolidation SoC drug acquisition (total expected cost*)	£1,523.13	£1,919.14
Consolidation SoC administration (total expected cost*)	£7,580.35	£9,118.04
Maintenance therapy acquisition (cost per week)	£10.53	£10.53
Maintenance therapy administration (cost per week)	£50.05	£50.05
Pre-/post-relapse alloSCT (once-only cost per procedure)‡	£97,157	
AE management (once-only cost)†	£3,096.81	£2,609.62
Subsequent-line therapy drug acquisition (once-only cost)‡	£71,259.93	£78,488.93
Subsequent-line therapy administration (once-only cost)‡	£8,096.12	£9,064.61
Terminal care costs (once-only cost)‡	£10,952.83	

SoC - standard of care; alloSCT - allogeneic stem cell transplant; AE - adverse event
** Total undiscounted cost of consolidation therapy, including percentage of patients starting each cycle and wastage adjustments*
† Applied in the first model cycle only
‡ Applied only during the first 5 years of the model time horizon

(i) Consolidation therapy costs

Drug acquisition costs for blinatumomab and each individual consolidation chemotherapy component are shown in Table 30. Dosing schedules for blinatumomab and SoC were based on the Study E1910 protocol.[11] Acquisition costs for all chemotherapy components include adjustments for wastage which are dependent on estimated distributions of BSA or weight, based on baseline patient characteristics in Study E1910. The cost of blinatumomab is based on its list price plus the PAS discount; the PAS price

per vial of blinatumomab is [redacted].[1] Unit costs of chemotherapy drugs used in the consolidation phase were taken from the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT)[79] and the British National Formulary (BNF).[80]

Unit costs associated with drug administration are summarised in Table 31. The costs of inpatient and outpatient hospital visits were based on NHS Reference Costs 2021/22.[81] The costs of blinatumomab administration include the cost of pump acquisition, maintenance and consumables. The cost of the pump assumes a 5-year life span for each device. Administration costs for oral drugs were assumed to be zero.

Table 30: Consolidation therapy – drug acquisition costs per dose including wastage

Drug	Preparation	Pack size (vials/ tabs)	Cost per pack	Dose per admin	Cost per dose (including wastage)*	Unit cost source
Blinatumomab (inc. PAS)	38.5mcg	1	[redacted]	28mcg/day	[redacted]	CS[1]
Cytarabine	100mg/ml vial	5	£13.76	75mg/m²	£2.75	eMIT[79]
Etoposide	20mg/ml vial	10	£13.40	100mg/m²	£1.34	eMIT[79]
Methotrexate	50mg/2ml vial	2	£14.72	12.5mg	£2.94	eMIT[79]
Pegaspargase	3,750mg/5ml vial	1	£1,296.79	2000IU/m²	£1,296.36	eMIT[79]
Daunorubicin	20mg/ml vial	10	£715.00	25mg/m²	£214.50	BNF[80]
Vincristine	2mg/2ml vial	5	£12.09	1.4mg/m²	£2.42	eMIT[79]
Cyclophosphamide	500mg powder for injection	1	£9.32	650mg/m²	£22.53	eMIT[79]
	1,000mg powder for injection	1	£13.12	650mg/m²		eMIT[79]
	2,000mg powder for injection	1	£27.50	650mg/m²		eMIT[79]
6-mercaptopurine	50mg tablet	25	£9.42	60mg/m²	£1.10	BNF[80]
Dexamethasone	2mg tablet	50	£2.32	10mg/m²	£0.45	eMIT[79]

PAS - Patient Access Scheme; CS - company's submission; eMIT - electronic Market Information Tool; BNF - British National Formulary
** Costs adjusted for patient BSA/weight based on characteristics of patients in Study E1910*

Table 31: Administration unit costs

Item	Unit cost	Cost source (NHS Reference Costs 2021/22[81])
Inpatient days	£577.45	Weighted mean of acute lymphoblastic leukaemia with CC score 0-5+, elective
Outpatient bag change	£349.41	Deliver subsequent elements of a chemotherapy cycle - outpatient [SB15Z]
Pump costs	£4.54	Specialist nursing, cancer related, adult, face to face [N10AF]
IV/IT (Outpatient)	£349.41	Deliver subsequent elements of a chemotherapy cycle - outpatient [SB15Z]
Oral	£0.00	Assumption

IV – intravenous; IT - intrathecal; CC - complication/comorbidity

The expected costs of drug acquisition and administration for each cycle of consolidation therapy in the blinatumomab plus SoC and SoC groups are summarised in Table 32 and Table 33, respectively.

Table 32: Consolidation therapy - drug acquisition and administration costs, blinatumomab plus SoC group

Treatment, frequency and proportion starting cycle				Drug acquisition		Drug administration					
Cycle	**Drug**	**Admins in cycle**	**Percent starting cycle**	**Expected cost**	**Expected total acquisition cost for cycle**	**IP days**	**OP bag changes**	**Pumps (28- IP days)**	**IV OP**	**Oral**	**Expected total admin cost for cycle**
Blinatumomab Cycle 1	Blinatumomab (cIV)	28	[redacted]	[redacted]	[redacted]	3	6	25			[redacted]
Blinatumomab Cycle 2	Blinatumomab (cIV)	28	[redacted]	[redacted]	[redacted]	2	6	26			[redacted]
Consolidation SoC Cycle 1	Cytarabine (IV/SC)	5	[redacted]	[redacted]	[redacted]	2			3		[redacted]
	Etoposide (IV)	5									
	Methotrexate (IT)	1									
	Pegaspargase (IV)	1									
Consolidation SoC Cycle 2	Cytarabine (IC/SC)	5	[redacted]	[redacted]	[redacted]	2			3		[redacted]
	Etoposide (IV)	5									
	Methotrexate (IT)	1									
Consolidation SoC Cycle 3	Daunorubicin hydrochloride (IV)	4	[redacted]	[redacted]	[redacted]	2			3		[redacted]
	Vincristine sulfate (IV)	4									
	Cyclophosphamide (IV)	1							1		
	Cytarabine (IV/SC)	8							8		
	Mercaptopurine (PO)	14								14	
	Methotrexate (IT)	1									
	Dexamethasone (PO)	14								12	
Blinatumomab Cycle 3	Blinatumomab (cIV)	28	[redacted]	[redacted]	[redacted]	2	6	26			[redacted]
Consolidation SoC Cycle 4	Cytarabine (IV/SC)	5	[redacted]	[redacted]	[redacted]	2			3		[redacted]
	Etoposide (IV)	5									
	Methotrexate (IT)	1									
Blinatumomab Cycle 4	Blinatumomab (cIV)	28	[redacted]	[redacted]	[redacted]	2	6	26			[redacted]

SoC - standard of care; IV - intravenous; SC - subcutaneous; IT - intrathecal; PO - per os (by mouth); cIV - continuous intravenous infusion; IP - inpatient; OP - outpatient

Table 33: Consolidation therapy - drug acquisition and administration costs, SoC group

Treatment, frequency and proportion starting cycle				Drug acquisition		Drug administration					
Cycle	**Drug**	**Admins/ cycle**	**Percent starting cycle**	**Expected cost**	**Expected total acquisition cost for cycle**	**IP days**	**OP bag changes**	**Pumps (28- IP days)**	**IV OP**	**Oral**	**Expected total admin cost for cycle**
Consolidation SoC Cycle 1	Cytarabine (IV/SC)	5	[redacted]	[redacted]	[redacted]	3			2		[redacted]
	Etoposide (IV)	5		[redacted]							
	Methotrexate (IT)	1		[redacted]							
	Pegaspargase (IV)	1		[redacted]							
Consolidation SoC Cycle 2	Cytarabine (IV/SC)	5	[redacted]	[redacted]	[redacted]	2			3		[redacted]
	Etoposide (IV)	5		[redacted]							
	Methotrexate (IT)	1		[redacted]							
Consolidation SoC Cycle 3	Daunorubicin hydrochloride (IV)	4	[redacted]	[redacted]	[redacted]	2			3		[redacted]
	Vincristine sulfate (IV)	4		[redacted]							
	Cyclophosphamide (IV)	1		[redacted]					1		
	Cytarabine (IV/SC)	8		[redacted]					8		
	Mercaptopurine (PO)	14		[redacted]						14	
	Methotrexate (IT)	1		[redacted]							
	Dexamethasone (PO)	14		[redacted]						12	
Consolidation SoC Cycle 4	Cytarabine (IV/SC)	5	[redacted]	[redacted]	[redacted]	2			3		[redacted]
	Etoposide (IV)	5		[redacted]							
	Methotrexate (IT)	1		[redacted]							

SoC - standard of care; IV - intravenous infusion; SC - subcutaneous; IT - intrathecal; PO - per os (by mouth); IP - inpatient; OP - outpatient

(ii) Maintenance therapy costs

The company's model assumes that patients receive maintenance chemotherapy after completing or discontinuing from consolidation therapy. Within the model, patients in both treatment groups are assumed to receive maintenance therapy for a maximum duration of 2.5 years (from model entry) or until they experience relapse.

The maintenance chemotherapy regimen assumed in the model follows the Study E1910 protocol[11] and includes the components listed in Table 34. All list prices for drugs were obtained from the BNF[80] or eMIT.[79] In line with the company's approach for estimating the costs of consolidation therapy, acquisition costs for all components were adjusted for wastage based on estimated distributions of BSA or weight in Study E1910.

Table 34: Maintenance therapy - acquisition costs per dose, including wastage

Drug	Preparation	Pack size (vials/ tabs)	Cost per pack	Dose per admin	Cost per dose (including wastage)*	Unit cost source
Mercaptopurine	50mg	25	£9.42	75mg/m²	£1.32	BNF[80]
Methotrexate (PO)	2.5mg tablet	24	£1.12	20mg/m²	£0.52	eMIT[79]
	2.5mg tablet	100	£3.18			
Vincristine sulfate	1mg/ml vial	5	£33.59	1.4mg/m²	£2.42	eMIT[79]
	2mg/2ml vial	5	£12.09			
Prednisolone	1mg tablet	28	£0.28	60mg/m²	£0.96	eMIT[79]
	5mg tablet	28	£0.41			
	25mg tablet	56	£11.76			
Methotrexate (IT)	1,000mg/10ml vial	1	£44.88	12.5mg	£2.94	eMIT[79]
	500mg/20ml vial	1	£10.05			
	50mg/2ml vial	5	£14.72			
	5,000mg/50ml vial	1	£183.12			

BNF - British National Formulary; eMIT - electronic Market Information Tool; IT - intrathecal; PO - per os (by mouth)
** Costs adjusted for patient BSA/weight based on characteristics of patients in E1910*

The model assumes that maintenance chemotherapy is administered exclusively in the outpatient setting. The expected costs of drug acquisition and administration for maintenance therapy for both treatment groups in the model are summarised in Table 35.

Table 35: Maintenance therapy - drug acquisition and administration costs, both groups

Treatment and frequency			Drug acquisition		Drug administration		
Drug	**Dosing schedule**	**Admins/ cycle**	**Weekly cost**	**Weekly acquisition cost**	**Administration**	**Weekly cost**	**Weekly admin cost***
Mercaptopurine	Daily	7	£9.23	£10.53	Oral	£0.00	£50.05
Methotrexate (PO)	Weekly	1	£0.52		Oral	£0.00	
Prednisolone	Days 1-5, every 3 months	0.38	£0.37		Oral	£0.00	
Vincristine sulfate	Days 1, every 3 months	0.08	£0.19		Intravenous - outpatient	£25.03	
Methotrexate (IT)	Days 1, every 3 months	0.08	£0.23		Intrathecal - outpatient	£25.03	

IT - intrathecal; PO - per os (by mouth)
** Values shown include an error in the company's original model. The corrected cost is £53.57 per week*

(iii) AlloSCT (pre- and post-relapse)

Patients in Study E1910[11] could undergo alloSCT before or after relapse. Unit costs associated with alloSCT are shown in Table 36. The costs associated with stem cell harvesting and transplant were taken from NHS Reference Costs 2021/22.[81] The costs of post-transplant follow-up were obtained from a report published by the UK Stem Cell Strategy Oversight Committee;[82] this source has been used in several previous appraisals of ALL therapies.[15, 19, 90] These costs were inflated to 2022/23 values using the NHS Cost Inflation Index (NHSCII, pay and prices index).[83] The expected cost per alloSCT procedure including 24-months of follow-up was estimated to be £97,157. The company's model applies this as a once-only cost to all patients undergoing pre-relapse alloSCT in the first model cycle, and to a proportion of patients who experience an RFS event and undergo post-relapse alloSCT in each model cycle up to the end of year 5 (see Table 37).

Table 36: Unit costs of alloSCT

Item	%	Unit cost	Expected cost
Stem cell harvesting*			
[SA18Z] Bone marrow harvest	15.41%	£5,808	2021/22: £5,441
[SA34Z] Peripheral blood stem cell harvest	84.59%	£5,375	2022/23: £5,824
Stem cell transplant*			
[SA20A] Bone marrow transplant, allogeneic graft (sibling), 19 years and over	0.93%	£35,641	2021/22: £39,980 2022/23: £42,791
[SA21A] Bone marrow transplant, allogeneic graft (volunteer unrelated donor), 19 years and over	0.00%	£0	
[SA22A] Bone marrow transplant, allogeneic graft (cord blood), 19 years and over	1.24%	£77,952	
[SA23A] Bone marrow transplant, allogeneic graft (haplo-identical), 19 years and over	0.00%	£0	
[SA38A] Peripheral blood stem cell transplant, allogeneic (sibling), 19 years and over	28.35%	£32,964	
[SA39A] Peripheral blood stem cell transplant, allogeneic (volunteer unrelated donor), 19 years and over	45.36%	£37,350	
[SA40A] Peripheral blood stem cell transplant, allogeneic (donor type not specified)	24.12%	£51,390	
[SA20A] Bone marrow transplant, allogeneic graft (sibling), 19 years and over	0.93%	£35,641	
Follow-up†			
Up to 6 months	90%	£28,390	2012/13: £39,275
6 to 12 months	48%	£19,502	2022/23: £48,542
12 to 24 months	31%	£14,073	
Total cost per alloSCT (2022/23 prices)			**£97,157**

AlloSCT - allogeneic stem cell transplant
** Percentage calculated from activity counts and unit costs from NHS Reference Costs 2021/22[81] (elective inpatient)*
† Percentage of alive patients and cost per event from UK Stem Cell Strategy Oversight Committee costing analysis[82]

Table 37: Summary of once-only costs of alloSCT

Health state	Proportion of patients		Expected once-only cost	
	Blinatumomab plus SoC	SoC	Blinatumomab plus SoC	SoC
Pre-relapse	[redacted]	[redacted]	[redacted]	[redacted]
Post-relapse	[redacted]	[redacted]	[redacted]	[redacted]

AlloSCT - allogeneic stem cell transplant; SoC - standard of care

(iv) Costs of managing AEs

The company's model includes the costs of managing Grade ≥3 TEAEs based on the frequencies observed in the blinatumomab plus SoC and SoC groups of Study E1910.[11] Unit costs were based on NHS Reference Costs 2021/22,[81] Jones *et al.*[83] and assumptions. The AE frequencies and unit costs applied in the model are summarised in Table 38. The total expected costs of managing AEs in the blinatumomab plus SoC and SoC groups were estimated to be £3,096.81 and £2,609.62, respectively.

Within the company's model, these expected AE costs are applied as once-only costs in the first model cycle. The model does not include the costs associated with AEs arising from subsequent-line therapies for treating R/R B-cell ALL.

Table 38: Grade ≥3 TEAE frequencies and unit costs

AE	Frequency - blin+SoC	Frequency - SoC	Unit cost*	Cost source (NHS Reference Costs 2021/22,[81] unless otherwise stated)
ALT increased	[redacted]	[redacted]	£808.79	Non-elective short stay liver failure disorders without interventions, with CC score 0-4 (GC01F)
Anaemia	[redacted]	[redacted]	£646.20	Weighted mean of non-elective short stay iron deficiency anaemia (SA04G-SA04L)
Aphasia	[redacted]	[redacted]	£661.85	Rehabilitation for other neurological disorders (VC12Z)
AST increased	[redacted]	[redacted]	£808.79	Non-elective short stay liver failure disorders without interventions, with CC score 0-4 (GC01F)
CRS	[redacted]	[redacted]	£9,865.09	Non-elective short stay liver failure disorders without interventions, with CC score 0-4 (GC01F)
Device related infection	[redacted]	[redacted]	£3,337.28	Weighted mean of non-elective short stay infections or other complications of procedures (WH07E-WH07G)
Diarrhoea	[redacted]	[redacted]	£609.11	Weighted mean of non-elective short stay non-malignant gastrointestinal tract disorders (FD10J-FD10M)
Fatigue	[redacted]	[redacted]	£646.20	Assumed to be the same as anaemia
Febrile neutropenia	[redacted]	[redacted]	£580.93	Weighted mean of non-elective short stay other haematological or splenic disorders (SA08G-SA08J)
Headache	[redacted]	[redacted]	£472.14	Weighted mean of non-elective short stay headache, migraine or SDF leak (AA31C-AA31E)
Hyperglycaemia	[redacted]	[redacted]	£613.47	Weighted mean of non-elective short stay diabetes with hyperglycaemic disorders (KB02G-KB02K)
Hypertension	[redacted]	[redacted]	£454.45	Hypertension (EB04Z)
Hypertriglyceridaemia	[redacted]	[redacted]	£56.00	PSSRU 2022,[83] cost assumed to be equal to 1 GP visit
Hypotension	[redacted]	[redacted]	£454.45	Assumed to be same as hypertension
Lymphocyte count decreased	[redacted]	[redacted]	£580.93	Weighted mean of non-elective short stay other haematological or splenic disorders (SA08G-SA08J)
Nausea	[redacted]	[redacted]	£609.11	Weighted mean of non-elective short stay non-malignant gastrointestinal tract disorders (FD10J-FD10M)
Neutrophil count decreased	[redacted]	[redacted]	£580.93	Weighted mean of non-elective short stay other haematological or splenic disorders (SA08G-SA08J)
Platelet count decreased	[redacted]	[redacted]	£748.20	Weighted mean of non-elective short stay thrombocytopenia (SA12G-SA12K)
Sepsis	[redacted]	[redacted]	£782.91	Weighted mean of non-elective short stay sepsis with multiple interventions (WJ06A-WJ06C), sepsis with single intervention (WJ06D-WJ06F), and sepsis without interventions (WJ06-WJ06J)

WBC count decreased	[redacted]	[redacted]	£580.93	Weighted mean of non-elective short stay other haematological or splenic disorders (SA08G-SA08J)
Expected total cost	**£3,096.81**	**£2,609.62**		

ALT - alanine aminotransferase; AST - aspartate aminotransferase; CRS - cytokine release syndrome; WBC - white blood cell; blin - blinatumomab; SoC - standard of care; PSSRU - Personal Social Services Research Unit
**Unit costs uplifted to 2021/22 values*

(v) Subsequent-line therapy costs

In current practice, patients who relapse may receive additional treatment with blinatumomab, inotuzumab ozogamicin, chemotherapy, and CAR T-cell therapy. They may also undergo alloSCT. The company's model excludes the possibility of patients receiving CAR-T therapy because brexucabtagene autoleucel is currently only available through the CDF, and tisagenlecleucel is recommended only for people up to the age of 25 years. As such, the model includes blinatumomab, inotuzumab ozogamicin, and chemotherapy (assumed to be FLAG-IDA) as possible drug-based subsequent therapies. The model assumes that amongst patients who relapse in the blinatumomab plus SoC group, [redacted] receive inotuzumab ozogamicin and the remaining [redacted] receive FLAG-IDA, whereas in the SoC group, [redacted] receive inotuzumab ozogamicin, [redacted] receive blinatumomab and [redacted] receive FLAG-IDA. These assumptions were based on clinical input obtained by the company.[17] The model applies the costs of subsequent treatments for relapsed B-cell ALL as once-only costs at the point of relapse based on the number of new RFS events in each model cycle. Patients are assumed to receive only one line of subsequent therapy for relapsed ALL.

The acquisition costs of subsequent therapies are presented in Table 39. The dose and administration of subsequent-line therapy covering whole treatment cycles followed the TOWER trial[66] for blinatumomab and FLAG-IDA, and estimates reported in TA541[17] for inotuzumab ozogamicin (see Table 40). Drug costs were obtained from the BNF,[80] eMIT[79] and the Monthly Index of Medical Specialities (MIMS).[86] Acquisition costs for all components were adjusted for wastage based on estimated distributions of BSA or weight.

Table 39: Subsequent-line therapy – acquisition costs per dose, including wastage

Drug	Preparation	Pack size (vials/ tabs)	Unit cost	Dose per admin	Cost per dose (including wastage)*	Unit cost source
Blinatumomab (inc. PAS)	38.5mcg	1	[redacted]	28mcg/day	[redacted]	CS[1]
Inotuzumab ozogamicin	1mg	1	£8,048.00	0.8mg/m² 0.5mg/m²	£8,048.00	BNF[80]
Fludarabine	50mg/2ml vial	1	£83.86	30mg/m²	£158.30	eMIT[79]
Cytarabine	20mg/ml vial	5	£4.19	2,000 mg/m²	£27.14	eMIT[79]
	100mg/ml vial	1	£7.72			
		1	£8.50			
		5	£2.75			
Idarubicin	1mg/ml vial	1	£87.36	8mg/m²	£323.82	MIMS[86]
	1mg/ml vial	1	£174.72			
Filgrastim	0.30mg/ml vial	5	£175.68	0.005mg/m²	£86.52	BNF[80]
	0.60mg/ml vial	7	£189.33			
	0.60mg/ml vial	1	£175.67			
	0.96mg/ml vial	5	£166.46			
	0.96mg/ml vial	7	£189.88			
	0.96mg/ml vial	5	£189.12			
	0.96mg/ml vial	1	£175.13			

PAS - Patient Access Scheme; CS - company's submission; eMIT - electronic Market Information Tool; BNF - British National Formulary; MIMS - Monthly Index of Medical Specialities
** Costs adjusted for patient BSA/weight based on characteristics of patients in E1910[11]*

Table 40: Drug acquisition and administration costs, subsequent-line therapy

Treatment, frequency and proportion starting cycle				Drug acquisition		Drug administration				
Cycle	**Drug**	**Admins/ cycle**	**Percent starting cycle***	**Expected cost**	**Expected total acquisition cost**	**IP days**	**OP bag changes**	**Pumps (28- IP days)**	**IV OP**	**Expected total admin cost**
Blin Cycle 1	Blinatumomab	24	[redacted]	[redacted]	[redacted]	10	4	[redacted]	-	[redacted]
Blin Cycle 2	Blinatumomab	28	[redacted]	[redacted]		2	6	[redacted]	-	
Blin Cycle 3	Blinatumomab	28	[redacted]	[redacted]		-	7	[redacted]	-	
Blin Cycle 4	Blinatumomab	28	[redacted]	[redacted]		-	7	[redacted]	-	
Blin Cycle 5	Blinatumomab	28	[redacted]	[redacted]		-	7	[redacted]	-	
Blin Cycle 6	Blinatumomab	28	[redacted]	[redacted]		-	7	[redacted]	-	
Blin Cycle 7	Blinatumomab	28	[redacted]	[redacted]		-	7	[redacted]	-	
Blin Cycle 8	Blinatumomab	28	[redacted]	[redacted]		-	7	[redacted]	-	
Blin Cycle 9	Blinatumomab	28	[redacted]	[redacted]		-	7	[redacted]	-	
Inotuzumab ozogamicin Cycles 1-3	Inotuzumab ozogamicin	9.5†		£76,375.52	£76,375.52	9.5†	-	-	7	£7,931.71
FLAG-IDA Cycle 1	Fludarabine	5	[redacted]	[redacted]	[redacted]	16.8‡	-	-	-	[redacted]
	Cytarabine	5		[redacted]						
	Idarubicin	3		[redacted]						
	Filgrastim	14		[redacted]						
FLAG-IDA Cycle 2	Fludarabine	5	[redacted]	[redacted]		16.8‡	-	-	-	
	Cytarabine	5		[redacted]						

Treatment, frequency and proportion starting cycle				Drug acquisition		Drug administration				
Cycle	**Drug**	**Admins/ cycle**	**Percent starting cycle***	**Expected cost**	**Expected total acquisition cost**	**IP days**	**OP bag changes**	**Pumps (28- IP days)**	**IV OP**	**Expected total admin cost**
	Idarubicin	3		[redacted]						
	Filgrastim	14		[redacted]						
FLAG-IDA Cycle 3	Fludarabine	5	[redacted]	[redacted]		16.8‡	-	-	-	
	Cytarabine	5		[redacted]						
	Idarubicin	3		[redacted]						
	Filgrastim	14		[redacted]						
FLAG-IDA Cycle 4	Fludarabine	5	[redacted]	[redacted]		16.8‡	-	-	-	
	Cytarabine	5		[redacted]						
	Idarubicin	3		[redacted]						
	Filgrastim	14		[redacted]						

Blin – blinatumomab; IV - intravenous; IP - inpatient; OP - outpatient

***** Based on the TOWER study*

† *Total number of doses across 3 cycles, based on information reported in the TA541 committee papers*[17]

‡ *Informed by TA893*[18] *and TA450*[16]

The estimated once-only costs for subsequent-line therapy are presented in Table 41. Similar to the post-relapse alloSCT costs, the company's model assumes that patients who remain relapse-free after five years are cured; hence, these subsequent-line treatment costs are applied only to patients who relapse during the first 5 years since model entry.

Table 41: Summary of subsequent-line therapy costs

	Cost		Distribution	
Treatment	**Acquisition**	**Admin**	**Blinatumomab plus SoC**	**SoC**
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]
Inotuzumab ozogamicin	£76,375.52	£7,931.71	[redacted]	[redacted]
FLAG-IDA	[redacted]	[redacted]	[redacted]	[redacted]
Once-only cost of treatment acquisition			[redacted]	[redacted]
Once-only cost of treatment administration			[redacted]	[redacted]

SoC - standard of care; FLAG-IDA - fludarabine, cytarabine, G-CSF and idarubicin

(vi) Terminal care costs

The costs of terminal care were estimated based on a weighted mean of non-elective long-stay and non-elective short-stay episodes for people with ALL with a complication/comorbidity (CC) score of 0, 2-4 or 5+, from NHS Reference Costs 2021/22.[81] The weighted mean cost was estimated to be £10,952.83 per patient.

Within the company's model, the once-only cost of terminal care is applied only to those patients who die within the first 5 years of the time horizon.

5.2.5. *Model evaluation methods*

The CS[1] presents cost-effectiveness results for blinatumomab plus SoC versus SoC using both the deterministic and probabilistic versions of the model. All results presented in the CS include the PAS discount for blinatumomab. All analyses apply a severity modifier of 1.0.

Within the PSA, the company used beta distributions for utility/disutility values and proportions/probabilities, gamma distributions for costs, AE durations and the SMR, Dirichlet distributions for the proportion of patients receiving subsequent-line therapies and multivariate normal distributions for survival distributions. The probabilistic ICER is based on 1,000 Monte Carlo simulations. The results of the PSA are presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs).

The CS[1] presents the results of deterministic sensitivity analyses (DSAs) using tornado plots. The CS also presents the results of eight probabilistic scenario analyses which explore: alternative discount rates for health outcomes and costs; the use of standard log-normal survival distributions for RFS and OS;

blinatumomab dose adjustments based on the observed dose in Study E1910[11] and two alternative MCMs for each of RFS and OS. No subgroup analyses are presented.

5.2.6. *Company's original model results*

Table 42 presents the central estimates of cost-effectiveness generated using the company's original submitted model, including the PAS for blinatumomab. The probabilistic version of the model suggests that blinatumomab is expected to generate an additional [redacted] discounted QALYs at an additional cost of [redacted]; the corresponding ICER is £32,539 per QALY gained. The deterministic version of the model suggests a slightly lower ICER of £31,643 per QALY gained.

Table 42: Company's base case results – blinatumomab plus SoC versus SoC, including blinatumomab PAS

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model†							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,539**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,643**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SoC - standard of care
** Undiscounted*
† Based on a re-run by the EAG

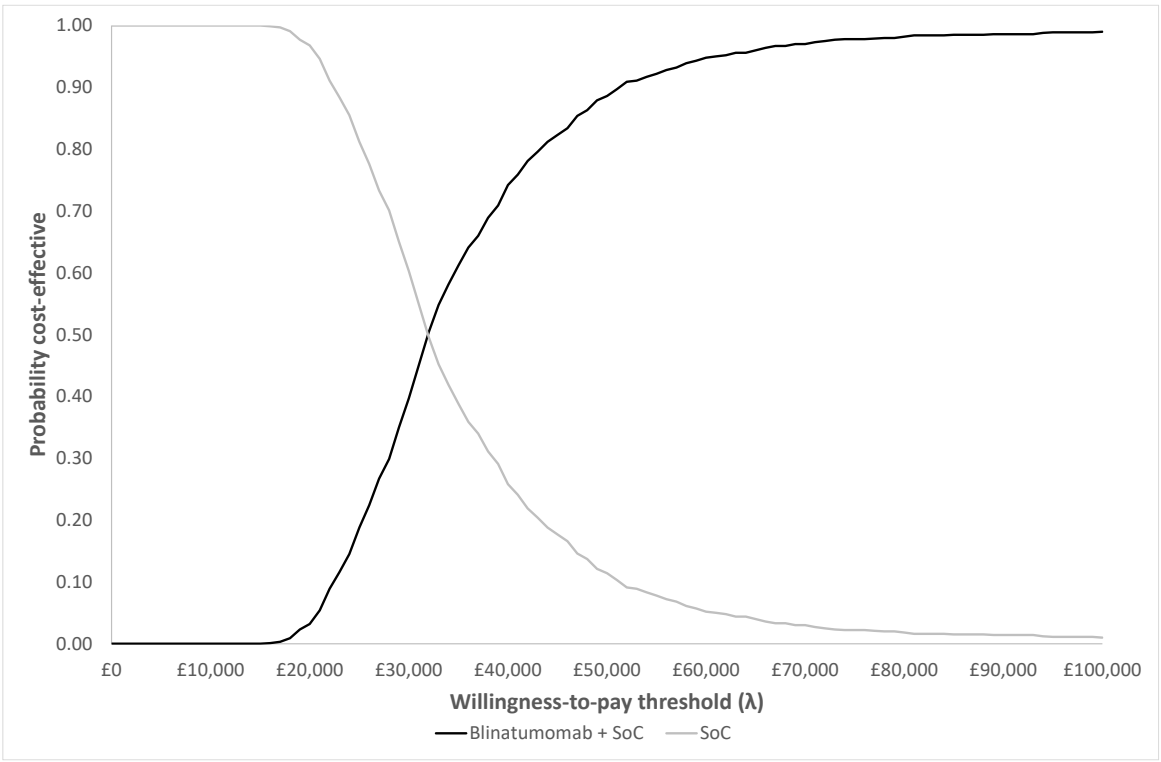
Company's PSA results

The results of the company's PSA are presented as a cost-effectiveness plane in Figure 18 and as CEACs in Figure 19. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the probability that blinatumomab generates more net benefit than BSC is expected to be approximately 0.03 and 0.40, respectively.

Figure 18: Cost-effectiveness plane, blinatumomab plus SoC versus SoC, including blinatumomab PAS (redrawn by the EAG)

Blin - blinatumomab; SoC - standard of care; QALY - quality-adjusted life year

Figure 19: Cost-effectiveness acceptability curves, blinatumomab plus SoC versus SoC, including blinatumomab PAS (redrawn by the EAG)

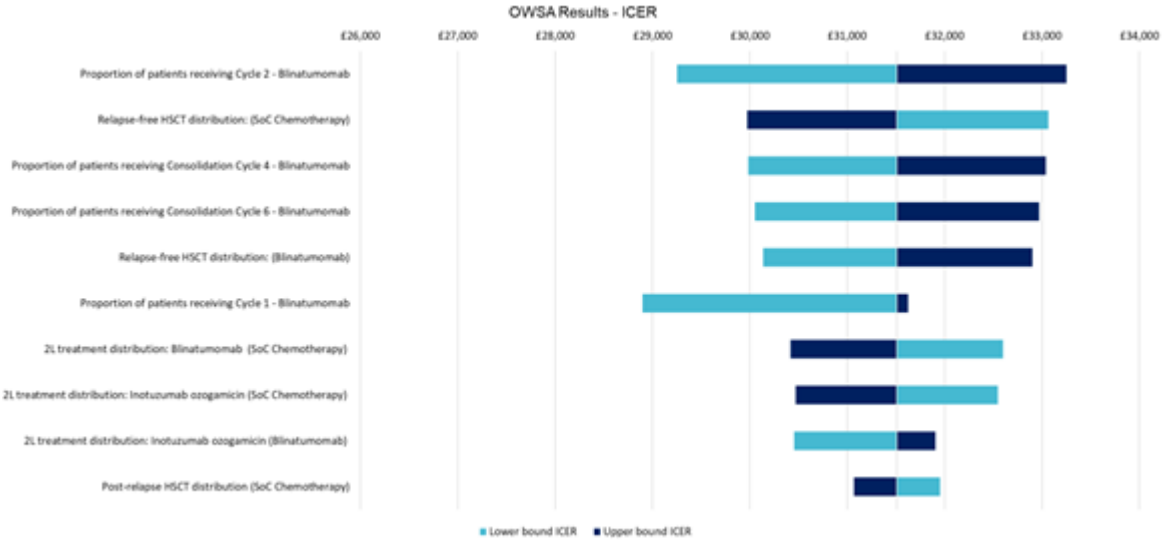


SoC - standard of care

Company's DSA results

Figure 20 presents the results of the company's DSAs using a tornado plot. The plot indicates that the ICER is somewhat sensitive to the proportion of patients receiving blinatumomab in each cycle of consolidation therapy, as well as the proportion of patients receiving alloSCT whilst relapse-free and the proportion of patients receiving blinatumomab or inotuzumab as subsequent therapy following relapse. The range of ICERs generated from the DSAs is fairly narrow, ranging from £28,898 per QALY gained (proportion of patients receiving blinatumomab in cycle 1 = [redacted]) to £33,254 per QALY gained (proportion of patients receiving blinatumomab in cycle 2 = [redacted]).

Figure 20: Company's tornado plot, blinatumomab plus SoC versus SoC, including blinatumomab PAS (reproduced from CS, Figure 26)



DSA - deterministic sensitivity analysis; ICER - incremental cost-effectiveness ratio; HSCT - haematopoietic stem cell transplant; SoC - standard of care

Company's scenario analysis results

Table 43 presents the results of the company's scenario analyses. As shown in the table, the ICER is substantially lower than the base case estimate when health outcomes and costs are discounted at a rate of 1.5%, and substantially higher when discounted at a rate of 5% (Scenarios S1 and S2, respectively). These scenarios reflect non-Reference Case discount rates. The company's clarification response[21] (question B21) states that the company does not intend to make a case in support of non-Reference Case discount rates in this appraisal; hence, these scenario analyses are unlikely to be useful for informing decision-making. The use of standard log-normal parametric survival models for RFS and OS suggest a lower ICER of £25,734 per QALY gained (Scenario S3); however, given that cure is expected for some patients, this approach may not be useful as it assumes a homogenous patient population which follows a single hazard function. Adjusting the blinatumomab dose according to the observed dose in Study E1910[11] reduces the ICER to £28,561 per QALY gained Scenario S4). The remaining scenarios (S5-S8) apply alternative MCMs for RFS and OS and indicate that selecting these alternative models has only a very limited impact on the ICER for blinatumomab.

Table 43: Company's scenario analysis results – blinatumomab plus SoC versus SoC, probabilistic, including blinatumomab PAS

No.	Scenario	Incremental QALYs gained	Incremental costs	ICER
-	Company's base case (deterministic)	[redacted]	[redacted]	**£31,643**
S1	Discount rates for health effects and costs = 1.5%	[redacted]	[redacted]	£23,683
S2	Discount rates for health effects and costs = 5%	[redacted]	[redacted]	£40,381
S3	RFS = standard log-normal distribution; OS = standard log-normal distribution	[redacted]	[redacted]	£25,734
S4	Blinatumomab dose adjusted according to the observed dose per treatment cycle in Study E1910	[redacted]	[redacted]	£28,561
S5	RFS = exponential MCM	[redacted]	[redacted]	£32,957
S6	RFS = log-logistic MCM	[redacted]	[redacted]	£32,783
S7	OS = gamma MCM	[redacted]	[redacted]	£32,075
S8	OS = log-logistic MCM	[redacted]	[redacted]	£32,173

S - scenario; MCM - mixture-cure model; RFS - relapse-free survival; OS - overall survival; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

5.3. Critical appraisal of the company's original economic analyses

This section presents the EAG's critical appraisal of the company's original economic model, as described in the CS.[1] Section 5.3.1 summarises the EAG's methods for the critical appraisal of the company's model. Section 5.3.2 describes the EAG's verification of the company's model. Section 5.3.3 describes the correspondence between the CS, the model inputs and their original sources. Section 5.3.4 describes the extent to which the company's economic analysis adheres to the NICE Reference Case.[91] Section 5.3.5 presents the EAG's critical appraisal of the company's model.

5.3.1. *Critical appraisal methods*

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[92, 93]
- Scrutiny and discussion of the company's model by the EAG.
- Double-programming the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.

- Where possible, checking parameter values used in the company's model against their original data sources.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2. *Model verification by the EAG*

Table 44 presents a comparison of the results of the deterministic version of the company's original model and the EAG's double-programmed model. As shown in the table, the results obtained from the EAG's rebuilt model are very similar to those generated using the company's model. However, the EAG's double-programming exercise revealed several minor programming errors; these are discussed in detail in Section 5.3.5.

Table 44: Comparison of results generated using the company's original model and the EAG's double-programmed model, including blinatumomab PAS, excludes correction of errors

Outcome	Company's model		EAG's double-programmed model	
	Blinatumomab plus Soc	SoC	Blinatumomab plus SoC	SoC
LYGs*	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]
ICER	**£31,643**		**£31,643**	

EAG - External Assessment Group; SoC - standard of care; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PAS - Patient Access Scheme
** Undiscounted*

5.3.3. *Correspondence between the model, the CS and original sources of parameter values*

Where possible, the EAG checked the company's model input values against their original sources. The parameters of the survival models were generated from analyses of IPD from Study E1910[11] which were not available to the EAG; as such, the EAG cannot verify that these analyses have been undertaken appropriately. The EAG was able to identify most of the other model parameters from their original sources. The EAG notes some minor discrepancies in the AE disutility values whereby the original reported values were rounded down unnecessarily in the model. In addition, the EAG was unable to locate the disutility value for hypotension and lymphocyte count decreased in the committee papers for TA783.[75] Some minor errors in drug costs and pack sizes were also identified; these discrepancies have been resolved as part of the EAG's exploratory analyses.

5.3.4. *Adherence to the NICE Reference Case*

Table 45 summarises the extent to which the company's economic model adheres to the NICE Reference Case.[91] Overall, the EAG believes that the company's model is generally in line with the Reference Case. The only deviation is the exclusion of alloSCT which was listed as a comparator in the final NICE scope.[20]

Table 45: Adherence to the NICE Reference Case

Element of HTA	Reference Case	EAG comments
Defining the decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is generally in line with the final NICE scope.[20] No economic subgroup analyses are presented.
Comparator(s)	As listed in the scope developed by NICE	The company's model includes SoC consolidation chemotherapy as the sole comparator. AlloSCT is not included as a comparator. Clinical advisors consulted by the company and the EAG agreed that alloSCT is not a relevant comparator for this appraisal and that a positive recommendation for blinatumomab would not lead to the displacement of alloSCT.
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The economic analysis adopts an NHS and PSS perspective, including health effects on patients. Impacts on caregivers are not included.
Perspective on costs	NHS and PSS	The model includes costs borne by the NHS and PSS.
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained for blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy alone.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 50-year (lifetime) time horizon.
Synthesis of evidence on health effects	Based on systematic review	RFS and OS outcomes for blinatumomab plus SoC and SoC alone are derived from Study E1910.[11] This is the pivotal trial of blinatumomab plus SoC consolidation chemotherapy identified from the company's SLR. The EAG considers this evidence source to be relevant to the decision problem.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	HRQoL data were not collected in Study E1910.[11] In line with TA589,[15] the utility value for relapse-free state is based on EQ-5D estimates of MRD-responders from the BLAST study,[66] and the utility value for post-relapse state is based on mapped EQ-5D estimates from the TOWER study.[85] The disutility of alloSCT is based on a VAS estimate reported by Sung *et al.*[68] Disutilities associated with AEs are based on the published literature and previous NICE TAs.
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	

Element of HTA	Reference Case	EAG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	No additional equity weighting is applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be values using the prices relevant to the NHS and PSS	Drug costs are valued at current prices. Other resource costs are valued using estimates from NHS Reference Costs 2021/22[81] and the PSSRU[83] which have been inflated to current prices.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% in the base case analysis. Results are also presented using non-Reference Case discount rates of 1.5% and 5% in sensitivity analyses.

EAG - External Assessment Group; HTA - health technology assessment; NHS - National Health Service; PSS - Personal Social Services; PSSRU - Personal Social Services Research Unit; QALY - quality-adjusted life year; EQ-5D - Euroqol 5 Dimensions; alloSCT - allogeneic stem cell transplant; SLR - systematic literature review; NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; HRQoL - health-related quality of life; RFS - relapse-free survival; OS - overall survival: MRD - minimal residual disease

5.3.5. *Main issues identified in EAG's critical appraisal*

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's original economic model. These issues are discussed in further detail in the subsequent sections. It should be noted that many of these issues have only a minor impact on the ICER for blinatumomab plus SoC.

Box 1: Main issues identified from the critical appraisal

(1) Model errors and other minor issues

(2) Issues relating to the model structure and assumptions

(3) Uncertainty around long-term RFS and OS

(4) Uncertainty around the utility values applied in the company's model

(5) Uncertainty around the resource costs applied in the company's model

(6) Limited sensitivity analyses

(1) Model errors and other minor issues

The double-programming exercise and additional cell-checking undertaken by the EAG revealed some errors in the company's original executable model. These errors are described below. With the exception of issues (g) and (h), these errors were identified before the EAG submitted the clarification letter. The issues raised in the EAG's letter were addressed in a revised version of the company's model provided as part of their clarification response.

(a) Use of inappropriate life tables

The company's model applies general population life tables for the UK.[65] The EAG believes that it would be more appropriate to use life tables for England.[94]

(b) Inconsistent application of SMR-adjusted hazards in the survival analysis

The model applies the SMR-uplifted life table mortality risks to the cured subgroup of the MCM (i.e., those represented by the cure fraction). General population mortality risks (excluding the SMR) are also applied as a constraint to the uncured subgroup of the MCM survivor function. The EAG believes that this introduces an inconsistency into the model, as it implies that some long-term survivors in the uncured portion of the MCM may be subject to lower mortality risks than those patients in the cured subgroup. Instead, the EAG believes that it would be more appropriate to apply the same SMR-uplifted mortality risks as a constraint for RFS and OS in the uncured group and to characterise the risk of death in the cured group of the MCM.

(c) Programming error in the =INDEX() function applied to estimate the costs of maintenance therapy in the SoC consolidation chemotherapy group

The company's model assumes that patients who discontinue consolidation therapy before completing the full course of treatment receive maintenance therapy for a longer duration compared with people who complete the full course of consolidation therapy. The model calculations which estimate the proportion of early discontinuers in the SoC group includes a programming error which erroneously refers to the proportion of early discontinuers in the blinatumomab plus SoC group.

(d) Error in uplifting some administration costs for maintenance therapy to current values

Administration costs associated with outpatient bag changes and IV infusions during maintenance therapy erroneously exclude uplifting of costs to current values.

(e) Programming error leading to inconsistent application of general population utility values to relapse-free patients

The model assumes that the HRQoL for patients who remain relapse-free after 5 years rebounds to general population levels. However, the model only applies general population utility values to the cured group of the MCM (those reflected by the cure fraction), rather than all patients who remain relapse-free at 5 years.

(f) Programming error leading to a higher proportion of patients receiving blinatumomab in cycle 4 versus cycle 3 in PSA samples

The PSA includes a minor programming error which frequently produces samples which allow the proportion of patients who receive blinatumomab in cycle 4 to be higher than the proportion of patients who receive blinatumomab in cycle 3.

(g) Minor errors in dose calculation

The model errneously applies a pack size of 5 for vincristine and a pack size of 10 for etoposide. According to eMIT,[79] these values should both be 1. The cost per pack of cytarabine should be £26.53 instead of £13.76. In addition, the EAG believes that the cost of 6-mercaptopurine should be based on the drug tariff price of £8.45 rather than the NHS indicative price of £9.42.

(h) The different pack sizes and costs of filgrastim and idarubicin

The EAG notes that some pack sizes and costs of filgrastim on BNF 2024 have recently been updated. This affects the lowest prices for the 30 million units/0.5 ml vial and the 48 million units/0.5 ml vial. The EAG also found that the unit costs of idarubicin in the eMIT are less expensive than those used in the company's model: £71.88 per 5mg/5ml vial and £145.13 per 10mg/10ml vial instead of £87.36 and £174.72, respectively.

(i) Exclusion of half-cycle correction

As noted in Section 5.2.2, the company's model includes the functionality to apply half-cycle correction, but this is excluded from the base case analysis. The EAG believes that half-cycle correction should be included. This is a very minor issue because the cycle length is short (1 week).

The company's clarification response[21] (questions B11, B13, B23-B26) acknowledges that issues (a)-(f) were errors in the original model. These issues were addressed in the updated version of the company's model provided as part of their clarification response. Issues (g)–(i) were identified by the EAG after the clarification letter was submitted and were therefore not addressed in the company's clarification response. The results of this updated model are summarised separately in Section 5.4. The correction of these errors results in a small reduction in the company's base case ICER.

(2) Issues relating to the model structure and assumptions

(a) Use of a partitioned survival model structure

In TA589,[15] the Evidence Review Group (ERG) raised concerns that a large proportion of MRD-positive patients receiving blinatumomab or standard care chemotherapy were assumed to undergo alloSCT, yet the company's economic analysis used a partitioned survival model structure which did not include a causal link between receipt of alloSCT and its impact on RFS and OS. The final guidance document for this appraisal states that this model was not suitable for decision-making. At the request of the NICE Appraisal Committee, the company subsequently submitted a revised model which used a semi-Markov approach and included an explicit causal link between the probability of undergoing alloSCT and RFS and OS in both treatment groups. This revised semi-Markov model was subsequently used to inform decision-making.

In the current appraisal of blinatumomab, the company's economic analysis is based on a partitioned survival model approach. The CS[1] (page 62) highlights that the proportion of patients who received alloSCT in Study E1910[11] was low and comparable between the treatment groups, and that the selected partitioned survival modelling approach produces predictions which are close to the observed comparative survival data.

The ERG's criticisms about the lack of a structural link between receipt of alloSCT and RFS and OS in TA589[15] could be argued to also apply in the current appraisal – ideally, the model structure should reflect the differential impact of alloSCT on subsequent event risks because alloSCT may lead to curative outcomes for some patients. However, the EAG agrees that the structural limitations of the company's partitioned survival model appear to be mitigated by the fact that the proportions of patients who underwent alloSCT in Study E1910[11] was similarly low in both treatment groups. The EAG also notes that the number of patients available to inform transitions between the health states with and without alloSCT would be small and any resulting model predictions would likely be highly uncertain. As such, the EAG considers the company's model structure to be generally appropriate in this case.

(b) Assumption of a 5-year cure time point

Whilst the company's economic model is informed by MCMs for RFS and OS, the model also includes a structural assumption of cure at 5 years. This cure time point was based on clinical opinion. The cure time point acts as a cap on costs and/or QALYs in the following parts of the model:

- Health utility for patients who remain relapse-free rebounds to age- and sex-matched general population norms after 5 years
- Costs of subsequent-line drug treatment and alloSCT are assumed to be zero after 5 years
- QALY losses associated with receipt of post-relapse alloSCT are not applied after 5 years
- Deaths occurring after 5 years are assumed to be unrelated to ALL; hence the terminal care QALY losses and costs are not applied after this time point.

The EAG notes that the uncured portions of the fitted MCMs for RFS in both treatment groups indicate that a small proportion of patients continue to experience relapse beyond 5 years and this can be seen in the model trace for both treatment groups. The model features listed above imply that even though some patients continue to experience relapse beyond 5 years, they are not treated with drug therapy or alloSCT and they do not suffer any loss of HRQoL due to post-relapse alloSCT. The EAG does not consider these assumptions to be appropriate - these costs and adverse health effects should be included in the model, regardless of when cure is expected. Applying a 5-year cap on costs and QALY losses associated with terminal care might be generally reasonable as a means of attributing these impacts only to ALL-related deaths rather than all deaths. However, the EAG notes that this approach will ignore some costs and QALY losses for patients who suffer late relapse but survive beyond the assumed 5-year cure time point.

(3) Uncertainty around long-term RFS and OS

Overall, the EAG considers that the company's survival analysis is reasonable, although some concerns have been identified. These concerns are discussed below based on the general considerations around model fitting and selection set out in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[87, 95]

(a) Consideration of suitability of joint models

The company investigated the appropriateness of fitting combined models by assessing the proportional hazards (PH) assumption using log cumulative hazard plots and Schoenfeld residual plots, and the accelerated failure time (AFT) assumption using quantile-quantile (Q-Q) plots. Given that there was evidence found against fitting combined models, the company concluded that fitting separate models to the available data for each treatment group was more appropriate. The EAG believes that this is a reasonable approach as it does not rely on the assumption that the observed treatment effect is maintained beyond the observed period of the trial.

(b) Range of candidate models assessed

The company fitted MCMs to the available data on RFS and OS. Candidate models included exponential, Weibull, gamma, Gompertz, log-logistic, log-normal and generalised gamma MCMs. The generalised gamma MCM was excluded from further consideration as it did not converge for OS and it provided low cure fractions for RFS. The Gompertz MCM was excluded as it provided unstable cure fraction for both RFS and OS. The EAG acknowledges the convergence issue with the generalised gamma and Gompertz MCMs.[96] In addition, the company fitted seven standard parametric survival distributions to the data for each arm of the trial, including the exponential, Weibull, gamma, Gompertz, log-logistic, log-normal and generalised gamma distributions. However, the results for these survival models were not included in the CS. The EAG agrees with the use of MCMs, but notes that providing the results of the standard parametric models in the CS may have been useful, if only to provide further evidence to justify their exclusion.

(c) Statistical and visual goodness-of-fit

Among other factors, the company's model selection process included consideration of statistical goodness-of-fit (AIC and BIC) and visual inspection. The EAG notes that the company summed the separate AIC/BIC values for each treatment group together to inform model selection. The EAG disagrees with this approach and believes that it is more informative to consider AIC/BIC for each model fitted to the data for each treatment group. In response to clarification question B8,[21] the company provided AIC/BIC values for each arm separately (see Table 22 and Table 24). When the generalised gamma and Gompertz MCMs are excluded, the remaining MCMs for RFS and OS all have generally similar AIC/BIC values for each treatment group.

(d) Consideration of nature of hazards

The CS[1] states that the company considered hazard plots to inform model selection; however, these plots were not provided or discussed in the CS. In response to the clarification question B3,[21] the company presented the empirical hazard plots and the hazard plots from the fitted MCMs. The empirical hazard for RFS has a decreasing trend for both treatment arms with a potential slight increase at the start of the SoC arm depending on the smoothing method used (see Figure 11 and Figure 12). The empirical hazard for OS first increases and then decreases (see Figure 15 and Figure 16). All of the fitted MCMs, apart from the exponential MCM for OS, appear to capture the general shape of the RFS and OS hazards well.

The EAG notes that each of the hazard plots provided in the company's clarification response[21] include a hazard function denoted "noisy." The EAG is unsure how these have been generated and considers them difficult to interpret. The EAG would have preferred to have seen the unsmoothed empirical hazards in a form that is easier to interpret (e.g., as a standard stepped hazard function); however, this is a minor criticism.

(e) Consideration of long-term clinical plausibility and cure assumptions

As discussed in Section 5.2.4, the company held clinical validation meetings to obtain clinical input on the cure assumption as well as the long-term clinical plausibility of selected MCMs.[88] The EAG notes that the estimated cure fractions from the MCMs vary for the SoC group, with a range of 0.28 (from 0.26 to 0.54) for OS and 0.11 (from 0.43 to 0.54) for RFS, whereas the use of different MCMs did not result in a marked difference in the estimated cure fractions for the blinatumomab plus SoC group, with a range of 0.06 (from 0.76 to 0.82) for OS and 0.03 (from 0.74 to 0.77) for RFS. During the clarification round, the EAG asked the company to comment on the plausibility of assuming different cure fractions between RFS and OS (see clarification response,[21] question B5). The company's response explains that it is plausible that the OS cure fraction should be slightly higher than the RFS cure fraction as further cure may be attained by relapsed patients through the use of subsequent-line therapies. This is consistent with the company's base case models, with an estimated cure fraction of 0.82 for blinatumomab plus SoC OS, 0.74 for blinatumomab plus SoC RFS, 0.53 for SoC OS and 0.47 for SoC RFS.

The EAG notes that in the second clinical validation meeting,[88] the log-logistic and Weibull MCMs for RFS and log-normal and the exponential MCMs for OS (which give the lowest long-term OS predictions) were not included in the clinical validation meeting slides.

The EAG sought further advice from their clinical advisors regarding the plausibility of the company's selected MCMs for RFS and OS. The EAG showed the advisors the company's MCM predictions for RFS and OS, including hybrid Kaplan-Meier survivor functions followed by SMR-uplifted general

population mortality risks after the last observation (see Figure 9, Figure 10, Figure 13 and Figure 14). Both clinical advisors expressed uncertainty in selecting a preferred model for OS. Both advisors stated that late relapse following chemotherapy can occur but that this is rare. The first clinical advisor considered the model predictions for the company's selected Weibull MCM for OS to be reasonable. They also commented that the company's selected log-normal MCM for RFS seemed reasonable and highlighted that this model produced the most pessimistic predictions for both treatment groups. They further stated that they considered it appropriate to apply the same RFS/OS model for both treatment groups. The second clinical advisor noted that there was little difference in RFS between the models. They stated that it was difficult to select a preferred model for OS, but highlighted that the log-normal and exponential MCMs for OS in the SoC group appeared to be overly pessimistic as they predict markedly lower OS compared with the other models (see Figure 14). Owing to uncertainty around long-term outcomes, the clinical advisors agreed that it was important to explore the impact of all of the models in sensitivity analyses.

Both clinical advisors highlighted that ALL treatments can lead to late effects such as secondary malignancy and increased risk of heart disease; however, they agreed that the use of a low SMR was appropriate for this population because few patients would receive alloSCT.

EAG conclusions on the company's survival analysis

Overall, the EAG considers the company's decision to apply log-normal MCMs for RFS and Weibull MCMs for OS is reasonable. The EAG notes that given that several other fitted MCMs have similar AICs and reasonable hazard shapes, these alternative models may also be potentially appropriate. The EAG's exploratory analyses include scenario analyses to demonstrate the impact of all of the fitted MCMs for RFS and OS on the ICER for blinatumomab plus SoC.

(4) Uncertainty around the utility values applied in the company's model

The EAG considers that the utility values for the relapse-free state (utility = 0.84 to 0.85, depending on whether patients receive blinatumomab in a given model cycle) are generally appropriate, although there is some uncertainty around whether HRQoL would fully rebound to general population levels after 5 years. The EAG's clinical advisors mentioned that some patients may experience lower long-term HRQoL as a consequence of the cumulative burden of toxicity from chemotherapy.

However, the EAG has concerns that the utility value of 0.692 applied in the post-relapse state is implausibly high. This same issue was raised by the ERG in TA589[15] and the final guidance document states that the Appraisal Committee considered that this value was *"too high."* Within the current appraisal, the EAG's clinical advisors both commented that this value was unreaslistically high. In response to a request for clarification from the EAG (see clarification response,[21] question B14), the

company stated that: *"The PRS utility of 0.692 was validated with UK clinical experts, who confirmed that this utility value reasonably represents the quality of life of the modelled PRS population."* However, the minutes of the company's clinical validation meeting include a comment from a clinical expert that [redacted] Overall, the EAG retains its view that the post-relapse utility value applied in the company's model is not plausible.

As part of the company's clarification response[21] (question B14), the company presented scenario analyses which apply lower post-relapse utility values of 0.50 and 0.25. The inclusion of these alternative utility values only resulted in small reductions in the ICER. These alternative scenarios are also included in the EAG's exploratory analyses (see Section 5.5).

(5) Concerns regarding costs included in the model

Overall, the EAG believes that the range of resource costs included in the company's model and the sources used to value these are generally appropriate. However, the EAG identified some minor concerns relating to the exclusion of clinic visit/monitoring costs, the exclusion of costs associated with AEs resulting from subsequent-line therapies following relapse, an implicit assumption that all RFS events are relapses which leads to the overestimation of subsequent-line therapy costs, and the use of an outdated unit cost for alloSCT follow-up. These issues are described below.

(a) Exclusion of monitoring-related resource costs

The company's model does not include any costs associated with clinician visits or monitoring tests, either before or after relapse. The EAG's clinical advisors stated that currently some patients undergo regular MRD testing to determine eligibility for treatment with blinatumomab. The advisors commented that MRD testing is done on bone marrow which is invasive and that the test is expensive. They stated that testing is usually performed on a 3-monthly basis to look for re-emergence of disease, but noted that there is variation in practice. They stated that if a patient was receiving blinatumomab then they would not monitor their marrow regularly if the patient was otherwise well. They also stated that although clinical practice is variable, patients typically also require regular clinic visits and blood counts after each cycle of consolidation therapy and during each maintenance cycle. After completing treatment, patients tend to attend clinic more often initially, with the frequency of clinic visits declining over time. These costs are not included in the company's model.

As part of the clarification process, the EAG asked the company to provide an updated economic model which includes the costs of clinic visits and monitoring (see clarification response,[21] question B15). The company's updated model includes the functionality to include HCRU costs associated with visits and

monitoring. This analysis includes the costs of visits with haematologists, radiologists, other specialists and GPs, assuming more frequent visits in years 1-2 versus years 3-5. Within the updated model trace, these costs are applied only to patients who have completed or discontinued consolidation therapy. Compared with the company's base case analysis, the inclusion of these costs leads to a small reduction in the ICER (see Table 47).

(b) Exclusion of costs of AEs associated with subsequent-line therapies

The company's model includes the costs of Grade ≥3 TEAEs observed in Study E1910.[11] The Clinical Study Report (CSR) for Study E1910 states that these TEAEs were captured during the Step 3 treatment period or within 30 days of Step 3 treatment end. Whilst the model assumes that all patients who relapse receive subsequent-line therapy, it excludes any further costs associated with AEs caused by those therapies.

The company's revised model includes additional functionality to include costs and QALY losses associated with AEs from subsequent-line therapies in the analysis (see clarification response,[21] question B16). This scenario analysis indicates that including subsequent-line AEs leads to a small reduction in the ICER (see Table 47).

(c) Assumption that all RFS events are relapses

The company's model estimates the costs associated with post-relapse alloSCT and subsequent-line therapies based on the number of new RFS events which occur in each model cycle. The costs of these interventions are then applied as once-only lump sum costs to newly relapsed patients. A similar approach is also applied to estimate QALY losses associated with post-relapse alloSCT. This approach implicitly assumes that all RFS events are relapses rather than deaths. However, in Study E1910,[11] [redacted] RFS events in the blinatumomab plus SoC group and [redacted] RFS events in the SoC group were deaths rather than relapses. As a consequence, the model likely overestimates the costs and negative health impacts associated with post-relapse treatments.

During the clarification round, the EAG asked the company to amend the model to address this issue (see clarification response,[21] question B22). The company's updated model includes the functionality to adjust the RFS probabilities to account for fatal events. This adjustment leads to a small increase in the ICER (see Table 47). The company's clarification response notes that: (a) the absolute number of pre-relapse deaths was similar between the treatment groups which affects the proportion of RFS events which are fatal and (b) that data collection on RFS in Study E1910[11] was less rigorous after 2 years which may have resulted in some inaccuracy. The EAG believes that the first issue simply reflects the observed data. The EAG acknowledges the second issue as a limitation, but notes that if the data

collection in Study E1910 did result in bias, this could have more far-reaching impacts on other aspects of the economic model e.g., the RFS extrapolation for the SoC group where later RFS and OS events were observed.

(d) The source used to inform alloSCT costs is outdated

The company's model includes the costs of alloSCT follow-up based on a costing analysis included in a 2014 report published by NHS Blood and Transplant.[82] This costing analysis was, in turn, informed by an earlier analysis von Agthoven *et al*. (2002).[98] The EAG notes that this source is more than 20 years old. However, this same source has been used in several other appraisals of ALL therapies[15, 19, 90] and the EAG is unaware of any better, more recent alternative sources. The EAG notes that the company's model is not sensitive to the cost of alloSCT.

(6) Limited sensitivity analyses

The CS[1] includes scenario analyses which include the use of two alternative MCMs and one standard parametric survival model for each time-to-event end point in the model (see Table 47). These analyses result in ICERs which are similar to or lower than the company's base case ICER. As noted in critical appraisal point 3, there are other potentially plausible MCMs which have not been considered in the company's base case analysis or scenario analyses. As such, the EAG considers the analyses presented in the CS to be limited. The EAG's exploratory analyses include consideration of all fitted MCMs for RFS and OS to explore their impact on the cost-effectiveness of blinatumomab.

5.4. Summary of the company's updated model

As part of the company's clarification response,[21] the company provided an updated version of their model. The company's updated base case model includes the following amendments:

- General population mortality risks were amended to reflect life tables for England and Wales
- General population utility values are applied to all patients who are relapse-free after 5 years (rather than just those patients represented by the cure fraction)
- The SMR was applied to both the cured and non-cured parts of the MCMs for RFS and OS.
- All drug administration costs were uplifted to 2022/23 values.
- The programming error relating to SoC maintenance therapy was corrected.
- The model calculations were amended to cap the proportion of patients receiving consolidation therapy in a current cycle at the level of use in the previous cycle. This amendment is applied to both treatment groups in the model.

In addition, the company's clarification response[21] includes the results of several additional scenario analyses which explore other issues raised in the EAG's clarification letter, including:

- Assuming that the relapse-free utility value does not rebound to general population norms
- Applying lower post-relapse utility values of 0.50 and 0.25
- Including HCRU costs for up to 5 years in relapse-free patients who have completed or discontinued consolidation therapy and for up to 5 years (from model entry) in people with relapsed disease
- Including costs and QALY losses due to AEs associated with subsequent-line treatments for relapsed ALL
- Adjusting costs and disutilities to account for the proportion of RFS events which are deaths.

The results of the company's updated base case analysis are summarised in Table 46. The results of the company's additional scenario analyses are summarised in Table 47. The company's updated base case model generates a slightly lower deterministic ICER compared with their original model (£31,505 versus £31,643 per QALY gained). The company's additional scenario analyses suggest that alternative assumptions around HRQoL decrements, post-relapse utility values, health state resource use, AEs and RFS fatality rates do not have a material impact on the ICER for blinatumomab – amongst the scenarios tested, the largest increase in the ICER was £629.

Table 46: Results of the company's original and updated base case analyses, deterministic, including blinatumomab PAS

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Company's original base case analysis							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,643**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's updated base case analysis (post-clarification)							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,505**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-

** Undiscounted*
Blin - blinatumomab; SoC - standard of care; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

Table 47: Results of the company's additional scenario analyses, deterministic, including blinatumomab PAS

Scenario	Incremental QALYs gained	Incremental costs	ICER
Updated base case	[redacted]	[redacted]	**£31,505**
Include HRQoL decrement for cured population	[redacted]	[redacted]	£32,134
Lower post-relapse utility: 0.50	[redacted]	[redacted]	£31,350
Lower post-relapse utility: 0.25	[redacted]	[redacted]	£31,149
Include HCRU up to 5 years	[redacted]	[redacted]	£31,214
Include 2L Tx. AE costs and disutilities	[redacted]	[redacted]	£31,454
Adjust 2L costs and disutilities for proportion of RFS events that are deaths (fatal rate)	[redacted]	[redacted]	£32,068

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; HRQoL - health-related quality of life; HCRU - health care resource use; 2L - second-line ; Tx - treatment; AE - adverse event; RFS - relapse-free survival

The EAG notes that the company's updated analyses are subject to two minor issues: (i) the updated analyses apply life tables for England and Wales rather than England alone, and (ii) the general population utility multiplier is erroneously applied to patients who are relapse-free (those not reflected by the cure fraction) after their utility has already rebounded to the general population utility values after 5 years. These issues are resolved in the EAG's exploratory analyses (see Section 5.5).

5.5. EAG's exploratory analyses

5.5.1. *Exploratory methods*

The EAG undertook exploratory analyses (EAs) using the updated model provided in the company's clarification response.[21] All analyses were undertaken using the deterministic version of the model. The results of the EAG's preferred analysis are presented using both the probabilistic and deterministic versions of the model.

All analyses were undertaken by one modeller and checked by a second modeller. All results presented in this section include the PAS discount for blinatumomab. The results of the analyses including price discounts for other treatments (inotuzumab ozogamicin and 6-mercaptopurine) are provided in a separate confidential appendix to this EAG report.

EAG's preferred analysis

EA1: Correction of errors and other minor issues

The following corrections were applied to the company's updated model within a single combined analysis:

(a) *EA1a:* The model was amended to use life tables for England.

(b) *EA1b:* Pack sizes for etoposide and vincristine were corrected to be 1 instead of 10 and 5, respectively. The cost per pack of cytarabine was corrected to £26.53. The cost of 6-mercaptopurine was based on its NHS tariff price (£8.45 per pack) rather than the indicative price listed on the BNF[80] (£9.42 per pack).
(c) *EA1c:* The general population utility multiplier was removed when the age-and sex-matched general population utility value is applied to relapse-free patients (those not reflected by the cure fraction) after 5 years.
(d) *EA1d:* The most recent pack sizes and costs of filgrastim are used, resulting in a slightly lower cost per dose of £84.25 instead of £86.52. For idarubicin, the cheaper costs from eMIT are used: £71.88 per 5mg/5ml vial and £145.13 per 10mg/10ml vial.
(e) *EA1e:* Half-cycle correction was included.

These error corrections were also applied in subsequent exploratory analyses EA2-5.

EA2: Adjustment of RFS to account for fatal events

Within this analysis, an adjustment was applied to account for the proportion of RFS events which are deaths. This was implemented using additional functionality included in the company's updated model. The company estimated the fatal progression rate by dividing the number of RFS death events by the total number of RFS events per treatment arm ([redacted] in the blinatumomab plus SoC group and [redacted] in the SoC group). Costs and QALY losses associated with subsequent-line therapies and alloSCT are then applied only to non-fatal events.

EA3: **Inclusion of HCRU costs with no 5-year cap for post-relapse state**

This analysis includes additional health care costs in the relapse-free and post-relapse health states. Upon completion of consolidation treatment, patients who are relapse-free patients are assumed to incur a weekly cost of £103.44 and £56.80 during years 1-2 and years 3-5, respectively. These estimates include costs of visits with haematologists, radiologists, other specialists and GPs.[21] In this EAG exploratory analysis, patients who relapse during the first 5 years of the time horizon are assumed to incur a cost of £385.57 per week. This was implemented using additional functionality included in the company's updated model. In addition, the EAG amended the company's updated model to remove the 5-year cap on health care resource use costs for relapsed patients, and applies the lower weekly cost of £56.80 for all cycles after 5 years.

EA4: No 5-year cap for subsequent-line treatment/alloSCT costs and QALY losses

The EAG believes that patients who relapse after 5 years would receive subsequent-line treatment. Therefore, the model should include the costs of the second-line drug treatments and the costs and QALY losses associated with post-relapse alloSCT for all patients who relapse, regardless of whether

this event occurs before or after the assumed 5-year cure time point. This analysis removes the 5-year cap on the costs of subsequent-line treatment and the costs and QALY losses of alloSCT in the model.

EA5: EAG-preferred analysis

This analysis combines EAs 1-4. Results are presented using both the deterministic and probabilistic versions of the model (EA5a and EA5b, respectively).

Additional sensitivity analyses

The following additional sensitivity analyses (ASAs) were conducted using the deterministic version of the EAG's preferred model (EA5a).

- *ASA1a-j: Alternative MCMs for RFS and OS.* The model was re-run using alternative MCMs for RFS and OS. Alternative MCMs were evaluated separately for each end point. The same functional form was applied in each treatment group. These analyses were conducted using existing functionality in the company's model.
- *ASA2a-b: Use of non-parametric (Kaplan-Meier) RFS and OS plus fixed cure time points.* This analysis assumes that RFS and OS follow the observed Kaplan-Meier estimates from Study E1910[11] up to a fixed cure time point and then the hazards switch to those estimated from SMR-uplifted age-and sex-matched general population life tables. Cure time points of 5 years and 7.5 years were explored.
- *ASA3a-b: Alternative SMRs*. This analysis explores the extent to which the ICER is sensitive to the SMR. The use of a higher SMRs of 2.0 and 3.0 are explored.
- *ASA4a-b: Alternative post-relapse utility values*. This analysis explores the use of lower post-relapse utility values of 0.50 and 0.25.
- *ASA5: Inclusion of second-line treatment AEs costs and QALY losses.* This analysis includes both management costs and QALY losses associated with AEs resulting from subsequent-line treatments for relapsed disease. This analysis was conducted using additional functionality included in the company's updated model.
- *ASA6: Alternative proportion of patients receiving pre-relaspe alloSCT.* In Study E1910,[11] approximately [redacted] of patients received alloSCT prior to relapse. The EAG's clinical advisors stated that in UK clinical practice, they would not expect patients with MRD-negative Ph-negative B-cell ALL to receive alloSCT prior to relapse due to risks of TRM. This sensitivity analysis assumes that no patients receive alloSCT in the relapse-free state; however, OS and RFS are not adjusted from the base case.
- *ASA7: Adjustment for fatal RFS events excluded.* This sensitivity analysis removes the adjustment of fatal RFS events applied in EA2.

- *ASA8: Health care resource use costs applied from the begnining of consolidation.* This sensitivity analysis assumes that all relapse-free patients incur HCRU costs from the beginning of the consolidation treatment phase (rather than the end).
- *ASA9: Relapse-free utility applied indefinitely (no rebound to general population utility)*. This sensitivity analysis removes the assumption that HRQoL for patients who remain relapse-free after 5 years rebounds to general population norms. Instead, the utility value of 0.85 estimated from BLAST is applied indefinitely in the relapse-free state.

5.5.2. *Exploratory results*

Results of the EAG's preferred analysis

The results of the EAG's preferred analyses are shown in Table 48. Each exploratory analysis (EA) was applied individually. EAs 2-5 include the error corrections applied in EA1. None of the EAG's individual amendments have a material impact on the ICER; the largest impact is in EA4 which reduces the ICER by less than £1,200. The EAG's preferred analysis results in a probabilistic ICER of £31,214 per QALY gained (EA5b) and a deterministic ICER of £30,815 per QALY gained (EA5a). These ICERs are slightly lower than the company's updated base case ICER.

Table 48: EAG's preferred model results, includes PAS discount for blinatumomab

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated base case (post-clarification), deterministic							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,505**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA1: Correction of remaining model errors and other minor issues							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,485**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA2: Adjustment of RFS for fatal events							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,047**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA3: Inclusion of HCRU costs with no 5-year cap for post-relapse state							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,165**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA4: No 5-year cap for subsequent-line treatment/alloSCT costs and QALY losses							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,317**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA5a: EAG-preferred analysis (EA1-4 combined), deterministic							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,815**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA5b: EAG-preferred analysis (EA1-4 combined), probabilistic							

Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,214**
SoC	[redacted]	[redacted]	[redacted]				

** Undiscounted*
EA - exploratory analysis, PAS - Patient Access Scheme; Blin - blinatumomab; SoC - standard of care; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; RFS - relapse-free survival; HCRU - health care resource use; alloSCT - allogenic stem cell transplant

Results of the EAG's additional sensitivity analysis

The results of the EAG's additional sensitivity analyses are presented in Table 49. Based on the selection of MCM models for RFS and OS, the ICERs are estimated to range from £22,643 per QALY gained (RFS = log-normal MCM, OS = exponential MCM) to £32,144 per QALY gained (RFS = exponential MCM, OS = Weibull MCM). The ICER is also sensitive to:

- The assumed SMR – the ICER increases to £34,908 when the SMR is assumed to be 2.0 and to £38,845 when the SMR is assumed to be 3.0 (ASAs 3a and 3b).
- The use of certain alternative RFS and OS distributions – the application of the empirical Kaplan-Meier functions with a 5-year cure time point increases the ICER to £38,834 per QALY gained (ASA2a). The ICER is decreased to £27,375 per QALY gained if a later cure time point of 7.5 years is assumed (ASA2b). This is because the 5-year cure time point analysis ignores later RFS and OS events observed in the SoC group (see Figure 4 and Figure 5).

The model results are not particularly sensitive to any of the other alternative assumptions tested in the EAG's additional sensitivity analyses.

Table 49: EAG's additional sensitivity analysis results, including PAS for blinatumomab

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA5a: EAG-preferred analysis (EA1-4 combined), deterministic							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,815**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1a: RFS = exponential MCM, OS = Weibull MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,144**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1b: RFS = Weibull MCM, OS = Weibull MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,097**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1c: RFS = Gompertz MCM, OS = Weibull MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,652**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1d: RFS = log-logistic MCM, OS = Weibull MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,333**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1e: RFS = gamma MCM, OS = Weibull MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,138**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1f: RFS = log-normal MCM, OS = exponential MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,643**

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1g: RFS = log-normal MCM, OS = Gompertz MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,220**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1h: RFS = log-normal MCM, OS = log-normal MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,088**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1i: RFS = log-normal MCM, OS = log-logistic MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,013**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA1j: RFS = log-normal MCM, OS = gamma MCM							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,128**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA2a: RFS and OS = Kaplan-Meier function with cure time point at 5 years							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,834**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA2b: RFS and OS = Kaplan-Meier function with cure time point at 7.5 years							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,375**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA3a: SMR=2.0							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,908**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA3b: SMR=3.0							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,845**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA4a: Post-relapse utility value = 0.50							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,663**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA4b: Post-relapse utility value = 0.25							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,466**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA5: Inclusion of second-line treatment AEs costs and disutilities							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,693**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA6: Pre-relapse alloSCT proportion = 0%							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,641**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA7: Adjustment for fatal RFS events excluded							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,996**

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA8: HCRU costs applied from start of consolidation							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,228**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
ASA9: Relapse-free utility applied indefinitely (no rebound to general population utility)							
Blin+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,430**
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-

** Undiscounted*

EAG - External Assessment Group; ASA - additional sensitivity analysis; EA - exploratory analysis; blin - blinatumomab; SoC - standard of care; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; RFS - relapse-free survival; OS - overall survival; MCM - mixture-cure model; HCRU – health care resource use; SMR - standardised mortality ratio; AE - adverse event; alloSCT - allogenic stem cell transplantation; PAS - Patient Access Scheme

5.6. Discussion

The company undertook an SLR of existing economic studies of frontline therapies for newly diagnosed Ph-negative B-cell ALL.[11] The review included three existing economic evaluations; however, the company did not consider any of these to be considered relevant to the current appraisal.

The company's submitted economic model assesses the incremental cost-effectiveness of blinatumomab plus SoC consolidation therapy versus SoC consolidation therapy alone in adults with Ph-negative CD19-positive MRD-negative B-precursor ALL. The population included in the model is consistent with the population enrolled in Study E1910[11] and reflects the group of MRD-negative patients who are expected to be included in the anticipated extension of the marketing authorisation for blinatumomab.[1, 21] No subgroup analyses are reported. A comparison against alloSCT is not included. The company's model uses a partitioned survival approach which includes three health states: (i) relapse-free, (ii) post-relapse and (iii) dead. The analysis adopts an NHS and PSS perspective over a 50-year (lifetime) horizon. Caregiver effects are not included. Clinical outcomes for both the intervention and comparator groups are based on MCMs fitted to the data on RFS and OS from Study E1910. Consistent with TA589,[15] health state utility values were based on analyses of data collected in the BLAST and TOWER studies,[29;66] whilst disutility values associated with alloSCT and AEs associated with consolidation therapy were taken from literature, previous NICE TAs and assumptions. Resource costs are based on E1910,[11] previous literature, previous NICE TAs, standard costing sources[79-81, 86] and clinical assumptions.

The probabilistic version of the company's original model suggests that the ICER for blinatumomab plus SoC consolidation therapy versus SoC consolidation therapy alone is expected to be £32,539 per QALY gained. The deterministic ICER is slightly lower at £31,643 per QALY gained. Based on the characteristics of the population and the expected QALY gain in the SoC group, additional severity-related QALY weighting is not applicable.[99] Following the clarification round, the company submitted

an updated economic model which includes the correction of errors as well as additional functionality which allows further scenario analyses to be conducted. The company's updated model suggests a probabilistic ICER of £31,361 per QALY gained and a deterministic ICER of £31,505 per QALY gained. This updated model includes two additional minor issues: (i) the updated analyses apply life tables for England and Wales rather than England alone, and (ii) the general population utility multiplier is erroneously applied to relapse-free people (those not reflected by cure fraction) after their utility has already rebounded to the general population utility values after 5 years.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The EAG also checked the amendments applied in the company's updated model. The EAG's critical appraisal of the original model identified limitations regarding the model structure and assumptions, some limitations and uncertainties in the company's survival analysis, and uncertainty around the health state utility values and certain costs. Most of these issues appear to be minor.

The EAG undertook exploratory analyses using the company's updated model to address the issues described above. The EAG's preferred model includes: (i) the correction of minor errors and the inclusion of updated costs and half-cycle correction; (ii) adjustments to account for fatal RFS events; (iii) the inclusion of HCRU costs, including ongoing costs for relapsed patients after 5 years, and (iv) the removal of the 5-year cap on costs/QALY losses associated with subsequent-line treatment and alloSCT. The probabilistic version of the EAG's preferred model suggests that the ICER for blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation therapy alone is expected to be £31,214 per QALY gained. The deterministic ICER is similar at £30,815 per QALY gained. These ICERs are slightly lower than the ICERs suggested by the company's updated model.

The EAG's additional sensitivity analyses indicate that:

- The ICER may be reduced if either the exponential MCMs or log-normal MCMs for OS are selected. However, these models produce very pessimistic predictions in the SoC group and the EAG's clinical advisors did not consider them to be plausible.
- The ICER is noticeably higher if a fixed cure time point of 5 years is assumed. However, this approach ignores some later RFS and OS events in the SoC group and does not account for background mortality risks in either group during intervals where the empirical Kaplan-Meier function remains flat.
- The ICER is increased if higher SMRs are applied (base case SMR=1.09; scenarios tested include SMRs of 2.0 and 3.0). However, the EAG's clinical advisors commented that it is

appropriate to use a lower SMR in this population because few MRD-negative patients will receive alloSCT.

None of the EAG's other sensitivity analyses had a material impact on the ICER.

6. OVERALL CONCLUSIONS

Clinical effectiveness conclusions

The CS presents data from the E1910 RCT of blinatumomab plus SoC consolidation chemotherapy versus SoC consolidation chemotherapy alone in 224 adult patients with CD19-positive Ph-negative MRD-negative B-cell precursor ALL in the frontline consolidation phase. The population enrolled in Study E1910 were aged ≥30 years and ≤70 years. MRD negative status at Step 3 in the trial was based on a threshold of 0.01%. The anticipated licence extension for blinatumomab is expected to relate to adults with CD19-positive, Ph- negative, B-cell precursor ALL in the consolidation phase, regardless of MRD status.

As of the 23rd June 2023 DCO, significant reductions in the risks of death (HR 0.44; 95% CI 0.25, 0.76, *p*=0.001) and relapse or death (HR 0.53; 95% CI 0.32, 0.88, *p*=0.006) were reported for the blinatumomab group versus the SoC group. Median OS and median RFS were not reached in either treatment group. HRQoL data were not collected in the trial. The most common Grade 3 or 4 TEAEs in the blinatumomab group (vs SoC) were: neutrophil count decreased ([redacted]); platelet count decreased ([redacted]); white blood cell count decreased ([redacted]); lymphocyte count decreased ([redacted]); anaemia ([redacted]) and febrile neutropenia ([redacted]). TEAEs of special interest included CRS ([redacted]) and neurologic events, most commonly headache ([redacted]) and tremor ([redacted]).

The EAG's clinical advisors considered Study E1910 to be some extent representative of UK clinical practice, but noted differences in terms of age and race. They also stated that they would expect blinatumomab to also be an effective treatment in younger adult patients who are under 30 years of age. They highlighted that including the age-cut-off or the MRD threshold applied in Study E1910 in any future positive NICE recommendation for blinatumomab in this indication would inappropriately restrict access to treatment.

Cost-effectiveness conclusions

The company's model assesses the cost-effectiveness of blinatumomab in combination with SoC consolidation therapy versus SoC consolidation therapy alone in adults with Ph-negative CD19-positive MRD-negative B-precursor ALL. The company's updated economic model suggests that a probabilistic ICER of £31,361 per QALY gained and a deterministic ICER of £31,505 per QALY gained. The EAG's preferred analysis includes: (i) the correction of minor errors and the inclusion of updated costs and half-cycle correction; (ii) adjustments to account for fatal RFS events; (iii) the inclusion of monitoring-related HCRU costs, including ongoing costs for relapsed patients after 5 years, and (iv) the removal of the 5-year cap on costs/QALY losses associated with subsequent-line treatment and alloSCT. The

EAG's preferred model suggests slightly lower ICERs than those suggested by the company's model: the EAG's probabilistic ICER is expected to be £31,214 per QALY gained and the deterministic ICER is similar at £30,815 per QALY gained.

The EAG's analyses indicate that the ICER for blinatumomab may be noticeably lower than the company's base case if log-normal or exponential MCMs are selected for OS, or noticeably higher if RFS and OS are based on Kaplan-Meier functions with a 5-year cure time point, or if a higher SMR is assumed. However, the EAG does not prefer any of these scenarios. The EAG's exploratory analyses around other model parameters indicate that these factors do not have a material impact on the ICER.

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8. APPENDICES

Appendix 1: Technical appendix – instructions for implementing the EAG's exploratory analyses

Scenario		Instructions
EAG exploratory analysis	1	Set C4 (a.EAG.EA1) to 'TRUE' in the 'EAG' worksheet
	2	Based on EA1, set C9 (a.EAG.EA2) to 'TRUE' in the 'EAG' worksheet
	3	Based on EA1, set C10 (a.EAG.EA3) to 'TRUE'' in the 'EAG' worksheet
	4	Based on EA1, set C12 (a.EAG.EA4) to 'TRUE' in the 'EAG' worksheet
EAG sensitivity analysis	1a-e	Set C18 (a.EAG.EA_S1_RFS) in the 'EAG' worksheet to - "1" for 1a - "6" for 1b - "3" for 1c - "4" for 1d - "2" for 1e
	1f-j	Set C19 (a.EAG.EA_S1_OS) in the 'EAG' worksheet to - "1" for 1f - "3" for 1g - "5" for 1h - "4" for 1i - "2" for 1j
	2a	Set C20 (a.EAG.EA_S2) to '2' in the 'EAG' worksheet
	2b	Set C20 (a.EAG.EA_S2) to '3' in the 'EAG' worksheet
	3a	Set C23 (a.EAG.EA_S3) to '2' in the 'EAG' worksheet
	3b	Set C23 (a.EAG.EA_S3) to '3' in the 'EAG' worksheet
	4a	Set C26 (a.EAG.EA_S4) to '2' in the 'EAG' worksheet
	4b	Set C26 (a.EAG.EA_S4) to '3' in the 'EAG' worksheet
	5	Set C29 (a.EAG.EA_S5) to 'TRUE' in the 'EAG' worksheet
	6	Set C30 (a.EAG.EA_S6) to 'TRUE' in the 'EAG' worksheet
	7	Set C9 (a.EAG.EA2) to 'FALSE' in the 'EAG' worksheet
	8	Set C32 (a.EAG.EA_S8) to 'TRUE' in the 'EAG' worksheet
	9	Set C33 (a.EAG.EA_S9) to 'TRUE' in the 'EAG' worksheet

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 7 October 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Minor Additional Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 73 (Section 5.2.1) states: "The treatment schedule for the intervention group is based on the design of Study E1910[11] and involves two consecutive cycles of blinatumomab administered as a continuous intravenous (IV) infusion at a dose of 28µg/day for 28 days, followed by a 14-day infusion-free interval in each cycle, followed by three consecutive cycles of	Please could the sentence be amended as follows: "The treatment schedule for the intervention group is based on the design of Study E1910[11] and involves two consecutive cycles of blinatumomab administered as a continuous intravenous (IV) infusion at a dose of 28µg/day for 28 days, followed by a 14-day infusion-free interval in each cycle, followed by three consecutive cycles of consolidation chemotherapy,	The Company consider the sentence as it stands to be unclear and requests for it to be adjusted in order to better reflect the treatment schedule of the intervention group (presented in Appendix M.1.1).	The EAG agrees. The company's suggested text has been added to the report. We have also mentioned the number of cycles of chemotherapy received in the comparator group.

<table>
<tr>
<td>consolidation chemotherapy, followed by alternating cycles of blinatumomab and standard consolidation chemotherapy for a further 3 cycles (including a total 4 cycles of blinatumomab and 4 cycles of chemotherapy)”</td>
<td>followed by alternating cycles of blinatumomab and standard consolidation chemotherapy for a further 3 cycles. In total, patients assigned to Arm C received 4 cycles of blinatumomab and 4 cycles of consolidation chemotherapy.”</td>
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<tr>
<td>Page 90 (Section 5.2.4) states

“The EAG notes that the impact of psychiatric disorders is not included in the model, despite its incidence being [redacted] in the blinatumomab group; the reasons for this are unclear.”</td>
<td>Please remove this sentence.</td>
<td>While the EAG are correct that ‘psychiatric disorders’ is not included in the model, and that the incidence of psychiatric disorders was ≥5.0% (****) in the blinatumomab group, ‘psychiatric disorders’ is a system organ class. Within this class, each of the specific adverse event (confusional state, depression, insomnia, mental status changes, anxiety) each had an incidence <5% (see table below and Table 14-6.6.4.of the CSR). For this reason, they were not included within the Company’s model, in alignment with the approach taken for all AEs.
<table>
<tr><th>System organ class PT, n (%)</th><th>Blinatumomab + SOC consolidation chemotherapy</th><th>SOC Consolidation chemotherapy ([redacted])</th><th>Overall ([redacted])</th></tr>
</table></td>
<td>Thanks for the clarification. The EAG has removed this sentence.</td>
</tr>
</table>

		<table><tr><td></td><td>(*****)</td><td></td><td></td></tr><tr><td>Psychiatric disorders</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Confusional state</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Depression</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Insomnia</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Mental status changes</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Anxiety</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>	
Page 115 (Section 5.3.5) states: “The EAG notes that some pack sizes and costs of filgrastim on BNF 2024 have recently been updated. This affects the lowest prices for the 12	Please could the EAG clarify how the pack costs have changed as this was unable to be verified by the Company. If this is an error, please could the EAG remove this from the report.	The BNF website for filgrastim reports the lowest cost for the 12 million units/0.2 ml vial as £113.60 from Accord-UK Ltd. This is the same pack cost included in the Company’s CEM (see cell J330 on the “Drug Cost” tab). Similarly, the lowest cost for the 48 million units/0.5 ml vial with 5 doses is £399.50 from Sandoz Ltd. This is also the same pack cost included in the Company’s CEM (see cell J333 on the “Drug Cost” tab). The Company agrees the eMIT costs for idarubicin have since changed and thank the EAG for correcting this.	The EAG report included a minor reporting error whereby we referred to an updated price for the 12 million units/0.2 ml vial, but this should instead have referred to an updated price for the 30 million units/0.5 ml vial. The lowest

million units/0.2 ml vial and 48 million units/0.5 ml vial.”			price for five doses of 30 million units/0.5ml vial is £246.50 from Pfizer Ltd. (the price in the company’s CEM is £52.7 for one dose). The EAG has corrected this minor error in the text. The lowest price for the 48 million units/0.5 ml vial for five doses is £395.25 (NHS indicative price) from Pfizer Ltd.
Page 115 (Section 5.3.5) states: “The company’s clarification response (questions B11, B13, B23-B26) acknowledges that issues (a)-(f) were errors in the original model. These issues were addressed in	The Company request the EAG update the report to provide important additional context here: “The company’s clarification response (questions B11, B13, B23-B26) acknowledges that issues (a)-(f) were errors in the original	The Company request the EAG amend their report to provide additional context to highlight issues (g) to (i) were not raised at clarification questions and therefore could not be addressed by the Company. The current wording could be misinterpreted to imply the Company actively did not address issues (g) – (i) during clarification questions, which is not accurate.	The EAG agrees. Text explaining the timing of error identification has been added to the report.

the updated version of the company's model provided as part of their clarification response."	model. These issues were addressed in the updated version of the company's model provided as part of their clarification response. **Issues (g) – (i) have been identified by the EAG since the Company provided responses to the clarification questions**."		

Issue 2 Data and confidentiality highlighting amendments

Location of incorrect data or marking	Description of incorrect data or marking	Amended marking	EAG response
Page 16 (Section 1.4.) and Page 133 Section 6 states "TEAEs of special interest included cytokine release syndrome (CRS) ([redacted] vs [redacted]) and	The percentage given for "headache" (TEAE of special interest) in the SoC chemotherapy arm is incorrect.	To align with the data reported in the CSR, Table 14-6.6.8, please could this sentence be amended as follows: "TEAEs of special interest included cytokine release syndrome (CRS) ([redacted]) and neurologic	The EAG agrees. This value has been amended throughout the report.

neurologic events; most commonly headache ([redacted] vs [redacted]), and tremor ([redacted] vs [redacted].”		events; most commonly headache ([redacted]), and tremor ([redacted]).”	
Page 40 (Section 4.2.1.) Figure 2.	The figure provided by the EAG does not align with the E1910 trial protocol. In Figure 2 of the EAG report, alloSCT is shown to be available to patients after being randomised to Arm C and given to patients *before and as an alternative to* blinatumomab cycles 1 and 2. However, as noted in the footnote for Figure 2 as well as indicated in Appendix M.1.1, Figures 5 – 7 and Document B, Figure 4, patients could receive alloSCT only **after** the first 2 cycles of blinatumomab in the blinatumomab plus SoC chemotherapy arm or at any time following intensification chemotherapy in the SoC chemotherapy arm.	Please could the EAG update Figure 2 in their report to more closely align with Document B, Figure 4, to avoid any confusion in the timing of availability of alloSCT in Arm C of the E1910 trial.	The EAG agrees that the alloSCT boxes in the diagram are potentially misleading. The figure has been amended to clarify the timing of alloSCT in each treatment group.

<table>
<tr>
<td>Page 45 (Section 4.2.6.).</td>
<td>Unpublished safety data from the E1910 trial are confidential. As such, confidentiality highlighting should be applied to the percentages of dropouts due to AEs.</td>
<td>Please can the confidentiality highlighting be added as follows:
“There were some imbalances in dropouts between the groups (blinatumomab vs SoC: disease progression/relapse; 6.3% vs 12.5%, AEs; [redacted], and patient withdrawal; 4.5% vs 8%).”</td>
<td>The confidentiality marking has been amended as requested.</td>
</tr>
<tr>
<td>Page 45 (Section 4.2.7.)</td>
<td>Unpublished safety data from the E1910 trial are confidential. As such, confidentiality should be applied to the number of patients in the SAS.</td>
<td>Please can the confidentiality highlighting be added as follows:
“Safety analyses were based on the Safety Analysis Set (SAS), which included all randomised patients who received at least one dose of protocol-specific treatments (N=[redacted]).”</td>
<td>The confidentiality marking has been amended as requested.</td>
</tr>
<tr>
<td>Page 48 (Section 4.2.8.). Table 8</td>
<td>Unpublished safety data from the E1910 trial are confidential. As such, confidentiality highlighting should be applied to the percentages given for “Adverse event/side effects/complications”.
In addition, the percentage given for “Infection” in the SoC chemotherapy arm is incorrect.</td>
<td>Please could the following confidentiality highlighting and data updates be applied in Table 8:
<table>
<tr><td></td><td>Blinatumomab plus SoC chemotherapy</td><td>SoC chemotherapy (N=112), n (%)</td></tr>
</table>
</td>
<td>The confidentiality marking has been amended as requested. Please note that we have also redacted Figure 3 as these values are also contained in the diagram.</td>
</tr>
</table>

			(N=112), n (%)		
		Adverse event/side effects/complications	[redacted]	[redacted]	
		Death on study	[redacted]	[redacted]	
		Infection	4 (3.6)	**2 (1.8)**	
Page 69 (Section 5.1) states “The company searched all relevant electronic bibliographic databases in July 2023”	The economic SLR was initially conducted on 12th September 2023, and an update was conducted on 16th April 2024, as noted in Appendix G and stated by the EAG in the previous sentence.	Please could this sentence be amended as follows: “The company searched all relevant electronic bibliographic databases in **September** 2023”			The EAG agrees. The month has been corrected in the report.
Page 72 (Section 5.2.1), Page 75 (Section 5.2.3) states “At model entry, patients are	The correct value for the proportion of patients assumed to be female is 50.4% as per the Table 20, Section B.3.3.1.	Please can the sentence be amended to read: “At model entry, patients are assumed to be 50.1 years of age			The EAG agrees. This value has been amended throughout the report.

<table>
<tr>
<td>assumed to be 50.1 years of age and 50.5% are assumed to be female”</td>
<td></td>
<td>and 50.4% are assumed to be female”</td>
<td></td>
</tr>
<tr>
<td>Table 38 (Section 5.2.4)</td>
<td>The correct values, as per the company’s original model, should be [redacted] and [redacted], for the blinatumomab + SOC consolidation chemotherapy arm and the SOC consolidation chemotherapy arm alone, respectively.</td>
<td>Please can the table be corrected as follows:
<table>
<tr><th>AE</th><th>Frequency - blin +SoC</th><th>Frequency - SoC</th><th>Unit cost *</th><th>Cost source (NHS Reference Costs 2021/22 ,81 unless otherwise stated)</th></tr>
<tr><td>WBC count decreased</td><td>[redacted]</td><td>[redacted]</td><td>£580.93</td><td>Weighted mean of non-elective short stay other haematological</td></tr>
</table>
</td>
<td>This appears to be a copy paste error in the original EAG report. The values have been corrected as requested.</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td><table><tr><td></td><td></td><td></td><td></td><td>or splenic disorders (SA08G-SA08J)</td></tr></table></td><td></td></tr>
<tr><td>Table 39 (Section 2.4)</td><td>Fludarabine preparation, as per Table 47, Section B.3.5.1, is 25 mg/2 ml vial.</td><td>Please can the table be corrected as follows:<table><tr><td>Drug</td><td>Preparation</td></tr><tr><td>Fludarabine</td><td>25mg/2ml vial</td></tr></table></td><td>From eMIT, there is only one price for fludarabine: £83.86 for a 50mg/2ml vial. In the company's CEM, the cost per vial (50mg/2ml vial) is £83.86, which is already correct. The EAG report has not been amended.</td></tr>
</table>

Issue 3 Typographical and formatting errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 76 (Section 5.2.3) states "The model includes two structural constraints: (i) the per-cycle risk of death in the target population cannot be lower than that of the SMR-uplifted age-and sex-matched general population, and (ii) the cumulative probability of RFS cannot	Please can the sentence be amended to read: "The model includes two structural constraints: (i) the per-cycle risk of death in the target population cannot be lower than that of the SMR-uplifted age-and sex-matched general population, and (ii) the cumulative probability of RFS cannot	In the Company's model, as noted in Table 54, Section B.3.8.2, the RFS risk was modelled to be *equal to or higher* than the OS risk at all times.	This is not a factual inaccuracy. In the context of survival analysis, the cumulative probability is the probability which is read from the survival function at

be higher than that of OS at any timepoint.”	be **lower** than that of OS at any timepoint.”		time *t*. The text is therefore already accurate in that the model applies a constraint which ensures that cumulative probability of RFS cannot be higher than that for OS (i.e., the RFS curve has to be below the OS curve). The EAG report has not been amended.