NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]

Contents:



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

Contains AIC, CIC

# Pre-meeting briefing
# Blinatumomab for previously treated B-precursor acute lymphoblastic leukaemia
# [ID804]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

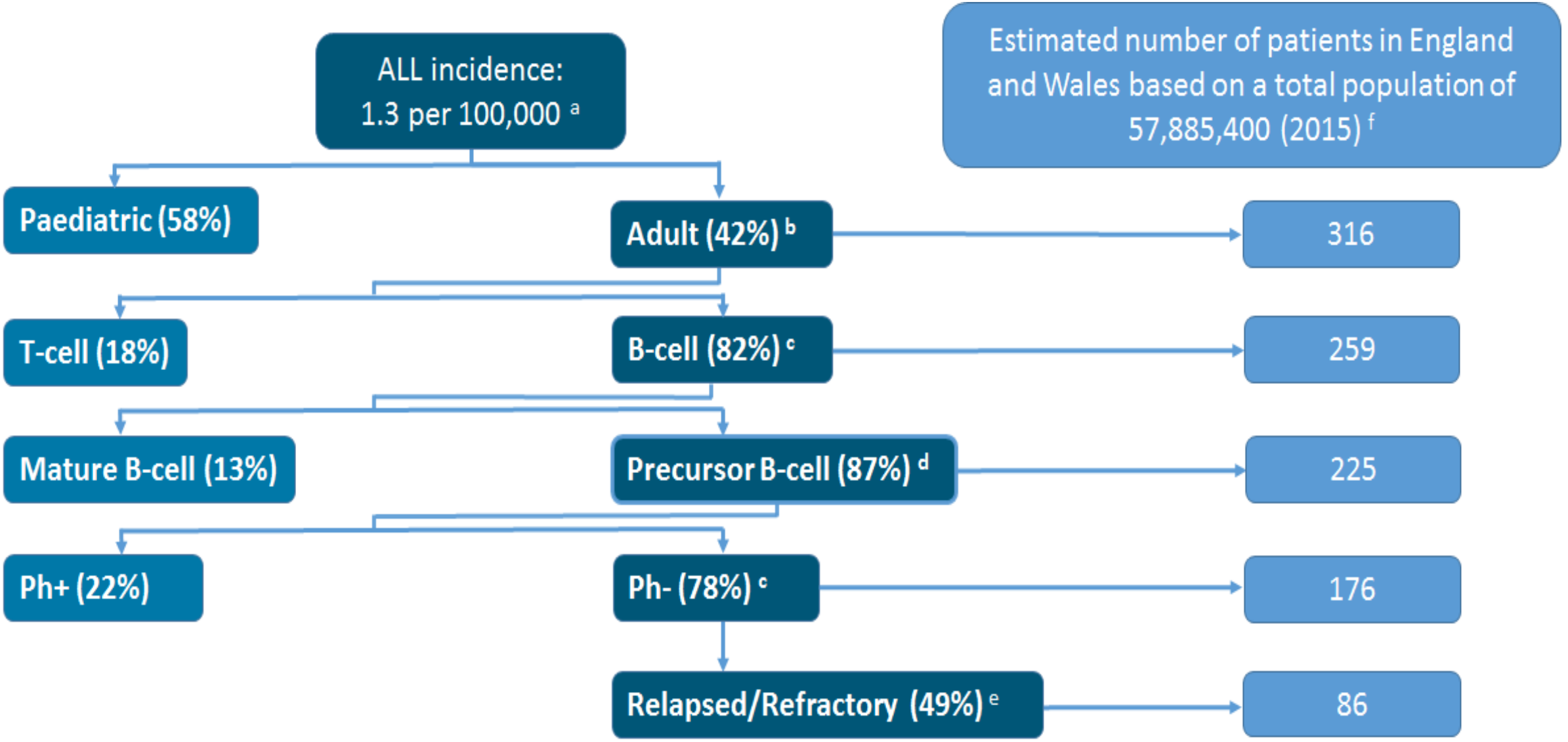
# Key decision points

- What is the prognosis for Philadelphia chromosome negative relapsed or refractory ALL?
- What is current standard of care for ALL? Is allo-SCT the only cure?
- The TOWER trial compared blinatumomab with clinicians choice. Is FLAG-IDA the most relevant comparator in clinical practice? Is clofarabine a relevant comparator for some people?
- How would blinatumomab fit into the current treatment pathway? Is it most likely to be for first relapse, and for how many cycles? Can it be used in the outpatient setting?
- How generalisable are the results of the clinical trials (which excluded people who had first relapse after 12m)?
- There was an OS benefit of 3.7 months and may be used as a bridge to transplant. What is the potential that blinatumomab alone to produce a durable long term effect?

# Acute lymphoblastic leukaemia: Disease background

- Acute form of cancer of the white blood cells
- Rare - 0.2% of new cancers in UK
- Predominately disease of childhood but affects adults too
- 42% of cases in adults
- Symptom include fatigue, breathlessness, infections, bleeding, bruising, fever & sweating
- Precursor B-cell is the most common type of ALL
- Approximately 22% of adults with precursor B-cell ALL have acquired chromosomal abnormality known as Philadelphia chromosome positive disease (Ph+)[a]
- Currently no NICE guidelines on treatment of ALL
  - TA408 recommends pegaspargase for untreated ALL
  - TKI inhibitors only used for treating Ph+

# Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia



# Current management

- Relapsed ALL currently treated by combination chemotherapy with poor response and considerable toxicity
- Most common regimen used is fludarabine, cytarabine and GCSF based combination chemotherapy with or without idarubicin (FLAG-IDA)
- Clofarabine-based regimens sometimes used
  - MA for monotherapy in paediatric patients only
  - Significant off-label use in clinical practice
  - CDF transition funding will remain in place until a commissioning decision is taken by the CDF 'off label process'
- Blinatumomab an alternative to these "salvage" therapies
- Treatment of ALL grouped into three main phases:
  - remission–induction
  - intensification / consolidation
  - continuation/ maintenance (including allogeneic stem cell transplant – a potentially curative option)

# Patient Perspective

- 64%[a] of ALL patients are diagnosed following an emergency presentation
- Most patients with relapsed or refractory ALL will be extremely ill, having undergone (and not responded well to) highly toxic treatment
- The majority of patients treated with highly toxic salvage chemotherapy would spend around half of their time in hospital
- Many patients (particularly older or less fit adults) are unable to tolerate these aggressive options and receive best supportive care. As such, there is an urgent need for these patients in this setting to access further treatment options
- The vast majority of patients (over 90%) will die from their disease within a short period of time, usually within a few months because there are such limited options for relapsed or refractory patients

# Technology

| | |
|---|---|
| Details of the technology | Blinatumomab (BLINCYTO®, Amgen) |
| Marketing authorisation | • Adults with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia<br>• European marketing authorisation was granted in November 2015 (on a conditional basis given the lack of available randomised controlled trial evidence at the time of approval) |
| Mechanism of action | • Blinatumomab is a T-cell engager antibody targeting CD19 and the CD3/T cell receptor<br>• When blinatumomab binds to both the cancer cell and T-cell, the T-cell is recruited and activated to destroy the cancer cell |
| Administration | • Continuous intravenous infusion for up to 96 hours at a dosage of 9 µg/day (starting dose; days 1–7) or 28 µg/day (subsequent doses)<br>• Each cycle of treatment is 28 days of continuous infusion<br>• Patients may receive 2 cycles of treatment, separated by a 14 day treatment-free interval<br>• Patients who achieve complete remission may receive up to 3 additional cycles of consolidation treatment<br>• Hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of subsequent cycles |
| Acquisition cost (excluding VAT) | • List price £2,017 per 38.5 µg vial<br>• The company has proposed a simple PAS which has been approved by the DoH |

# Final NICE scope

| | |
|---|---|
| Population | People with Philadelphia-chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukaemia |
| Intervention | Blinatumomab |
| Comparator | • Fludarabine, cytarabine and GCSF based combination chemotherapy, with or without idarubicin<br>• Clofarabine-based combination chemotherapy<br>• Best supportive care (including palliative care) |
| Outcomes | • Overall survival<br>• Event-free survival<br>• Relapse-free survival<br>• Treatment response rates<br>• Time to and duration of response<br>• Rate of stem cell transplant<br>• Adverse effects<br>• Health-related quality of life |
| Subgroups | • People for whom allo-SCT is considered an appropriate treatment option |

# Company Decision Problem – Changes from Final Scope

| | **Company comment** | **ERG comment** |
|---|---|---|
| Population | **Adults** – MA does not include children | N/A |
| Comparator | • **Fludarabine, cytarabine and GCSF based combination chemotherapy *with* idarubicin (FLAG-IDA)**<br>  • Most common salvage chemotherapy in clinical practice<br>  • Availability of clofarabine in adults remains unclear since the expiration of CDF (included in scenario analysis)<br>  • Blinatumomab likely an alternative to other salvage chemotherapies rather than an alternative to BSC | • ERG clinical advisor agreed that BSC not a useful comparator and that FLAG-based regimens used in vast majority of cases<br>• Noted that clofarabine is sometimes used for ALL |
| Subgroups to be considered | • **People who have not received prior salvage therapy**<br>  • Appropriateness for allo-SCT cannot be determined in a robust/uniform way in a clinical study<br>  • Blinatumumab likely to be used early in the treatment pathway (i.e. before salvage therapy) | • Decision to undertake allo-SCT requires significant clinical judgment<br>• Therefore, decision to not present subgroup analyses for the scoped subgroup reasonable |

# Expert Comments

- Adult patients with relapsed ALL have “an appalling prognosis”:
  - Conventional chemotherapy: zero long term survival
  - Allogeneic stem cell transplant + salvage chemotherapy: ~ 25% survival at 5 years
- Despite the poor overall prognosis it is possible to be cured (with allo-SCT)
- Blinatumomab potentially a “huge” advance for patients in terms of both outcomes and experience
- Easier to deliver than combination chemotherapy and could allow patients to receive therapy as outpatients due to lower toxicity – saving weeks of inpatient stay
- No agreed standard of care in this setting with several different regimens used, as reflected in the phase 3 trial
- Most patients respond (complete remission) within 1 course of treatment
- “No point to continue” beyond 2 courses for non-responders

*NCRI-ACP-RCP; RCPath*

# Clinical effectiveness

# Clinical Evidence Summary

- Systematic review by the company found two relevant studies:
  - TOWER - Open-label, multicentre phase 3 RCT
  - MT103-211 - Phase 2, single-arm, multicentre, open-label study

- The ERG regarded that all relevant evidence had been included

# Blinatumomab Clinical Evidence -TOWER

| | |
|---|---|
| **Design** | Open-label, multicentre phase 3 RCT |
| **Location (sites)** | 101 sites in 21 countries (5 sites in the UK = 5.2% of enrolled patients) |
| **Population** | • Patients were eligible if they were adults with R/R Ph- B-precursor ALL and were:<br>  • Refractory to primary induction therapy or salvage therapy<br>  • In untreated first relapse with first remission duration < 12 months<br>  • In untreated second or greater relapse<br>  • In relapse at any time after allo-SCT<br>Following intensive combination chemotherapy as initial treatment or subsequent salvage therapy |
| **Intervention and comparator** | • Patients randomised (2:1 ratio) to either blinatumomab or one of 4 standard of care chemotherapy regimens:<br>FLAG ± anthracycline based regimen ([redacted])<br>  • High-dose methotrexate based regimen ([redacted])<br>  • Clofarabine or clofarabine based regimen ([redacted])<br>  • HiDAC based regimen ([redacted]) |
| **Primary outcome measures** | OS |
| **Secondary outcome measures** | Complete remission (CR), duration of CR, minimum residual disease remission, post baseline allo-SCT, HRQoL, safety |

# TOWER Baseline Characteristics

| | Blinatumomab (N=271) | SOC Chemotherapy (N=134) |
|---|---|---|
| Age (years), mean (IQR) | 40.8 (25.0, 54.0) | 41.1 (26.0, 58.0) |
| Male, n (%) | 162 (59.8) | 77 (57.5) |
| Prior allo-SCT, n (%) | 94 (34.7) | 46 (34.3) |
| Prior salvage therapy (per randomised strata)[a], n (%) | [redacted] | [redacted] |
| **Key ALL entry criterion, n (%)** | | |
| Refractory to primary or salvage therapy | 115 (42.4) | 54 (40.3) |
| In 1st relapse with 1st remission < 12 months | 76 (28.0) | 37 (27.6) |
| In untreated 2nd or greater relapse | 32 (11.8) | 16 (11.9) |
| Relapse after allo-SCT | 46 (17.0) | 27 (20.1) |
| No criteria met | 2 (0.7) | 0 (0) |

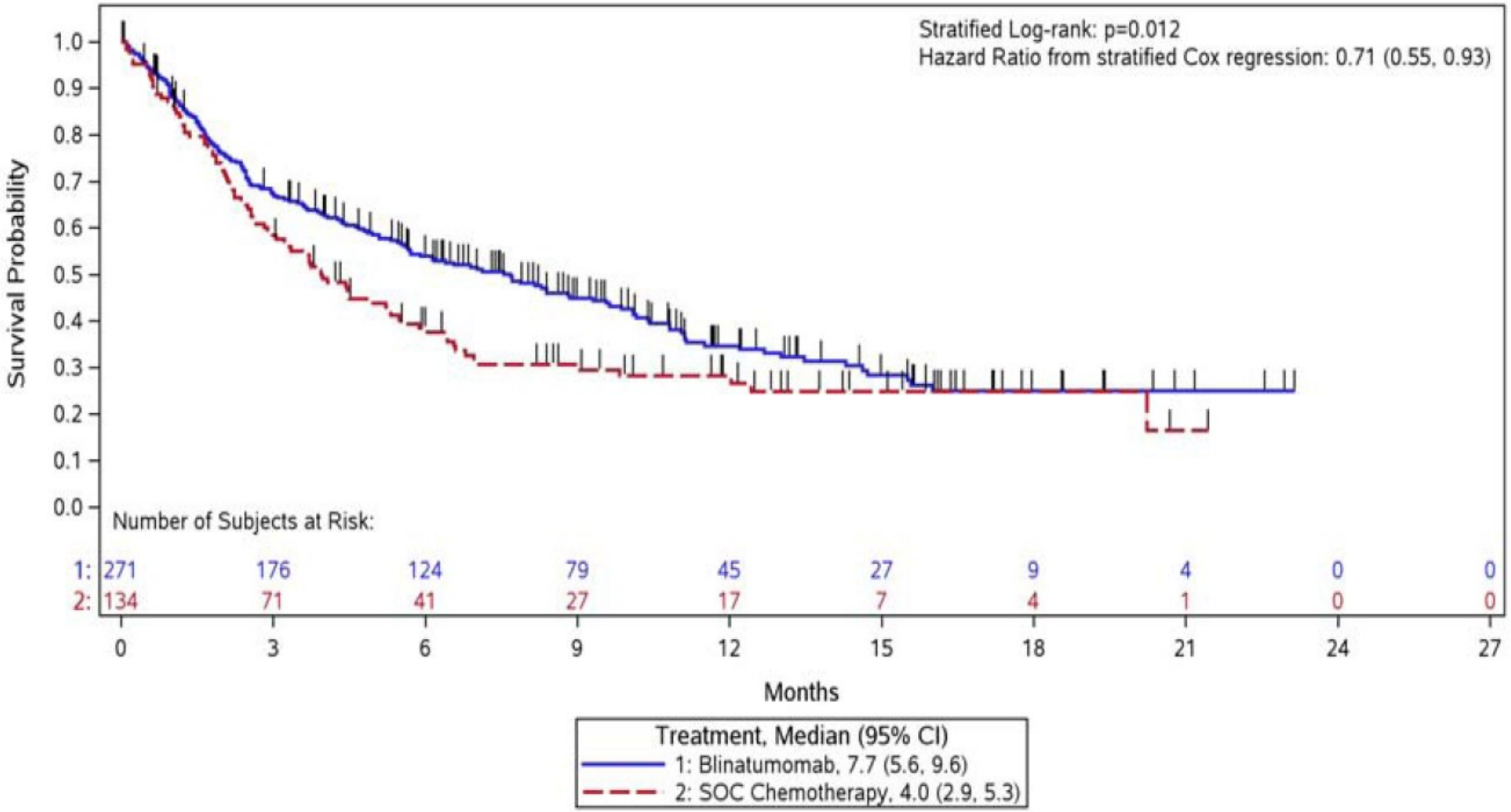
ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; FLAG, fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim); HiDAC, high-dose cytarabine; IQR, interquartile range; SOC, standard of care.

# TOWER Results

| | | Blinatumomab (N=271) | SOC Chemotherapy (N=134) |
|---|---|---|---|
| Overall survival | OS duration, median months (95% CI) | 7.7 (5.6, 9.6) | 4.0 (2.9, 5.3) |
| | Hazard ratio (95% CI) | 0.71 (0.55, 0.93) | |
| Complete remission within 12 weeks of treatment initiation | CR/CRh*/CRi, % (95% CI) | 43.9 (37.9, 50.0) | 24.6 (17.6, 32.8) |
| | Duration of response, median months (95% CI) | 7.3 ([redacted]) | 4.6 ([redacted]) |
| | CR, % (95% CI) | 33.6 (28.0, 39.5) | 15.7 (10.0, 23.0) |
| | Duration of response, median months (95% CI) | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Event free survival | Events, n (%) | [redacted] ([redacted]) | [redacted] ([redacted]) |
| | Hazard ratio (95% CI) | [redacted] ([redacted]), [redacted] | |
| Allo-SCT | Post-baseline % (95% CI) | 24.0 ([redacted]) | 23.9 ([redacted]) |
| MRD among responders | % (95% CI) | 76.3 ([redacted]) | 48.5 ([redacted]) |

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological response; CRi, complete remission with incomplete haematological response; MRD, minimal residual disease remission

# Kaplan–Meier plot of overall survival (TOWER)




A censored subject is indicated by a Vertical Bar |.

# TOWER Pre-specified Subgroup Analyses of Overall Survival

| Subgroup | OS, HR (95% CI) |
|---|---|
| Overall ITT population | 0.71 (0.55, 0.93) |
| *Age (per randomised strata)* | |
| <35 years | [redacted] |
| ≥35 years | [redacted] |
| *Number of prior salvage therapies* | |
| 0 | [redacted] |
| 1 | [redacted] |
| ≥2 | [redacted] |
| *Prior allo-HSCT (per randomised strata)* | |
| Yes | [redacted] |
| No | [redacted] |
| *Intended SOC chemotherapy regimen* | |
| Clofarabine or clorfarabine based regimen | [redacted] |
| FLAG with or without anthracycline based regimen | [redacted] |
| HIDAC based regimen | [redacted] |
| High-dose methotrexate based regimen | [redacted] |

allo-SCT, allogeneic stem cell transplant; CI, confidence interval; FLAG, fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating

# TOWER adverse events

| **Treatment-emergent adverse event** | **Blinatumomab (N= [redacted])** n(%) | **SOC Chemotherapy (N= [redacted])** n(%) |
|---|---|---|
| *Treatment emergent AEs* | | |
| Total | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Grade ≥ 3 | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Serious AE | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Led to interruption of treatment | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Led to discontinuation of treatment | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Life-threatening | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Fatal TEAEs | [redacted] ([redacted]) | [redacted] ([redacted]) |
| *Treatment-related AEs* | | |
| Total | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Grade ≥ 3 | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Serious AE | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Led to interruption of treatment | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Led to discontinuation of treatment | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Life-threatening | [redacted] ([redacted]) | [redacted] ([redacted]) |
| Fatal TEAEs | [redacted] ([redacted]) | [redacted] ([redacted]) |

# Blinatumomab Clinical Evidence -MT103-211

| | |
|---|---|
| **Design** | Phase 2, single-arm, multicentre, open-label study |
| **Location (sites)** | 23 sites in Europe and 14 sites in the United States |
| **Population** | • Patients were eligible if they were adults with R/R Ph- B-precursor ALL and were:<br>  • Primary refractory after induction<br>  • Relapsed within 12 months of first remission<br>  • Relapsed within 12 months of allo-SCT<br>  • No response to or relapse after salvage therapy |
| **Intervention and comparator** | Blinatumomab.<br>• As this was a single-arm study, the company compared with an historical cohort<br>• The ERG did not regard the single-arm trial per se as relevant and thus focused on the comparison between the single-arm trial and the historical cohort. |
| **Primary outcome measures** | Proportion of patients achieving CR/CRh* within the first two cycles (i.e., 12 weeks) of blinatumomab treatment |
| **Secondary outcome measures** | OS, RFS, EFS, CR, CRh*, post-baseline allo-SCT |

# Non-randomised evidence - Study MT103-211 Baseline Characteristics

| | **Blinatumomab (N=189)** |
|---|---|
| Age (years), median (range) | 39 (18-79) |
| Male, n (%) | 119 (63.0) |
| Prior allo-SCT, n (%) | 64 (33.9) |
| Prior salvage therapy, n (%) | 151 (79.9) |
| **Key ALL entry criteria, n (%)** | |
| Primary refractory | 16 (8.5) |
| Relapse within 12 months of allo-SCT | 39 (20.6) |
| Entering first salvage with first remission duration ≤ 12 months | 23 (12.2) |
| Entering second or greater salvage therapies | 108 (57.1) |
| No disease stage entry criteria met | 3 (1.6) |

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; FLAG, fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim); HiDAC, high-dose cytarabine; IQR, interquartile range; SOC, standard of care.

# Non-randomised evidence - Study MT103-211 Results

| | | **Blinatumomab (N=189)** |
|---|---|---|
| Complete remission within first two treatment cycles (primary endpoint) | CR, % (95% CI) | 33.3 (26.7, 40.5) |
| | CRh*, % (95% CI) | 9.5 (5.3, 10.4) |
| Overall survival duration, median months (95% CI) | Primary analysis | 6.1 (4.2, 7.5) |
| | Secondary analysis | 6.4 (4.3, 7.7) |
| | Additional ad-hoc analysis | 6.5 (4.4, 7.7) |
| Relapse-free survival, median months (95% CI) | Primary analysis (Oct 2013) | 5.9 (4.8, 8.3) |
| | Secondary analysis (Jun 2014) | 6.8 (5.0, 10.0) |
| | Additional ad-hoc analysis (Jul 2015) | 6.8 (5.0 10.0) |

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological response. Primary analysis: 10 October 2013 data cut-off date. At the time of the data cut-off for the secondary analysis (20 June 2014) and additional ad-hoc analysis (15 July 2015), 77.7% (147/189) and 88.4% (167/189) of patients in the primary analysis set had ended the study, respectively.

# Comparative analysis

- As Study MT103-211 was a single-arm study, the company presented a comparison with an historical cohort (Study 20120310)

| **Study 20120310** | |
|---|---|
| **Design** | Retrospective pooled analysis of historical data available from 1990 to 2013 for 1139 adult patients (694 patients with data on CR and 1112 patients with OS data) |
| **Population** | Patients were eligible if they were adults with R/R Ph- B-precursor ALL and were:<br>• In first relapse or salvage treatment after a first remission duration of ≤ 12 months<br>• Refractory to initial treatment,<br>• R/R after first or later salvage, or<br>• R/R disease within 12 months of allo-SCT |
| **Primary endpoint** | Rate of CRsg following relapse or salvage treatment, defined as:<br>• < 5% blasts in bone marrow<br>• Full or partial/incomplete haematologic recovery |
| **Secondary endpoint** | • OS<br>• RFS<br>• Proportion of patients receiving allo-SCT following salvage therapy |

# Comparative analysis

- Company used weighted analysis to compare patients in Study MT103-211 with the historical cohort
- Two approaches were used to address differences in patient characteristics across studies
- In the reweighted analysis patients were stratified based on known prognostic factors (e.g. age, prior allo-SCT and prior salvage therapy)
- In the propensity score analysis, patient characteristics (e.g. age, prior allo-SCT, prior salvage therapy) were also used to weight the estimates using inverse probability of treatment weighting methodology

# Weighted analysis: comparison of haematological remission rates from historical cohort and Study MT103-211

| Stratum | | Historical cohort | | Blinatumomab (Study MT103-211)[c] | |
|---|---|---|---|---|---|
| Age, years | Prior lines of treatment | N (stratum %) | CRsg % (95% CI) | N (stratum %) | CR/CRh* % (95% CI) |
| < 35 | allo-SCT[a] | 48 (6.9) | 29 (17, 44) | 40 (21.2) | 38 (21, 54) |
| < 35 | In 1st salvage[b] | 119 (17.1) | 44 (35, 53) | 10 (5.3) | 70 (35,93) |
| < 35 | In 2nd+ salvage[b] | 150 (21.6) | 18 (12, 25) | 40 (21.2) | 43 (27, 59) |
| ≥ 35 | allo-SCT[a] | 41 (5.9) | 27 (14, 43) | 24 (12.7) | 58 (37, 78) |
| ≥ 35 | In 1st salvage[b] | 187 (26.9) | 30 (24, 38) | 19 (10.1) | 26 (9, 51) |
| ≥ 35 | In 2nd+ salvage[b] | 149 (21.5) | 17 (11, 24) | 56 (29.6) | 41 (28,55) |
| Combined weighted estimate | | 694 | 24 (20, 27) | 189 | 43 (36, 50) |

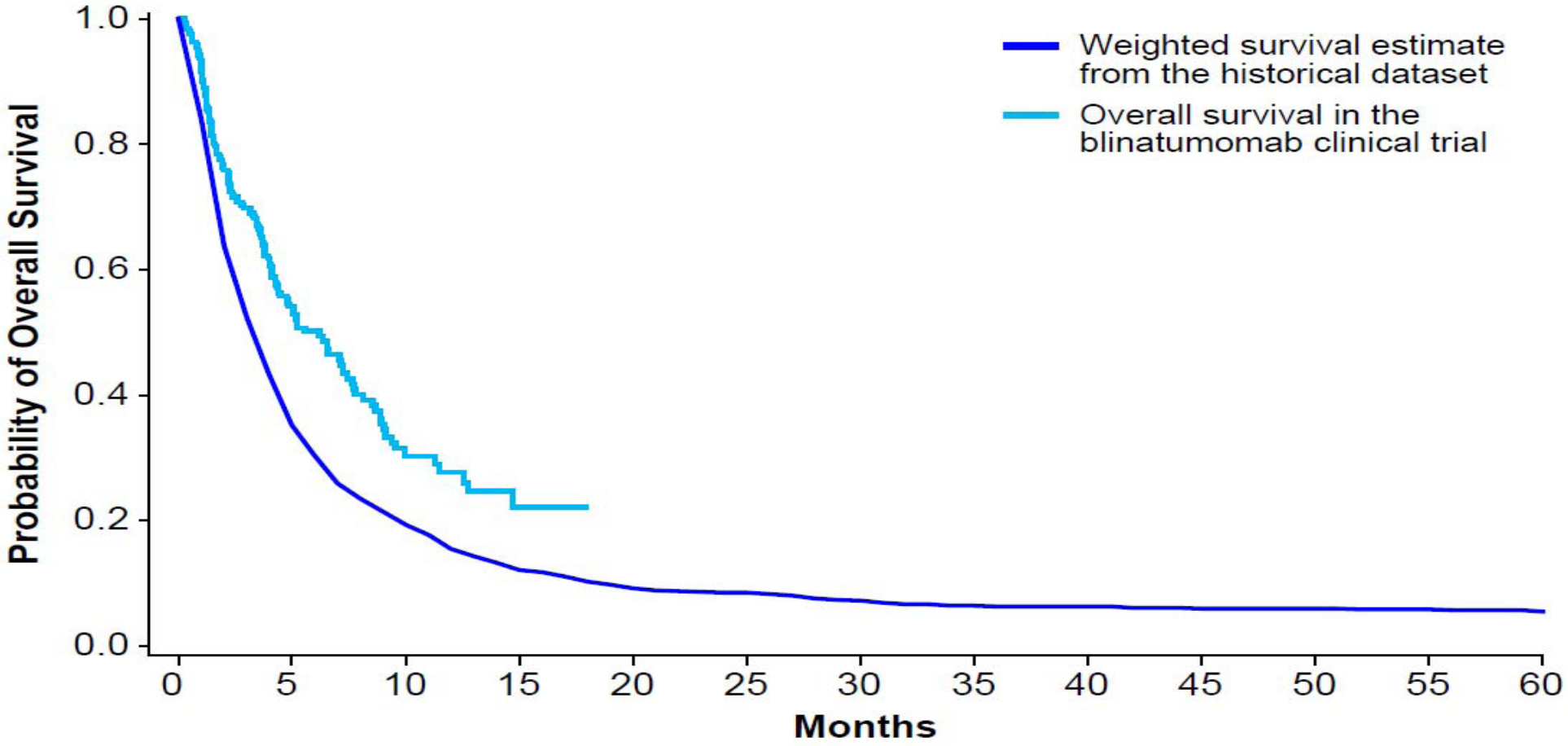
[a] All patients with a history of allo-SCT (could be in 1st, 2nd or greater salvage)
[b] All patients without a history of allo-SCT
[c] Primary analysis data cut-off date (10 Oct 2013)
allo-SCT, allogeneic stem cell transplant, CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRsg, complete remission per study groups/sites.

# Weighted analysis: comparison of OS from historical cohort and Study MT103-211

| Stratum | | Historical cohort | | Blinatumomab (Study MT103-211)[c] | |
|---|---|---|---|---|---|
| Age, years | Prior lines of treatment | N (stratum %) | Median OS, months (95% CI) | N (stratum %) | Median OS, months (95% CI) |
| < 35 | allo-SCT[a] | 108 (9.7) | 3.8 (2.9, 4.5) | 40 (21.2) | 7.6 (3.5, 9.4) |
| < 35 | In 1st salvage[b] | 258 (23.2) | 5.7 (4.9, 6.3) | 10 (5.3) | NE (4.1, NE) |
| < 35 | In 2nd+ salvage[b] | 161 (14.5) | 2.9 (2.3,4.0) | 40 (21.2) | 6.3 (3.7, 12.6) |
| ≥ 35 | allo-SCT[a] | 79 (7.1) | 4.0 (2.8, 4.7) | 24 (12.7) | 9.3 (3.3, NE) |
| ≥ 35 | In 1st salvage[b] | 341 (30.7) | 3.7 (3.2, 4.4) | 19 | 5.1 (2.8, 7.0) |
| ≥ 35 | In 2nd+ salvage[b] | 165 (14.8) | 2.2 (1.7, 2.9) | 56 | 3.7 (1.9, 6.5) |
| Combined weighted estimate | | 1112 | 3.3 (2.8, 3.6) | 189 | 6.1 (4.2, 7.5) |

[a] All patients with a history of allo-SCT (could be in 1st, 2nd or greater salvage)
[b] All patients without a history of allo-SCT
[c] Primary analysis data cut-off date (10 Oct 2013)
allo-SCT, allogeneic stem cell transplant; CI, confidence interval; NE,not estimable; OS, overalll survival.

# Weighted analysis: comparison of OS from historical cohort and Study MT103-211



# Comparative analysis – propensity score analysis

| | Historical cohort N=1112 (Study 20120310) | Blinatumomab N=189 (Study MT103-211) |
|---|---|---|
| 6 month survival, % (95% CI) | 33 (31, 36) | 58 (55, 60) |
| 12 month survival, % (95% CI) | 17 (15, 19) | 39 (36, 42) |
| OS, HR (95% CI) | | 0.54 (0.40, 0.73) |
| Complete remission[a], predicted % (95% CI) | 26 (23, 30) | 49 (33, 65) |
| CR/CRh* vs. CRsg, OR (95% CI) | | 2.68 (1.67, 4.31) |

[a] CRsg (historical cohort) and CR/CRh* (MT103-211)

CI, confidence interval, CR, complete remission; CRh*, complete remission with partial haematological recovery, CRsg, complete remission with or without full haematological recovery depending on study group in historical cohort, OS, overall survival, OR, odds ratio, HR, hazard ratio

# ERG critique of clinical effectiveness - TOWER

- The trial as a whole was large and generally of good quality, with clear and appropriate approach to outcome selection and trial statistics and included patients generalisable to those in England
- TOWER was not powered to undertake  subgroup analyses
- In TOWER, dropout was imbalanced between arms (and was higher in the standard of care chemotherapy arm, 18.7% vs 1.5%), though this did not affect balance on known demographic characteristics
- Data presented for TOWER drew from interim analyses, and thus the study data presented are not at full maturity (although CR/CRh*/CRi data are)
- [redacted] of patients in the blinatumomab arm received more than the five cycles of blinatumomab described in the marketing authorisation
- [redacted] of patients in the standard of care chemotherapy arm received blinatumomab subsequently
- TOWER was an open-label trial
- Consolidation criteria used in TOWER to determine if further treatment after two cycles is appropriate does not match precisely the consolidation criteria in the marketing authorisation
- It is unclear the degree to which the standard of care chemotherapy arm in TOWER is an appropriate substitute for FLAG-IDA, the scoped comparator

# ERG Critique of clinical effectiveness - Study MT103-211

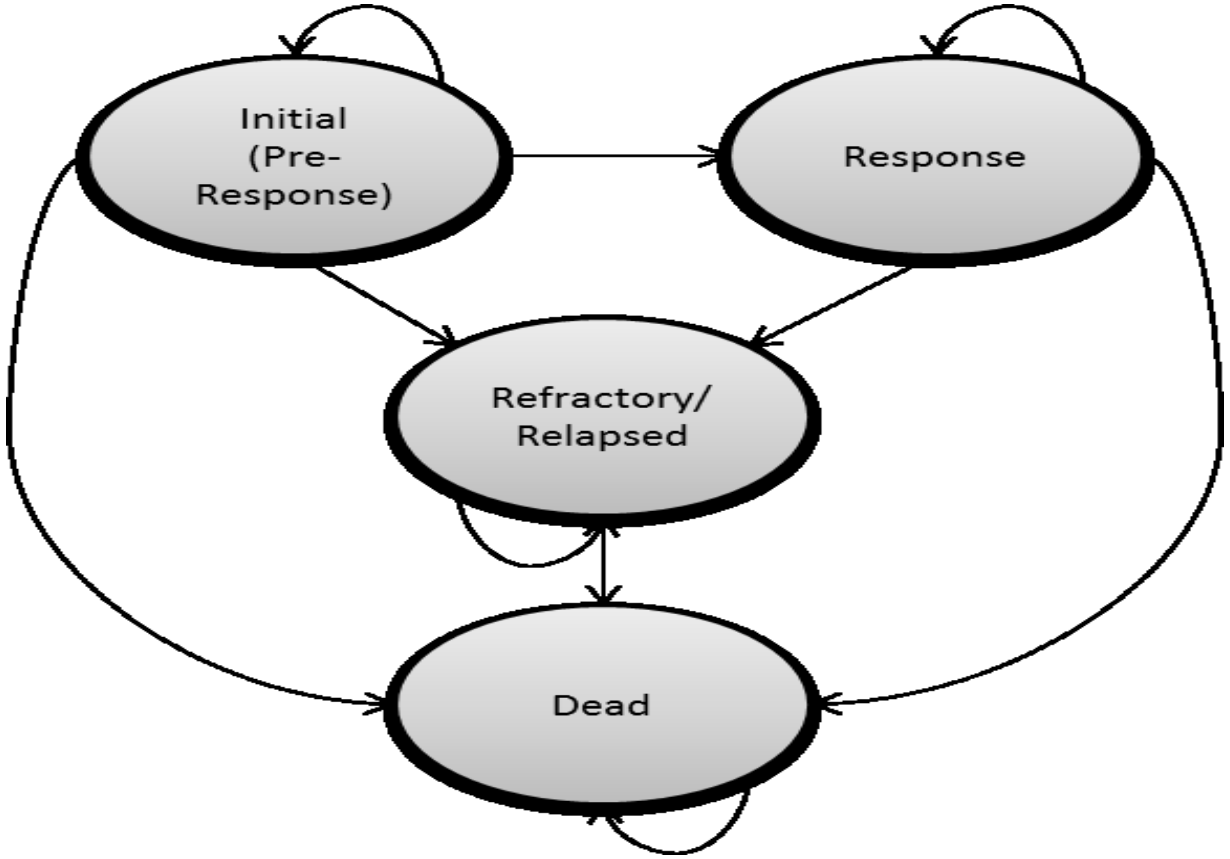
- The ERG did not regard the single-arm trial per se as relevant and thus focused on the comparison between the single-arm trial and the historical cohort
- Note that magnitude of effectiveness comparable to TOWER
- In the non-randomised comparison provided, the definition of complete remission was inconsistent between the blinatumomab arm and the standard of care chemotherapy natural history comparator, and was heterogeneous within the standard of care arm
- Populations in Study MT103-211 and the historical comparator are non-equivalent
- Matched weighting analysis presented by company -the arms were not significantly different once matched except for on region
- Note that the company did not provide evidence of covariate balance using the remission analyses

# Cost effectiveness evidence

# Key issues: cost effectiveness

- The population of the model (and trials) excludes people who have relapsed after 12 months. Does the committee consider the clinical and cost effectiveness to be applicable to people who have a better prognosis?
- Does the committee consider standard of care used in TOWER (base case model) or FLAG-IDA to be the most appropriate comparator?
- Does the committee consider the extrapolation of OS and EFS in the company model to be appropriate?
- Are all of the benefits of blinatumomab included in the QALY calculation?
- To what extent will blinatumomab be admininstered in an outpatient setting?
- Does the committee consider end-of-life criteria to be met?
- Does the committee consider the company or the ERG model to represent the most plausible ICER?

# Model structure




- Partitioned survival model
- Patients enter model in “initial” state and remain in this state for 12 weeks (unless they die)
- After 12 weeks either enter the “refractory/relapsed” state or “response” state
- Weekly model cycle
- 50-year time horizon
- Baseline characteristics from TOWER

# Model details

- Model uses a partitioned survival model approach – which captures the difference in area between OS and EFS survival curves
- Patients receive either blinatumomab or FLAG-IDA
- Effectiveness of the whole SOC chemotherapy arm of TOWER used as a proxy for the effectiveness of FLAG-IDA
  - Costs based on FLAG-IDA
- All clinical parameters in base case derived from TOWER RCT (ITT population)
- OS and EFS among responders extrapolated by company with parametric survival curves fitted to the Kaplan Meier plots
- Patients with relapse after greater than 12 months in remission were not represented in the model as they were not included in TOWER
- Patients alive after 4 years cured - same HR for OS for with blinatumomab and SOC
- Costs considered in the model included drug acquisition and administration costs for blinatumomab and FLAG-IDA, cost of allo-SCT, the costs of subsequent salvage therapy, and terminal care costs
- These costs were calculated independently of the model states

# Overall survival in submitted clinical evidence (AIC)

# Company overall survival extrapolation (AIC)

## Restricted Gompertz

# Extrapolation of outcomes – ERG critique

- OFS and EFS have been estimated based on fitting parametric curves to Kaplan-Meier plots of observed blinatumomab data and assuming proportional hazards to determine the treatment effect
- ERG consider that the proportional hazard assumptions not met, given that the Kaplan-Meier plots appear to cross from month 15 through the remainder of the trial time horizon
  - Company reject this argument, saying that very few patients at risk at time point after curves overlap
- Company assume that patients alive at 4 years are cured - hazard rates for OS are the same for blinatumomab and SOC chemotherapy after 4 years
  - ERG clinical advisor suggests people who survive 5 years or more are likely to be cured
- Parametric fit was chosen by a combination of visual inspection of goodness-of-fit, long-term plausibility informed by historical data and expert opinion, and using the Bayesian Information Criterion (BIC)
- Gompertz model was used in OS base case analysis- this is the 8$^{th}$ best fitting model (BIC)
- ERG explored alternative survival curves in the model but were limited by data availability and were unable to find a more clinically plausible OS curve

# Other clinical parameters

| Parameter | Blinatumomab | FLAG-IDA | Source |
|---|---|---|---|
| Response rate (%) | 43.9 | 24.6 | TOWER |
| Duration of benefit (months) | 48 | - | Company assumption |
| *Parameters used in calculating costs only* | | | |
| Patients receiving allo-SCT (%) | 24.4 | 23.9 | TOWER |
| Patients receiving subsequent innovative therapies (%) | [redacted] | [redacted] | TOWER |
| Patients receiving other subsequent therapies (%) | [redacted] | [redacted] | TOWER |

# Health-related quality of life – Utility values

| Health states | Blinatumomab (N=271) Mean (SE) | SOC Chemotherapy (N=134) Mean (SE) |
|---|---|---|
| Initial (Pre-response) | [redacted] | [redacted] |
| Response | [redacted] | [redacted] |
| Relapsed/refractory | [redacted] | [redacted] |
| Terminal decrement | [redacted] | |

- TOWER collected information on HRQoL (EORTC QLQ-C30) which was mapped to EQ-5D by the company with an algorithm developed using data from 771 patients enrolled in three studies of patients with breast cancer, lung cancer, and multiple myeloma
- All observed adverse events were assumed to occur while people are on treatment and receiving inpatient/outpatient care, and would have been captured by the EORTC QLQ-C30.
- Utility values from the general population were used for people surviving more than four years - unclear if any uncertainty around these estimates was used to inform the probabilistic sensitivity analyses

EQ-5D, EuroQol five dimensions; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30; FAS, full analysis set; SD, standard deviation; SOC, standard of care.

# Utility values – ERG critique

- Assessment should be based on information collected at baseline and one or more time point – company did not include baseline utility values or adjust for baseline differences
- Failure to adjust for these imbalances in utility values could result in misleading cost-effectiveness results
- ERG-preferred approach would have been to include and control for baseline differences, then map these values from the EORTC QLQ-C30 to the EQ-5D
  - Lack of access to patient-level data prevented this
- Changes in utility values assumed to reflect actual treatment effects although no statistical justification provided
- Utility values from the general population were used for people surviving more than four years - unclear if any uncertainty around these estimates was used to inform the probabilistic sensitivity analyses

# Costs

| | Costs (£) | Sources |
|---|---|---|
| *Blinatumomab costs (based on TOWER – see next slide)* | | |
| Drug acquisition (per 38.5 µg vial) | 2,017 | Amgen, list price<br>Dosing regimens from TOWER |
| Inpatient day for drug administration* | 682 | NHS Reference Costs, 14/15 |
| Outpatient infusion centre visit | 204 | NHS Reference Costs, 14/15 |
| Home infusion pump per day of use | 3.84 | UK oncology nurses |
| **Total cost per patient entering model** | [redacted] | |
| *Other costs* | | |
| FLAG-IDA cost per patient entering model | 14,240 | BNF (2016); NHS Generic Pharmaceuticals eMit (2015) |
| Total allo-SCT costs | 104,000 | UK Stem Cell Strategy Oversight Committee 2014 |
| Subsequent innovative salvage therapy | [redacted] | Assumed same as Blinatumomab |
| Subsequent systemic salvage therapy | 14,240 | Assumed same as FLAG-IDA |
| Terminal care | 8,602 | Kings Fund 2008<br>Marie Curie 2012 |

*Hospitalisation implemented in accordance with minimum stated in SmPC:9 days in Cycle 1, 2 days in Cycle 2 and 14 days hospitalisation during Cycle 1 for patients with a history or presence of clinically relevant CNS pathology.

# Costs – ERG critique

- Based on correspondence with the ERG's clinical expert, note the lack of infrastructure in hospitals for the outpatient administration of blinatumomab
- People receiving blinatumomab treatment are therefore likely to spend four weeks in care for both cycles 1 and 2 and consolidation cycles
  - Considerably higher than what the company suggested
  - The ERG has explored this in a scenario analysis
- ERG advisor suggests that patients frequently hospitalised for the entirety of the treatment cycle
  - ERG has undertaken scenario analyses whereby people received all treatment in inpatient care
- Note that company assume no drug wastage

# Cycles of Blinatumomab -TOWER

- Drug acquisition costs for blinatumomab include up to 9 cycles as per TOWER
- Blinatumomab only licensed for up to 5 cycles
- Zero cost for cycle 6+ explored in scenario analysis – adjusted effectiveness not available

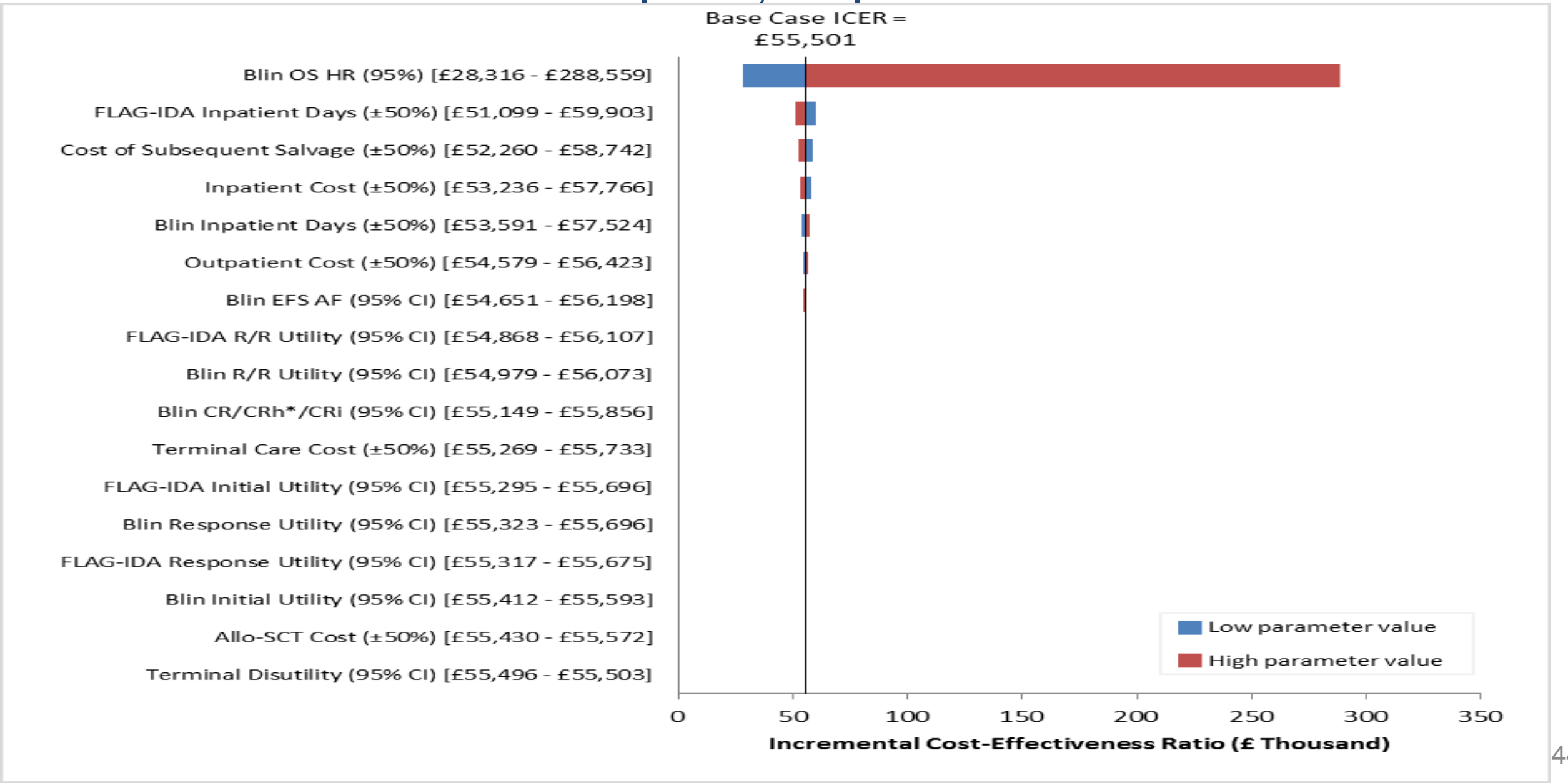
| Cycle | % Starting cycle (TOWER) | % Completing cycle (TOWER) |
|---|---|---|
| Cycle 1 | [redacted] | [redacted] |
| Cycle 2 | [redacted] | [redacted] |
| Cycle 3 | [redacted] | [redacted] |
| Cycle 4 | [redacted] | [redacted] |
| Cycle 5 | [redacted] | [redacted] |
| Cycle 6 | [redacted] | [redacted] |
| Cycle 7 | [redacted] | [redacted] |
| Cycle 8 | [redacted] | [redacted] |
| Cycle 9 | [redacted] | [redacted] |

# Company base-case deterministic results for all patients – blinatumomab PAS price

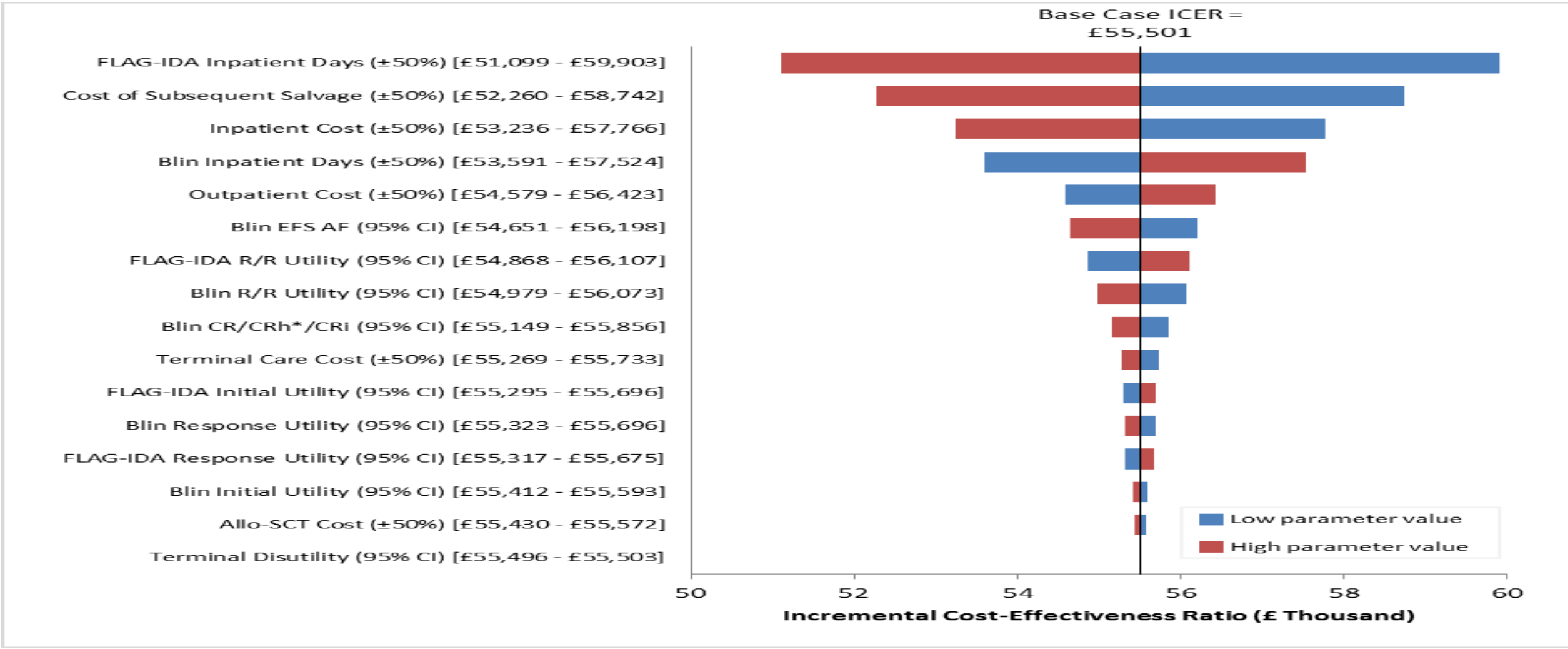
| Treatment | Total | | | Incremental | | | ICER (£) |
|---|---|---|---|---|---|---|---|
| | Cost (£) | LYs | QALYs | Cost (£) | LYs | QALYs | |
| Blinatumomab | 144,611 | 4.38 | 3.35 | 80,446 | 1.78 | 1.45 | 55,501 |
| FLAG-IDA | 64,165 | 2.61 | 1.90 | 80,446 | | | |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life-years.

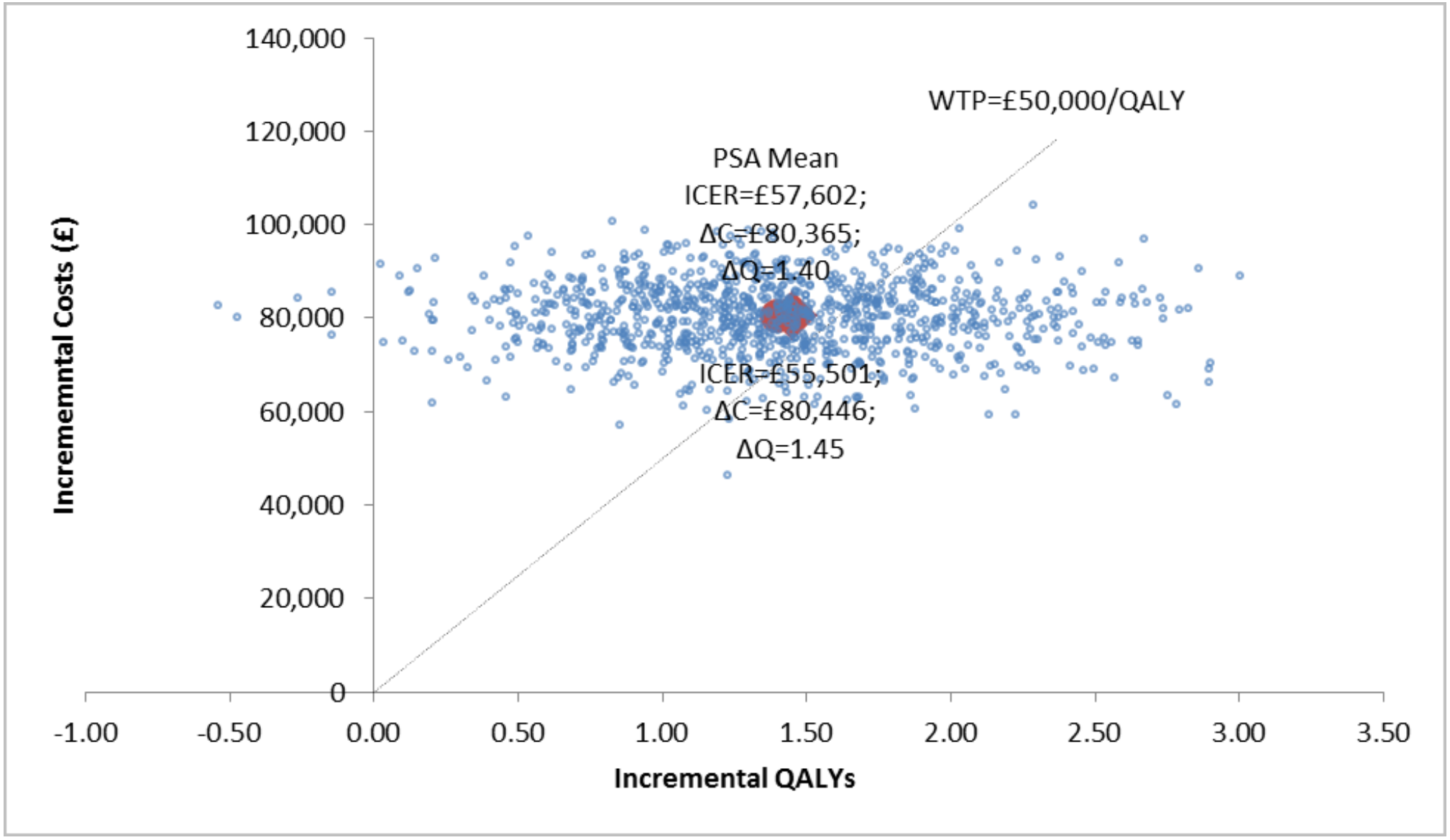
# Tornado diagram (blinatumomab vs FLAG-IDA, all patients) – PAS price, all parameters



# Tornado diagram (blinatumomab vs FLAG-IDA, all patients) – PAS price, excluding sensitivity analysis on OS



# Probabilistic sensitivity analysis results for all patients - blinatumomab PAS price



# Company subgroup analysis- patients with no prior salvage therapy, blinatuomomab PAS price

| Treatment | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Cost (£) | QALYs | ICER (£/QALY) | Cost (£) | QALYs | ICER (£/QALY) |
| Blinatumomab | 171,879 | 3.91 | 49,190 | 172,220 | 3.59 | 58,884 |
| FLAG-IDA | 74,703 | 1.94 | | 75,125 | 1.94 | |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

**ERG**: "…there is still considerable uncertainty in terms of the treatment efficacy, as the TOWER trial was not powered to detect these differences, and clinical results for the difference between subgroups did not reach statistical significance"

# Scenario analysis results- all patients, PAS price

| Scenario number | Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|
| | Base Case | 80,446 | 1.45 | 55,501 |
| 1 | Safety analysis set | 74,256 | 1.34 | 55,314 |
| 2 | Subgroup of patients that were intended to receive a FLAG-IDA SOC therapy regimen at randomization | 78,459 | 2.42 | 32,371 |
| 2 | OS Based on RCS Log-Logistic | 80,824 | 0.47 | 171,487 |
| 3 | Survivors Cured - 36 Months | 78,866 | 1.81 | 43,527 |
| 4 | Survivors Cured - 48 Months | 79,280 | 1.60 | 49,485 |
| 5 | Survivors Cured - 60 Months | 79,572 | 1.45 | 55,017 |
| 6 | EFS Based on Lognormal | 80,461 | 1.45 | 55,659 |
| 7 | 36-Month Duration of Benefit | 80,446 | 1.39 | 57,754 |
| 8 | 60-Month Duration of Benefit | 80,444 | 1.47 | 54,696 |
| 9 | 10-Year Model Timeframe | 80,466 | 0.63 | 126,896 |
| 10 | 20-Year Model Timeframe | 80,455 | 1.02 | 78,878 |
| 11 | 60-Year Model Timeframe | 80,444 | 1.46 | 55,135 |
| 12 | 1.5% Discount Rate | 80,852 | 1.97 | 41,081 |
| 13 | 10 Inpatient Days Blinatumomab All Cycles | 88,069 | 1.45 | 60,760 |
| 14 | Zero cost for Blinatumomab Cycle 6+ | 72,179 | 1.45 | 49,798 |
| 15 | Blinatumomab home IV bag changes for Cycle 3+ | 79,677 | 1.45 | 54,971 |
| 16 | Clofarabine Included in FLAG-IDA | 76,206 | 1.45 | 52,576 |
| 17 | Rate of allo-SCT from MT103-211 | 87,085 | 1.45 | 60,081 |
| 18 | EORTC-8D Utilities | 80,446 | 1.49 | 53,910 |
| 19 | TTO Utilties from Vignette Study | 80,446 | 1.40 | 57,438 |

# Scenario analysis results
# Patients with no prior salvage therapy, PAS price

| Scenario number | Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|
| | Base Case (No Prior Salvage) | 97,176 | 1.98 | 49,190 |
| 1 | Safety analysis set (No Prior Salvage) | 74,070 | 1.58 | 46,821 |
| 2 | OS Based on RCS Log-Logistic | 97,624 | 0.79 | 123,824 |
| 3 | Survivors Cured - 36 Months | 95,114 | 2.59 | 36,761 |
| 4 | Survivors Cured - 48 Months | 95,678 | 2.32 | 41,211 |
| 5 | Survivors Cured - 60 Months | 96,078 | 2.12 | 45,339 |
| 6 | EFS Based on Lognormal | 97,140 | 1.98 | 49,114 |
| 7 | 36-Month Duration of Benefit | 97,166 | 1.82 | 53,389 |
| 8 | 60-Month Duration of Benefit | 97,177 | 2.05 | 47,291 |
| 9 | 10-Year Model Timeframe | 97,214 | 0.95 | 102,439 |
| 10 | 20-Year Model Timeframe | 97,206 | 1.46 | 66,788 |
| 11 | 60-Year Model Timeframe | 97,174 | 1.98 | 49,055 |
| 12 | 1.5% Discount Rate | 97,621 | 2.61 | 37,336 |
| 13 | 10 Inpatient Days Blinatumomab All Cycles | 107,383 | 1.98 | 54,356 |
| 14 | Zero cost for Blinatumomab Cycle 6+ | 82,931 | 1.98 | 41,979 |
| 15 | Blinatumomab home IV bag changes for Cycle 3+ | 96,070 | 1.98 | 48,630 |
| 16 | Clofarabine Included in FLAG-IDA | 92,806 | 1.98 | 46,978 |
| 17 | Rate of allo-SCT from MT103-211 | 108,862 | 1.98 | 55,105 |
| 18 | EORTC-8D Utilities | 97,176 | 2.03 | 47,881 |
| 19 | TTO Utilties from Vignette Study | 97,176 | 1.81 | 53,680 |

# ERG Comments

- Several areas of uncertainty in the economic model
- Generalisability of SOC chemotherapy to FLAG-IDA uncertain
- TOWER not powered for subgroup analysis
- Concerns over extrapolation of treatment effectiveness
  - Conservative interpretation of Kaplan-Meier plots is that additional costs and benefits are unlikely to accrue past the trial time horizon, and extrapolation of effectiveness beyond the trial time horizon is thus unnecessary
  - ERG explored a “within-trial” analysis, which assumes no treatment effect beyond the 2-year trial period based on OS curves overlapping at 15 months
  - Caution that this may underestimate costs and benefits, given that some SOC patients received subsequent treatment with blinatumomab or other therapies
  - ERG was limited by data availability in exploring the feasibility of alternative survival curves in the economic model
- Concerns over health care utilisation
  - ERG clinical advisor suggests that the minimum hospitalisation requirements used in model are unrealistic – hopsitalisation for entirety of first two treatments likely
  - ERG believe that daily bag changing for intravenous chemotherapy more likely

# ERG Analysis

- ERG undertook the following scenario analyses, based on their concerns with the company base case:
  - Two-year time horizon
  - Additional inpatient treatment
    - Inpatient stay for cycles one and two
    - Assuming blinatumomab is administered in an inpatient setting (five cycles with inpatient stays)
  - Intravenous bag changes daily, as opposed to every four days
- **ERG preferred base case**: inpatient treatment in cycles one and two, daily bag changes in subsequent cycles

# ERG preferred base case – PAS price

## inpatient treatment in cycles one and two, daily bag changes in subsequent cycles

| Treatment | Deterministic | | | Probabilistic | | |
|---|---|---|---|---|---|---|
| | Cost (£) | QALYs | ICER (£/QALY) | Cost (£) | QALYs | ICER (£/QALY) |
| Blinatumomab | 167,644 | 3.35 | 69,746 | 167,590 | 3.22 | 73,383 |
| FLAG-IDA | 66,550 | 1.90 | | 66,543 | 1.85 | |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

# ERG Deterministic scenario analysis – two-year time horizon ("within- trial" analysis), PAS price

| Treatment | Total | | Incremental | | ICER (£) |
|---|---|---|---|---|---|
| | Cost (£) | QALYs | Cost (£) | QALYs | |
| Blinatumomab | 144,120 | 0.57 | 80,442 | 0.19 | 432,478 |
| FLAG-IDA | 63,678 | 0.38 | | | |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life-years.

# Innovation as per company submission

- First-in-class mechanism of action that harnesses the body's own immune system to recognise and eliminate malignant cancer cells
- There are no targeted treatments licensed specifically for this disease
- Patients also experience a high treatment burden as a result of the significant toxicities associated with salvage chemotherapy regimens
- Blinatumomab can be administered in an outpatient setting
- Additional benefits associated with blinatumomab are unlikely to be captured:
  - minimising hospitalisation (benefit to patients, families, wider society)
- As blinatumomab is indicated for a very rare condition (86 patients per year in England) demonstrating cost effectiveness is challenging
- Applying the standard approach to evaluating medicines for this very small group of patients is likely to be unfairly biased against blinatumomab
- The company have requested that blinatumomab be evaluated taking into account a wider range of criteria about the benefits and costs, as NICE does for HST appraisals

# End of Life Criteria

| Criteria | Normal range | TOWER (months) |
|---|---|---|
| Short life expectancy | <24 months | 4.0 |
| Extension to life | ≥3 months | 3.7 |

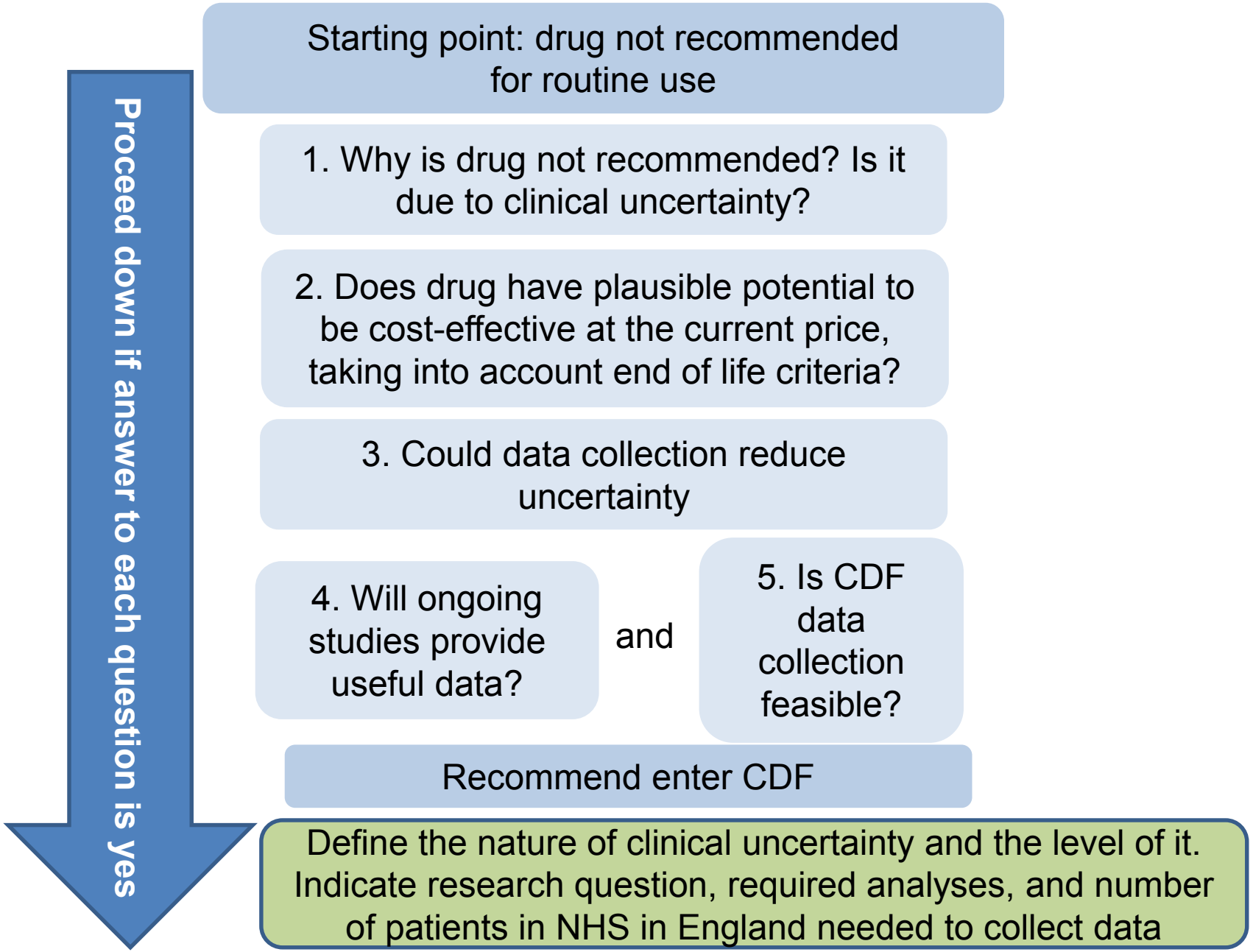
- Company state that blinatumomab for the treatment of adult patients with R/R Ph- B-precursor ALL meets the NICE end-of-life criteria
- ERG “agrees that a case exists” for blinatumomab fulfilling NICE end-of-life criteria.

# Equality

- No equality issues relating to use of blinatumomab for the treatment of adult R/R Ph- B-precursor ALL were identified at scoping stage or in submissions

# Back-up slides

# CDF Recommendation Decision Pathway



# Highly specialised technologies criteria

- For a topic to be selected for HST, all of the following criteria need to be met:
  - The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;
  - The target patient group is distinct for clinical reasons;
  - The condition is chronic and severely disabling;
  - The technology is expected to be used exclusively in the context of a highly specialised service;
  - The technology is likely to have a very high acquisition cost;
  - The technology has the potential for life long use;
  - The need for national commissioning of the technology is significant.

# ERG Deterministic scenario analysis – inpatient stay changed, intravenous bag changes every 4 days as per company model, PAS price

| Treatment | Total | | Incremental | | ICER (£) |
|---|---|---|---|---|---|
| | Cost (£) | QALYs | Cost (£) | QALYs | |
| **Patients hospitalised for first two cycles** | | | | | |
| Blinatumomab | 163,842 | 3.35 | 97,686 | 1.45 | 67,395 |
| FLAG-IDA | 66,156 | 1.90 | | | |
| **Patients hospitalised for five cycles (maximum in MA)** | | | | | |
| Blinatumomab | 175,941 | 3.35 | 108,532 | 1.45 | 74,878 |
| FLAG-IDA | 67,409 | 1.90 | | | |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life-years.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

## Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia

## Scope

### Remit

To appraise the clinical and cost effectiveness of blinatumomab within its marketing authorisation for previously treated B-precursor acute lymphoblastic leukaemia.

### Background

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. Lymphocytes are white blood cells that are vital for the body's immune system. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood. ALL can be classified into 3 groups based on immunophenotyping: B-precursor ALL (also known as precursor-B-cell ALL), mature B-cell ALL and T-cell ALL. B-cell ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22 and CD79a expression.

ALL is most common in children, adolescents and young adults, with 65% of cases diagnosed in people aged under 25 years. A second increase in incidence is observed in people aged over 60 years. In England, 536 people were diagnosed with ALL in 2011 and 202 people died from ALL in 2012. Approximately 20–30% of adults with ALL have the Philadelphia chromosome.[1]

The aim of treatment in ALL is to achieve a cure. Treatment can take up to 3 years to complete and is generally divided into 3 phases; induction phase, consolidation and maintenance. The choice of chemotherapy regimen can depend on the phase and although selection of drugs, dose schedules and treatment duration may differ slightly between different subtypes of ALL, the basic treatment principles remain similar. There is currently no NICE guidance for treating ALL. During induction, newly diagnosed ALL is generally treated with chemotherapy combinations including vincristine, an anthracycline and asparaginase. During the consolidation phase, intensified chemotherapy is used, which may include high dose methotrexate with mercaptopurine, high dose asparaginase, or a repeat of the induction therapy. During the maintenance phase low dose chemotherapy is used, which typically consists of weekly methotrexate and daily mercaptopurine for an extended period of time to prevent relapse. In adults with high risk acute ALL, stem cell

transplantation and chemotherapy are both considered first line treatment options.[2]

Relapse or refractory to initial treatment occurs in approximately 45% of people with newly diagnosed B-cell ALL. The overall survival rate at 5 years is approximately 10%[3]. Although there is currently no standard of care for people with relapsed or refractory ALL, adults are usually treated with a combination chemotherapy regimen of fludarabine, cytarabine and granulocyte colony-stimulating factor, with or without idarubicin, followed by stem cell transplantation where a suitable donor can be found, or best supportive care (including palliative care). Clofarabine is also used outside its marketing authorisation in clinical practice in England through the Cancer Drugs Fund.

## The technology

Blinatumomab (Amgen) is a T-cell engager antibody targeting CD19 and the CD3/T cell receptor. When blinatumomab binds to both the cancer cell and T-cell, the T-cell is recruited and activated to destroy the cancer cell. It is administered intravenously.

Blinatumomab has a marketing authorisation in the UK for "adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)".

| | |
|---|---|
| **Intervention** | Blinatumomab |
| **Population** | People with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia |
| **Comparators** | • Fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy, with or without idarubicin<br>• Clofarabine based combination chemotherapy<br>• Best supportive care (including palliative care) |

| | |
|---|---|
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• event-free survival<br>• relapse-free survival<br>• treatment response rates (including minimal residual disease and haematologic responses and complete remission)<br>• time to and duration of response<br>• rate of stem cell transplant<br>• adverse effects of treatment<br>• health-related quality of life |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective. |
| **Other considerations** | If the evidence allows the following subgroup will be considered:<br>• people for whom allogeneic stem cell transplantation is considered an appropriate treatment option<br>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. |
| **Related NICE recommendations and NICE Pathways** | Appraisals in development (including suspended appraisals)<br>'Pegaspargase for treating acute lymphoblastic leukaemia'. NICE technology appraisal [ID863]. Publication expected September 2016.<br>'Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia'. NICE technology |

| | |
|---|---|
| | appraisal [ID671]. Publication expected May 2017.<br><br>'Erythrocyte encapsulated asparaginase for treating acute lymphoblastic leukaemia in adults and children after treatment with escherichia coli derived asparaginase' NICE technology appraisal [ID864]. Publication expected June 2017.<br><br>'Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia' Proposed NICE technology appraisal [ID893]. Publication date to be confirmed.<br><br>Terminated appraisals:<br><br>'Dasatinib for the treatment of acute lymphoblastic leukaemia' (terminated appraisal; 2008). NICE technology appraisal [ID386].<br><br>Related Guidelines:<br><br>'Suspected cancer: recognition and referral' (2015). NICE guideline NG12.<br><br>'Improving outcomes in children and young people with cancer' (2005). Cancer Service Guideline<br><br>'Improving outcomes in haematological cancers' (October 2003) Cancer Service Guideline.<br><br>Related Quality Standards:<br><br>'Children and young people with cancer' (February 2014) NICE quality standard 55<br><br>Related NICE Pathways:<br><br>Suspected cancer recognition and referral (2015) NICE pathway<br><br>Blood and bone marrow cancers (2014) NICE Pathway |
| **Related National Policy** | Specialist cancer services for children and young people, Chapter 106, Manual for Prescribed Specialised Services 2013/14<br><br>http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf<br><br>Blood and marrow transplantation services (all ages), Chapter 29, Manual for Prescribed Specialised Services 2013/14<br><br>http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf<br><br>Department of Health, NHS Outcomes Framework 2015/16, Dec 2014. Domains 1 and 2 |

| | |
|---|---|
| | https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf |

## References

1 Cancer Research UK (2014) Acute lymphoblastic leukaemia (ALL) statistics, Accessed October 2015

2 Macmillan Cancer Support (2014) Treatment overview for acute lymphoblastic leukaemia, Accessed October 2015

3 Oriol A (2010), Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica Apr 2010, 95 (4) 589–596

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal
## Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]

### Matrix of consultees and commentators

| Consultees | Commentators (no right to submit or appeal) |
|---|---|
| Company<br>• Amgen (blinatumomab)<br><br>Patient/carer groups<br>• African Caribbean Leukaemia Trust<br>• Anthony Nolan<br>• Black Health Agency<br>• Bloodwise<br>• Cancer Black Care<br>• Cancer Equality<br>• Cancer52<br>• Delete Blood Cancer<br>• HAWC<br>• Helen Rollason Cancer Charity<br>• Independent Cancer Patients Voice<br>• Leukaemia Cancer Society<br>• Leukaemia CARE<br>• Lymphoma Association<br>• Macmillan Cancer Support<br>• Maggie's Centres<br>• Marie Curie Cancer Care<br>• Muslim Council of Britain<br>• Rarer Cancers Foundation<br>• South Asian Health Foundation<br>• Specialised Healthcare Alliance<br>• Tenovus cancer care<br><br>Professional groups<br>• Association of Cancer Physicians<br>• British Committee for Standards in Haematology<br>• British Geriatrics Society<br>• British Institute of Radiology<br>• British Psychosocial Oncology Society<br>• British Society for Haematology<br>• Cancer Research UK | General<br>• Allied Health Professionals Federation<br>• Board of Community Health Councils in Wales<br>• British National Formulary<br>• Care Quality Commission<br>• Department of Health, Social Services and Public Safety for Northern Ireland<br>• Healthcare Improvement Scotland<br>• Medicines and Healthcare products Regulatory Agency<br>• National Association of Primary Care<br>• National Pharmacy Association<br>• NHS Alliance<br>• NHS Commercial Medicines Unit<br>• NHS Confederation<br>• Scottish Medicines Consortium<br><br>Possible comparator companies<br>• Accord Healthcare (cytarabine, filgrastim, fludarabine)<br>• Allergan (fludarabine)<br>• Chugai Pharma UK (lenograstim)<br>• Hospira UK (cytarabine, filgrastim, fludarabine)<br>• Pfizer (cytarabine, idarubicin)<br>• Sandoz (filgrastim , fludarabine)<br>• Sanofi (fludarabine, clofarabine)<br>• Teva Pharma (lipegfilgrastim)<br><br>Relevant research groups<br>• Cochrane Haematological Malignancies Group<br>• Elimination of Leukaemia Fund<br>• Institute of Cancer Research<br>• Leuka |

| **Consultees** | **Commentators (no right to submit or appeal)** |
|---|---|
| • Royal College of General Practitioners<br>• Royal College of Nursing<br>• Royal College of Pathologists<br>• Royal College of Physicians<br>• Royal College of Radiologists<br>• Royal Pharmaceutical Society<br>• Royal Society of Medicine<br>• Society and College of Radiography<br>• UK Clinical Pharmacy Association<br>• UK Health Forum<br>• UK Oncology Nursing Society<br><br><u>Others</u><br>• Department of Health<br>• NHS England<br>• NHS Richmond CCG<br>• NHS South East Staffordshire & Seisdon Peninsular CCG<br>• Welsh Government | • Leukaemia Busters<br>• MRC Clinical Trials Unit<br>• National Cancer Research Institute<br>• National Cancer Research Network<br>• National Institute for Health Research<br>•<br><u>Associated Guideline groups</u><br>• National Clinical Guidelines Centre<br><br><u>Associated Public Health groups</u><br>• Public Health England<br>• Public Health Wales |

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

***PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS***

**Definitions:**

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal (STA)

# Blinatumomab for previously treated B-precursor acute lymphoblastic leukaemia

## Company evidence submission

## Prepared by:

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| | 1.1 (without PAS) | Yes<br>AIC and CIC redacted | 02 March 2017 |

# Acronyms and abbreviations

| | |
|---|---|
| AE | Adverse event |
| ALL | Acute lymphoblastic leukaemia |
| allo-SCT | Allogeneic stem cell transplantation |
| ALLSS | Acute lymphoblastic leukaemia symptom scale |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ANZCTR | Australian New Zealand Clinical Trials Registry |
| ASCO | American Society of Clinical Oncology |
| ASH | American Society of Hematology |
| AST | Aspartate aminotransferase |
| AWMSG | All Wales Medicines Strategy Group |
| BIC | Bayesian Information Criterion |
| BNF | British National Formulary |
| BSC | Best supportive care |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CEAC | Cost-effectiveness acceptability curve |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CI | Confidence interval |
| CNS | Central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRD | Centre for Reviews and Dissemination |
| CR | Complete remission |
| CRh* | Complete remission with partial haematological recovery |
| CRi | Complete remission with incomplete haematologic recovery |
| CrIs | Credible intervals |
| CRS | Cytokine release syndrome |
| CRsg | Complete remission per study groups |
| CSR | Clinical study report |
| DMC | Data monitoring committee |
| DoH | Department of Health |
| ECOG | Eastern Cooperative Oncology Group |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |

| | |
|---|---|
| EED | Economic Evaluation Database |
| 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 |
| EORTC-8D | European Organisation for Research and Treatment of Cancer eight dimension |
| EPAR | European Public Assessment Report |
| EQ-5D | EuroQoL Five Dimensions health status questionnaire |
| ESMO | European Society for Medical Oncology |
| EU | European Union |
| EU CTR | European Clinical Trials Register |
| EWALL | European Working Group for Adult ALL |
| FAS | Full analysis set |
| FDA | United States Food and Drug Administration |
| FLAG-AMSA | Fludarabine, cytarabine, filgrastim, amsacrine |
| FLAG | Fludarabine, cytarabine, granulocyte colony stimulating factor |
| FLAG-IDA | Fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin |
| GCSF | Granulocyte colony-stimulating factor |
| GEE | Generalised estimating equations |
| GGT | Gamma-glutamyl transferase |
| GHS/QoL | Global Health Status/Quality of Life |
| GLM | Generalised linear model |
| GVHD | Graft-versus-host disease |
| HCHS | Healthcare and hospital services |
| HCP | Healthcare practitioner |
| HiDAC | High-dose cytarabine |
| HIT | Home infusion treatment |
| HRG | Healthcare Resource Group |
| HRG | Healthcare Resource Group |
| HRQoL | Health-related quality of life |

| | |
|---|---|
| HST | Highly Specialised Technology |
| HTA | Health Technology Assessment |
| Hyper-CVAD | Hyperfractionated, cyclophosphamide, vincristine, doxorubicin |
| ICER | Incremental cost-effectiveness ratio |
| ICTRP | International Clinical Trials Registry Platform |
| ICTRP | International Clinical Trials Registry Platform |
| IPTW | Inverse probability of treatment weighting |
| IQR | Interquartile range |
| ITT | Intent to treat |
| IV | Intravenous |
| IVRS | Interactive voice/response system |
| KM | Kaplan–Meier |
| LALA | Leucémie Aiguës Lymphoblastique de l'Adulte |
| LY | Life-year |
| MAE | Mean absolute errors |
| MAR | Missing at random |
| MeSH | Medical Subject Heading |
| MMRM | Model for repeated measures |
| MRD | Minimal residual disease |
| MVH | Measurement and Valuation of Health |
| N/A | Not applicable |
| NCCN | National Comprehensive Cancer Network |
| NE | Not estimable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIH | National Institute of Health |
| NR | Non-response |
| ONS | Office for National Statistics |
| OS | Overall survival |
| PAS | Primary analysis set |
| PAS | Patient access scheme |
| PASLU | PAS Liaison Unit |
| PCR | Polymerase chain reaction |

| | |
|---|---|
| PETHEMA | Programa Español de Tratamientos en Hematologica |
| PFS | Progression-free survival |
| Ph- | Philadelphia chromosome–negative |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PSA | Probabilistic sensitivity analysis |
| PSS | Personal Social Services |
| PSSRU | Personal Social Services Research Unit |
| QALY | Quality-adjusted life-year |
| QoL | Quality of life |
| R/R | Relapsed or refractory |
| RCS | Restricted cubic spline |
| RCT | Randomised controlled trial |
| RFS | Relapse-free survival |
| RMSE | Root-mean squared errors |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Safety analysis set |
| SD | Standard deviation |
| SEM | Standard error of the mean |
| SE | Standard error |
| SLR | Systematic literature review |
| SMC | Scottish Medicines Consortium |
| SmPC | Summary of Product Characteristics |
| SOC | Standard of care |
| SSE | Sum of squared errors |
| STA | Single technology appraisal |
| TA | Technology appraisal |
| TEAE | Treatment-emergent adverse event |
| TTHR | Time-to-haematological relapse |
| TTO | Time trade-off |

| | |
|---|---|
| UKALL XII | UK Medical Research Council Acute Lymphoblastic Leukaemia Trial XII |
| ULN | Upper limit of normal |
| US | United States |
| VAT | Value added tax |
| WBC | White blood cell |
| WHO | World Health Organization |
| WTP | Willingness to pay |
| YLL | Years of life lost |

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# 1 Executive summary

## *1.1 Introduction*

Adult relapsed or refractory Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia (R/R Ph- B-precursor ALL) is a very severe, rare, and complex haematological malignancy that specifically affects lymphoblasts; proliferating lymphoblasts crowd out and suppress the production of normal blood cells in the bone marrow. It is estimated that there are just 86 adult patients per year with Ph- B-precursor ALL in England and Wales who will relapse or become refractory to treatment. The prognosis for these patients is extremely poor and they face imminent risk of death; median overall survival (OS) is estimated to be only around 3 to 6 months, and approximately 75% of patients die within a year of starting their first salvage therapy. Adult patients with Ph- B-precursor ALL have a median age of 34 to 39 years at diagnosis, and it is estimated that patients die, on average, 30 years prematurely. These years of life lost (YLLs) far exceed those in other more common haematological and solid tumour malignancies.

Meaningful progress in the treatment of adult R/R Ph- B-precursor ALL has been lacking for decades and, with the exception of blinatumomab, there are no targeted treatments licensed specifically for the disease in the UK. Active treatment options are limited to a range of poorly effective and highly toxic salvage chemotherapy regimens, with or without allogenic stem cell transplant (allo-SCT) which is currently the only potentially curative treatment option. There is no clearly defined treatment pathway and a lack of specific recommendations around patient management in available European clinical guidelines and regional National Health Service (NHS) protocols, reflecting the absence of any clearly superior salvage chemotherapy. FLAG-IDA, a combination comprising fludarabine, cytarabine, and granulocyte colony-stimulating factor (GCSF) in combination with idarubicin (an anthracycline) represents the most commonly used salvage chemotherapy regimen in clinical practice in England and Wales, and is therefore considered the relevant comparator for this appraisal. There is an urgent need for new, effective treatment options for adult patients with R/R Ph- B-precursor ALL that prolong OS, improve rates and duration of haematological remission to give patients a better chance of being considered eligible for allo-SCT, and reduce toxicities to preserve quality of life (QoL).

Blinatumomab is a novel bispecific T-cell engaging immunotherapy, with a first-in-class mechanism of action that harnesses the body's own immune system to recognise and eliminate cancer cells. It was conditionally approved by the European Medicines Agency (EMA) following an accelerated assessment based on compelling results from a phase 2 study (including a comparison with a historical cohort), reflecting that blinatumomab is an important medicine with major public health interest, addresses a substantial unmet need, and represents a major therapeutic innovation. TOWER is a phase 3 confirmatory randomised controlled trial (RCT) that evaluated blinatumomab against investigator choice of protocol-specified standard of care (SOC) chemotherapy in adult patients with R/R Ph- B-precursor ALL, and was stopped early for efficacy after a significant OS benefit for blinatumomab was demonstrated. In TOWER, blinatumomab was associated with a near-doubling of median OS, more than doubling of complete remission (CR) rates, fewer of the common toxicities seen with SOC chemotherapy, and improved health-related QoL (HRQoL). TOWER is the first study in several decades to show a significant survival benefit for a new therapy versus SOC in R/R

ALL. Blinatumomab therefore offers adult R/R Ph- B-precursor ALL patients prolonged survival and an improved likelihood of achieving haematological remission, thus giving them a better chance of being considered eligible for allo-SCT. Blinatumomab also offers patients the chance to receive treatment in the outpatient setting after a short minimum period of hospitalisation (the first 9 days of the first cycle and the first 2 days of the second cycle), which is likely to be significant for patients and their families. As such, blinatumomab represents a step change in the management of patients with this devastating and highly aggressive disease that responds poorly to current salvage chemotherapy regimens and is associated with very poor survival.

The cost-effectiveness analyses presented in this submission are based on the list price of blinatumomab. Amgen has proposed a simple patient access scheme (PAS) which has been approved by the Department of Health (DoH); analyses incorporating the PAS are included in the PAS addendum to this submission. Using current National Institute for Health and Care Excellence (NICE) methodology, demonstrating cost effectiveness of blinatumomab is challenging for this extremely rare disease, even with the application of end-of-life criteria (and corresponding willingness-to-pay threshold) and a simple PAS. Additional benefits associated with blinatumomab are unlikely to be captured within the standard NICE incremental cost-utility framework, specifically, the benefits to patients and their families of minimising hospitalisation requirements and to wider society of treating a younger patient population (median age at diagnosis 34-39 years) with an effective treatment option that may lead to more patients achieving long-term remission and survival. Given that blinatumomab is indicated for a rare condition in a very small number of patients (86 per year) who have a huge unmet medical need and who stand to gain substantially from access to blinatumomab, it meets many of the criteria for appraisal under the Highly Specialised Technology (HST) framework. Consequently, blinatumomab should be evaluated taking into account a wider range of criteria about the benefits and costs, as NICE does for HST appraisals. Applying the standard approach to evaluating medicines for this very small group of patients is likely to be unfairly biased against blinatumomab. Given the huge unmet need and the significant clinical benefit, including additional benefit not captured by the quality-adjusted life-year (QALY), blinatumomab is proposed for use in England and Wales for the full licensed population (i.e., in all adult patients with R/R Ph- B-precursor ALL).

## *1.2 Statement of decision problem*

Table 1-1 summarises the decision problem addressed in this submission.

**Table 1-1. 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 relapsed or refractory B-precursor acute lymphoblastic leukaemia | Adults with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia | Blinatumomab does not have a marketing authorisation for use in paediatric patients. |
| Intervention | Blinatumomab | Per final scope | N/A |
| Comparator (s) | • Fludarabine, cytarabine and GCSF based combination chemotherapy, with or without idarubicin<br>• Clofarabine-based combination chemotherapy<br>• Best supportive care (including palliative care) | Fludarabine, cytarabine and GCSF based combination chemotherapy with idarubicin (FLAG-IDA) | • FLAG-IDA is considered to represent the relevant comparator for blinatumomab based on feedback from UK clinical experts, and data suggesting it is the most common salvage chemotherapy regimen used in clinical practice in the UK. Clinical effectiveness estimates were derived from the whole SOC chemotherapy arm of TOWER to maximise the use of the data from TOWER, and because the SOC chemotherapy arm was considered to be broadly generalisable to FLAG-IDA by UK clinical experts. An informative cost-effectiveness scenario analysis was conducted in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation. As the OS HR for blinatumomab versus SOC chemotherapy was more favourable in this subgroup, the base-case approach is potentially conservative.<br>• Clofarabine is licensed as a monotherapy for the paediatric population and is due to be appraised by |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | | | NICE in 2017 for paediatric use in patients who have received at least two prior therapies. Funding and routine availability of clofarabine in the adult population remains unclear since the expiration of the previous Cancer Drug Fund. Although not considered a relevant comparator, a cost-effectiveness scenario analysis was conducted incorporating costs for clofarabine; similar to the base-case analysis versus FLAG-IDA, clinical effectiveness estimates were based on the whole SOC chemotherapy arm of TOWER (which included clofarabine or clofarabine based regimens as one of four protocol-specified investigator choice regimens).<br>• BSC is generally reserved for patients who do not respond to salvage chemotherapy, have reached end-of-life, and have experienced substantial toxicity with salvage chemotherapy. Blinatumomab, which is likely to be used as an alternative to other salvage chemotherapies rather than as an alternative to BSC, would therefore be used before BSC in the treatment pathway. |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| Outcomes | • OS<br>• EFS<br>• RFS<br>• Treatment response rates (including MRD and haematologic responses)<br>• Time to and duration of response<br>• Rate of stem cell transplant<br>• AEs of treatment<br>• HRQoL<br>• | Per final scope | N/A |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from a NHS and Personal Social Services perspective. | Per final scope | N/A |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| Subgroups to be considered | People for whom allo-SCT is considered an appropriate treatment option | People who have not received prior salvage therapy | • The criteria clinicians use to determine patient eligibility for allo-SCT are heterogeneous, and there is no robust/uniform way in which appropriateness can be defined in the context of a clinical study.<br>• It is likely that blinatumomab will be used early in the treatment pathway (i.e., in patients who have not received prior salvage therapy). This is because treating patients earlier in the treatment pathway (i.e., patients with a better prognosis) with a more effective therapy is likely to lead to improvements in both absolute and relative OS. The subgroup of patients who have not received prior salvage therapy is therefore a pertinent subgroup. Data for this subgroup come from pre-specified subgroup analyses of TOWER (stratification factor subgroup). |
| Special considerations including issues related to equity or equality | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. | Per final scope | N/A |

allo-SCT, allogeneic stem cell transplant; AEs, adverse events; EFS, event-free survival; FLAG ± anthracycline, fludarabine, cytarabine, granulocyte colony stimulating factor ± anthracycline; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; GCSF, granulocyte colony-stimulating factor; HR, hazard ratio; 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; RFS, relapse-free survival.

## 1.3 Description of the technology being appraised

A brief overview of blinatumomab is provided in Table 1-2.

**Table 1-2. Technology being appraised**

| | |
|---|---|
| UK approved name and brand name | Blinatumomab (Blincyto®) |
| Marketing authorisation/CE mark status | A conditional marketing authorisation was approved by the EC on 23 November 2015 (EU/1/15/1047/001).<br><br>Conditional approval was subject to the provision of data from the confirmatory phase 3 TOWER RCT; these data were submitted to the EMA via Type II variation procedure on 11 November 2016. |
| Indications and any restriction(s) as described in the SmPC | Blinatumomab is indicated for the treatment of adults with R/R Ph- B-precursor ALL |
| Method of administration and dosage | • Blinatumomab solution for infusion is administered as a continuous IV infusion delivered at a constant flow rate using an infusion pump over a period of up to 96 hours.<br>• Hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle,[a] and the first 2 days of subsequent cycles<br>• A therapeutic dose of 9 µg/day (starting dose; days 1–7) or 28 µg/day (subsequent doses) should be administered to the patient by infusing a total of 240 mL blinatumomab solution for infusion at one of four constant infusion rates and associated infusion durations:<br>▪ Infusion rate of 10 mL/h for a duration of 24 hours<br>▪ Infusion rate of 5 mL/h for a duration of 48 hours<br>▪ Infusion rate of 3.3 mL/h for a duration of 72 hours<br>▪ Infusion rate of 2.5 mL/h for a duration of 96 hours |

[a] Or first 14 days if presence of clinically relevant CNS pathology

ALL, acute lymphoblastic leukaemia; CNS, central nervous system; EC, European Commission; EMA, European Medicines Agency; EU, European Union; IV, intravenous; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory; SmPC, summary of product characteristics.

## 1.4 Summary of the clinical effectiveness analysis

### 1.4.1 Overview of the clinical evidence base

The main clinical evidence presented in this submission for blinatumomab in adult patients with R/R Ph- B-precursor ALL comes from TOWER (N = 405), a phase 3, randomised, open-label study designed to assess the superiority of blinatumomab over investigator choice of one of four protocol-specified SOC chemotherapy regimens: FLAG ± anthracycline-based; high-dose cytarabine (HiDAC)-based; high-dose methotrexate-based; or clofarabine-based. The most common intended SOC chemotherapy regimen in patients randomised to SOC chemotherapy was FLAG ± anthracycline ([redacted]). As a planned interim analysis of OS showed

that TOWER had achieved its primary objective of demonstrating that blinatumomab improves OS compared with SOC chemotherapy, the study was stopped early for efficacy based on recommendations from an independent data monitoring committee (DMC), and long-term follow-up was discontinued prematurely.

Important additional evidence on the clinical effectiveness of blinatumomab comes from the key registrational, phase 2, single-arm study of 189 adult patients with R/R Ph- B-precursor ALL (Study MT103-211), including a comparison with a historical cohort receiving SOC chemotherapy using appropriate statistical methodology.

Both TOWER and Study MT103-211 enrolled particularly difficult-to-treat adult R/R Ph- B-precursor ALL patient populations as patients in untreated first relapse with a first remission duration ≥ 12 months (i.e., patients with a better prognosis) were not eligible for the studies.

### 1.4.2 Results of RCT evidence (TOWER)

A summary of results for the key efficacy endpoints from TOWER is provided in Table 1-3.

**Table 1-3. Summary of results for the key efficacy endpoints in TOWER (FAS)**

| | **Blinatumomab (N = 271)** | **SOC chemotherapy (N = 134)** |
|---|---|---|
| Overall survival (primary endpoint) | | |
| Median, months (95% CI) | 7.7 (5.6, 9.6) | 4.0 (2.9, 5.3) |
| Hazard ratio (95% CI) | 0.71 (0.55, 0.93) | |
| p-value | 0.012[a] | |
| CR within 12 weeks of treatment initiation (key secondary endpoint) | | |
| n, (%) | 91 (33.6) | 21 (15.7) |
| p-value | < 0.001 [a] | |
| CR/CRh*/CRi within 12 weeks of treatment initiation (key secondary endpoint) | | |
| n, (%) | 119 (43.9) | 33 (24.6) |
| p-value | < 0.001 [a] | |

Note: Primary analysis (4 January 2016 data cut-off date)

[a] Statistically significant.

CI, confidence interval; CR, complete mission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; SOC, standard of care.

Survival Outcomes: Blinatumomab was associated with a statistically significant improvement in OS compared with SOC chemotherapy (Hazard ratio [HR] 0.71; p = 0.012); median OS was almost doubled from 4.0 months in the SOC chemotherapy arm to 7.7 months in the blinatumomab arm. A pre-specified sensitivity analysis of OS with patients censored at the time of allo-SCT showed that the survival benefit associated with blinatumomab is independent of transplant (HR: 0.66; p = 0.004). Blinatumomab also improved event-free survival (EFS) compared with SOC chemotherapy (HR 0.55; descriptive p < 0.001).

Haematological remission outcomes: Significantly more patients treated with blinatumomab achieved a haematological remission than with SOC chemotherapy within 12 weeks of treatment initiation (CR: 33.6% vs. 15.7%, $p < 0.001$; CR/CRh* [complete remission with partial haematological recovery]/CRi [complete remission with incomplete haematological recovery]: 43.9% vs. 24.6%, $p < 0.001$). Haematological remission was more durable in patients treated with blinatumomab than with SOC chemotherapy (CR: median duration [redacted] months; CR/CRh*/CRi: median duration 7.3 months vs. 4.6 months). Further, more CR/CRh*/CRi responders achieved minimal residual disease (MRD) remission with blinatumomab than with SOC chemotherapy underlining the high quality and depth of remissions associated with blinatumomab (76.3% vs. 48.5%; descriptive p = [redacted]).

Rates of allo-SCT: Rates of post-baseline allo-SCT were similar across study arms with 24.0% of patients in the blinatumomab arm and 23.9% of patients in the SOC chemotherapy arm receiving transplant. These similar rates, which may seem counter-intuitive, are likely due to clinicians adopting a different approach to the management of patients dependent on study arm and patient characteristics. Among patients who achieved a haematological remission (CR/CRh*/CRi within 12 weeks of treatment initiation), a higher proportion of patients in the blinatumomab arm had received a prior allo-SCT than patients in the SOC chemotherapy arm ([redacted]), thus making them less likely to receive a post-baseline allo-SCT based on feedback from a UK clinical expert (a TOWER investigator). In addition, among patients who achieved a haematological remission, patients in the SOC chemotherapy arm were transplanted earlier than in the blinatumomab arm (median time to allo-SCT [redacted]). Patients in the SOC chemotherapy arm were also more likely than patients in the blinatumomab arm to be transplanted even when haematological remission was not achieved (10.4% vs. 5.5% among patients who did not achieve a CR/CRh*/CRi within 12 weeks of treatment initiation). Taken together, these data indicate that some of the TOWER investigators may have believed blinatumomab-treated patients were more under control. This may have biased OS results in favour of SOC chemotherapy.

Patient-reported outcomes: Blinatumomab delayed time to clinically meaningful deterioration in HRQoL (10-point decrease in European Organisation for Research and Treatment of Cancer quality of life questionnaire-C30 [EORTC QLQ-C30] Global Health Status /QoL [GHS/QoL]) or EFS event (HR 0.67; descriptive p = 0.0051). Blinatumomab also improved EORTC QLQ-C30 scores from baseline relative to SOC chemotherapy (descriptive p = [redacted] for overall treatment effect during Cycle 1 for the main GHS/QoL scale).

Subgroup analyses: Results from a pre-specified stratification factor subgroup analysis of OS by prior salvage therapy (yes vs. no) suggest that patients who have not received prior salvage therapy are likely to benefit more from treatment with blinatumomab than patients who have received prior salvage therapy (HR [redacted] vs. [redacted]). Median OS in patients who had not received prior salvage therapy was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months). For patients who had received prior salvage therapy, median OS was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months). Clinical experts consulted by Amgen consider this to be highly clinically plausible, given that treating patients earlier in the treatment pathway (i.e., patients with a better prognosis) with a more effective therapy is likely to lead to improvements in both absolute and relative OS. This subgroup analysis is pertinent to the decision problem as clinicians are likely to use blinatumomab early in the

treatment pathway (i.e., in patients who have not received prior salvage therapy) given the above. The OS treatment effect also favoured blinatumomab in the pre-specified subgroup of patients who were intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm. The HR in the FLAG ± anthracycline based regimen ([redacted]) was lower than in any of the other SOC chemotherapy regimen subgroups, and than in the primary OS analysis in the TOWER FAS. Although FLAG-IDA is considered the relevant comparator for this appraisal, treatment-effect estimates from the whole SOC chemotherapy arm have been used to inform the base-case cost-effectiveness analysis. This represents a potentially more conservative approach than using treatment-effect estimates from the subgroup of patients intended to receive a FLAG ± anthracycline based regimen, and is supported by UK clinical experts consulted by Amgen who confirmed that the relative efficacy of blinatumomab versus SOC chemotherapy is unlikely to vary by SOC chemotherapy regimen. An OS benefit was consistently observed for blinatumomab over SOC chemotherapy in most other pre-specified subgroups of a reasonable sample size, including subgroups for age, prior allo-SCT, and proportion of bone marrow blasts. Similarly, improvements in the proportions of patients achieving a CR and CR/CRh*/CRi within 12 weeks of treatment initiation, and EFS benefits were consistently observed in most pre-specified subgroups with a reasonable sample size.

Safety and tolerability outcomes: Blinatumomab was generally well tolerated relative to SOC chemotherapy, despite the substantially longer treatment exposure in the blinatumomab arm ([redacted] subject years vs. [redacted] subject years). The incidence of the most common treatment-emergent adverse events (TEAEs), including ≥ Grade 3 adverse events (AEs), such as neutropaenia, febrile neutropaenia, anaemia, thrombocytopaenia, and infections (e.g., pneumonia) was lower in the blinatumomab arm than in the SOC chemotherapy arm. There was a higher incidence of cytokine release syndrome (CRS) and neurologic AEs in the blinatumomab arm than in the SOC chemotherapy arm, consistent with the known safety profile of blinatumomab. Rates of ≥ Grade 3 neurologic AEs were similar across study arms, and CRS AEs led to treatment discontinuation in few patients. Specific safety warnings and corresponding management recommendations are detailed in the blinatumomab summary of product characteristics (SmPC).

Overall, blinatumomab demonstrated a favourable risk-benefit profile in TOWER.

### 1.4.3 Results of non-RCT evidence (Study MT103-211)

A summary of results for the key results from Study MT103-211 and the comparison with the historical cohort receiving SOC chemotherapy is provided in Table 1-4.

**Table 1-4. Summary of key results from Study MT103-211 and comparison with the historical SOC chemotherapy cohort**

| Source | Outcome | Blinatumomab | SOC chemotherapy |
|---|---|---|---|
| Study MT103-211 (PAS; N = 189) | CR/CRh* within 2 cycles, % (95% CI) (primary endpoint) | 43 (36, 50) | N/A |
| | CR within 2 cycles, % (95% CI) (secondary endpoint) | 33 (27, 41) | N/A |
| | OS, median months (95% CI) (secondary endpoint) | Primary analysis:[a] 6.1 (4.2, 7.5) Additional ad-hoc analysis:[b] 6.5 (4.4, 7.7) | N/A |
| Historical SOC chemotherapy data (weighted to match MT103-211 population)[a] | CRsg, % (95% CI) | N/A | N = 694 24 (20, 27) |
| | OS, median months (95% CI) | N/A | N = 1112 3.3 (2.8, 3.6) |
| Study MT103-211 vs. historical comparator: propensity score analysis[a] | CR/CRh* ('211) and CRsg (historical control), % (95% CI) | 49 (33, 65) | 26 (23, 30) |
| | OS, hazard ratio (95% CI) | 0.54 (0.40, 0.73) | |

[a]Primary analysis data cut-off date (10 Oct 2013) for Study MT103-211 data
[b]Additional ad-hoc analysis data cut-off date (15 July 2015)

CI, confidence interval, CR, complete remission; CRh*, complete remission with partial haematological recovery; CRsg, complete remission per study groups/sites; N/A, not applicable; PAS, primary analysis set; SOC, standard of care.

The proportions of patients achieving a CR/CRh* and CR within the first two cycles (i.e., 12 weeks) of treatment in Study MT103-211 were 42.9% and 33.3%, respectively. This is consistent with the proportions of patients achieving a CR/CRh*/CRi (43.9%) and CR (33.6%) in the blinatumomab arm of TOWER. Based on the most recent data cut-off date (15 July 2015), median OS was 6.5 months and median relapse-free survival (RFS) in patients achieving CR/CRh* was 6.8 months. This median OS is similar to the 7.7 months seen in the blinatumomab arm of TOWER. Also consistent with TOWER, pre-specified subgroup analyses of Study MT103-211 by numbers of prior salvage therapies showed that median OS was higher in patients who had received no prior salvage therapy than in patients who had received prior salvage therapy. In Study MT103-211, 25% of patients, irrespective of response, went on to undergo allo-SCT.

A comparison of blinatumomab data from Study MT103-211 with historical SOC chemotherapy control data, using appropriate analytical methods to address imbalances in prognostic factors (weighted analysis and propensity score analysis), showed more favourable haematological remission rates and OS outcomes with blinatumomab. The proportion of patients achieving a CR/CRh* and median OS for blinatumomab in Study MT103-211 were approximately double the CRsg rate (complete remission with or without full haematological

recovery depending on study group) and median OS seen in the historical cohort, which is consistent with the relative treatment effects seen for blinatumomab versus SOC chemotherapy in TOWER. The proportion of patients receiving allo-SCT after salvage therapy, irrespective of response, was 18% in the weighted historical cohort.

### 1.4.4 Strengths and limitations of the clinical evidence base

The clinical evidence base for blinatumomab presented in this submission includes data from TOWER, a large, international phase 3 RCT which represents the highest quality evidence for evaluating clinical efficacy. This in itself should be considered an important strength given the dearth of RCT evidence in the disease area. The results from the primary and key secondary outcomes measured in TOWER were consistent in a range of pre-specified sensitivity analyses and subgroup analyses. Key outcomes from TOWER (i.e., OS and haematological remission rates) are also consistent with both Study MT103-211 and with the comparison of Study MT103-211 with the historical SOC comparator cohort.

Both TOWER and Study MT103-211 included a broad spectrum of adult patients with R/R Ph-B-precursor ALL (with most patients enrolled in Europe), and the patient populations in these studies were considered broadly generalisable to clinical practice in England and Wales by UK clinical experts. Treatment with blinatumomab in TOWER and Study MT103-211 was broadly consistent with the marketing authorisation for blinatumomab, with the notable exception that patients could receive additional blinatumomab maintenance cycles in TOWER (after two cycles of initial treatment and three cycles of consolidation treatment). Although the proportion of patients in the blinatumomab arm who received more than the maximum of five cycles permitted by the marketing authorisation in TOWER was small ([redacted]%), this should be considered a limitation of the clinical evidence base.

Additional limitations of the clinical evidence base include the open-label design of TOWER, which is common and often unavoidable in RCTs evaluating complex treatment regimens where it would be difficult and unethical to conduct double-blind studies. In addition, there was a high number of drop-outs in TOWER, including a large imbalance of patients who dropped out before receiving their allocated study drug (mostly in the SOC chemotherapy arm and primarily due to patient choice). However, any potential resulting bias is likely to be small as demonstrated by sensitivity analyses of OS and key secondary outcomes in the safety population (i.e., patients who received at least one dose of study drug). Another limitation of TOWER is that more patients in the SOC chemotherapy arm received subsequent anticancer therapies than in the blinatumomab arm ([redacted]% vs. [redacted]% among patients who received study drug), including a higher proportion of innovative anticancer therapies. This could have biased efficacy results in favour of the SOC chemotherapy arm; however, use of subsequent therapies in an RCT of patients with such life-threatening diseases as R/R Ph- B-precursor ALL is unavoidable.

Given the above mentioned limitations of the TOWER RCT which may have confounded clinical effectiveness results, Study MT103-211 and the comparison with the historical comparator cohort (a robust non-randomised study and analysis with low risk of bias) should be considered an important additional source of clinical effectiveness evidence.

## 1.5 Summary of the cost-effectiveness analysis

The cost-effectiveness of blinatumomab was determined using a de novo partitioned survival semi-Markov model developed in Microsoft® Excel. The model comprised four health states and the probabilities of being in each of the health states were calculated from data from the phase 3 TOWER RCT on the proportion of patients achieving haematological remission (CR/CRh*/CRi within 12 weeks of treatment initiation), EFS (among responders), and OS. Cost inputs including acquisition and administration of initial and subsequent salvage therapies were also mainly derived from TOWER; similarly, QALYs were estimated using oncology-specific HRQoL outcome data (EORTC QLQ-C30) collected in TOWER and mapped to EuroQol-5D (EQ-5D).

Amgen has proposed a simple PAS which has been approved by the DoH; analyses incorporating the PAS are included in the PAS addendum to this submission. The base-case comparison versus FLAG-IDA is based on the TOWER FAS (i.e. intent-to-treat [ITT] population) (**Error! Reference source not found.**) and shows that blinatumomab resulted in 1.45 additional QALYs and an incremental cost (with blinatumomab at the list price) of £[redacted] leading to an incremental cost-effectiveness ratio (ICER) of £[redacted] per QALY.

**Sensitivity and scenario analyses indicated that in the base-case analysis, the model were most sensitive to the parameters predicting the OS for blinatumomab relative to IDA, blinatumomab treatment duration, and time horizon. The majority of the tested and scenario analyses did not have a large impact on the ICER, suggesting that the cases presented reflect a realistic estimate of the ICER for blinatumomab. An scenario analysis was conducted on the pre-specified subgroup of patients intended a FLAG ± anthracycline based regimen at randomisation, and the resulting ICER was to £[redacted] (Table 1-5. Base case incremental cost-effectiveness results (TOWER, FAS)**

| Technology (and comparators) | Total costs (£) | Total life years | Total QALYs | Incremental costs (£) | Incremental life years | Incremental QALYs | ICER versus baseline (£) |
|---|---|---|---|---|---|---|---|
| FLAG-IDA | 64,165 | 2.61 | 1.90 | - | - | - | - |
| Blinatumomab | [redacted] | 4.38 | 3.35 | [redacted] | 1.78 | 1.45 | [redacted] |

FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Table 1-6Table 1-6), suggesting that the base-case approach is potentially conservative. In another relevant scenario analysis using an alternative discount rate of 1.5% for health outcomes as recommended in the NICE reference case when considering treatment effects that are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the ICERs for the TOWER FAS population are reduced to £[redacted] (Table 1-6).

A comprehensive subgroup analysis was also performed using TOWER data for the pre-specified stratification factor subgroup of patients who had not received prior salvage therapy, as this subgroup represent a clinically relevant subgroup of patients likely to benefit even further from receiving blinatumomab. Using the same modelling assumptions, the base-case ICER in this subgroup was £[redacted] (Table 1-7).

**Table 1-5. Base case incremental cost-effectiveness results (TOWER, FAS)**

| Technology (and comparators) | Total costs (£) | Total life years | Total QALYs | Incremental costs (£) | Incremental life years | Incremental QALYs | ICER versus baseline (£) |
|---|---|---|---|---|---|---|---|
| FLAG-IDA | 64,165 | 2.61 | 1.90 | - | - | - | - |
| Blinatumomab | [redacted] | 4.38 | 3.35 | [redacted] | 1.78 | 1.45 | [redacted] |

FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

**Table 1-6. Incremental cost-effectiveness results (TOWER, FAS; key scenario analyses)**

| | Technology (and comparators) | Total costs (£) | Total life years | Total QALYs | Incremental costs (£) | Incremental life years | Incremental QALYs | ICER versus baseline (£) |
|---|---|---|---|---|---|---|---|---|
| Planned FLAG ± anthracycline based regimen at randomisation | FLAG-IDA | 61,377 | 1.36 | 0.98 | - | - | - | - |
| | Blinatumomab | [redacted] | 4.41 | 3.40 | [redacted] | 3.04 | 2.42 | [redacted] |
| 1.5% discount rate | FLAG-IDA | 64,594 | 3.42 | 2.53 | - | - | - | - |
| | Blinatumomab | [redacted] | 5.86 | 4.50 | [redacted] | 2.44 | 1.97 | [redacted] |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

**Table 1-7. Incremental cost-effectiveness results (TOWER, subgroup of patients with no prior salvage therapy)**

| Technology (and comparators) | Total costs (£) | Total life years | Total QALYs | Incremental costs (£) | Incremental life years | Incremental QALYs | ICER versus baseline (£) |
|---|---|---|---|---|---|---|---|
| FLAG-IDA | 74,703 | 2.65 | 1.94 | - | - | - | - |
| Blinatumomab | [redacted] | 5.06 | 3.91 | [redacted] | 2.40 | 1.98 | [redacted] |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

# 2 The technology

## *2.1 Description of the technology*

### 2.1.1 UK approved and brand name

Blinatumomab (brand name: Blincyto®)

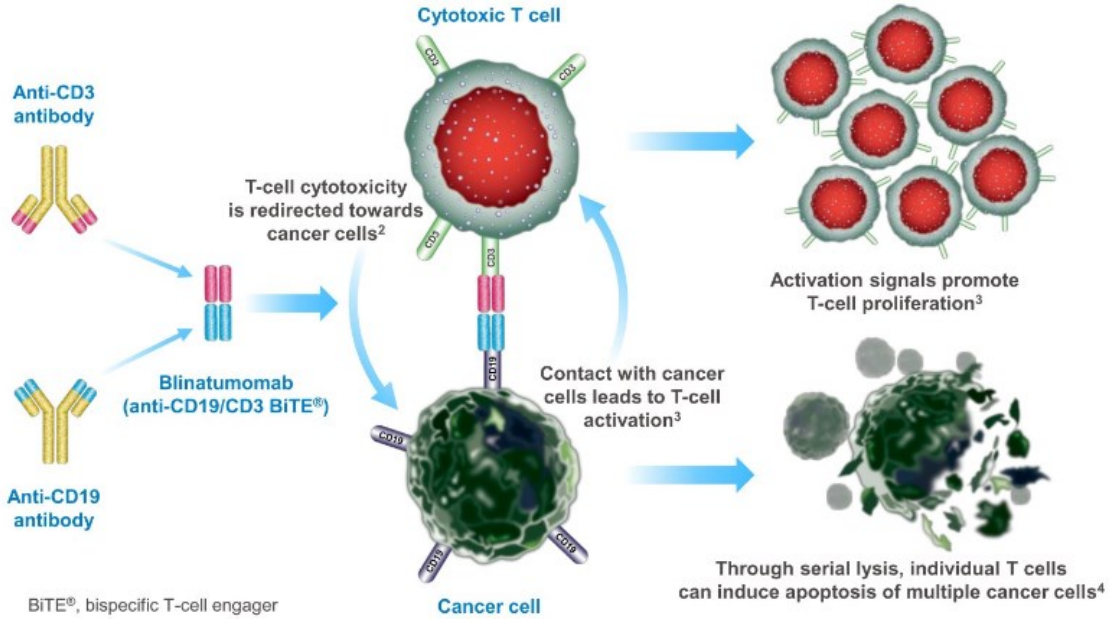
### 2.1.2 Therapeutic class

Therapeutic class: Blinatumomab is classified as an 'other antineoplastic agent' and further sub-classified as a monoclonal antibody (ATC code: L01XC19).

### 2.1.3 Mechanism of action

Blinatumomab is a first-in-class, bispecific T-cell engager (BiTE®) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin, and to CD3 expressed on the surface of T-cells.[1] Blinatumomab activates endogenous T-cells by connecting CD3 expressed on the T-cell receptor (TCR) complex with CD19 expressed on benign and malignant B-cells.[2-4] Blinatumomab mediates the formation of a cytolytic immunological synapse between the T-cell and the malignant B-cell, triggering release of proteolytic enzymes to kill target cells.[3] Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, all of which results in elimination of CD19+ cells (Figure 2-1).[2,3] It is the unique action of bringing T-cells into close proximity with malignant B-cells much more frequently than without blinatumomab that greatly augments the surveillance and cytotoxic abilities of the patient's own T-cells.[1] Thus, blinatumomab harnesses the body's own immune system to fight cancer.[4]

**Figure 2-1. Blinatumomab structure and mechanism of action**




References: [1]Baeuerle *et al.*, 2009[5], [2]Bargou *et al*., 2008[6], [3]Klinger *et al*., 2012[7], [4]Hoffmann *et al*., 2005[8]

BiTE®, bispecific T-cell engager

## *2.2 Marketing authorisation/CE marking and health technology assessment*

### 2.2.1 Marketing authorisation

Blinatumomab was granted orphan designation by the European Commission (EC) in 2009.[9] A European marketing authorisation application (MAA) for blinatumomab was submitted in October 2014.[10] On an accelerated assessment basis (reflecting that blinatumomab is an important medicine with major public health interest), the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for this MAA in September 2015,[11,12] and a conditional MA for blinatumomab in all European Union member states was approved by the EC on 23 November 2015.[12] The approved indication is detailed below.

**European Medicines Agency indication (2015)**

| |
|---|
| Blinatumomab is indicated for the treatment of adults with relapsed or refractory (R/R) Philadelphia chromosome negative (Ph-) B-precursor acute lymphoblastic leukaemia (ALL) |

Although the clinical benefit of blinatumomab was considered 'established' based on the registrational studies, the European Medicines Agency (EMA) granted approval on a conditional basis in the European Union (EU) given the lack of available randomised controlled trial (RCT) evidence at the time of approval, as highlighted in the European Public Assessment Report (EPAR). The lack of RCT data is addressed in this submission with data from the phase 3 TOWER RCT (Section 4.2), which was stopped early (and long-term follow-up discontinued)

after meeting its primary efficacy endpoint. Data from TOWER were submitted to the EMA on 11 November 2016 via a Type II variation procedure.

A second point highlighted by the EMA in the blinatumomab EPAR is the limited number of late first relapse patients (> 12 months) enrolled in the registrational studies, although efficacy was still considered 'established' in this patient population. It is anticipated that further efficacy data will be collected for this population as part of a planned post-approval safety registry study (20150136).

The summary of product characteristics (SmPC) and EPAR for blinatumomab are provided in Appendix I.

### 2.2.2 Health technology assessments

Heath technology assessments (HTAs) for blinatumomab have been conducted by the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). On 13 June 2016, blinatumomab was accepted for use by the SMC in accordance with its full marketing authorisation.[13] Similarly, AWMSG recommended blinatumomab in accordance with its full marketing authorisation on 27 July 2016.[14]

### 2.2.3 UK launch date

Blinatumomab was launched in the UK in December 2015.[15]

### 2.2.4 Regulatory approval outside the UK

In addition to its conditional marketing approval in the UK and 27 other EU member states, blinatumomab has been approved for use in several other jurisdictions, including the US, Canada, South Korea, Mexico, Norway, Iceland, Switzerland, Liechtenstein, Lebanon and Australia.

The United States (US) Food and Drug Administration (FDA) granted breakthrough therapy, priority review, and finally accelerated approval for blinatumomab in December 2014 for the treatment of adult R/R Ph- B-precursor ALL, reflecting the major public health interest in this patient population.[1] In September 2016, the FDA extended the licensed indication to include paediatric patients with R/R Ph- B-precursor ALL under a conditional accelerated approval pathway based on the results from a phase 1/2 trial.[16]

## 2.3 Administration and costs of the technology

### 2.3.1 Administration and costs

An overview of administration and costs of blinatumomab is provided in Table 2-1.

**Table 2-1. Administration and costs of blinatumomab**

| | Details of administration/costs | Source |
|---|---|---|
| Pharmaceutical formulation | 38.5 µg of powder for concentrate and solution for infusion | Blinatumomab SmPC[3] |
| Acquisition cost (excluding VAT) | £2,017 per 38.5 ug vial (list price) | N/A |
| Method of administration | IV | Blinatumomab SmPC[3] |
| Doses | 9 µg/day and 28 µg/day | Blinatumomab SmPC[3] |
| Dosing frequency | A therapeutic dose of 9 µg/day (starting dose; Days 1–7 of Cycle 1) or 28 µg/day (subsequent doses) should be administered to the patient by infusing a total of 240 mL blinatumomab solution for infusion at one of four constant infusion rates and associated infusion durations:<br>• Infusion rate of 10 mL/h for a duration of 24 hours<br>• Infusion rate of 5 mL/h for a duration of 48 hours<br>• Infusion rate of 3.3 mL/h for a duration of 72 hours<br>• Infusion rate of 2.5 mL/h for a duration of 96 hours | Blinatumomab SmPC[3] |
| Average length of a course of treatment (i.e., a cycle) | A single cycle of treatment is 4 weeks of continuous infusion followed by a 2-week treatment-free interval. | Blinatumomab SmPC[3] |
| Average cost of a course of treatment (i.e., a cycle) | The average cost of blinatumomab per cycle at the blinatumomab list price is:<br>• £48,408 in Cycle 1 (9 µg/day starting dose during Days 1–7 followed by 28 µg/day Days 8–28; 24 vials)<br>• £56,476 in all subsequent cycles (28 µg/day for Days 1–28; 28 vials) | N/A |
| Anticipated average interval between courses of treatments | Patients receive a 2-week treatment-free interval between cycles. | Blinatumomab SmPC[3] |

| | Details of administration/costs | Source |
|---|---|---|
| Anticipated number of repeat courses of treatments | • Patients may receive two cycles of treatment. Patients who have achieved complete remission (CR/CRh*) after two treatment cycles may receive up to three additional cycles of blinatumomab consolidation treatment, based on an individual benefits-risks assessment.<br>• In Study MT103-211, the mean number of cycles per patient was 1.6[b] | Blinatumomab SmPC[3] |
| Dose adjustments[a] | Temporary or permanent discontinuation should be considered following severe (Grade 3) or life-threatening (Grade 4) AEs.<br><br>No dose adjustment is necessary in elderly patients or in patients with renal or hepatic impairment. | Blinatumomab SmPC[3] |
| Anticipated care setting | Hospital and outpatient | Blinatumomab SmPC[3] |

[a] For further information on recommended dose adjustments to manage treatment-related toxicities, refer to the blinatumomab SmPC.
[b] The mean number of completed cycles in the TOWER RCT was [redacted] (Section 4.12.1.1), however 10.1% of patients received additional cycles of protocol-permitted maintenance therapy beyond the maximum of five induction/consolidation cycles permitted by the marketing authorisation.

AEs, adverse events; CR, complete remission; CRh*, complete remission with partial haematological recovery; IV, intravenous; N/A. not applicable; SmPC, summary of product characteristics; VAT, value added tax.

### 2.3.2 Patient access scheme (PAS)

Amgen has proposed a simple PAS which has been approved by the DoH; analyses incorporating the PAS are included in the PAS addendum to this submission.

### 2.3.3 Changes in service provision and management

Blinatumomab is administered via continuous intravenous (IV) infusion and requires the assistance of a healthcare professional (HCP) to handle and prepare the medicinal product. In addition, the infusion bag must be changed at least every 96 hours by a HCP.[3] No additional diagnostic tests are required to identify patients eligible for treatment with blinatumomab. No additional National Health Service (NHS) infrastructure is expected to be needed to incorporate blinatumomab into the clinical pathway of care.

Hospitalisation is recommended for patients receiving blinatumomab for a minimum of 9 days of the first cycle (or 14 days if presence of clinically relevant central nervous system [CNS] pathology) and the first 2 days of the second cycle.[3] For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended. This recommendation does not represent an additional burden to healthcare providers as hospitalisation during the treatment period is routine clinical practice with current treatment options. A recent retrospective chart review of the healthcare burden of hospitalisation in France during salvage chemotherapy treatment

showed that patients spent on average, almost half (46%) of the chemotherapy treatment period (mean: 87 days) in hospital.[17] Given that blinatumomab may be administered in the outpatient setting other than recommended hospitalisation outlined above, it has the potential to reduce duration of hospitalisation compared with current salvage chemotherapy regimens.

Recommended monitoring for blinatumomab includes:[3]

- Monitoring for signs and symptoms of neurologic events (with e.g., a writing test), infection, cytokine release syndrome (CRS), tumour lysis syndrome (including renal function and fluid balance in the first 48 hours after the first infusion), pancreatitis (with e.g., physical examination, laboratory evaluation of serum amylase and serum lipase, and abdominal imaging), and progressive multifocal leukoencephalopathy
- Monitoring of laboratory parameters (including, but not limited to white blood cell count and absolute neutrophil count) related to neutropaenia and febrile neutropaenia
- Monitoring of laboratory parameters related to elevated liver enzymes i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during treatment especially during the first 48 hours of the first two cycles

Most of these monitoring requirements would be part of routine clinical practice for adult patients with R/R Ph- B-precursor ALL being treated with current salvage chemotherapy regimens. One exception is the recommended neurological examination which is performed in patients prior to starting blinatumomab therapy. Patients should be clinically monitored for signs and symptoms of neurologic events, and management of any events to resolution may require either temporary interruption or permanent discontinuation of blinatumomab. Another exception is CRS, and patients should be monitored closely for signs and symptoms including pyrexia, asthaenia, headaches, hypotension, increased bilirubin, and nausea.

The following concomitant medications are recommended for use with blinatumomab:[3]

- Dexamethasone 20 mg IV, administered one hour prior to initiation of each cycle
- Antipyretic (e.g., paracetamol) to reduce pyrexia during the first 48 hours of each treatment cycle
- Intrathecal chemotherapy prophylaxis before and during treatment to prevent CNS ALL relapse

These medications are commonly used in the management of R/R Ph- B-precursor ALL, and are not specific to treatment with blinatumomab.

The main resource use and costs associated with the introduction of blinatumomab are anticipated to be drug acquisition costs and costs associated with administration of blinatumomab (e.g., reconstitution prior to administration, costs associated with IV infusion, and costs associated with hospitalisation). No additional NHS infrastructure is expected to be needed to incorporate blinatumomab into the clinical pathway of care.

## 2.4 Innovation

Meaningful progress in the treatment of adult R/R Ph- B-precursor ALL has been lacking for decades and, with the exception of blinatumomab, there are no targeted treatments licensed specifically for this disease (Section 3.4.2). Patients face imminent risk of death with a median overall survival (OS) of around 3 to 6 months (Section 3.2.2). Patients also experience a high treatment burden as a result of the significant toxicities associated with salvage chemotherapy regimens and substantial hospitalisation requirements – patients may spend half of the salvage chemotherapy treatment period in hospital (Section 3.3).

Blinatumomab is a novel single-agent bispecific T-cell engaging immunotherapy with a first-in-class mechanism of action that harnesses the body's own immune system to recognise and eliminate malignant cancer cells (Section 2.1.3). Blinatumomab was conditionally approved by the EMA (subject to provision of data from the TOWER RCT) on an accelerated assessment pathway based on compelling results from a phase 2 single-arm study (Study MT103-211), including a comparison with a historical standard of care (SOC) cohort (Section 2.2.1). This reflects that blinatumomab is an important medicine with major public health interest, addresses a substantial unmet need, and represents a major therapeutic innovation. These results were confirmed by the phase 3 TOWER RCT which showed that blinatumomab was associated with a near-doubling of median OS compared with SOC chemotherapy (7.7 months vs. 4.0 months; hazard ratio [HR] 0.71, p = 0.012) (Section 4.7). Haematological remission rates for patients in the blinatumomab arm were also significantly higher than in the SOC chemotherapy arm (complete remission [CR]/CR with partial haematological remission [CRh*]/CR with incomplete haematological remission [CRi], 44% vs. 25%; $p < 0.001$; CR, 34% vs. 16%; $p < 0.001$). In addition, incidence of important adverse events (AEs) commonly associated with cytotoxic SOC chemotherapies such as neutropaenia, febrile neutropaenia, anaemia, thrombocytopaenia, and infections (e.g., pneumonia) were lower in the blinatumomab arm than SOC chemotherapy arm (Section 4.12).

Blinatumomab also provides the option of an effective therapy that can be administered in the outpatient setting (Section 0), and therefore has the potential to reduce duration of hospitalisation compared with current salvage chemotherapy regimens. This is of particular significance for patients with R/R Ph- B-precursor ALL where quality of life (QoL) and time spent at home with family is extremely important. In addition, blinatumomab is likely to bring benefits to wider society of treating a younger patient population (median age at diagnosis 34-39 years) with an effective treatment option that may lead to more patients achieving long-term remission and survival. These benefits will not be fully captured within the standard National Institute for Health and Care Excellence (NICE) incremental cost-utility framework.

Based on the above, blinatumomab represents a major therapeutic innovation and a step change in the management of patients with this devastating and highly aggressive disease that responds poorly to current salvage chemotherapy regimens and is associated with very poor survival.

# 3 Health condition and position of the technology in the treatment pathway

## *3.1 Disease overview*

- ALL is a complex haematological malignancy that specifically affects lymphoblasts; proliferating lymphoblasts crowd out and suppress the production of normal blood cells in the bone marrow
- The severe and rapidly progressing symptoms require urgent medical attention, and the disease is generally diagnosed within a few weeks after the onset of symptoms
- ALL is typically sub-classified as being of B- or T-cell lineage, by maturity of affected B- and T-cells, by presence of the most common genetic aberration (the Philadelphia chromosome), and by whether patients have relapsed or are refractory to treatment

Leukaemia is a complex haematological malignancy that is progressive in nature and characterised by the increased production of immature or abnormal blood cells by bone marrow and other blood-forming organs. Leukaemia is classified into four main types based on the aggressiveness of disease progression (acute or chronic) and the type of blood cell precursors that are affected (lymphoid [white blood cells or lymphocytes] or myeloid [platelet, monocyte, and macrophage]).[18]

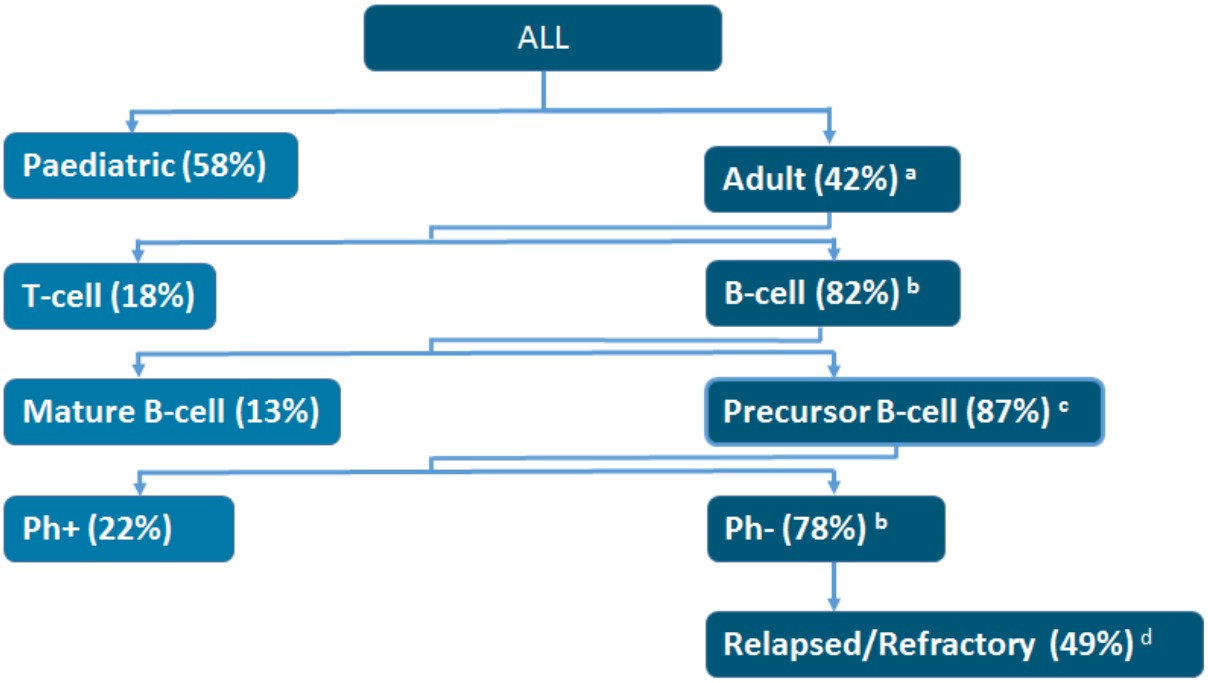
ALL specifically affects immature lymphocytes (lymphoblasts) that are derived from B- or T-lymphocyte stem cells. Proliferating lymphoblasts crowd out and supress the production of normal blood cells in the bone marrow, causing haematological deficiencies, including anaemia, immune system impairment, and platelet count deficiency.[18,19] ALL can also spread to the CNS.[20] The leukaemic lymphoblasts express the same antigens as normally developing B- and T-cells. Clinically, the recognised phenotypes are T-cells, mature B-cells, and precursor B-cells. Precursor B-cells typically express CD10, CD19, and CD34 cell surface markers.[19] Immunophenotyping is an important part of the diagnostic work-up for ALL to classify cases, for immunologic monitoring of minimal residual disease (MRD; defined as the detection of more than 1 cancerous cell per 10,000 normal cells), and for treatment with targeted cellular immunotherapy.[19]

In most patients with ALL, the disease is diagnosed within a few weeks of the onset of symptoms, which include overwhelming fatigue, intolerance to physical exercise, bruising, bleeding, enlarged lymph nodes, fever with infections, headache, vomiting, and lethargy.[24,25] The severity of these symptoms causes patients to seek urgent medical attention. An abnormal test of peripheral blood is generally followed by bone marrow aspiration/biopsy. If the bone marrow contains more than 20% lymphoblasts, the diagnosis is confirmed.[18,21,22] Diagnosis invariably leads to urgent hospital admission.

An overview of the sub-classifications of ALL is provided in Figure 3-1. ALL is classified as being of either B-cell or T-cell lineage. In adults, B-cell lineage accounts for approximately 82% of ALL cases.[23,24] B-cell ALL is further classified as either immature B-cell (B-precursor ALL) or mature B-cell ALL. In approximately 87% of adult B-cell ALL cases, the malignancy

occurs in the immature B-cells (B-precursor ALL).[23] B-precursor ALL is further classified based on the presence of most frequent genetic aberration in ALL patients, the Philadelphia chromosome (Ph); this translocation is present in approximately 22% of adult B-precursor ALL cases.[23,24] The remaining 78% of patients are Ph-. Approximately half of patients with Ph- B-precursor ALL do not respond to or relapse after initial treatment with multi-drug, marrow-ablative chemotherapy or after allo-SCT in eligible patients.[25]. Patients whose disease returns after responding to treatment are referred to as relapsed; patients who do not respond to treatment are referred to as refractory to treatment.

**Figure 3-1. ALL sub-classifications**




[a] Calculated from UK age-specific ALL incidence data reported by Cancer Research UK (2011-2013 estimate).[26] Since data were only provided for 5-year age groups, the 15-19 year age group was split such that 60% of the population projection for this age group was considered 15-17, and the remaining 40% were considered 18-19 and included in the estimate for adult patients.
[b] Weighted average of data from (i) a UK cytogenetic population-based study of 349 patients (> 15 years of age) with ALL diagnosed between 1983 and 2001 (Moorman *et al.,* 2010);[23] and (ii) an analysis of cytogenetic data from 1522 patients (15 years to 65 years of age) with ALL enrolled on the MRC UKALLXII/ECOG 2993 study (Moorman *et al.,* 2007).[24] Data on T- and B-cell lineage from Moorman *et al.,* 2007[24] was calculated using separately reported proportions of patients with T-cell lineage in subsets of patients with Ph+ ALL and Ph- ALL.
[c] Based on UK data from a cytogenetic population-based study of 349 patients (> 15 years of age) with ALL diagnosed between 1983 and 2001 (Moorman *et al.,* 2010).[23]
[d] Based on data from 1508 newly diagnosed ALL patients (15 years to 60 years of age) enrolled on the UKALL12/ECOG E2993 study, of whom 136 died or failed to achieve remission in induction (refractory) and 609 who relapsed after achieving a remission (Fielding *et al.,* 2007).[25]

ALL, acute lymphoblastic leukaemia; Ph-, Philadelphia chromosome negative; Ph+, Philadelphia chromosome positive.

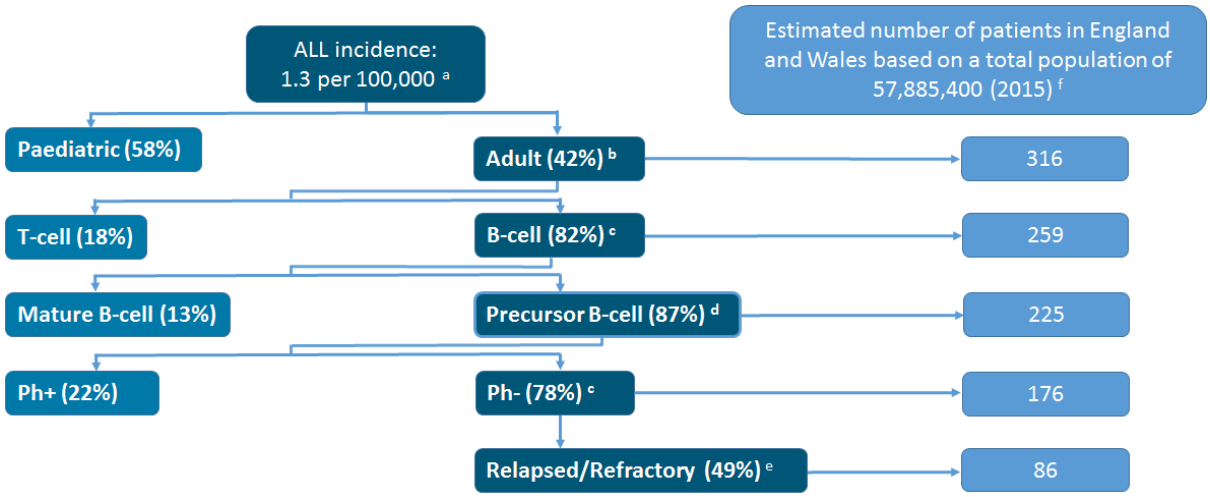
## 3.2 Epidemiology and survival

- Adult R/R Ph- B-precursor ALL is an extremely rare disease; an estimated 86 patients were diagnosed in England and Wales in 2015.
- The prognosis for adult patients with R/R Ph- B-precursor ALL is extremely poor and patients face imminent risk of death; survival is estimated to be only around 3 to 6 months, and around 75% of patients die within a year of starting their first salvage therapy

### 3.2.1 Incidence and prevalence

ALL is an orphan disease with an estimated incidence of 1.3 per 100,000 population in the UK.[27] Using this estimate, alongside literature reporting the proportions of patients with different sub classifications of ALL and most recent available population estimates from the Office for National Statistics (ONS), the annual number of incident adult R/R Ph- B-precursor ALL patients (i.e., the number of patients who would become eligible for treatment with blinatumomab per its marketing authorisation) is estimated to be 86 as of 2015 (Figure 3-2).

**Figure 3-2. Estimated incidence of adult R/R Ph- B-precursor ALL in England and Wales**




[a] Cancer Research UK (2013 estimate)[27]
[b] Calculated from UK age-specific ALL incidence data reported by Cancer Research UK (2011-2013 estimate).[26] Since data were only provided for 5-year age groups, the 15-19 year age group was split such that 60% of the population projection for this age group was considered 15-17, and the remaining 40% were considered 18-19 and included in the estimate for adult patients.
[c] Weighted average of data from (i) a UK cytogenetic population-based study of 349 patients (> 15 years of age) with ALL diagnosed between 1983 and 2001 (Moorman *et al.,* 2010);[23] and (ii) an analysis of cytogenetic data from 1522 patients (15 years to 65 years of age) with ALL enrolled on the MRC UKALLXII/ECOG 2993 study (Moorman *et al.,* 2007).[24] Data on T- and B-cell lineage from Moorman *et al.,* 2007 was calculated using separately reported proportions of patients with T-cell lineage in subsets of patients with Ph+ ALL and Ph- ALL.
[d] Based on UK data from a cytogenetic population-based study of 349 patients (> 15 years of age) with ALL diagnosed between 1983 and 2001 (Moorman *et al.,* 2010).[23]
[e] Based on data from 1508 newly diagnosed patients (15 to 60 years of age) with ALL enrolled on the MRC UKALLXII/ECOG 2993 study, of whom 136 died or failed to achieve remission in induction (refractory) and 609 who relapsed after achieving a remission (Fielding *et al.,* 2007).[25]
[f] Office of National Statistics (2015 estimate).[28]

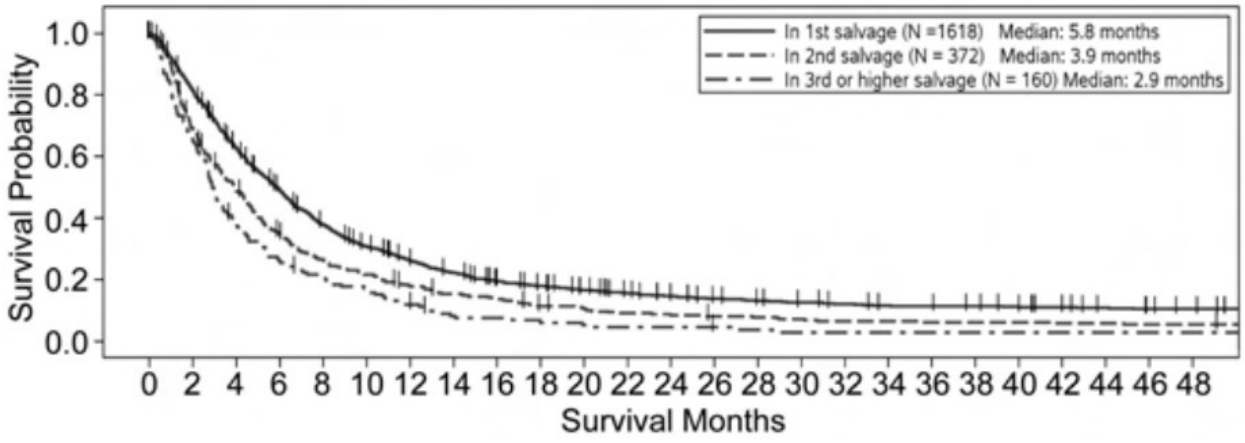
ALL, acute lymphoblastic leukaemia; Ph-, Philadelphia chromosome negative; Ph+, Philadelphia chromosome positive; R/R, relapsed or refractory.

Due to an extremely poor life expectancy (Section 3.2.2), adult R/R Ph- B-precursor ALL is mostly considered as an incident disease and there is a lack of published prevalence data.

### 3.2.2 Survival

The prognosis is extremely poor for adult patients with R/R Ph- B-precursor ALL, and patients face imminent risk of death with a life expectancy of around 3 to 6 months.[29] A large, international, retrospective study of 1706 adult patients with R/R Ph- B-precursor ALL diagnosed between 1990 and 2013 in Europe and the US (including 427 patients from the UK) showed that the overall median OS was 5.8 months, 3.9 months, and 2.9 months from the start of first, second, and third or later salvage, respectively (Figure 3-3).[29] Of the patients in first salvage, 49% were alive after 6 months, 26% were alive after 1 year, and just 11% were alive after 3 years. Although median OS from the start of first salvage therapy appears to have improved over time, it remained low at 6.5 months in the most recent cohort of patients (2005-2013). Findings from this study are consistent with UK-relevant data from a retrospective analysis of outcomes in 609 adult newly diagnosed ALL patients enrolled in the MRC UKALL12/ECOG 2993 study where median survival after relapse was 24 weeks (5.5 months).[25] Feedback from UK clinical experts consulted by Amgen confirmed that an average survival of around 6 months from the start of first salvage therapy is reflective of outcomes typically seen in clinical practice in England and Wales.

**Figure 3-3. Overall survival curves from the start of first, second, and third or later salvage therapy in a retrospective study of adult patients with R/R Ph- B-precursor ALL (1990-2013)**




Reference: Gokbuget *et al.*, 2016[29]

ALL, acute lymphoblastic leukaemia; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory.

## 3.3 Effects of R/R Ph- B-precursor ALL on patients, carers, and society

Adult patients with R/R Ph- B-precursor ALL are extremely ill with symptoms such as overwhelming fatigue, intolerance to physical exercise, bruising, bleeding, enlarged lymph nodes, fever with infections, headache, vomiting, and lethargy.[21,22] Their health is further compromised by highly toxic salvage chemotherapy regimens that are associated with a range of toxicities, including haematological toxicities such as neutropaenia and thrombocytopaenia (Section 3.4.5.2).[21,22,30] Consequently, adult patients with R/R Ph- B-precursor ALL almost always require inpatient admission, and patients spend around half the salvage chemotherapy treatment period in hospital.[17,31,32] For example, a recent retrospective chart review of the healthcare burden of hospitalisation in France in 33 adult R/R Ph- B-precursor ALL patients treated during 2003–2014 showed that patients spent on average, almost half (46%) of the salvage chemotherapy treatment period in hospital.[17] The mean number of hospitalisations per patient was 2.2 and the mean length of stay was 16.8 days per hospitalisation. As well as representing a substantial burden to patients, hospitalisation is a key driver of direct costs to healthcare providers.

Published data on the effects of R/R Ph- B-precursor ALL on QoL of patients and carers are sparse. In a small study focusing on the QoL of adult ALL patients treated with salvage chemotherapy, fatigue, pain, neuropathy, and depression were all commonly reported symptoms.[33]

Adult patients diagnosed with Ph- B-precursor ALL have a median age of 34 to 39 years.[34-36] Recent research to estimate the years of life lost (YLL) due to Ph- B-precursor ALL in the US found that adult patients with the disease die, on average, 30 years prematurely.[37] These YLL estimates far exceed those seen in other more common haematological and solid tumour malignancies, such as chronic lymphocytic leukaemia (10 years), prostate (6 years), colorectal (10 years), lung (12 years) and breast (14 years) cancers.[37,38] This means that the long-term societal and economic consequences of each premature death, including the substantial number of working years lost, are much greater than in many other oncologic diseases.

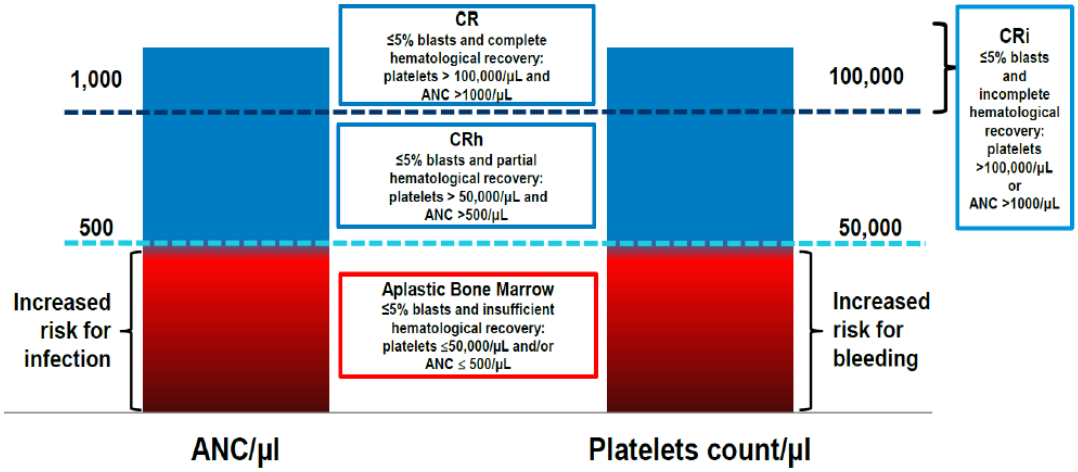
## 3.4 Summary of current treatment options, clinical guidelines/technology appraisal guidance, and treatment patterns

- Meaningful progress in the treatment of adults with R/R Ph- B-precursor ALL has been lacking for decades, and there are no targeted treatments specifically licensed for the management of adult R/R Ph- B-precursor ALL in the UK.
- Active treatment options are limited to a range of poorly effective and highly toxic salvage chemotherapy regimens, with or without allo-SCT which is currently the only potentially curative treatment.
- There are no relevant published NICE clinical guidelines or technology appraisal guidance; other available European guidelines and regional NHS protocols provide limited specific recommendations around the management of adult patients with R/R Ph- B-precursor ALL.
- UK treatment patterns data and feedback from UK clinical experts suggest that FLAG-IDA is the most commonly used regimen for the treatment of adult patients with R/R Ph- B-precursor ALL in England and Wales. UK Treatment patterns data also show that there is substantial heterogeneity around the approach to allo-SCT in clinical practice
- There is an urgent need for new effective treatment options for adult patients with R/R Ph- B-precursor ALL that prolong OS, improve rates and duration of haematological remission to give patients a better chance of being considered eligible for allo-SCT, and reduce toxicities to preserve QoL.

### 3.4.1 Aims of treatment

The current primary treatment goals for Ph- B-precursor ALL are reaching and maintaining haematological remission (e.g., CR) to enable patients to receive allo-SCT (the only potentially curative treatment option), and ultimately prolonging OS.[39,40] In Ph- B-precursor ALL, CR is typically defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full haematological recovery (absolute neutrophil count [ANC] > 1,000/μL and platelet count > 100,000/μL) (Figure 3-4). Patients who achieve a CR (or CRh* or CRi) may have an option to receive an allo-SCT.[40,41]

**Figure 3-4. Haematological recovery levels in patients with ≤ 5% blasts in bone marrow**




References: Cheson *et al.,* 2003[42]; Appelbaum *et al.,* 2007[40]; Topp *et al.,* 2015[43]

ANC, absolute neutrophil count; CR, complete remission; CRh, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery.

In addition, treatment goals include extending disease-free survival (e.g., relapse free survival [RFS]), managing disease complications and treatment-related toxicities, as well as preserving normal performance and QoL for as long as possible. Treatment selection is highly individualised and dependent on many factors such as response to previous treatments, duration of remission, the AE profile of treatment options, comorbidities and fitness, regional practice patterns, and clinician preference.[39,44,45]

### 3.4.2 Overview of current treatment options

Meaningful progress in the treatment of adult R/R Ph- B-precursor ALL has been lacking for decades and, with the exception of blinatumomab, there are no targeted treatments licensed specifically for the disease in the UK. Active treatment options are highly limited, and consist of another round of poorly effective and highly toxic salvage chemotherapy, with or without allo-SCT.[19,21,46] Allo-SCT is currently the only potentially curative treatment option for patients with R/R Ph- B-precursor ALL.[39] Some patients may also enrol in clinical trials of novel agents.

Examples of salvage chemotherapy regimens that may be used for adult R/R Ph- B-precursor ALL based on clinical guidelines, clinical studies, and published literature include:[39,45,47-49]

- FLAG-based regimens - a combination of fludarabine, cytarabine, and granulocyte colony-stimulating factor (GCSF), often given in combination with an anthracycline e.g., idarubicin (FLAG-IDA)
- Hyper-CVAD-based regimens – a combination of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
- High-dose cytarabine (HiDAC)-based regimens
- Methotrexate with L-asparaginase-based regimens
- Clofarabine-based regimens
- Vincristine sulfate liposome-based regimens

Intrathecal chemotherapy, with or without radiation to the brain, also forms part of current chemotherapy regimens to prevent CNS relapse.[50]

### 3.4.3 Clinical guidelines and technology appraisal guidance

#### *3.4.3.1 NICE clinical guidelines and technology appraisal guidance*

There are currently no published NICE clinical guidelines relevant to the management of adult R/R Ph- B-precursor ALL.

Pegaspargase was recommended in NICE TA408 (October 2016) as a treatment option for children, young people, and adults with ALL, but the manufacturer submission and subsequent recommendation was limited to patients with newly-diagnosed disease.[51] This technology appraisal (TA) is therefore not considered relevant to the current appraisal.

Two other potentially-relevant NICE TAs are planned/in development:

- 'Erythrocyte encapsulated asparaginase for treating acute lymphoblastic leukaemia in adults and children after treatment with *Escherichia coli* derived asparaginase' (for the treatment of people with ALL who are intolerant or allergic to asparaginase, or have disease that has relapsed on asparaginase treatment) [ID864].[52] Suspended as of 28 October 2016.
- 'Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia' [ID893].[53] Publication expected September 2017.

#### *3.4.3.2 Other clinical guidelines and recommendations*

A web-based, double-blind clinician survey conducted in 2013 of 75 haemato-oncologists and haematologists based in France, Germany, Italy, Spain, and the UK, found that UK clinicians (n = 15) typically consult trial protocols and international guidelines for management of adult R/R Ph- B-precursor ALL, including:[45]

- The UK Medical Research Council Acute Lymphoblastic Leukaemia Trial XII (UKALL XII) trial protocol for newly diagnosed ALL (2005)[47]
- Guidelines from the American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) on the treatment of adults with ALL (2008)[46]
- Guidelines from the European Working group for ALL on the treatment of adult patients (EWALL) (2011)[48]

Other relevant international guidelines include the European Society for Medical Oncology (ESMO) guidelines for and US-based National Comprehensive Cancer Network (NCCN) guidelines.[54,55]

These guidelines and recommendations provide few specific details around the management of adult patients with R/R Ph- B-precursor ALL, and generally recommend offering patients the opportunity to enter into a clinical trial. Where details are provided, these are typically a list of potential salvage chemotherapy treatment options without any specific stated preference, reflecting the lack of widely accepted treatment protocol, and lack of RCT evidence for this disease. An exception is the recently published NCCN guidelines, which state that blinatumomab is a preferred option.[54]

In addition, there are several different regional NHS protocols that relate to the management of R/R ALL, which clinicians may use to inform decision-making in UK clinical practice.[56-63] Much like the international guidelines and trial protocols, these provide few specific details around the management of adult patients with R/R Ph- B-precursor ALL, generally recommending patients enter into a clinical trial if possible, and list a range of potential salvage chemotherapy treatment options (without stating any given preference), with FLAG-IDA commonly highlighted as a potential option.

### 3.4.4 Current treatment pathway and treatment patterns

#### *3.4.4.1 Current treatment pathway*

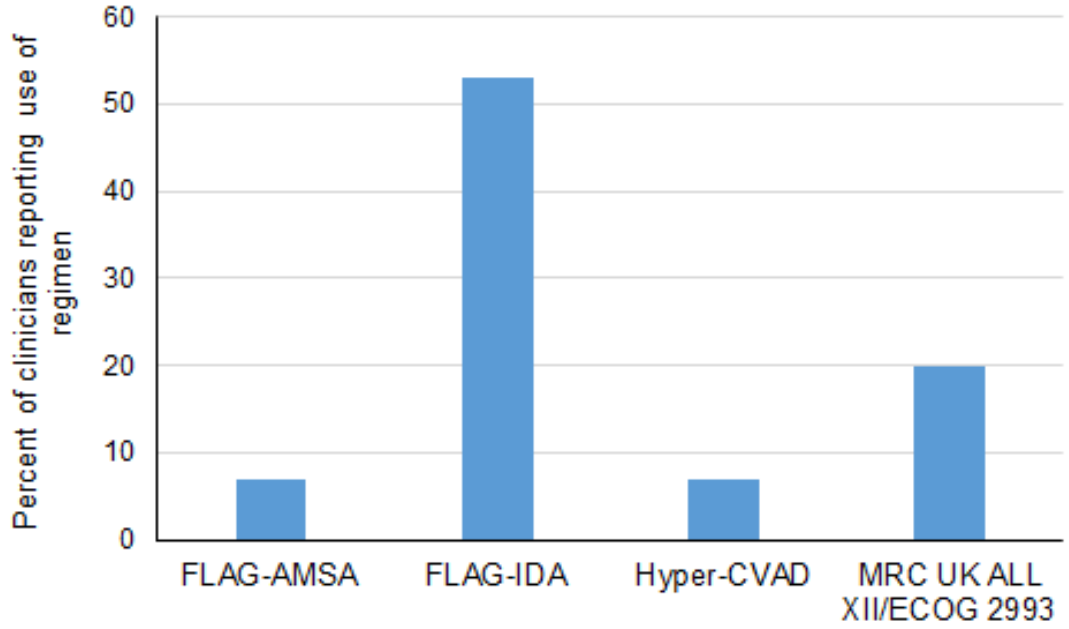
Standard first line treatment for adult patients with newly diagnosed Ph- B-precursor ALL is combination chemotherapy, including an induction phase (with e.g., vincristine, an anthracycline, and asparginase), consolidation phase with intensified chemotherapy (with e.g., high-dose methotrexate), and a maintenance phase with low-dose chemotherapy.[44,48,57,63,64] Eligible patients may also receive allo-SCT during first line treatment.

There are limited treatment options for patients who have relapsed or are refractory to first line treatment, and there is no clearly defined treatment pathway for these patients. As described in Section 3.4.1, there is no clearly superior salvage chemotherapy regimen and the choice of regimen depends on many factors, including response to previous treatments, duration of remission, the AE profile of therapeutic options, patient comorbidities and fitness, regional practice patterns, and clinician preference. Eligible R/R patients may also receive an allo-SCT during salvage treatment.

#### *3.4.4.2 Treatment patterns*

Data from the aforementioned clinician survey (Section 3.4.3.2) showed that of the 15 UK respondents, FLAG-based regimens were the most commonly used treatment options in adult patients with R/R Ph- B-precursor ALL (60%).[45] FLAG-IDA was the most commonly used FLAG-based regimen, with more than half (53%) of the clinicians reporting use of FLAG-IDA or a modified version of this regimen (Figure 3-5). UK clinical experts consulted by Amgen confirmed that FLAG-IDA represents the most common regimen for the management of adult R/R Ph- B-precursor ALL in clinical practice in England and Wales.

**Figure 3-5. Use of R/R Ph- B-precursor ALL salvage chemotherapies reported by UK clinicians**




Reference: Saltman *et al.,* 2015[45]

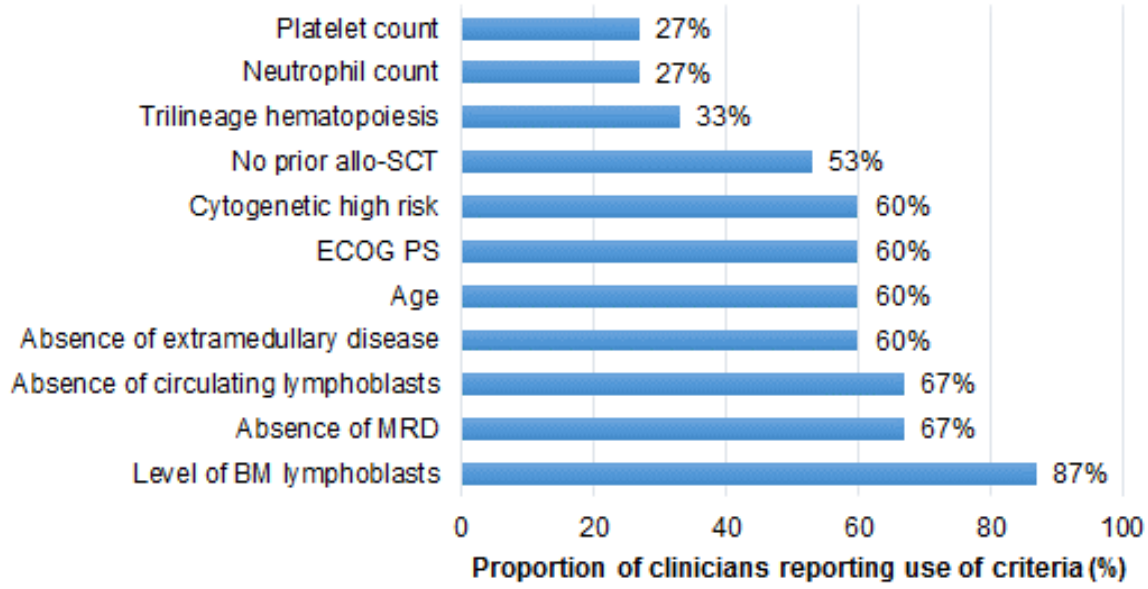
ALL, acute lymphoblastic leukaemia; FLAG-AMSA, fludarabine, cytarabine, filgrastim, amsacrine; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; hyper-CVAD, hyperfractionated, cyclophosphamide, vincristine, doxorubicin; MRC UK ALL XII/ECOG 2993, daunorubicin, vincristine, L-asparaginase, methotrexate; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory.

### 3.4.5 Issues and uncertainty with the current treatment pathway

#### *3.4.5.1 Uncertainty with the current treatment pathway*

As outlined in 3.4.4, there is significant uncertainty with management of adult R/R Ph-B-precursor ALL patients given the lack of any clearly defined treatment pathway. Further, data from the aforementioned clinician survey (Section 3.4.3.2) showed that of the 15 UK respondents, there is substantial heterogeneity around the approach to allo-SCT in adult R/R Ph- B-precursor ALL, and the criteria used to determine patient eligibility. In the UK respondents, the proportion of bone marrow blasts was the most commonly used criteria to determine eligibility for allo-SCT (87%), though other common criteria included absence of MRD, absence of circulating lymphoblasts and extramedullary disease, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and cytogenetic risk (Figure 3-6).

**Figure 3-6. Use of criteria for determining patient eligibility for allo-SCT reported by UK clinicians**




Reference: Amgen data on file, 2014[37,65]

allo-SCT, allogenic stem cell transplant; BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MRD, minimal residual disease.

In addition, although the majority of clinicians (67%) required the allo-SCT eligibility criteria to be met at a time point after completion of treatment, regardless of how long these criteria were maintained, around one quarter (27%) of clinicians required the criteria to be maintained throughout consolidation. [37,65] Further data from the survey suggest that use of allo-SCT may be driven by clinician preference and location (i.e., clinicians based at transplant centres may be more inclined to transplant than clinicians not based at transplant centres). In the location with the highest proportion of clinicians providing allo-SCT at their centre (London; 30%), 51% of patients received allo-SCT. In contrast, in locations with the lowest proportion of clinicians providing allo-SCT at their centre (South-West, East-Midlands, and Scotland; 10%), rates of allo-SCT ranged between just 2% and 4%.

### *3.4.5.2 Issues with the current treatment pathway and unmet medical need*

The prognosis for adult R/R Ph- B-precursor ALL patients with current salvage chemotherapy regimens is extremely poor, and patients face an imminent risk of death with a median survival of around 3 to 6 months (Section 3.2.2). The EWALL guidelines note that in four large-scale trials reporting the general outcome of patients with R/R ALL (MD Anderson Cancer Center, The French-Belgium-Swiss-Australasian Leucémie Aiguës Lymphoblastique de l'Adulte (LALA) intergroup, the Medical Research Council of the United Kingdom Adult ALL Working Party, and the Spanish Programa Español de Tratamientos en Hematologica (PETHEMA) group) the type of salvage chemotherapy did not appear to impact patient outcomes.[25,66-68] Long-term post-relapse OS was uniformly poor across all treatments, ranging from 3% to 7% at 5 years.[48]

Adult patients with R/R Ph- B-precursor ALL also have poor haematological remission rates with existing salvage chemotherapy regimens (around 20% to 30%).[4,49,69] Furthermore, the chance of achieving CR decreases with the number of applied SOC chemotherapy regimens, not only because of cumulative toxicity, but also as a secondary result of chemo resistance.[39] Among adult patients with R/R disease who respond to salvage chemotherapy, remissions are typically not long-term, and about 80% of patients relapse again. Even among patients who achieve haematological remission, many may still have MRD following chemotherapy, which is predictive of relapse and poor outcomes following allo-SCT.[70,71]

As well as having highly limited effectiveness, current salvage chemotherapy regimens are associated with significant toxicities such as thrombocytopaenia (which can lead to bleeding), neutropaenia (which can lead to fever and infections), anaemia, cardiotoxicities, hepatotoxicities, and neuropathy.[21,22,30,45] Treatment mortality (i.e., death within 15 days of the start of therapy and death during the first course of therapy) occurs in as many as 11% to 23% of patients.[69,72] Furthermore, toxicities associated with salvage chemotherapy regimens mean that patients spent almost half of the salvage chemotherapy treatment period in hospital.[17,31,32] The number of agents and dosing regimens renders SOC chemotherapy regimens extremely complex; the decision to continue or resume regimens in the face of toxicities can be difficult, and because of the rarity of the disease, many treating clinicians have not accumulated wide experience with the toxicities of the drug combinations.[46]

There is an urgent need for new, effective treatment options for adult patients with R/R Ph- B-precursor ALL that prolong OS, improve rates and duration of haematological remission to give patients a better chance of being considered eligible for allo-SCT, and reduce toxicities to preserve QoL.

## *3.5 Proposed use of blinatumomab in England and Wales and relevant comparators*

Blinatumomab is proposed for use in England and Wales in accordance with its full marketing authorisation i.e., in all adult patients with R/R Ph- B-precursor ALL given that all patients within the licensed indication would hugely benefit from access to it.

The final NICE scope for this appraisal included three comparators: FLAG ± anthracycline, clofarabine-based combination chemotherapy, as well as best supportive care (BSC) including palliative care.

FLAG-IDA is considered to represent the most relevant comparator for blinatumomab, given that FLAG-based regimens, particularly FLAG-IDA, are those most commonly used in clinical practice in England and Wales based on UK-specific data from a survey of haemato-oncologists and haematologists, as well as feedback from UK clinical experts consulted by Amgen (Section 3.4.4.2).

Clofarabine-based combination chemotherapy is not considered a relevant comparator as:

- Clofarabine is licensed as a monotherapy only for paediatric use in patients who have received at least two prior regimens and where there is no other treatment option

anticipated to result in a durable response,[73] and is most commonly used for paediatric patients in UK clinical practice.[74]

- Clofarabine is due to be appraised by NICE only in paediatric patients who have received at least two prior regimens in 2017 (ID 1033).[75]
- Funding and routine availability of clofarabine in the adult population remains unclear since the expiration of the previous Cancer Drug Fund (which listed clofarabine)[74] in March 2016.

Best supportive care (including palliative care) is not considered a relevant comparator as it is typically reserved for patients who do not respond to salvage therapy, are nearing the end of life, and have usually experienced substantial treatment-related toxicity.[76] Blinatumomab, which is likely to be used as an alternative to other salvage therapies rather than as an alternative to BSC, would therefore be used before BSC in the treatment pathway.

## *3.6 Equality*

No equality issues relate to use of blinatumomab for the treatment of adult R/R Ph- B-precursor ALL.

# 4 Clinical effectiveness

## *4.1 Identification and selection of relevant studies*

- A comprehensive systematic literature review was used to identify relevant RCT and observational evidence.
- One relevant RCT and one relevant non-RCT were identified that evaluated the efficacy and safety of blinatumomab.

### 4.1.1 Systematic literature review

A comprehensive systematic literature review (SLR) was conducted in October 2015 and updated in November 2016 to identify RCTs and observational studies reporting the efficacy and safety of current treatments for adult patients with R/R Ph- B-precursor ALL. Additional exclusion criteria were applied to the broad review to identify those studies most relevant for inclusion in this submission (i.e., those assessing blinatumomab and that enrolled ≥ 50 patients) as detailed below. The SLR was conducted in accordance with the requirements of NICE and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[77-79]

### 4.1.2 Search strategies

Three databases were simultaneously searched during the clinical literature search (Table 4-1). Searches were conducted combining the appropriate syntax for each database with Medical Subject Heading (MeSH) terms relevant to leukaemia, free-text terms and study type filters where appropriate. The searches were updated for the final time on 16 November 2016 and no papers published after this date were considered. See Appendix II for full details of the search strategies.

**Table 4-1. Main databases searched for the clinical efficacy/safety SLR**

| Clinical evidence |
|---|
| • Ovid MEDLINE® In-Process & Non-Indexed Citations and Ovid MEDLINE® [database coverage 1946 to Week 2 November 2016] |
| • EMBASE® [1988 to Week 2 November 2016] |
| • Cochrane Central Register of Controlled Trials (CENTRAL) [All papers included in the database as of Week 2 November 2016] |

The reference lists of all identified reviews were cross-checked to identify additional primary studies, clinical experts, and relevant organisations and websites. In addition, supplementary hand searches of conference proceedings, HTAs, systematic reviews, and grey literature were conducted using the sources shown in Table 4-2.

**Table 4-2. Supplementary searches included in the clinical efficacy/safety SLR**

| Conference abstracts and trial entries from 2013 to 2016 | Existing health technology assessments (HTAs), systematic reviews, and protocols relating to pharmacological treatment from 1950 to November 2016 | Grey literature databases to November 2016 |
|---|---|---|
| • American Society of Clinical Oncology (ASCO) http://www.asco.org/<br>• European Hematology association (EHA) http://www.ehaweb.org/<br>• American Society of Hematology (ASH) http://www.hematology.org/<br>• National Institute of Health (NIH) ClinicalTrials.gov http://www.clinicaltrials.gov/<br>• WHO International Clinical Trials Registry Platform (ICTRP) http://www.who.int/ictrp/en/<br>• Australian New Zealand Clinical Trials Registry (ANZCTR) http://www.anzctr.org.au/<br>• European Clinical Trials Register (EU CTR) https://www.clinicaltrialsregister.eu/<br>• PharmaNet.Bund http://www.pharmnet-bund.de/static/de/index.html | • Cochrane Database of Systematic Reviews (CDSR) [All papers included in the database as of November 2016]<br>• Health Technology Assessment database (HTA) [All papers included in the database as of November 2016] | • US Food & Drug Administration (FDA) http://www.fda.gov/default.htm<br>• EPAR (European Public Assessment Reports) - European Medicines Agency (EMA) http://www.ema.europa.eu/ema/<br>• National Institute for Health and Care Excellence (NICE) Guidance http://www.nice.org.uk/<br>• Scottish Medicines Consortium (SMC) http://www.scottishmedicines.org.uk/Home<br>• All Wales Medicines Strategy Group (AWMSG) http://www.awmsg.org/<br>• Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca |

### 4.1.3 Study selection

Abstracts identified through the electronic database searches and web searching (summarised in Section 4.1.2) were independently screened by title and abstract by two researchers. Discrepancies were addressed through discussion, and disagreements were resolved by a third independent reviewer. All publications excluded during the secondary (full text) screening process for the broad SLR were documented along with the reasons for exclusion (Appendix II). Table 4-3 summarises the eligibility criteria used in the study selection process for the clinical studies.

**Table 4-3. Eligibility criteria used in the study selection process across the clinical efficacy/safety SLR**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | • Adult (≥ 15 years) R/R ALL<br>• Adult R/R Ph- B-precursor ALL | • Only paediatric, non-R/R ALL, T-cell patients, animal studies, or in vitro studies |
| Intervention | • Blinatumomab<br>• All other available pharmacological interventions (licensed and/or routinely used) to treat R/R ALL alone or in combination (salvage chemotherapies) | • N/A |
| Comparators | • Placebo<br>• Best supportive care<br>• Any active interventions (including dose-to-dose comparisons) | • N/A |
| Outcomes | • For efficacy: rates and duration of response, OS, PFS, clinically-relevant PFS, disease-free survival, time-to-treatment failures<br>• For safety: rates and duration of Grade 1-5 AEs, treatment discontinuations due to AEs or treatment-related AEs, treatment interruptions due to AEs, and dose modifications due to AEs | • Only genetic, biomarker, or laboratory outcomes |
| Trial design | • RCTs, including crossover studies<br>• Non-randomised clinical trials; observational studies (prospective and retrospective cohort studies); case control; and single arm studies | • Case reports, guidelines, letters, editorials, pharmacokinetic studies, or narrative reviews[b] |

AEs, adverse events; ALL, acute lymphoblastic leukaemia; OS, overall survival; PFS, progression-free survival; RCTs, randomised clinical trials; R/R, relapsed or refractory; SLR, systematic literature review.

#### *4.1.3.1 Identification of studies most relevant for inclusion in the submission*

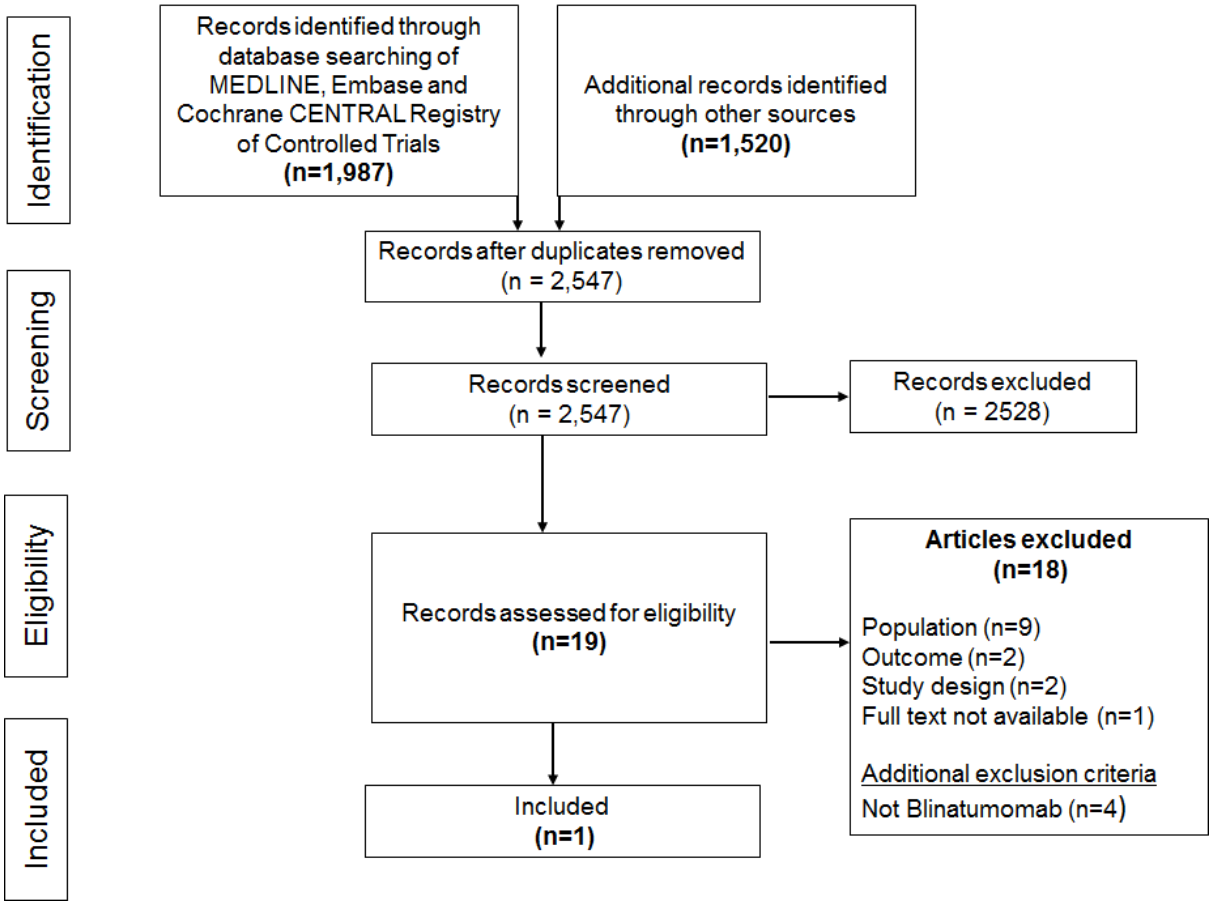
Additional exclusion criteria were applied to identify those studies most relevant for inclusion in the NICE submission: Studies were excluded if they did not assess the intervention of interest as defined in the decision problem (i.e., blinatumomab) or enrolled less than 50 patients.

### 4.1.4 Flow diagram for clinical evidence

The following PRISMA diagrams show the SLR process including the total number of records identified in the searches, and the reasons for study exclusion. A full list of excluded publications is provided in Appendix II with the reason for exclusion.

Figure 4-1 presents the PRISMA flow diagram for the RCT study selection. The RCT search identified one study (reported in one article) which is discussed in more detail in Section 4.2.

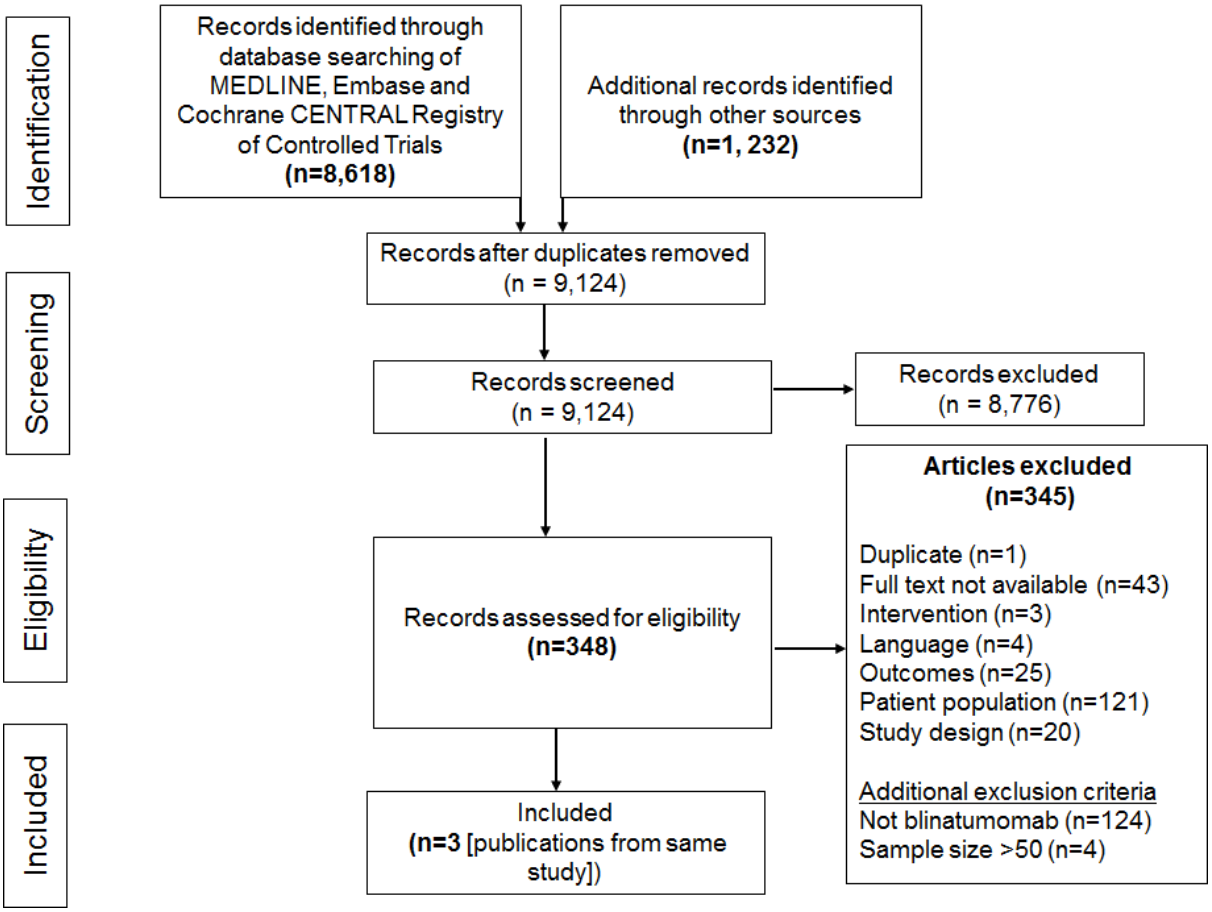
**Figure 4-1. RCT PRISMA flow diagram**




RCT, randomised controlled trial

Figure 4-2 presents the PRISMA flow diagram for the non-RCT study selection. The non-RCT search identified one study (reported in three articles) which is discussed in more detail in Section 4.11

**Figure 4-2. Non-RCT PRISMA flow diagram**




RCT, randomised controlled trial

## 4.2 List of relevant randomised controlled trials

- One relevant phase 3 RCT was identified that evaluated blinatumomab compared with SOC chemotherapy in adult patients with R/R Ph- B-precursor ALL (TOWER).

The SLR identified one Amgen-sponsored phase 3 relevant RCT reported in one publication assessing the efficacy/safety of blinatumomab in adult patients with R/R Ph- B-precursor ALL (TOWER) (Table 4-4). As a planned second interim analysis of OS showed that TOWER had achieved its primary objective of demonstrating that blinatumomab improves OS compared with SOC chemotherapy, the study was stopped early for efficacy and long-term follow-up was discontinued prematurely.[80]

**Table 4-4 List of relevant randomised controlled trials**

| Study number (acronym) | Population | Intervention | Comparator | Primary study references |
|---|---|---|---|---|
| 00103311 (TOWER) | Adult patients with R/R Ph- B-precursor ALL | Blinatumomab | SOC chemotherapy | • Topp *et al*., 2016 (EHA conference proceeding abstract)[81]<br>• TOWER primary analysis clinical study report (4 January 2016 data cut-off date)[80] |

ALL, acute lymphoblastic leukaemia; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory; SOC, standard of care.

## 4.3 Summary of TOWER methodology

- TOWER (N = 405) is a randomised, open-label, phase 3 RCT of adult patients with R/R Ph- B-precursor ALL.
- The primary endpoint of TOWER is OS; secondary and exploratory endpoints included the proportions of patients achieving haematological remission (CR and CR/CRh*/CRi) within 12 weeks of treatment initiation, EFS, duration of haematological remission, MRD remission, incidence of post-baseline allo-SCT, and AE rates.

### 4.3.1 Overview of study design

TOWER is a randomised, controlled, open-label, multicentre phase 3 study that randomised 405 adult patients with R/R Ph- B-precursor ALL. Patients were randomised in a 2:1 ratio to receive blinatumomab or treatment with investigator choice of one of four protocol-specified SOC chemotherapy regimens. Randomisation was stratified by age (< 35 vs. ≥ 35 years), prior salvage therapy (yes vs. no), and prior allo-SCT (yes vs. no). Patients were eligible if they had R/R Ph- B-precursor ALL and were:

- Refractory to primary induction therapy or salvage therapy
- In untreated first relapse with first remission duration < 12 months
- In untreated second or greater relapse
- In relapse at any time after allo-SCT

As patients in untreated first relapse with a first remission duration ≥ 12 months (i.e., patients with a better prognosis)[29] were not eligible, the population enrolled in TOWER therefore represents a particularly difficult-to-treat R/R Ph- B-precursor ALL population.

A brief summary of the TOWER study design and comprehensive list of eligibility criteria is provided in Table 4-5.

**Table 4-5. Overview of TOWER location and settings, study design, and eligibility criteria**

| | |
|---|---|
| **Location** | • 101 sites in 21 countries in Europe, North America, Israel, and Asia-Pacific<br>• 265 patients across 69 centres (65.4% of randomised patients) were enrolled in Europe, and 21 patients across 5 centres (5.2% of randomised patients) were enrolled in the UK |
| **Study design** | • Phase 3, randomised, controlled, open-label, multicentre study<br>• Patients were randomised in a 2:1 ratio to receive blinatumomab or investigator choice of one of four protocol-specified SOC chemotherapy regimens<br>• Patients were stratified by age (< 35 vs. ≥ 35 years), prior salvage therapy (yes vs. no), and prior allo-SCT (yes vs. no) |
| **Eligibility criteria for participants** | Inclusion criteria<br>• Age ≥ 18 years<br>• Ph- B-precursor ALL<br>▪ Refractory to primary induction therapy or salvage therapy<br>▪ Untreated first relapse with first remission duration < 12 months<br>▪ Untreated second or greater relapse<br>▪ Relapse at any time after allo-SCT<br>• Received intensive combination chemotherapy for treatment of ALL for initial treatment or subsequent salvage therapy<br>• > 5% blasts in the bone marrow<br>• ECOG PS 0-2<br>• Informed consent<br><br>Exclusion criteria<br>• Malignancy other than ALL within 5 years before treatment[a]<br>• Diagnosis of Burkitts leukaemia according to WHO classification<br>• HIV or chronic infection with hepatitis B or C<br>• History or presence of clinically relevant CNS pathology[b]<br>• Active ALL in the CNS or testes<br>• Isolated extramedullary disease<br>• Current autoimmune disease or history of autoimmune disease with potential CNS involvement<br>• Autologous SCT within 6 weeks or allo-SCT within 12 weeks before start of protocol-specified therapy<br>• Active acute Grade 2–4 GvHD or active chronic GvHD that requires systemic treatment, or any systemic therapy against GvHD within 2 weeks before start of protocol-specified therapy |

| | |
|---|---|
| | • Known exclusion criteria to investigator choice of SOC chemotherapy<br>• Cancer chemotherapy[c] or radiotherapy within 2 weeks before start of protocol-specified therapy, or immunotherapy within 4 weeks before start of protocol-specified therapy<br>• Prior anti-CD19 therapy<br>• Prior blinatumomab or previously randomised in TOWER<br>• Currently receiving treatment or received treatment within 30 days in another study; other investigational procedures whilst participating in TOWER were excluded<br>• Known sensitivity to immunoglobulins or any of the products or components to be administered during dosing<br>• Likely to not be available to complete all protocol-required study visits and/or not be able to comply with all required study procedures<br>• Abnormal laboratory values (ALT, AST or ALP ≥ 5 x ULN]; total bilirubin or creatinine ≥ 1.5 x ULN, or calculated creatinine clearance < 60 mL/min<br>• Pregnancy or breast feeding, or possibility of pregnancy within 3 months after the last dose of protocol-specified therapy[d]<br>• History or evidence of any other clinically significant disorder, condition, or disease that would pose a risk to subject safety or interfere with the study |
| **Settings and locations where the data were collected** | Secondary care (hospital) setting |

Reference: TOWER primary analysis CSR[80] and TOWER protocol[82]

[a] With exception of adequately treated non melanoma skin cancer, cervical carcinoma in situ, or breast ductal carcinoma in situ without evidence of disease; prostatic intraepithelial neoplasia without evidence of prostate cancer; and malignancy treated with curative intent and with no known active disease present for 5 years before enrolment and felt to be at low risk for recurrence by the treated physician
[b] With exception of history of CNS leukaemia controlled with intrathecal therapy
[c] With exception of intrathecal chemotherapy and dexamethasone
[d] Female patients of childbearing potential and male patients with partners of childbearing potential must be willing to use two highly effective forms of contraception during treatment with and until 24 hours after the last dose of protocol-specified therapy. Male patients with pregnant partners must be willing to use a condom during treatment with and for 3 months after the last dose of protocol-specified therapy.

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CNS, central nervous system; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematologic recovery; CSR, clinical study report; EFS, event-free survival; GvHD, graft versus host disease; MRD, minimal residual disease; OS, overall survivalSOC, standard of care; WHO, World Health Organization.

### 4.3.2 Study drugs and concomitant medications

A detailed overview of TOWER study drugs and required, permitted and disallowed concomitant medications is provided in Table 4-6.

Patients randomised to the blinatumomab arm received two 6-week induction cycles of blinatumomab administered as a continuous IV infusion over 4 weeks (9 µg/day during Week 1 of Cycle 1 then 28 µg/day for the remainder of the cycle) followed by a treatment-free interval

of 2 weeks.[80] Patients who achieved a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi could receive up to three additional 6-week consolidation cycles (28 µg/day for 4 weeks followed by a 2-week treatment-free interval). Patients who continued to have a bone marrow response or CR/CRh*/CRi after the consolidation phase could receive up to an additional 12 months treatment with blinatumomab in 12-week cycles (28 µg/day for 4 weeks and an 8-week treatment-free interval). Blinatumomab was administered in the inpatient setting for at least the first 9 days of the first induction cycle and the first 2 days of each subsequent cycle, as well as after any additional changes in dose. Afterward, treatment could be continued in the outpatient setting.

Patients randomised to the SOC chemotherapy arm received one of four protocol-specified, investigator-chosen regimens:[80]

- FLAG (fludarabine, cytarabine arabinoside, and GCSF) ± anthracycline-based regimen
- HiDAC (high-dose cytarabine arabinoside)–based regimen ± anthracycline and/or other drugs such as native *Escherichia coli* asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents
- High-dose methotrexate-based regimen in combination with native *Escherichia coli* asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents.
- Clofarabine as a single agent as recommended in the prescribing information or clofarabine-based regimens.

Similar to the blinatumomab arm, patients in the SOC chemotherapy arm received two induction cycles, and could go on to receive up to three additional consolidation cycles and up to 12 months additional maintenance treatment pending achievement/maintenance of bone marrow response or CR/CRh*/CRi in the preceding treatment phase.

**Table 4-6. Overview of TOWER study drugs and concomitant medications**

| | |
|---|---|
| **Study drugs** | Blinatumomab<br>• Induction phase: two 6-week cycles of blinatumomab (4-week treatment of continuous IV of 9 µg/day during Week 1 of Cycle 1 then 28 µg/day for the remainder of the cycle), followed by 2-week treatment-free interval<br>• Consolidation phase: Patients who achieved a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase could receive up to three additional 6-week cycles of blinatumomab (28 µg continuous IV per day for 4 weeks followed by a 2-week treatment-free interval)<br>• Maintenance phase: Patients with continued bone marrow response or CR/CRh*/CRi at the end of the consolidation phase could receive blinatumomab for up to an additional 12 months (or until investigator discretion, allo-SCT, treatment toxicity, relapse, or excluded medication use [e.g., anti-tumour or immunosuppressive therapy not included in the protocol, or other investigational agents]). During the maintenance phase, blinatumomab was administered in 12-week cycles (28 µg continuous IV per day for 4 weeks with an 8-week treatment-free interval)<br><br>SOC chemotherapy |

| | |
|---|---|
| | • Four SOC chemotherapy regimens were available at the investigators' discretion for patients in the SOC chemotherapy arm of the study:<br>▪ FLAG ± anthracycline-based regimen (such as idarubicin 10 mg/m$^2$ Days 1 and 3; fludarabine 30 mg/m$^2$ Days 1 to 5; cytarabine arabinoside 2 g/m$^2$ Days 1 to 5)[a]<br>▪ HiDAC–based regimen ≥ 1 g/m$^2$ per day ± anthracycline and/or other drugs such as native *Escherichia coli* asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents<br>▪ High-dose methotrexate-based regimen (500 mg/m$^2$ to 3 g/m$^2$ infused up to 24 hours) in combination with native *Escherichia coli* asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents<br>▪ Clofarabine as a single agent as recommended in the prescribing information or clofarabine-based regimens with 20 mg/m$^2$/day for up to 5 days<br>• As in the blinatumomab arm, patients received their SOC chemotherapy regimen for two induction cycles, up to three additional consolidation cycles in patients who achieved a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi at the end of the induction phase, and maintenance cycles for up to an additional 12 months (or until investigator discretion, allo-SCT, treatment toxicity, relapse, or excluded medication use [e.g., anti-tumour or immunosuppressive therapy not included in the protocol, or other investigational agents]) in patients who continued to have a bone marrow response or CR/CRh*/CRi at the end of the consolidation phase |
| **Permitted and disallowed concomitant medications** | <u>Required concomitant medications</u><br>• Patients in the blinatumomab arm with a high tumour load received pre-phase dexamethasone,[b] and all patients treated with blinatumomab received pre-dose dexamethasone as a prophylaxis against CRS. No dexamethasone pretreatment regimen was mandated with SOC chemotherapy<br>• Patients in both study arms were required to receive intrathecal CNS prophylaxis (e.g., methotrexate, cytosine arabinoside, or dexamethasone) within 10 days prior to start of treatment and following each induction and consolidation treatment cycle. Intrathecal CNS prophylaxis during maintenance treatment was at the investigator's discretion<br><br><u>Disallowed concomitant medications</u><br>• Any antitumour therapy other than the protocol-specified therapy (i.e., radiation therapy, immunotherapy, cytotoxic or cytostatic drugs)<br>• Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent); any other immunosuppressive therapies (except transient use of corticosteroids)<br>• Any other investigational agent<br>• Nonsteroidal anti-inflammatory drugs were avoided to prevent the potential for endothelial stress, if possible |

Reference: TOWER primary analysis CSR[80] and TOWER protocol[82]

[a] Patients > 60 years of age: idarubicin 5 mg/m$^2$ Day 1 and 3; fludarabine 20 mg/m$^2$ Day 1 to 5; cytarabine arabinoside1 g/m$^2$ Day 1 to 5

[b] Pre-phase treatment with dexamethasone was required for patients with proportion of blasts > 50% or peripheral blood blast count ≥ 15,000 µ/L, and recommended if LDH indicates rapidly progressing disease or if signs of extramedullary disease showed high tumour load.

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; CNS, central nervous system; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete

remission with incomplete haematologic recovery; CRS, cytokine release syndrome; CSR, clinical study report; EFS, event-free survival; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine arabinoside; MRD, minimal residual disease; OS, overall survival; SOC, standard of care.

### 4.3.3 Study endpoints and pre-specified subgroups

An overview of pre-specified endpoints and subgroups from TOWER is provided in Table 4-7.

The primary endpoint in TOWER was OS. Key secondary endpoints were the proportions of patients achieving CR and CR/CRh*/CRi within 12 weeks of treatment initiation, and EFS. Additional secondary endpoints included duration of CR and CR/CRh*/CRi, MRD remission rates, rates of post-baseline allo-SCT, and time to 10-point decrease in EORTC QLQ-C30 Global Health Status /QoL (GHS/QoL) or EFS event.

**Table 4-7. Study endpoints and pre-specified subgroups**

| | |
|---|---|
| **Primary outcome** | OS, defined as time since randomisation until death due to any cause[a] |
| **Secondary/tertiary outcomes** | <u>Key secondary endpoints</u><br>• CR (within 12 weeks of treatment initiation)[a]<br>▪ CR was defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/µL, **and** ANC > 1,000/µL)<br>• CR/CRh*/CRi (within 12 weeks of treatment initiation)[a]<br>▪ CR was defined as above. CRh* was defined as ≤ 5% blasts in the bone marrow, but with partial recovery of peripheral blood counts (platelets > 50,000/µL and ANC > 500/µL). CRi was defined as ≤ 5% blasts in the bone marrow, but with incomplete recovery of peripheral blood counts (platelets > 100,000/µL **or** ANC > 1000/µL)<br>• EFS[a]<br>▪ EFS was defined as time since randomisation until the date of relapse after achieving a CR/CRh*/CRi or death, whichever occurred first<br>▪ Patients who failed to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation were considered treatment failures and assigned an EFS duration of 1 day<br><br><u>Other secondary endpoints</u><br>• Duration of CR[a]<br>▪ Calculated from the date a CR was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first.<br>• Duration of CR/CRh*/CRi[a]<br>▪ Calculated from the date a CR/CRh*/CRi was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first.<br>• MRD remission (within 12 weeks of treatment initiation)[a]<br>▪ MRD remission was defined as MRD level below $10^{-4}$ by quantitative PCR or flow cytometry |

| | |
|---|---|
| | • Allo-SCT with or without blinatumomab treatment[a]<br>• Time to a 10-point decrease from baseline in HRQoL (EORTC QLQ-C30 GHS/QoL scale) or EFS event[a]<br>• Safety (incidence of AEs, 100-day mortality after allo-SCT, incidence of blinatumomab antibody formation, laboratory parameters)[a]<br><br><u>Exploratory endpoints</u><br>• HRQoL (ALLSS score at measured time points)[a]<br>• Blinatumomab steady state concentration<br>• Investigation for mutations in the tumour DNA to predict resistance to blinatumomab treatment |
| **Pre-planned subgroups** | <u>OS, CR within 12 weeks of treatment initiation, CR/CRh*/CRi within 12 weeks of treatment initiation, and EFS</u><br><br>Pre-specified subgroup analyses were carried out for the stratification factors (age [< 35 vs. ≥ 35 years], prior salvage therapy [yes vs. no], and prior allo-SCT [yes vs. no]), as well as for each of the 8 stratum formed by the combination of stratification factors (e.g., patients < 35 years with prior salvage therapy and a prior allo-SCT).<br><br>Additional pre-specified subgroup analyses were carried out on sex, race/ethnicity, region, alternate age grouping, number of prior salvage therapies (repeated for patients without prior allo-SCT), relapsed/refractory status (repeated for subjects without a prior allo-SCT), central laboratory baseline bone marrow blasts, central laboratory baseline platelet count, intended SOC chemotherapy regimen at randomisation, CD20 status, and CD22 status |

Reference: TOWER primary analysis CSR[80] and TOWER protocol[82]

[a] Relevant to the decision problem (i.e., included in the final scope for this appraisal); see Section 1.1

Note: Disease status was assessed until relapse using central bone marrow aspiration and local peripheral counts at the end of each treatment cycle during the treatment period and at the safety follow-up visit (30 days after the last dose of protocol-specified therapy). In the long-term follow-up period, disease status (in patients still in remission) and survival was to be assessed every three months until the 330$^{th}$ death is reported. HRQoL (EORTC QLQ C30 and ALLSS) was assessed on D1, D8, D15 and D29 in Cycles 1 and 2, D1, D15 and D29 in each consolidation cycle. HRQoL was not assessed during maintenance treatment.

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; ALLSS, acute lymphoblastic leukaemia symptom scale; ANC, absolute neutrophil count; CNS, central nervous system; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematologic recovery; CSR, clinical study report; EFS, event-free survival; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Global Health Status/Quality of Life; MRD, minimal residual disease; OS, overall survival; PCR, polymerase chain reaction; SOC, standard of care.

## 4.4 Statistical analysis in the TOWER study

The primary analysis of efficacy presented in this submission was performed on all randomised patients (the full analysis set [FAS]) analysed according to their randomised study regimen irrespective of treatment received, which is consistent with the intent-to-treat (ITT) principle.[80] The primary analysis of HRQoL (EORTC QLQ-C30) was performed on patients who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item (EORTC analysis set). The primary analysis of safety was performed on the safety analysis set (SAS) which included all patients who received protocol-specified therapy analysed according to the treatment they received.

TOWER was designed to randomise approximately 400 subjects and the primary analysis was scheduled to occur when 330 deaths were observed, assuming a hazard ratio of 0.70 for the primary endpoint. Two formal interim analyses were planned to assess OS when approximately 50% and 75% of the total number of OS events were observed. Stopping for efficacy was based on an O'Brien-Fleming type alpha spending function; the critical p-values corresponding to this spending function were 0.0031 for the first interim analysis, 0.0183 for the second interim analysis, and 0.044 for the final) analysis. The study could also stop for futility or on the basis of safety concerns. The interim analyses were overseen by an independent data monitoring committee (DMC), who made recommendations to Amgen regarding continuation of the study.

To preserve the overall significance level, inferential testing of the primary and key secondary endpoints was planned to follow a hierarchical structure in the following order in the pre-specified final analysis:

- OS
- CR within 12 weeks of treatment initiation
- CR/CRh*/CRi within 12 weeks of treatment initiation
- EFS

An overview of the statistical analysis methods for the primary and secondary endpoints in TOWER, sample size and power calculations, and data management and patient withdrawals is provided in Table 4-8.

**Table 4-8. Summary of pre-specified statistical analyses in the TOWER study**

| Trial number (acronym) | Hypothesis objective | Statistical analysis | Sample size and power calculations | Data management, patient withdrawals |
|---|---|---|---|---|
| Study 00103311 (TOWER ) | This study was conducted to determine whether blinatumomab was superior to SOC chemotherapy with respect to the primary efficacy endpoint of OS | <u>OS (primary endpoint)</u><br>• For the primary OS analysis, a 2-sided stratified log rank test stratified by age group, prior salvage therapy, and prior allo-SCT was used to determine whether blinatumomab improved OS compared with SOC chemotherapy.<br>• In addition, a HR with a 95% CI was estimated from a stratified Cox regression model. KM estimates were also generated.<br><u>CR and CR/CRh*/CRi within 12 weeks of treatment initiation (key secondary endpoints)</u><br>• A 2-sided Cochran-Mantel-Haenszel test, adjusted for the aforementioned stratification factors, was used to assess whether patients in the blinatumomab arm had a significantly higher response rate compared with the SOC chemotherapy arm.<br>• The percentage of patients in each treatment arm with a CR was summarised with an exact binomial 95% CI.<br><u>EFS (key secondary endpoint)</u><br>• EFS was analysed in the same way as OS.<br>• In addition, to address the potential bias of different cycle lengths across study arms, EFS times were grouped into discrete times[a]<br><u>Other secondary efficacy endpoints</u> | • In the FAS, if 330 deaths were observed, the study would be powered at approximately 85% for a 2-sided log-rank test with an overall alpha of 0.05 with a 2:1 randomisation ratio and an assumed HR of 0.70.<br>• 400 randomised patients were needed to observe 300 deaths and assumed a control arm median of 4.2 months (a conservative approximation based on two published studies of patients meeting the key entry criterion of the study)[69,72] a staggered 25-month enrolment period, a 7-month follow-up period after the last subject is enrolled, and a 10% | • Patients who withdrew from the study were not replaced<br>• For patients who withdrew before completion of all protocol-required visits and who were unable or unwilling to continue scheduled assessments, the investigator could search publicly available records to ascertain survival status (where allowed by local regulations)<br>• For rates of CR, CR/CRh*/CRi, and MRD patients without a post-baseline disease assessment were assumed not to have achieved a response<br>• For EFS, patients without a post-baseline disease assessment were assumed to have had an event on the day of randomisation, and patients who had missing disease assessments followed by non-missing assessments were censored |

| | | | | |
|---|---|---|---|---|
| | | • The duration of CR and CR/CRh*CRi was analysed for patients who achieved a CR and CR/CRh*/CRi and results presented as KM summaries<br>• MRD response and incidence of allo-SCT was analysed in the same way as the CR and CR/CRh*/CRi within 12 weeks of treatment initiation secondary endpoints<br>• Time to 10-point decrease from baseline EORTC QLQ C30 GHS/QoL or EFS event was analysed in the same way as EFS | drop-out rate over the 32-month study<br>• If 300 deaths were observed in the study the unconditional power decreased to approximately 80%. | on the day of the last non-missing assessment |

Reference: TOWER primary analysis CSR [80] and TOWER SAP[83]

[a] Patients who failed to achieve a CR/CRh*/CRi within the first two cycles were assigned an EFS duration of 1 day, EFS times based on a Cycle 2 assessment (those who responded at the end of Cycle 1, but relapsed in Cycle 2) were assigned to study Day 57 (29+28), EFS times based on a Cycle 3 assessment were assigned to study Day 85 (57+28), EFS times based on a Cycle 4 assessment were assigned to study Day 113 (85+28), and so on; death events were still reported as the actual death date

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematologic recovery; CSR, clinical study report; EFS, event-free survival; EORTC QLQ C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status/Quality of Life; HR, hazard ratio; FAS, full analysis set; KM, Kaplan–Meier; OS, overall survival; MRD, minimal residual disease; R/R, relapsed or refractory; SAP, statistical analysis plan; SOC, standard of care.

## *4.5 Participant flow in TOWER*

### 4.5.1 Patient disposition in TOWER

A Consolidated Standards of Reporting Trials (CONSORT) participant flow diagram as of the data cut-off date for the primary analysis (4 January 2016) is provided in Figure 4-3.

In TOWER, 405 patients were randomised and were included in the primary efficacy analyses (FAS); 376 patients received at least one dose of study drug and informed the safety analyses (SAS).[80]

Of note, a higher proportion of patients randomised to SOC chemotherapy did not receive study drug (n = 25, 18.7%) than in patients randomised to blinatumomab (n = 4, 1.5%). The most common reason for patients not receiving study drug in the SOC chemotherapy arm was patient choice (n = 22, 16.4%), which is unsurprising given the extremely poor prognosis and substantial toxicity associated with SOC chemotherapy (Section 3.2.2).

The most common reason for treatment discontinuation in both study arms was due to protocol-specified criteria (e.g., premature end of induction due to progression without prior CR/CRh*/CRi, and intention to receive allo-SCT or other therapy). The most common reason for study discontinuation in both study arms was death.

**Figure 4-3. TOWER CONSORT flow diagram**

Reference: TOWER primary analysis CSR [80]

AE, adverse event; allo-SCT, allogeneic stem cell transplantation; CONSORT, Consolidated Standards of Reporting Trials; CNS, central nervous system; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematologic recovery; CSR, clinical study report; GvHD, graft versus host disease; SOC, standard of care.

### 4.5.2 Baseline demographic, disease-related, and prior treatment characteristics

Baseline characteristics of participants are described in Table 4-9 and were similar across study arms in the FAS. The median age of patients was [redacted] years, with almost half ([redacted]%) of patients aged 18 to < 35 years. Slightly over one-third of patients (39.8%) had received no prior salvage therapy, 41.7% were refractory to their last therapy, and around one-third (34.6%) had received a prior allo-SCT. The most common intended SOC chemotherapy regimen at randomisation was FLAG ± anthracycline-based regimen ([redacted]%).

**Table 4-9. Summary of demographic, disease-related, and prior treatment characteristics (TOWER, FAS)**

| Baseline characteristic | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | Total (N = 405) |
|---|---|---|---|
| Sex, n (%) | | | |
| Men | 162 (59.8) | 77 (57.5) | 239 (59.0) |
| Women | 109 (40.2) | 57 (42.5) | 166 (41.0) |
| Age | | | |
| Median (IQR), years | [redacted] | [redacted] | [redacted] |
| Mean (IQR), years | 40.8 (25.0, 54.0) | 41.1 (26.0, 58.0) | 40.9 (26.0, 56.0) |
| < 35 years, n (%) | [redacted] | [redacted] | [redacted] |
| 35 to 54 years, n (%) | [redacted] | [redacted] | [redacted] |
| 55 to 64 years, n (%) | [redacted] | [redacted] | [redacted] |
| ≥ 65 years, n (%) | [redacted] | [redacted] | [redacted] |
| Maximum of central/local bone marrow blasts, n (%) | | | |
| < 50% | 69 (25.4) | 30 (22.4) | 99 (24.5) |
| ≥ 50% | 201 (74.2) | 104 (77.6) | 305 (75.3) |
| Unknown | 1 (0.4) | 0 (0) | 1 (0.2) |
| Key ALL entry criterion, n (%) | | | |
| Refractory to primary or salvage therapy | 115 (42.4) | 54 (40.3) | 169 (41.7) |
| In 1st relapse with 1st remission < 12 months | 76 (28.0) | 37 (27.6) | 113 (27.9) |
| In untreated 2nd or greater relapse | 32 (11.8) | 16 (11.9) | 48 (11.9) |
| Relapse after allo-SCT | 46 (17.0) | 27 (20.1) | 73 (18.0) |
| No criteria metPri | 2 (0.7) | 0 (0) | 2 (0.5) |
| Prior salvage therapy (per randomised strata), n (%) | | | |
| Yes | [redacted] | [redacted] | [redacted] |
| No[a] | [redacted] | [redacted] | [redacted] |
| Number of prior salvage regimens, n (%) | | | |
| 0[a] | 114 (42.1) | 65 (48.5) | 179 (44.2) |

| Baseline characteristic | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | Total (N = 405) |
|---|---|---|---|
| 1 | 91 (33.6) | 43 (32.1) | 134 (33.1) |
| 2 | 45 (16.6) | 16 (11.9) | 61 (15.1) |
| 3 | 14 (5.2) | 5 (3.7) | 19 (4.7) |
| > 3 | 7 (2.6) | 5 (3.7) | 12 (3.0) |
| Prior allo-SCT, n (%) | 94 (34.7) | 46 (34.3) | 140 (34.6) |
| Intended SOC chemotherapy regimen at randomisation | | | |
| FLAG ± anthracycline based regimen | [redacted] | [redacted] | [redacted] |
| High-dose methotrexate based regimen | [redacted] | [redacted] | [redacted] |
| Clofarabine or clofarabine based regimen | [redacted] | [redacted] | [redacted] |
| HiDAC based regimen | [redacted] | [redacted] | [redacted] |

Reference: TOWER primary analysis CSR (Tables 9-7, 14-2.3, and 14-4.4.5)[80]

[a]Numbers are not the same as data for prior salvage yes vs. no (stratification factor) is based on the IVRS and data on the number of lines of prior salvage regimens is based on the CRFs.

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; CRF, case report form; CSR, clinical study report; FAS, full analysis set; FLAG, fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim); HiDAC, high-dose cytarabine; IVRS, interactive voice/response system; IQR, interquartile range; SOC chemotherapy; WBC, white blood cell.

## *4.6 TOWER quality assessment*

In order to assess the risk of bias and generalisability of the TOWER study, quality assessment was conducted using guidance from 'Systematic reviews: Centre for Reviews and Dissemination (CRD)'s guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)'.[84] The instrument for evaluation of RCTs consists of seven items regarding randomisation, blinding, and reporting of withdrawals and dropouts.

A summary of the quality assessment is provided in Table 4-10. Quality assessment was conducted using the full clinical study report (CSR), as the study had not been fully published at the time of preparation of this submission. Randomisation and concealment of treatment allocation was appropriately conducted via use of an interactive voice response system (IVRS), both groups were well balanced for prognostic factors, and an ITT analyses was conducted for efficacy outcomes. Due to practical and ethical considerations associated with clinical trials of a single-agent intervention versus a complex combination SOC chemotherapy in this population, blinding was not possible. Additionally, dropout rates were imbalanced between groups following randomisation.

Overall, the study was well conducted when considering these limitations and represents the largest phase 3 trial in this population to date.

**Table 4-10. Quality assessment of the TOWER study**

| | |
|---|---|
| **Was randomisation carried out appropriately?** | Yes, after eligibility into the study was confirmed, patients were randomised in a 2:1 ratio to receive blinatumomab or SOC chemotherapy using an IVRS. |
| **Was the concealment of treatment allocation adequate?** | Yes, allocation was concealed by using an IVRS. |
| **Were the groups similar at the outset of the study in terms of prognostic factors?** | Yes, baseline characteristics were well balanced between treatment groups. |
| **Were the care providers, participants and outcome assessors blind to treatment allocation?** | • No, the study was open label so care providers, participants, and investigators were not blinded to treatment.<br>• The complexity of combination SOC chemotherapy regimens means that it would have been extremely difficult and unethical to conduct a double-blind study of a single-agent intervention in this disease area. |
| **Were there any unexpected imbalances in drop-outs between groups?** | • Yes, following randomisation there was a greater number of dropouts in the SOC chemotherapy arm (18.7%) than in the blinatumomab arm (1.5%). The most common reason for drop-out in patients who did not receive their allocated intervention in the SOC chemotherapy arm was patient choice, which is unsurprising given the extremely poor prognosis and substantial morbidity associated with SOC chemotherapy.<br>• However, no overall imbalance in drop outs was reported in patients who received at least one dose of study drug. |
| **Is there any evidence to suggest that the authors measured more outcomes than they reported?** | • Yes, data on the secondary endpoint of time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event and exploratory endpoint of changes in ALLSS scores over time were not included in the expedited primary analysis CSR – PRO outcomes will be reported at a later date in a separate report.<br>• However, data on the secondary endpoint of time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event have been included in this dossier as data were available for analysis at the time of submission. |
| **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?** | Yes, an ITT analysis was reported for all efficacy outcomes. |

ALLSS, acute lymphoblastic leukaemia symptom scale; CSR, clinical study report; EFS, event-free survival; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Global Health Status/Quality of Life; ITT, intention-to-treat; IVRS, interactive voice-response system; PRO, patient reported outcome; SOC, standard of care.

## 4.7 Clinical effectiveness results of the TOWER Study

- A statistically significant improvement in OS was observed for blinatumomab compared with SOC chemotherapy (HR 0.71; p = 0.012); median OS was almost doubled from 4.0 months in the SOC chemotherapy arm to 7.7 months in the blinatumomab arm.
- A pre-specified sensitivity analysis of OS with patients censored at the time of allo-SCT shows that the survival benefit associated with blinatumomab is independent of transplant (HR: 0.66; p = 0.004).
- Significantly more patients treated with blinatumomab achieved a haematological remission than with SOC chemotherapy within 12 weeks of treatment initiation (CR: 33.6% vs. 15.7%, p < 0.001; CR/CRh*/CRi: 43.9% vs. 24.6%, p < 0.001).
- Haematological remission was more durable in patients treated with blinatumomab than with SOC chemotherapy (CR: median duration [redacted] months; CR/CRh*/CRi: median duration 7.3 vs. 4.6 months).
- More CR/CRh*/CRi responders achieved MRD remission with blinatumomab than with SOC chemotherapy, underlining the high quality and depth of remissions associated with blinatumomab (76.3% vs. 48.5%; descriptive p = [redacted]).
- Blinatumomab improved EFS compared with SOC chemotherapy (HR 0.55; descriptive p < 0.001).
- Rates of post-baseline allo-SCT were similar across study arms with 24.0% of patients in the blinatumomab arm and 23.9% of patients in the SOC chemotherapy arm receiving transplant. These similar rates, which may seem counter-intuitive, are likely due to clinicians adopting a different approach to the management of patients dependent on study arm and patient characteristics. This may have biased OS results in favour of SOC chemotherapy.
- Blinatumomab delayed time to clinically-meaningful deterioration in HRQoL (10-point decrease in EORTC QLQ-C30 GHS/QoL) or EFS event (HR 0.67; descriptive p = 0.0051). Blinatumomab also improved EORTC QLQ-C30 scores from baseline relative to SOC chemotherapy (descriptive [redacted] for overall treatment effect during Cycle 1 for the main GHS/QoL scale).

### 4.7.1 Overview of data presentation

The primary analysis was triggered by the positive second interim analysis result when 75% (248 patients) of the total number of deaths (330) were observed. On 28 January 2016, the DMC recommended that the study be stopped for efficacy because the p-value = 0.011 was less than the pre-specified O'Brien-Fleming early stopping boundary of 0.0183. Amgen notified the regulatory authorities of the DMC recommendation and Amgen's decision to end the study early. On 2 March 2016 all regulatory authorities were notified that the long-term follow-up part of the study was discontinued prematurely. The data cut-off date for the primary analysis and for the DMC interim analysis was 4 January 2016.[80] All efficacy data reported below are based on this data cut-off-date.

In the snapshot of this primary analysis, 251 deaths were reported (i.e., 76.1% information time) resulting in a critical p-value of [redacted] (i.e., the threshold for statistical significance) based on the O'Brien-Fleming-type alpha-spending function. As of the data cut-off date for this primary analysis (4 January 2016), 22 patients randomised to blinatumomab continued to

receive blinatumomab treatment. A final analysis will occur after these patients have completed treatment and their 30-day safety follow-up visit (estimated to be in Q1 2017).

According to the statistical analysis plan, testing of key secondary efficacy endpoints in the second interim analysis was planned to be descriptive only, with formal testing of these endpoints planned only for the final analysis. However, information for CR and CR/CRh*/CRi had reached 100% by the time of data cut-off due to the fact that all patients had reached the end of the period for response evaluation (i.e., 12 weeks from treatment initiation), and no further update on CR and CR/CRh*/CRi response rates are expected in the final analysis. Therefore, the analysis for CR and CR/CRh*/CRi was considered final in the primary analysis and a two-sided alpha of 0.05 was used for hypothesis testing.

All TOWER pre-specified primary and secondary efficacy endpoints are presented in detail in the main submission as all are relevant to the decision problem and included in the final scope for this appraisal (Table 4-11). In addition, results from the pre-specified secondary safety endpoint of 100-day mortality following post-baseline allo-SCT is presented alongside the rates of post-baseline allo-SCT.

An exploratory post-hoc analysis of EORTC QLQ-C30 scales and single items over time is also presented as HRQoL is included in the final scope for this appraisal and EORTC QLQ-C30 data from TOWER are used inform the cost-effectiveness analysis. Results from the exploratory HRQoL endpoint of ALLSS score over time were not available for analysis at the time of this appraisal and are therefore not reported in this submission.

**Table 4-11. Overview of TOWER outcome data presented in detail in the main submission**

| | |
|---|---|
| **Pre-specified primary endpoint** | • OS primary analysis<br>▪ Pre-specified sensitivity analysis of patients who received at least one dose of study drug<br>▪ Pre-specified sensitivity analysis of patients where patients who received post-baseline allo-SCT were censored at the time of allo-SCT |
| **Pre-specified secondary endpoints** | <u>Pre-specified key secondary endpoints</u><br>• CR (within 12 weeks of treatment initiation)<br>• CR/CRh*/CRi (within 12 weeks of treatment initiation)[a]<br>• EFS<br><u>Other pre-specified secondary endpoints</u><br>• Duration of CR<br>• Duration of CR/CRh*/CRi<br>• MRD remission (within 12 weeks of treatment initiation)<br>• Allo-SCT with or without blinatumomab treatment<br>• 100-day mortality after allo-SCT (safety endpoint)<br>• Time to a 10-point decrease from baseline in HRQoL (EORTC QLQ-C30 GHS/QoL scale) or EFS event |
| **Post-hoc analysis** | EORTC QLQ-C30 GHS/QoL change from baseline over time |

Allo-SCT, allogenic stem cell transplant; CR, complete response; CRh*, complete response with partial haematological recovery; CRi, complete response with incomplete haematological recovery; EFS, event-free survival; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality

of Life Questionnaire-Core 30 Global Health Status/Quality of Life; HRQoL, health-related quality of life; OS, overall survival.

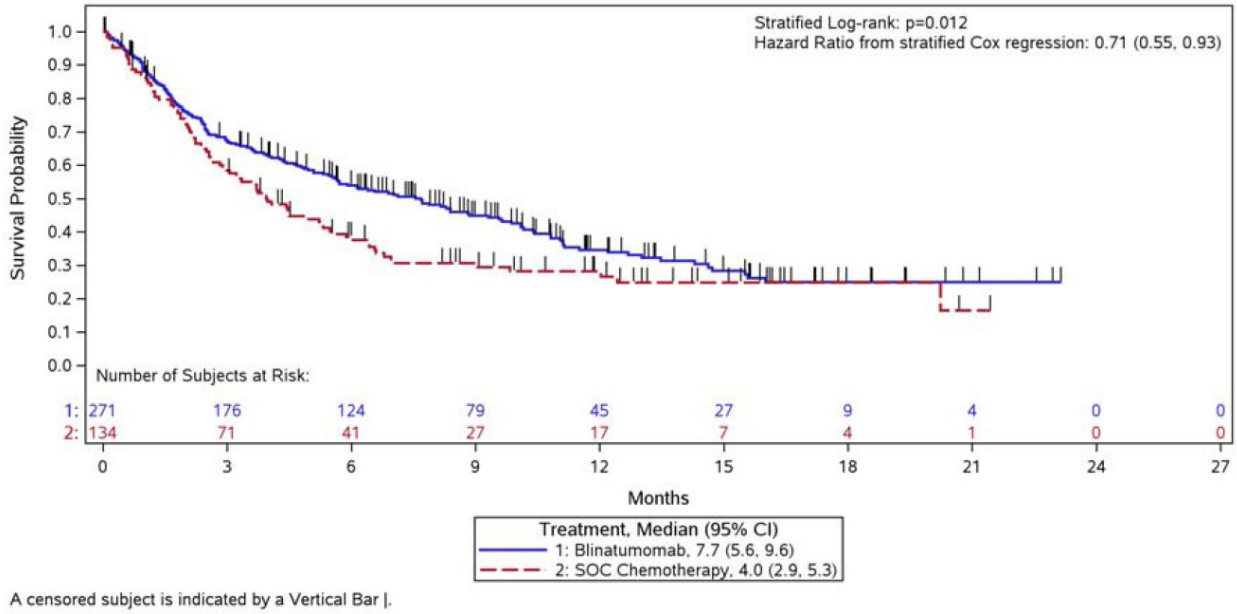
### 4.7.2 Overall survival (primary efficacy endpoint)

The TOWER study achieved its primary objective by demonstrating that blinatumomab improves OS compared with SOC chemotherapy (Figure 4-4 and Table 4-12).

A total of 251 (62.0%) patients had died at the time of data cut-off, [redacted] in the blinatumomab arm and [redacted] in the SOC chemotherapy arm. A statistically significant improvement in OS was observed for blinatumomab compared with SOC chemotherapy (HR 0.71; p = 0.012); median OS was almost doubled from 4.0 months in the SOC chemotherapy arm to 7.7 months in the blinatumomab arm. This p-value was below the critical p-value of 0.0194 for this interim analysis of OS. As of the data cut-off date, the median follow-up time for OS was 11.7 months in the blinatumomab arm and 11.8 months in the SOC chemotherapy arm.

Although the Kaplan–Meier plots clearly diverge within the first 3 months after randomisation and separation becomes more pronounced over time, the divergence appears to be limited to approximately 15 months. This should be interpreted in the context of the small patient numbers at risk at and beyond 15 months, the resulting highly limited statistical power to detect significant differences in treatment effects in later months of follow-up (Table 4-13), and the potential confounding effects of allo-SCT and crossover to subsequent treatment (Section 4.13.1.2).

**Figure 4-4. Kaplan–Meier plot of overall survival (TOWER, FAS)**




Reference: TOWER primary analysis CSR (Figure 10-1)[80]

FAS, full analysis set; CI, confidence interval; CSR, clinical study report; SOC, standard of care.

**Table 4-12. Overall survival (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| Died, n (%) | [redacted] | [redacted] |
| Censored, n (%) | [redacted] | [redacted] |
| OS duration, median months (95% CI) | 7.7 (5.6, 9.6) | 4.0 (2.9, 5.3) |
| Hazard ratio blinatumomab: SOC (95% CI) | 0.71 (0.55, 0.93) | |
| p-value[a] | 0.012 | |
| Median follow-up for OS, months (IQR) | 11.7 ([redacted]) | 11.8 ([redacted]) |

Reference: TOWER primary analysis CSR (Tables 10-1 and 14-4.5.1)[80]

[a]Log rank p-value from Cox regression model stratified by age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no) and prior allo-SCT (yes vs.no).

allo-SCT, allogenic stem cell transplant; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IQR, interquartile range; OS, overall survival; SOC, standard of care.

**Table 4-13. Summary of statistical power for overall survival at different time points from baseline (TOWER)**

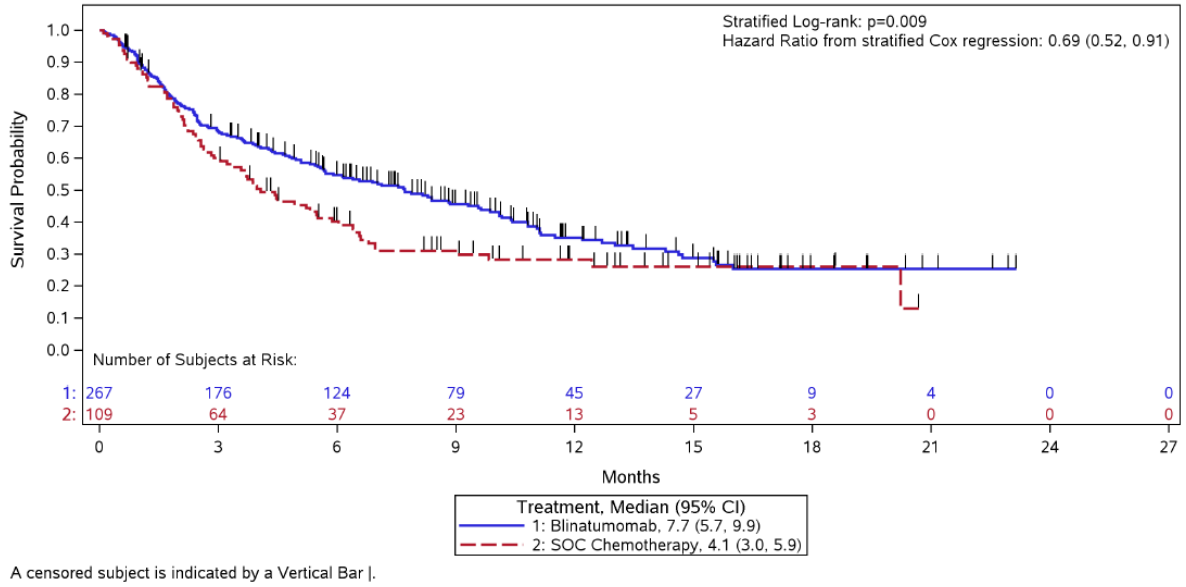
| Time point from baseline | Power of detecting a significant treatment effect between blinatumomab and SOC chemotherapy |
|---|---|
| 6 months | [redacted] |
| 12 months | [redacted] |
| 18 months | [redacted] |

Reference: Amgen data on file, 2016[85]

SOC, standard of care.

A range of pre-specified sensitivity analyses, including analyses of patients who received at least one dose of study drug (SAS; Figure 4-5) and analyses of patients in the FAS who were censored at the time of allo-SCT (Figure 4-6) were consistent with the primary analyses presented above in demonstrating an OS benefit for blinatumomab over SOC. In the sensitivity analysis of patients in the FAS who were censored at the time of allo-SCT, the survival benefit for blinatumomab versus SOC chemotherapy was maintained (HR: 0.66 [95% CI 0.50, 0.88]; p = 0.004), showing that the survival benefit associated with blinatumomab is independent of transplant. The survival curves in the Kaplan–Meier plot continue to remain separated over the duration of follow-up. Detailed results for all of the sensitivity analyses are provided in Appendix III.

**Figure 4-5. Kaplan–Meier plot of overall survival (TOWER, SAS)**

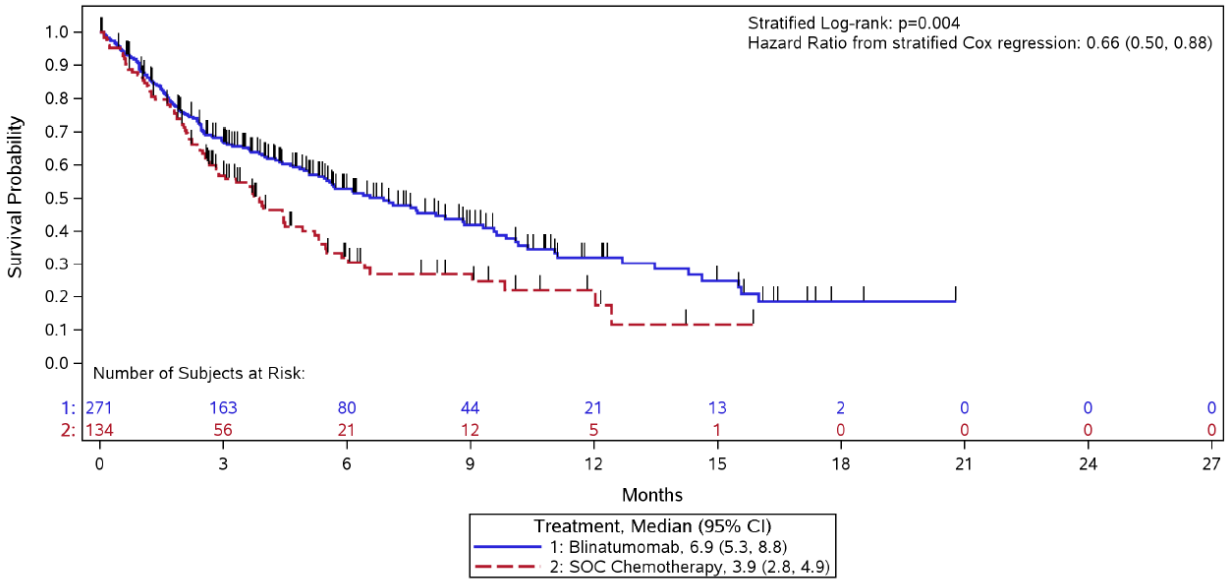



A censored subject is indicated by a Vertical Bar |.

Reference: TOWER primary analysis CSR (Figure 14-4.1.2)[80]

CI, confidence interval; CSR, clinical study report; SAS, safety analysis set; SOC, standard of care.

**Figure 4-6. Kaplan–Meier plot of overall survival with patients censored at the time of allo-SCT (TOWER, FAS)**




A censored subject is indicated by a Vertical Bar |.

Reference: TOWER primary analysis CSR (Figure 14-4.1.3)[80]

allo-SCT, allogenic stem cell transplant; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; SOC, standard of care.

### 4.7.3 Rates of CR and CR/CRh*/CRi within 12 weeks of treatment initiation (key secondary efficacy endpoints) and duration of response (secondary efficacy endpoints)

The proportion of patients achieving a CR within 12 weeks of treatment initiation was statistically significantly more than doubled in the blinatumomab arm compared with the SOC chemotherapy arm (33.6% vs. 15.7%; p < 0.001) (Table 4-14). Similarly, the proportion of patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation was statistically significantly almost doubled in the blinatumomab arm compared with the SOC chemotherapy arm (43.9% vs. 24.6%, p < 0.001).

**Table 4-14. Rates of CR and CR/CRh*/CRi within 12 weeks of treatment initiation (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| CR, n (%) | 91 (33.6) | 21 (15.7) |
| 95% CI | (28.0, 39.5) | (10.0, 23.0) |
| p-value[a] | < 0.001 | |
| CR/CRh*/CRi, n (%) | 119 (43.9) | 33 (24.6) |
| 95% CI | (37.9, 50.0) | (17.6, 32.8) |
| p-value[a] | < 0.001 | |

Reference: TOWER primary analysis CSR (Table 10-3)[80]

[a] Descriptive p-value from Cochran-Mantel-Haenszel test after adjusting for stratification factors of age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no), and prior allo-SCT (yes vs.no).

allo-SCT, allogenic stem cell transplant; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological response; CRi, complete remission with incomplete haematological response; CSR, clinical study report; FAS, full analysis set; SOC, standard of care.

A range of pre-specified sensitivity analyses, including pre-specified analyses of patients who received at least one dose of study drug (SAS) and of patients who had at least one post-baseline disease assessment were consistent with the primary analyses presented above in demonstrating higher rates of haematological remission for blinatumomab compared with SOC chemotherapy. Detailed results for all of the sensitivity analyses are provided in Appendix III.

Of the patients who achieved best response of CR or CR/CRh*CRi, median durations of response were longer in the blinatumomab arm (Table 4-15). The median duration of response for patients who achieved a CR was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm. For patients who achieved CR/CRh*/CRi the difference was even more pronounced with a median duration of response of 7.3 months in the blinatumomab arm and 4.6 months in the SOC chemotherapy arm.

**Table 4-15. Duration of haematological response (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| CR, n (%) | 91 (33.6) | 21 (15.7) |
| Events, n (%) | [redacted] | [redacted] |
| Censored, n (%) | [redacted] | [redacted] |
| Median time to event Kaplan–Meier, months (95% CI) | [redacted] | [redacted] |
| Median follow-up time, months | [redacted] | [redacted] |
| CR/CRh*/CRi | 119 (43.9) | 33 (24.6) |
| Events, n (%) | [redacted] | [redacted] |
| Censored, n (%) | [redacted] | [redacted] |
| Median time to event Kaplan–Meier, months (95% CI) | 7.3 (5.8, 9.9) | 4.6 (1.8, 19.0) |
| Median follow-up time, months | [redacted] | [redacted] |

Reference: TOWER primary analysis CSR (Tables 10-8 and 14-4.1.1)[80]

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological response; CRi, complete remission with incomplete haematological response; CSR, clinical study report; FAS, full analysis set; SOC, standard of care.

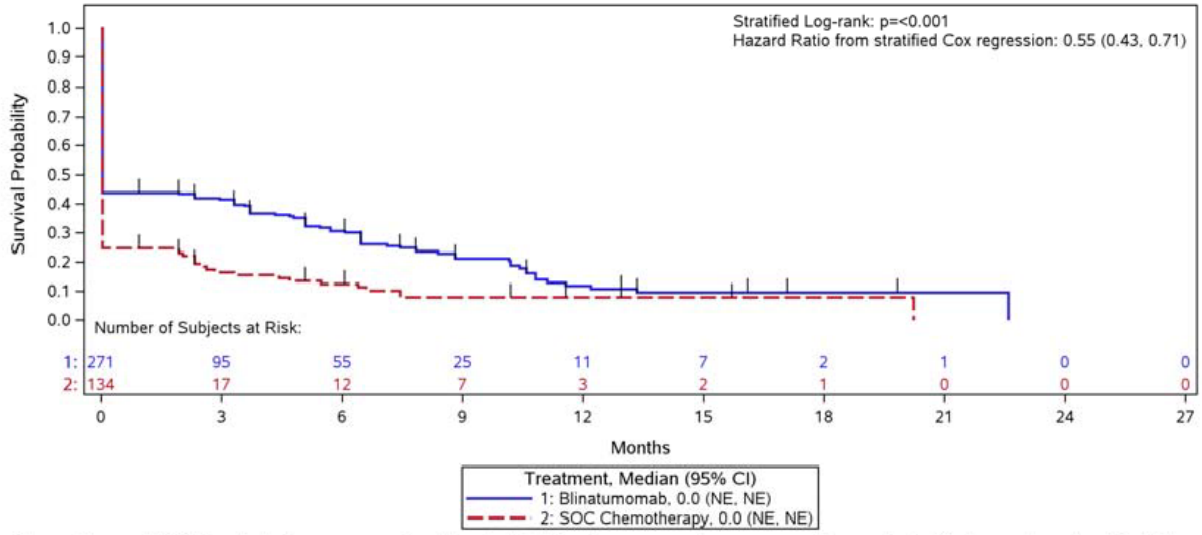
A pre-specified sensitivity analysis of duration of response with censoring at the time of allo-SCT in CR/CRh*/CRi responders was consistent with the primary analysis in showing a longer duration of response for patients in the blinatumomab arm. However, the duration of response in the equivalent analysis for CR responders was longer in the SOC chemotherapy arm ([redacted] months vs. [redacted] months). This is possibly due to the small number of patients and events in the SOC chemotherapy arm (n = [redacted] events) relative to the blinatumomab arm (n = [redacted] events). Full details of these sensitivity analyses are provided in Appendix III.

### 4.7.4 Event-free survival (key secondary efficacy endpoint)

A total of [redacted] patients ([redacted]) in the blinatumomab arm and [redacted] patients ([redacted] )in the SOC chemotherapy arm had an EFS event. Blinatumomab improved EFS compared with the SOC chemotherapy with a HR of 0.55 (descriptive p < 0.001) (Figure 4-7 and Table 4-16). The proportion of patients alive and in remission at 6 months was 30.7% ([redacted]) in the blinatumomab arm and 12.5% ([redacted]) in the SOC chemotherapy arm.[80]

A total of 56.1% patients in the blinatumomab arm and 75.4% patients in the SOC chemotherapy arm did not achieve a CR/CRh*/CRi within the first two cycles, and were assigned an EFS duration of 1 day (this approach is recommended for acute leukaemia by the EMA[86]). Hence, the median time to EFS was 1 day (rounded to 0 months) in both study arms (Figure 4-7 and Table 4-16).

**Figure 4-7. Kaplan–Meier plot of event-free survival (TOWER, FAS)**




Observed/censored EFS times for both arms are assigned the scheduled time the assessment was supposed to occur in the blinatumomab arm to mitigate the potential bias associated with different treatment cycle lengths between arms;
Death events will still be reported as the actual death date. A censored subject is indicated by a Vertical Bar |.

Reference: TOWER primary analysis CSR (Figure 10-3)[80]

CI, confidence interval; CSR, clinical study report; EFS, event-free survival; FAS, full analysis set; NE, not estimable; SOC, standard of care.

**Table 4-16. Event-free survival (TOWER, FAS)**

| | **Blinatumomab (N = 271)** | **SOC chemotherapy (N = 134)** |
|---|---|---|
| Events, n (%) | [redacted] | [redacted] |
| Censored, n (%) | [redacted] | [redacted] |
| EFS duration, median months (95% CI) | 0.0 ([redacted]) | 0.0 ([redacted]) |
| Hazard ratio blinatumomab: SOC (95% CI) | 0.55 (0.43, 0.71) | |
| p-value[a] | < 0.001 | |

Reference: TOWER primary analysis CSR (Table 14-4.7.1)[80]

Note: Patients who did not achieve a CR/CRh*/CRi within 12 weeks of treatment initiation were assigned an EFS duration of 1 day.
[a] Descriptive log rank p-value from Cox regression model stratified by age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no) and prior allo-SCT (yes vs.no).

allo-SCT, allogenic stem cell transplant; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; CSR, clinical study report; EFS, event-free survival; FAS, full analysis set;OS, overall survival; NE, not estimable; SOC, standard of care.

A range of pre-specified sensitivity analyses, including pre-specified analyses of patients who received at least one dose of study drug (safety analysis set) and of patients who had at least one post-baseline disease assessment were consistent with the primary analyses presented above in demonstrating improved EFS for blinatumomab compared with SOC chemotherapy. Detailed results for all of the sensitivity analyses are provided in Appendix III.

### 4.7.5 Minimal residual disease remission (secondary efficacy endpoint)

Although the pre-specified primary statistical analyses were to be conducted on the FAS, it is considered more clinically meaningful to assess the proportion of patients with MRD remission amongst those who achieved a CR/CRh*/CRi and had a post-baseline MRD assessment. This is because MRD remission represents a deeper response than CR/CRh*/CRi, and therefore patients achieving an MRD remission represent a subset of patients who have achieved a CR/CRh*/CRi.

In the blinatumomab arm, 76.3% of CR/CRh*/CRi responders with at least one post-baseline MRD disease assessment had an MRD remission compared with 48.5% in the SOC chemotherapy arm (descriptive [redacted]) (Table 4-17). MRD remission rates consistently favoured blinatumomab when all randomised patients (i.e., the FAS) was used as the denominator rather than patients who achieved a CR/CRh*/CRi and had at least one post-baseline MRD assessment ([redacted]%; Appendix III).

**Table 4-17. MRD remission within 12 weeks of treatment initiation (TOWER, patients in the FAS who achieved a CR/CRh*/CRi and had a post-baseline MRD assessment)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| Number of patients with post-baseline assessment | [redacted] | [redacted] |
| Number of patients with CR/CRh*/CRi | 97 | 33 |
| MRD remission, n (%) | 74 (76.3) | 16 (48.5) |
| 95 % CI | [redacted] | [redacted] |
| p-value[a] | [redacted] | |

Reference: TOWER primary analysis CSR (Table 10-9)[80]

[a] Descriptive p-value from Cochran-Mantel-Haenszel test after adjusting for stratification factors of age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no), and prior allo-SCT (yes vs.no).

allo-SCT, allogenic stem cell transplant; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological response; CRi, complete remission with incomplete haematological response; CSR, clinical study report; FAS, full analysis set. MRD, minimal residual disease; SOC, standard of care

### 4.7.6 Incidence of post-baseline allo-SCT (secondary efficacy endpoint) and 100-day mortality following allo-SCT (secondary safety endpoint)

Overall, the incidence of allo-SCT was similar across treatment arms. In the blinatumomab arm, 65 patients (24.0%) underwent allo-SCT compared with 32 (23.9%) patients in the SOC chemotherapy arm (descriptive p = [redacted]) (Table 4-18).

**Table 4-18. Incidence of post-baseline allo-SCT (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| Patients receiving post-baseline allo-SCT, n (%) | 65 (24.0) | 32 (23.9) |
| 95% CI | [redacted] | [redacted] |
| p-value[a] | [redacted] | |

Reference: TOWER primary analysis CSR (Table 10-10)[80]

[a] Descriptive p-value from Cochran-Mantel-Haenszel test after adjusting for stratification factors of age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no), and prior allo-SCT (yes vs.no).

allo-SCT, allogenic stem cell transplant; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; SOC, standard of care.

Although these data might seem counter-intuitive given the substantially higher haematological remission rates in the blinatumomab arm (Section 4.7.3), there are important potential reasons for this:

- Among patients who achieved a haematological remission (CR/CRh*/CRi within 12 weeks of treatment initiation), a higher proportion of patients in the blinatumomab arm had received a prior allo-SCT than patients in the SOC chemotherapy arm ([redacted]),[85] thus making them less likely to receive a post-baseline allo-SCT based on feedback from a UK clinical expert (a TOWER investigator). In addition, among patients who achieved a haematological remission, patients in the SOC chemotherapy arm were transplanted earlier than in the blinatumomab arm (median time to allo-SCT [redacted] months).[80] This suggests that for patients randomised to blinatumomab, clinicians may have been more inclined to adopt a 'watch and wait' approach because of the risk associated with the SCT procedure, availability of protocol-permitted maintenance treatment with blinatumomab in TOWER and potential for long-term remission with blinatumomab, and the favourable tolerability profile of blinatumomab compared with SOC chemotherapy. This assertion is supported by feedback from a UK clinical expert (a TOWER investigator).
- For patients randomised to SOC chemotherapy, allo-SCT may have been considered by TOWER investigators to be only route to long-term remission and potential cure for the vast majority of patients. Clinicians may therefore have been more inclined to undertake allo-SCT even in patients who were not in remission. The incidence of allo-SCT in the SOC chemotherapy arm (10.4%) was almost double than in the blinatumomab arm (5.5%) in patients who did not achieve a haematological remission (CR/CRh*/CRi within 12 weeks of treatment initiation).[80]
- Taken together, these data above indicate that some of the TOWER investigators may have believed blinatumomab-treated patients were more under control

The rate of allo-SCT is therefore an outcome influenced by a range of clinician-driven considerations and subject to substantial potential confounding. In order to reduce the potential impact of confounding, 100-day mortality following post-baseline allo-SCT was assessed only in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation and did not receive additional anticancer therapy prior to allo-SCT. Of these patients, 38 patients in the blinatumomab arm and 12 patients in the SOC chemotherapy arm had a post-baseline allo-SCT (Table 4-19). The Kaplan–Meier estimate of 100-day mortality rate following

post-baseline allo-SCT in these patients was [redacted] in the blinatumomab arm and [redacted] in the SOC chemotherapy arm. This should be interpreted in the context of the similar overall proportion of patients who had mortality events following allo-SCT, and the small numbers of patients and observed events.

**Table 4-19. 100-day mortality post allo-SCT in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation and did not receive other anticancer therapies before allo-SCT (TOWER)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| Number of patients with allo-SCT, n[a] | 38 | 12 |
| Died, n (%) | 10 (26.3) | 3 (25.0) |
| Censored, n (%) | [redacted] | [redacted] |
| 100-day mortality (Kaplan–Meier estimate), % (95% CI) | [redacted] | [redacted] |

Reference: TOWER primary analysis CSR (Table 10-12)[80]

[a]Patients achieved CR/CRh*/CRi within 12 weeks of treatment initiation and did not receive other anticancer therapies before allo-SCT

allo-SCT, allogenic stem cell transplant; CI, confidence interval; CSR, clinical study report; NE, not estimable; SOC, standard of care.

### 4.7.7 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated patient reported outcome (PRO) questionnaire comprising multi-item scales and single-item measures rated from 0 to 100 used to assess health-related QoL in cancer patients who participate in clinical trials.[87] In the EORTC QLQ-C30, a main GHS/QoL scale, five other functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning), three symptom scales (fatigue, pain, nausea), and six single items are assessed. For the GHS/QoL scale and functional scales, a higher score is indicative of better QoL. For symptom scales/single items, a lower score is indicative of better QoL. Changes of between 5 and 10 points on the EORTC QLQ-C30 scales can be considered clinically meaningful.[88-90]

#### *4.7.7.1 Time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event (secondary efficacy endpoint)*

Blinatumomab delayed the time to clinically meaningful 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event. The HR for the blinatumomab versus the SOC chemotherapy arm was 0.67 (descriptive p = 0.0051).[85] Similarly to the EFS endpoint, as patients who did not achieve a CR/CRh*/CRi within the first two cycles were assigned an EFS duration of 1 day, the median time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event was 1 day (rounded to 0 months) in both study arms.

**Figure 4-8. Kaplan–Meier plot of time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event (TOWER, EORTC analysis set)**

Reference: Amgen data on file, 2016[85]

Note: The EORTC analysis set included patients who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item.

BLIN, blinatumomab; C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; OL, open-label; SOC, standard of care.

#### *4.7.7.2 Change from baseline in EORTC QLQ-C30 scales and single items (post-hoc exploratory analysis)*

Baseline scores were similar across study arms at baseline for all EORTC QLQ-C30 scales and single items (Appendix III). In general, patients in the blinatumomab arm had improved post-baseline HRQoL compared with patients in the SOC chemotherapy across all scales and single items based on visual inspection (Figure 4-9 and Figure 4-10). As early as Day 8 of Cycle 1, mean changes from baseline suggested worsening in HRQoL in almost all scales and single items in the SOC chemotherapy arm; in contrast, mean changes from baseline suggested improvement in HRQoL in almost all scales and single items in the blinatumomab arm. The change from baseline in EORTC QLQ-C30 GHS/QoL scores in Cycle 1 were compared between treatment groups using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) under the assumption of missing at random (MAR). The model included effects of treatment, visit, treatment-by-visit interaction, and the baseline score, and the p-value for overall treatment effect was [redacted].

Detailed results for scores and change from baseline at each scheduled visit during Cycle 1 for each scale and single item are provided in Appendix III. As small patient numbers in the

SOC chemotherapy arm (< [redacted] patients) limits comparisons across study arms beyond Cycle 1, data for the remainder of follow-up is provided in Appendix III for all EORTC QLQ C30 scales and single items.

**Figure 4-9. Mean change from baseline in EORTC QLQ-C30 GHS/QoL and other functional scales by scheduled visit in Cycle 1 (TOWER, EORTC analysis set)**

Reference: Amgen data on file, 2016[85]

Descriptive [redacted] for GHS/QoL overall treatment effect during Cycle 1 using a restricted maximum likelihood-based mixed model for repeated measures under the assumption of missing at random. The EORTC analysis set included patients who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item.

D, day; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status/Quality of Life; CSR, clinical study report; SOC, standard of care.

**Figure 4-10. Mean change from baseline in EORTC QLQ-C30 symptom scales and single items by scheduled visit in Cycle 1 (TOWER, EORTC analysis set)**

Reference: Amgen data on file, 2016[85]

The EORTC analysis set included patients who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item.

D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SOC, standard of care.

## 4.8 Subgroup analysis

- Results from a pre-specified stratification factor subgroup analysis of OS suggest that patients who have not received prior salvage therapy are likely to benefit more from treatment with blinatumomab than patients who have received prior salvage therapy (HR [redacted]). Median OS in patients who had not received prior salvage therapy was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months). For patients who had received prior salvage therapy, median OS was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months).
- UK clinical experts consulted by Amgen consider this to be highly clinically plausible given that treating patients earlier in the treatment pathway (i.e., patients with a better prognosis) with a more effective therapy is likely to lead to improvements in both absolute and relative OS. This subgroup analysis is pertinent to the decision problem as clinicians are likely to use blinatumomab early in the treatment pathway (i.e., in patients who have not received prior salvage therapy) given the above.
- The OS treatment effect also favoured blinatumomab in the subgroup of patients who were intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm. The HR in the FLAG ± anthracycline based regimen ([redacted]) was lower than in any of the other SOC chemotherapy regimen subgroups and than in the primary OS analysis in the TOWER FAS. Although FLAG-IDA is considered the relevant comparator for this appraisal, treatment-effect estimates from the whole SOC chemotherapy arm have been used to inform the base-case cost-effectiveness analysis. This represents a potentially more conservative approach than using treatment-effect estimates from the FLAG ± anthracycline subgroup, and is supported by UK clinical experts consulted by Amgen who confirmed that the relative efficacy of blinatumomab versus SOC chemotherapy is unlikely to vary by SOC chemotherapy regimen
- An OS benefit was consistently observed for blinatumomab over SOC chemotherapy in most other subgroups with a reasonable sample size, including subgroups for age, prior allo-SCT, and proportion of bone marrow blasts.
- Similarly, improvements in the proportions of patients achieving a CR and CR/CRh*/CRi within 12 weeks of treatment initiation and EFS benefits were consistently observed in most subgroups with a reasonable sample size.

### 4.8.1 Overview of pre-specified subgroups and methodology

Pre-specified subgroup analyses were defined by a range of baseline variables and were conducted for the primary outcome OS, and key secondary outcomes measured in TOWER (CR within 12 weeks of treatment initiation, CR/CRh*/CRi within 12 weeks of treatment initiation, EFS) (Table 4-20). The analysis principles for the subgroup analyses were consistent with those conducted for the primary analysis of each endpoint. For subgroup analyses of CR and CR/CRh*/CRi within 12 weeks of treatment initiation, a continuity correction of 0.67 and 0.33 was added to blinatumomab arm and the SOC chemotherapy arm, respectively, to enable estimation of an odds ratio when subgroups with zero events within a treatment group occurred.[80] This reflects the 2:1 randomisation of patients to blinatumomab and SOC chemotherapy.

In addition, interaction tests were performed to explore the consistency of treatment effects in the subgroups using an unstratified Cox model, with a p-value < 0.10 pre-specified to be suggestive of a potential interaction.[80] Patients with a missing covariate value were not included in the model.

**Table 4-20. Overview of pre-specified subgroups in TOWER**

| | Subgroup and definition |
|---|---|
| Stratification factors | • Age (< 35 years vs. ≥ 35 years)<br>• Prior salvage therapy (yes vs. no)<br>• Prior allo-SCT (yes vs. no)<br>• Stratum formed by combination of stratification factors (< 35 years/prior salvage/prior allo-SCT vs. ≥ 35 years/prior salvage/prior allo-SCT vs. < 35 years/no prior salvage/prior allo-SCT vs. ≥ 35 years/no prior salvage/prior allo-SCT vs. < 35 years/prior salvage/no prior allo-SCT vs. ≥ 35 years/prior salvage/no prior allo-SCT vs. < 35 years/no prior salvage/no prior allo-SCT vs. ≥ 35 years/no prior salvage/no prior allo-SCT) |
| Baseline demographics | • Alternate age grouping (< 35 years vs. 35 to 54 vs. 55 to 64 vs. ≥ 65 years)<br>• Sex (male vs. female)<br>• Race/ethnicity (white vs. Asian vs. other)<br>• Geographic region (United States vs. Europe vs. rest of world) |
| Baseline organ function and comorbid conditions | • Central laboratory baseline bone marrow blasts (< 50% vs. ≥ 50% vs. unknown)[a]<br>• Central laboratory baseline platelet count (< 50,000 vs. 50,000 to 100,000 vs. > 100,000/µL) |
| Baseline disease characteristics[b] | • CD20 status (positive vs. negative)<br>• CD22 status (positive vs. negative) |
| ALL treatment history | • Number of prior salvage therapies (0 vs. 1 vs. ≥ 2) (repeated for patients without a prior allo-SCT)<br>• R/R status (primary refractory vs. 1 prior relapse vs. ≥ 2 prior relapses vs. unknown) (repeated for patients without a prior allo-SCT)[a] |
| Intended SOC chemotherapy regimen | • Intended SOC chemotherapy regimen collected for all patients before randomisation (FLAG ± anthracycline based regimen vs. clofarabine or clofarabine-based regimen vs. HiDAC based regimen vs. high-dose methotrexate based regimen) |

References: TOWER primary analysis CSR[80]

[a]Minor changes were made to the subgroup definition reported in the TOWER SAP prior to unblinding. The R/R status subgroup definition was changed from primary refractory or 1 prior relapse vs. ≥ 2 prior relapses to primary refractory vs. 1 prior relapse vs. ≥ 2 prior relapses vs. unknown. The central laboratory baseline bone marrow blast subgroup definition was changed from < 50% vs. ≥ 50% to < 50% vs. ≥ 50% vs. unknown.

[b] Due to the sparsity of sites that collected CD20 and CD22 status, these subgroups were not analysed

allo-SCT, allogenic stem cell transplant; CSR, clinical study report; R/R, relapsed/refractory; SAP, statistical analysis plan; SOC, standard of care.

### 4.8.2 Results of the pre-specified subgroup analyses

An OS benefit was consistently observed for blinatumomab over SOC chemotherapy in most subgroups with a reasonable sample size, including subgroups for age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no), prior allo-SCT (yes vs. no), and proportion of bone marrow blasts.[80] A summary of OS results in key subgroups of interest is provided in Figure 4-11, and detailed results for all subgroups are provided in Appendix IV.

Of particular relevance to the decision problem:

- Results from the analysis of the prior salvage therapy (yes vs. no) stratification factor subgroup showed an improved OS treatment effect for blinatumomab versus SOC chemotherapy in patients who had not received prior salvage ([redacted]) than for patients who had received prior salvage therapy ([redacted]).[80] Median OS in patients who had not received prior salvage therapy was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months).[85] For patients who had received prior salvage therapy, median OS was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months). Although the p-value for interaction testing ([redacted]) in this subgroup analysis of OS was larger than the value pre-specified to be suggestive of an interaction ([redacted]), it should be noted that TOWER was not primarily designed to detect significant treatment effects within baseline covariate subgroups, and consequently lacked power to detect significant treatment-covariate interaction.[80] Further, as this subgroup analysis was based on a stratification factor subgroup, the principles of randomisation are retained and baseline characteristics remained similar across study arms in the subgroup (Appendix IV). UK clinical experts consulted by Amgen considered it to be highly clinically plausible that treating patients earlier in the treatment pathway (i.e., patients with a better prognosis) with a more effective therapy such as blinatumomab is likely to lead to improvements in both absolute OS and relative OS versus SOC chemotherapy. This subgroup analysis is pertinent to the decision problem as clinicians are likely to use blinatumomab early in the treatment pathway (i.e., in patients who have not received prior salvage therapy) given the above.
- The OS treatment effect favoured blinatumomab in patients who were intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm.[80] The HR in the FLAG ± anthracycline based regimen ([redacted]) was lower than in any of the other SOC chemotherapy regimen subgroups and than in the primary OS analysis in the ITT population. Although FLAG-IDA is considered the relevant comparator for this appraisal, treatment-effect estimates from the whole SOC chemotherapy arm have been used to inform the base-case cost-effectiveness analysis (Section 5.3). This represents a potentially more conservative approach than using treatment effect estimates from the FLAG ± anthracycline subgroup, and is supported by UK clinical experts consulted by Amgen who confirmed that the relative efficacy of blinatumomab versus SOC chemotherapy is unlikely to vary by SOC chemotherapy regimen.

**Figure 4-11. Key subgroup analyses of overall survival (TOWER, FAS)**

Reference: TOWER primary analysis CSR[80]

allo-SCT, allogeneic stem cell transplant; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; NE, not estimable; SOC, standard of care.

Similarly to the subgroup analyses of OS, improvements in the proportions of patients achieving a CR and CR/CRh*/CRi within 12 weeks of treatment initiation and EFS benefits were consistently observed in most subgroups with a reasonable sample size. Detailed CR, CR/CRh*/CRi, and EFS results for all pre-specified subgroups are provided in Appendix IV.

## *4.9 Meta-analysis*

No meta-analyses were carried out as only one RCT (TOWER) was identified.

## *4.10 Indirect and mixed treatment comparisons*

No indirect comparisons were explored as the relevant RCT (TOWER) and additional non-RCT evidence adequately address the decision problem.

## *4.11 Non-randomised and non-controlled evidence*

- Important additional evidence on the clinical effectiveness of blinatumomab comes from a registrational, phase 2, single-arm study (Study MT103-211) of 189 patients with R/R Ph- B-precursor ALL, including a comparison with a historical cohort receiving SOC chemotherapy.
- The proportions of patients achieving a CR/CRh* and CR within the first two cycles of treatment in Study MT103-211 was 42.9% and 33.3%, respectively. This is highly consistent with the proportions of patients achieving a CR/CRh*/CRi (43.9%) and CR (33.6%) in the blinatumomab arm of the phase 3 TOWER RCT.
- Based on the most recent data cut-off date (15 July 2015), median OS was 6.5 months and median RFS in patients achieving CR/CRh* was 6.8 months. This median OS is similar to the 7.7 months seen in the blinatumomab arm of TOWER.
- Also consistent with TOWER, pre-specified subgroup analyses of Study MT103-211 by numbers of prior salvage therapies showed that median OS was higher in patients who had received no prior salvage therapy than in patients who had received prior salvage therapy.
- A comparison of blinatumomab data from Study MT103-211 with historical SOC chemotherapy control data, using appropriate analytical methods to address imbalances in prognostic factors (weighted analysis and propensity score analysis), showed more favourable haematological remission rates and OS outcomes with blinatumomab.
- The proportion of patients achieving a CR/CRh* and median OS for blinatumomab in Study MT103-211 were approximately double the CRsg rate (complete remission with or without full haematological recovery depending on study group) and median OS seen in the historical cohort, which is consistent with the relative treatment effects seen for blinatumomab versus SOC chemotherapy in TOWER.
- In Study MT103-211, 25% of patients irrespective of response, went on to undergo allo-SCT. The proportion of patients receiving allo-SCT after salvage therapy, irrespective of response, was 18% in the weighted historical cohort.

### 4.11.1 List of relevant non-randomised and non-controlled evidence

Due to the very low incidence and extreme severity of R/R ALL, and the lack of a widely established SOC, conducting large randomised clinical studies in this patient population is complex and RCT data are limited. The broad clinical efficacy/safety SLR (Section 4.1) identified 179 non-RCT studies that met the criteria for inclusion. Following application of additional exclusion criteria to identify those studies most relevant to the decision problem (studies with blinatumomab as the intervention and that enrolled > 50 patients), one relevant non-RCT study reported in three articles was identified (Study MT103-211). Table 4-21 provides an overview of this study.

Study MT103-211 is considered particularly relevant for inclusion in this submission as it was the key study underpinning the conditional EMA marketing authorisation, and provides information on outcomes of interest per the final scope of this appraisal that were not assessed in the phase 3 TOWER RCT (RFS and time to response). MT103-211 was a phase 2, multicentre, open-label, single-arm trial that evaluated the efficacy and safety of blinatumomab in adult patients with R/R Ph- B-precursor ALL.[4] As one of the largest prospective studies conducted in patients with R/R Ph- B-precursor ALL to date, it included 189 patients who were primary refractory after induction or who had relapsed within 12 months of first remission, relapsed within 12 months of receiving allo-SCT, or not responded to or relapsed after first salvage therapy or beyond. Information on Study MT103-211 is presented in Sections 4.11.2 to 4.11.6.1. A comparison of MT103-211 results with historical control data was also identified as a relevant non-RCT publication by the SLR,[91] and data from this analysis are presented in Section 4.11.6.2.

**Table 4-21. List of relevant non- randomised and non-controlled evidence**

| Study number (acronym) | Objective | Population | Intervention | Comparator | Primary study reference | Justification for inclusion/exclusion |
|---|---|---|---|---|---|---|
| NCT01466179 Study MT103-211[4,43,91] | To determine the efficacy of blinatumomab in R/R Ph- B-precursor ALL[4,43] | Aged ≥ 18 years, Ph-, B-precursor ALL, who were primary refractory after induction or relapsed within 12 months of 1st remission or allo-SCT, or who had not responded to or had relapsed after 1st salvage or beyond; ≥ 10% bone marrow blasts and ECOG ≤ 2 (N = 189) | Blinatumomab | N/A | Topp *et al.,* 2015[4] | • Key study supporting conditional marketing authorisation<br>• Provides information on time to response[a]<br>• Clinical effectiveness data from this study are used in the cost-effectiveness analysis to complement data from the phase 3 TOWER RCT |
| | To compare outcomes for blinatumomab vs. historical controls receiving SOC chemotherapy (Study 20120310) [91] | As above for blinatumomab.<br>Similar population for historical control cohort. | Blinatumomab | SOC chemo-therapy (historical cohort) | Gokbuget *et al.,* 2016[91] | • Enables a comparison of outcomes from MT103-211 with historical control data<br>• Clinical effectiveness data from this analysis are used in the cost-effectiveness analysis to complement data from the phase 3 TOWER RCT |

[a] Time to response is an outcome of interest included in this final scope for this appraisal but was not pre-specified endpoint in the TOWER RCT

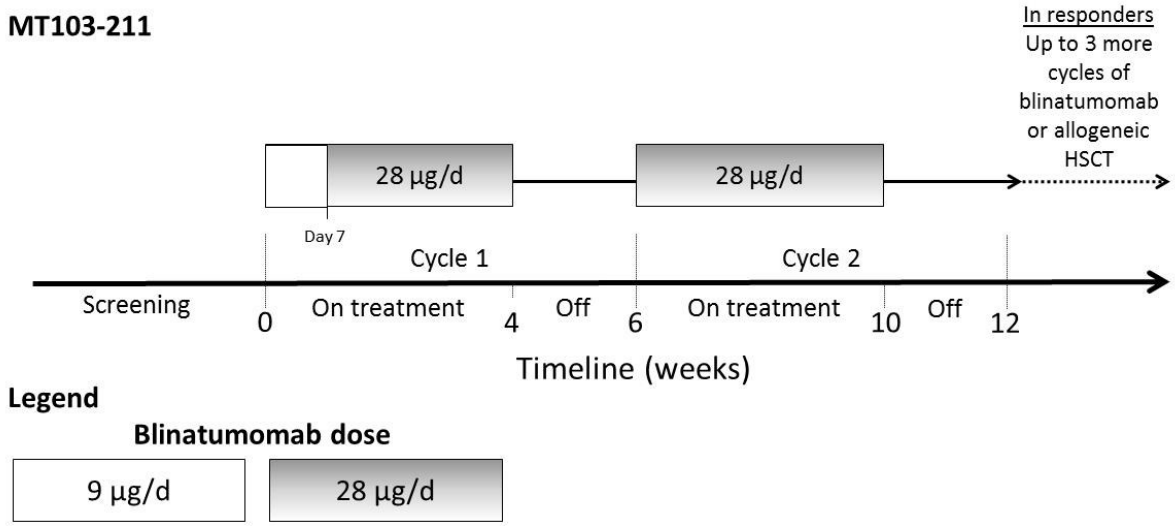
allo-SCT, allogeneic stem cell transplant; ALL, acute lymphoblastic leukaemia; ECOG, Eastern Cooperative Oncology Group; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory; RCT, randomised clinical trial; SOC, standard of care.

### 4.11.2 Summary of Study MT103-211 methodology

Study MT103-211 was a phase 2, single-arm, multicentre, open-label study that assessed the efficacy and safety of blinatumomab in patients with R/R Ph- B-precursor ALL.[4,92] The study was conducted at 23 centres in Europe and 14 centres in the United States. Eligible patients included adults with Ph- B-precursor ALL (primary refractory after induction or relapsed within 12 months of first remission, relapsed within 12 months of allo-SCT, or no response to or relapse after first salvage or beyond) and had $\geq$ 10% blasts in bone marrow and ECOG PS $\leq$ 2. As patients in untreated first relapse with a first remission duration ≥ 12 months (i.e., patients with a better prognosis)[29] were not eligible, the population enrolled in Study MT103-211 therefore represents a particularly difficult-to-treat R/R Ph- B-precursor ALL population. Important exclusion criteria were the presence of active disease in the CNS or testis, or a history or presence of clinically relevant CNS pathology. Full study eligibility criteria are reported in the Study MT103-211 CSR.[92]

The design of Study MT103-211 is summarised in Figure 4-12. Blinatumomab was administered as a continuous IV infusion over 4 weeks, followed by a 2-week treatment-free period, for up to five consecutive cycles. In Cycle 1, the dose was 9 µg/day for the first 7 days followed by 28 µg/day for the remaining 3 weeks of the treatment period. In subsequent cycles, the dose of blinatumomab was 28 µg/day for all 4 weeks of the treatment period. Patients who achieved CR or CRh* during the first two cycles could receive up to three additional cycles of blinatumomab or proceed to allo-SCT. Patients who relapsed during the follow-up period could receive up to an additional three cycles of treatment; therefore, the maximum possible exposure was eight cycles.

**Figure 4-12. Summary of MT103-211 study design**




d, day; HSCT, haematopoietic stem cell transplantation.

The core study duration consisted of a screening period of up to 3 weeks followed by a treatment period of up to 30 weeks, followed by an end of core study visit 30 days after the end of the last cycle. Following the core study, patients were followed periodically for efficacy for 24 months from treatment start. After 24 months (or after allo-SCT), haematological relapse

and survival information was gathered by phone/mail every 6 months until death or at least 3 years after treatment start.

MT103-211 followed a Simon two-stage design[93] followed by a third stage (extension) and an additional evaluation cohort to evaluate CNS symptoms.

The pre-specified primary endpoint was the proportion of patients achieving CR/CRh* within the first two cycles (i.e., 12 weeks) of blinatumomab treatment. Similarly to the TOWER RCT (Section 4.3.3), CR was defined as having ≤ 5% bone marrow blasts, no evidence of disease, and full haematological recovery (platelets > 100,000/μL and ANC > 1,000/μL). CRh* was defined as having ≤ 5% bone marrow blasts, no evidence of disease, and partial haematological recovery (platelets > 50,000/μL and ANC > 500/μL). Pre-specified secondary endpoints included:

- The proportions of patients achieving CR, CRh*, partial remission (PR; 6% to 25% bone marrow blasts with ≥ 50% reduction from baseline), and aplastic bone marrow response (6% to 25% bone marrow blasts, no evidence of disease, and partial haematological recovery [platelets > 50,000/μL and ANC > 500/μL]) within two cycles of treatment
- OS (time to death due to any cause)
- RFS (time to relapse or death due to any cause in patients who achieved a CR/CRh* during the core study)
- EFS (time to relapse or death due to any cause, with patients who didn't achieve a CR/CRh* during the core study assigned an EFS duration of 1 day)
- Time-to-haematological relapse (TTHR) (time to relapse or death due to disease progression in patients who achieved a CR/CRh* during the core study)
- The proportion of patients eligible for allo-SCT who underwent the procedure after treatment with blinatumomab.
- Severity and incidence of AEs
- 100-day mortality after allo-SCT

Pre-specified exploratory endpoints included the proportion of patients achieving MRD remission within two cycles of treatment and time to haematological remission (CR and CR/CRh*).

Further detail on study methodology is provided in the primary study publication and the MT103-211 clinical study report.[4,92]

### 4.11.3 Statistical analysis in Study MT103-211

The Primary Analysis Set (PAS) included all patients enrolled in the first three study stages who received any infusion of blinatumomab (N = 189). This was the main analysis set for efficacy and results presented in this submission focus on this population.

The primary analysis (10 October 2013 data cut-off date) was conducted when all patients in the PAS had completed the relevant assessments for the primary endpoint. A secondary analysis was conducted once all patients (including the additional evaluation cohort) completed treatment plus their 30-day safety follow-up visit (20 June 2014 data cut-off date). An additional ad-hoc analysis proving information for a safety update and for survival

extrapolation was performed with a data cut-off date of 15 July 2015. The final analysis will be performed after the last patient completes the last follow-up visit.

Response endpoints were reported as response rates with exact two-sided 95% CIs. Patients with non-evaluable or missing response assessments were counted as non-responders. Time-to-event endpoints were analysed using Kaplan–Meier methodology. For RFS, patients without documented relapse or who did not die were censored at the time of their last bone marrow assessment or last follow-up visit confirming remission.

The potential bias associated with the lack of a comparator arm in this study has been addressed by a comparison of MT103-211 results with historical control data using statistical techniques to adjust the historical control data to the MT103-211 study population. This analysis is reported in Section 4.11.6.2.

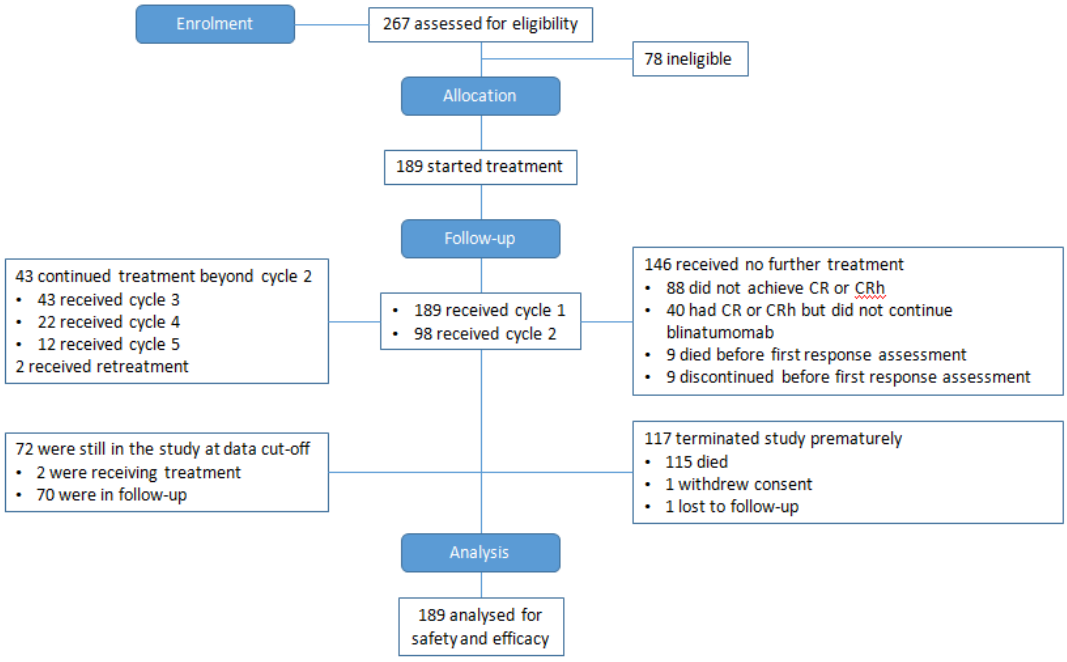
### 4.11.4 Participant flow in Study MT103-211

#### *4.11.4.1 Patient disposition*

A CONSORT participant flow diagram as of the data cut-off date for the primary analysis (10 October 2013) is provided in Figure 4-13.

A total of 189 patients were enrolled and received at least one infusion of blinatumomab in the first three stages of the study and were included in the PAS. At the time of the data cut-off for the primary analysis 61.9% (117/189) of patients had discontinued the study, and no patients had completed the follow-up period.

**Figure 4-13. Study MT103-211 CONSORT flow diagram (PAS)**




Reference: Topp *et al.,* 2015[4]

Note: Primary analysis (10 October 2013 data cut-off date)

CONSORT, Consolidated Standards of Reporting Trials; PAS, primary analysis set

At the time of the data cut-off for the secondary analysis (20 June 2014) and additional ad-hoc analysis (15 July 2015), 77.7% (147/189) and 88.4% (167/189) of patients in the PAS had ended the study, respectively.[94]

*4.11.4.2 Baseline demographic, disease-related, and prior treatment characteristics*

Baseline characteristics of participants in the PAS are described in Table 4-22. The median age of patients was 39 years. Around one-fifth of patients (20.1%) had received no prior salvage therapy, and around one-third (33.9%) had received a prior allo-SCT.

**Table 4-22. Summary of demographic, disease-related, and prior treatment characteristics (Study MT103-211, PAS)**

| Baseline characteristic | N = 189 |
|---|---|
| Sex n (%) | |
| Men | 119 (63.0) |
| Women | 70 (37.0) |
| Age | |
| Median (range), years | 39 (18-79) |
| < 35 years, n (%) | 90 (47.6) |
| 35 to 54 years, n (%) | 46 (24.3) |
| 55 to 64 years, n (%) | 28 (14.8) |
| ≥ 65 years, n (%) | 25 (13.2) |
| Bone marrow blast count, n (%) | |
| < 50% | 59 (31.2) |
| ≥ 50% | 130 (68.8) |
| Number of prior salvage regimens, n (%) | |
| 0 | 38 (20.1) |
| 1 | 77 (40.7) |
| 2 | 42 (22.2) |
| ≥ 3 | 32 (16.9) |
| Prior allo-SCT, n (%) | 64 (33.9) |
| Key ALL entry criteria, n (%) | |
| Primary refractory | 16 (8.5) |
| Relapse within 12 months of allo-SCT | 39 (20.6) |
| Entering first salvage with first remission duration ≤ 12 months | 23 (12.2) |
| Entering second or greater salvage therapies | 108 (57.1) |
| No disease stage entry criteria met | 3 (1.6) |

References: Topp *et al.,* 2015,[4] and Study MT103-211 primary analysis CSR[92]

Note: Primary analysis (10 October 2013 data cut-off date)

allo-SCT, allogeneic stem cell transplant; ALL, acute lymphoblastic leukaemia; CSR, clinical study report; PAS, primary analysis set.

### 4.11.5 Quality assessment of the non-RCT evidence

The quality of Study MT103-211 and the comparison with the historical control cohort was independently assessed by two reviewers using the STROBE quality assessment checklist.[95] The checklist pertains to the estimation of treatment effectiveness from non-randomised studies and assesses steps taken to minimise confounding, heterogeneity in treatment effect, statistical rationale and the assessment of uncertainty (NICE Decision Support Unit (DSU) Technical Support Document 17[96]). Discrepancies were resolved through discussion or the intervention of a third reviewer.

The detailed quality assessment is provided in Appendix V. Overall, Study MT103-211 and the comparison with the historical control cohort were considered to have a low risk of bias. In general, the studies demonstrated clear reporting of eligibility criteria, interventions, and results with no discrepancies. In addition, there was low risk of sampling and reporting bias, appropriate statistical analyses were used, and the outcomes were considered to be valid and reliable.

### 4.11.6 Clinical-effectiveness results of the relevant non-randomised and non-controlled evidence

*4.11.6.1 Study MT103-211*

Proportion of patients achieving a CR/CRh* within two cycles of treatment (pre-specified primary endpoint) and other pre-specified best haematological response secondary endpoints

In the primary analysis, the proportion of patients achieving a best haematological response of CR/CRh* within the first two cycles of treatment was 42.9% (Table 4-23). Of the patients with a CR/CRh* response, most experienced CR (CR 33.3%, CRh* 9.5%). Three of the 18 patients who achieved a CRh* as best haematological response within two cycles of treatment achieved a CR in later cycles.[4]

These results are consistent with those seen in the blinatumomab arm of the TOWER RCT (Section 4.7.3) where a CR rate of 33.5% and a CR/CRh*/CRi rate of 43.9% was observed within 12 weeks (i.e., two cycles) of treatment initiation. The latter includes patients with CRi and therefore would be expected to be higher than the CR/CRh* rate seen in Study MT103-211.

**Table 4-23. Best haematological response within the first two cycles of treatment (Study MT103-211, PAS)**

| Best Response | n (%) | (95% CI) |
|---|---|---|
| CR/CRh* (primary endpoint) | 81 (42.9) | (35.7%, 50.2%) |
| CR | 63 (33.3) | (26.7%, 40.5%) |
| CRh* | 18 (9.5) | (5.7%, 14.6%) |
| Blast-free hypoplastic or aplastic bone marrow | 17 (9.0) | (5.3%, 14.0%) |
| Partial remission | 5 (2.6) | (0.9%, 6.1%) |
| Reference: Topp *et al.,* 2015[4]<br><br>Note: Primary analysis (10 Oct 2013 data cut-off date) | | |

| Best Response | n (%) | (95% CI) |
|---|---|---|
| CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; PAS, primary analysis set. | | |

Overall survival, relapse-free survival, and event-free survival (pre-specified secondary endpoints)

OS and RFS data are presented in Table 4-24 for the primary analysis, secondary analysis and additional ad-hoc analysis. Kaplan–Meier plots for these outcomes based on the most recent analysis (i.e., the additional ad-hoc analysis) are provided in Figure 4-14 and Figure 4-15, respectively. Kaplan–Meier plots based on the primary and secondary analyses are provided in Appendix V.

Median OS was 6.5 months (95% CI 4.4, 7.7) in the additional ad-hoc analysis based on a median follow-up of 27.8 months. This is similar to the median OS of 7.7 months seen in the blinatumomab arm of the TOWER RCT (Section 4.7.2).

Among patients who achieved a CR/CRh* during the core study, median RFS in the additional ad-hoc analysis was 6.8 months (95% CI 5.0, 10.0) based on a median follow-up of 26.9 months. This is similar to the median time to haematological response of 7.3 months seen in those achieving a CR/CRh*/CRi in the blinatumomab arm of the TOWER RCT (Section 4.7.3); both endpoints were defined as time to first relapse or death from any cause.

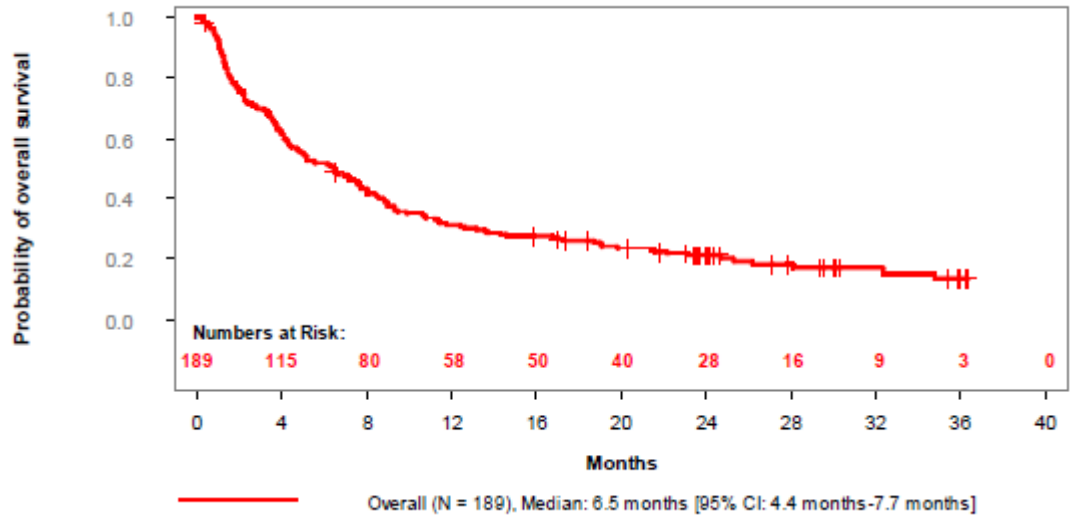
**Table 4-24. Overall survival and relapse-free survival (Study MT103-211, PAS)**

| Endpoint | N | Events n (%) | Censored n (%) | Median (95% CI) (months) | Median follow up (months) |
|---|---|---|---|---|---|
| OS | | | | | |
| Primary analysis[a] | 189 | 116 (61.4) | 73 (38.6) | 6.1 (4.2, 7.5) | 9.8 |
| Secondary analysis[b] | 189 | 142 (75.1) | 47 (24.9) | 6.4 (4.3, 7.7) | 17.7 |
| Additional ad-hoc analysis[c] | 189 | 153 (81.0) | 36 (19.0) | 6.5 (4.4, 7.7) | 27.8 |
| RFS[d] | | | | | |
| Primary analysis[a] | 82 | 45 (54.9) | 37 (45.1) | 5.9 (4.8, 8.3) | 8.9 |
| Secondary analysis[b] | 84 | 58 (69.0) | 26 (31.0) | 6.8 (5.0, 10.0) | 15.6 |
| Additional ad-hoc analysis[c] | 84 | 65 (77.4) | 19 (22.6) | 6.8 (5.0 10.0) | 26.9 |

[a] 10 October 2013 data cut-off date, reference: Topp *et al.,* 2015[4] and Study MT103-211 primary analysis CSR[92]
[b] 20 June 2014 data cut-off date, reference: MT103-211 secondary analysis CSR[94]
[c] 15 July 2015 data cut-off date, reference: Amgen data on file, 2015[97]
[d] RFS was assessed in patients who achieved a CR/CRh* during the core study.

CI, confidence interval; CSR, clinical study report; OS, overall survival; PAS, primary analysis set; RFS, relapse-free survival

**Figure 4-14. Kaplan–Meier plot of overall survival (Study MT103-211, PAS)**

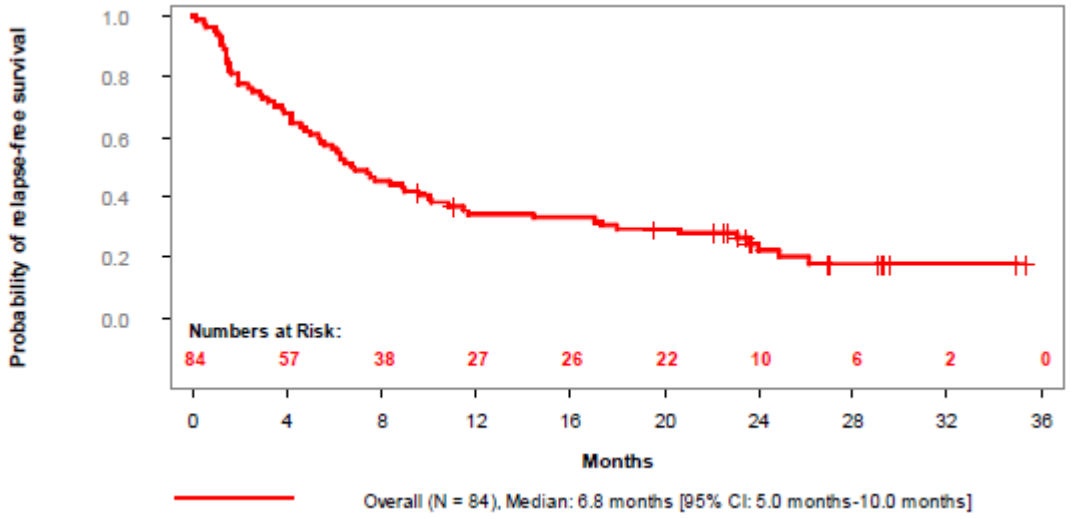



Reference: Amgen data on file, 2015[97]

Note: Additional ad-hoc analysis (15 Jul 2015 data cut-off date)

CI, confidence interval; OS, overall survival; PAS, primary analysis set

**Figure 4-15. Kaplan–Meier plot of relapse-free survival (Study MT103-211, PAS)**




Reference: Amgen data on file, 2015[97]

Note: Additional ad-hoc analysis (15 Jul 2015 data cut-off date). RFS was only assessed in patients who achieved a CR/CRh* during the core study.

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; PAS, primary analysis set; RFS, relapse–free survival.

More than 50% of patients had not achieved CR/CRh* during the core study and were assigned an EFS duration of 1 day. Median EFS was therefore 1 day, rounded to 0 months.[97] Full details of the most recent EFS analysis are available in the Study MT103-211 secondary analysis CSR.[97]

Results from analyses of other relevant pre-specified secondary and exploratory endpoints

Analyses of other pre-specified relevant secondary and exploratory outcomes in the primary analysis of Study MT103-211 (10 October 2013) showed that:

- The median time to CR/CRh* was 2.3 months (95% CI 1.7, 2.3) and median time to CR was 2.5 months (95% CI 2.3, 4.1).[92]
- The median time to haematological relapse was 6.7 months (95% CI 5.1, NE) for patients achieving CR/CRh* within the core study.[92]
- Of the 81 patients achieving CR/CRh* within the first two cycles of treatment, 32 (39.5%) went on to undergo allo-SCT.[4] The overall 100-day mortality post allo-SCT was 11.3% (95% CI 0.0, 23.4). [92] The rate of allo-SCT irrespective of haematological remission status was 25.4%.[92]
- Of the 73 MRD-evaluable patients achieving CR/CRh* within the first two cycles, 82% (n = 60) were MRD negative. [4] This is similar to the rate seen in the blinatumomab arm of TOWER for those who achieved CR/CRh*/CRi within 12 weeks, i.e., two cycles (76.3%). Median RFS for MRD responders was 6.9 months versus 2.3 months for non-responders, while median OS was 11.5 months versus 6.7 months, respectively.[4]

Results of pre-specified subgroup analyses

A summary of results from the pre-specified subgroup analyses of OS is presented for key subgroups of interest in Table 4-25, with a detailed overview of results for other pre-specified subgroups provided in the Study MT103-211 CSR.[94] Results are based on the most recent data cut-off date for which subgroup analyses were conducted (secondary analysis; 20 Jun 2014). There was a trend towards more favourable median OS for patients with fewer previous salvage therapies (0 prior therapies: 7.9 months; 1 prior therapy: 7.6 months; 2 prior therapies: 3.7 months; > 2 therapies: 4.7 months). This is consistent with the subgroup analyses of OS in TOWER (Section 4.8). Patients with < 50% blasts at baseline had longer median OS compared with those with ≥ 50% blasts (9.3 months vs 4.2 months).[94]

**Table 4-25. Pre-specified subgroup analyses of overall survival in key subgroups of interest (Study MT103-211, PAS)**

| | N | Events n (%) | Censored n (%) | Median (95% CI) (months) |
|---|---|---|---|---|
| Age | | | | |
| 18 to < 35 years | 90 | 62 (69) | 28 (31) | 7.6 (5.1, 20.7) |
| 35 to < 55 years | 46 | 35 (76) | 11 (24) | 5.1 (2.2, 8.5) |
| 55 to < 65 years | 28 | 24 (86) | 4 (14) | 4.4 (1.8, 9.3) |
| ≥ 65 years | 25 | 21 (84) | 4 (16) | 4.7 (3.5, 9.0) |
| Number of prior salvage therapies | | | | |
| 0 | 38 | 30 (79) | 8 (21) | 7.9 (5.0, 12.4) |
| 1 | 78 | 55 (71) | 23 (29) | 7.6 (4.3, 10.6) |
| 2 | 41 | 31 (76) | 10 (24) | 3.7 (2.1, 6.5) |
| > 2 | 32 | 26 (81) | 6 (19) | 4.7 (1.6, 8.6) |

| | N | Events n (%) | Censored n (%) | Median (95% CI) (months) |
|---|---|---|---|---|
| Prior allo-SCT | | | | |
| No | 125 | 95 (76) | 30 (24%) | 5.1 (3.9, 7.1) |
| Yes | 64 | 47 (73) | 17 (27%) | 8.5 (4.2, 11.2) |
| Central laboratory baseline bone marrow blasts | | | | |
| < 50% | 59 | 40 (68) | 19 (32%) | 9.3 (7.1, 14.3) |
| ≥ 50% | 130 | 102 (78) | 28 (22%) | 4.2 (3.1, 6.4) |

Reference: MT103-211 secondary analysis CSR[94]

Note: Secondary analysis (20 Jun 2014 data cut-off date). Subgroup analyses were not conducted for the more recent ad-hoc analysis of OS.

CI, confidence interval; CSR, clinical study report; NE, not estimable; OS, overall survival; PAS, primary analysis set;

The proportion of patients achieving CR/CRh* within the first two cycles of treatment and RFS outcomes are presented for key subgroups of interest in Appendix V, with a detailed overview of results for other pre-specified subgroups provided in the Study MT103-211 CSRs.[92,94]

*4.11.6.2 Comparison of MT103-211 results with historical control data*

The single-arm design of MT103-211 precludes direct comparison with comparator treatment regimens for R/R Ph- B-precursor ALL. Examination of the published literature revealed limitations that prevented the construction of a comparable literature-based population to that enrolled in MT103-211. Therefore, an observational historical comparator study (Study 20120310) was conducted to assess outcomes with SOC salvage chemotherapy regimens in a comparable patient population to MT103-211.[91] The historical comparator data was collected from experienced research groups in the EU (Germany, France, Spain, Italy, Poland, UK, Czech Republic) and the US. Clinical data from 1139 patients who had received SOC chemotherapy regimens, who were diagnosed with R/R Ph- B-precursor ALL after 1 January 1990 and had similar patient characteristics to those enrolled in Study MT103-211 were included in the analysis.

Table 4-26 summarises the design of the historical comparator study (Study 20120310).
The primary objective was to estimate the rate of complete remission per study groups (CRsg), defined as the percentage of patients who achieve < 5% bone marrow blasts with full or partial haematological recovery. Estimation of OS was a key secondary objective.

**Table 4-26. Overview of design for historical comparator study (Study 20120310)**

| | |
|---|---|
| **Study description** | Retrospective pooled analysis of historical data available from 1990 to 2013 for 1139 adult patients |
| **Patient population eligibility** | Adult patients with R/R Ph-* B-precursor ALL, who had received SOC chemotherapy frontline treatment and some type of standard-of-care post-relapse therapy, and who met one of the following criteria:<br>• In first relapse or salvage treatment after a first remission duration of ≤ 12 months<br>• Refractory to initial treatment,<br>• R/R after first or later salvage, or<br>• R/R disease within 12 months of allo-SCT |
| **Important exclusion criteria** | • CNS involvement at relapse<br>• Isolated extramedullary relapse<br>• Previous treatment with blinatumomab |
| **Primary endpoint** | Rate of CRsg following relapse or salvage treatment, defined as:<br>• < 5% blasts in bone marrow<br>• Full or partial/incomplete haematologic recovery |
| **Key secondary endpoints** | • OS<br>• RFS<br>• Proportion of patients receiving allo-SCT following salvage therapy |
| Reference: Gokbuget *et al.,* 2016[91] | |

allo-SCT, allogeneic stem cell transplant; ALL, acute lymphoblastic leukaemia; CRsg, complete remission per study groups/sites; CNS, central nervous system; OS, overall survival; Ph-, Philadelphia chromosome–negative; RFS, relapse-free survival; R/R, relapsed or refractory.

Although the inclusion criteria for the historical comparator study were similar to Study MT103-211, the percentage of patients with specific baseline characteristics differed across the studies. The percentage of first salvage patients in the historical comparator study was substantially higher than in Study MT103-211 (67% vs. 20%), an indication that the Study MT103-211 population was at higher risk of unfavourable outcomes than the historical cohort.[98] In addition there were fewer patients with a prior allo-SCT and fewer patients who had received multiple salvage treatments in the historical cohort.[91] In order to address these differences in patient characteristics and allow a meaningful comparison of outcomes across studies, two approaches were taken: a weighted analysis and a propensity score analysis.

Weighted analysis methodology

A weighted average of study outcomes from the historical cohort was derived based on the frequency distribution of known prognostic factors for R/R ALL in Study MT103-211. Six strata were defined by a combination of age (< 35 or ≥ 35 years) and prior lines of treatment (allo-SCT, in first salvage, in second or greater salvage).[91]

The proportion of patients who achieved a CR was estimated within each stratum of the historical cohort with an exact 95% CI. The proportions across strata were then pooled into a

combined estimate with each stratum weighted to the percentage of patients observed in that stratum from Study MT103-211. A 95% CI was estimated for the combined estimate via bootstrapping.[91] The same approach was used to assess the proportion of patients receiving allo-SCT after salvage therapy.

For OS, the Kaplan–Meier median and Kaplan–Meier proportions at 6 and 12 months were estimated within each stratum of the historical cohort together with 95% CIs. The same stratum weighted approach described above was used to derive combined estimates.[91].

Propensity score analysis methodology

A propensity score analysis was performed to balance measured patient characteristics in the historical cohort and Study MT103-211.[91] Available covariates included age, sex, duration between initial diagnosis and salvage therapy, region (US, Europe), prior allo-SCT, prior number of salvage therapies, primary refractory and in first salvage (yes, no) and refractory to last salvage therapy (yes, no). An estimated propensity score (the predicted probability of participating in Study MT103-211 if it were being conducted during the period of the historical comparator study) was assigned to each patient based on their set of covariates. Regression modelling and standardised differences were used to assess the balance of covariates. When estimating treatment effects, the propensity scores were used to adjust for patient differences between the historical cohort and Study MT103-211 using inverse probability of treatment weighting (IPTW) methodology. A logistic regression model was used to analyse CRsg and CR/CRh* rates with a treatment indicator covariate and propensity score-based weights. OS was analysed using a Cox proportional hazards model with a treatment indicator covariate and propensity score-based weights.

Results from the weighted analysis

Analysis in the historical cohort was based on 694 patients with CRsg data and 1112 patients with OS data.[91]

CR rates for the historical cohort (by stratum and combined across stratum) and the Study MT103-211 are provided in Table 4-27. The weighted CRsg rate in the historical cohort was 24% (95% CI 20%, 27%) compared with a CR/CRh* rate of 43% (95% CI 35%, 50%) in Study MT103-211. Sensitivity analyses showed a slightly higher CRsg rate in historical control patients treated more recently (26% for the year 2000 onward, 30% for 2005 onward). However, when restricting this analysis to sites providing data throughout the time period, CRsg rates were similar over time (19% for 1990 to 1999, 19% for 2000 onward).[91] Rates of CRsg in the historical cohort decreased with each line of salvage therapy (34%, 25%, 13% and 11% for first, second, third and fourth or higher line of salvage).

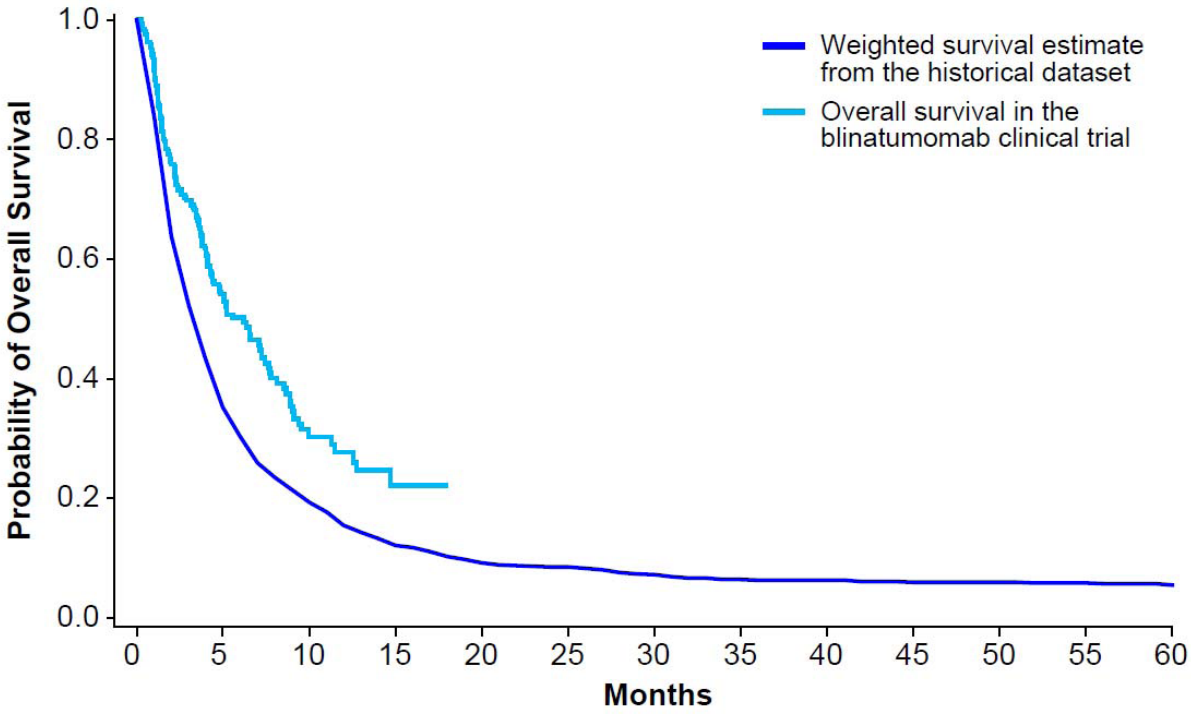
OS data for the historical cohort (by stratum and combined across stratum) and Study MT103-211 are provided in Table 4-28. Survival curves are shown in Figure 4-16. The weighted median OS in the historical cohort was 3.3 months (95% CI 2.8, 3.6) compared with 6.1 months (4.2, 7.5) in Study MT103-211. The weighted 6- and 12-month survival percentages were 30% and 15% in the historical cohort compared with 50% and 28% in Study MT103-211. Sensitivity analyses showed an increase in median OS over time for the historical cohort (3.8 months for 2000 onward, 4.2 months for 2005 onward). When restricting this analysis to sites providing

data throughout the time period, there remained an increase over time (2.4 months for 1990 to 1999, 3.2 months for 2000 onward).[91]

Of the 186 patients achieving a CRsg in the historical cohort, only 108 (58%) had available RFS data.[98] In addition, missing RFS data were not missing at random (the shorter the OS, the more likely RFS data were to be missing). Therefore, it was not considered appropriate to interpret RFS in the historical cohort and these data are not presented.

The weighted proportion of patients receiving allo-SCT after salvage therapy, irrespective of response, was 18% (95% CI, 15%, 21%) in the historical cohort.[98] In study MT103-211, 25% of patients, irrespective of response, went on to undergo allo-SCT.[4]

**Figure 4-16. Weighted analysis: comparison of OS from historical cohort and Study MT103-211**




Reference: Gokbuget *et al.,* 2016[91]

Note: 'blinatumomab clinical trial' refers to Study MT103-211. Data based on primary analysis data cut-off date (10 October 2013) for Study MT103-211.

OS, overall survival.

**Table 4-27. Weighted analysis: comparison of haematological remission rates from historical cohort and Study MT103-211**

| Stratum | | Historical cohort | | | | Blinatumomab (Study MT103-211)[c] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Age, years** | **Prior lines of treatment** | **N** | **Stratum %** | **Number with CRsg** | **CRsg % (95% CI)** | **N** | **Stratum %** | **Number with CR/CRh*** | **CR/CRh* % (95% CI)** |
| < 35 | allo-SCT[a] | 48 | 6.9 | 14 | 29 (17, 44) | 40 | 21.2 | 15 | 38 (21, 54) |
| < 35 | In 1st salvage[b] | 119 | 17.1 | 52 | 44 (35, 53) | 10 | 5.3 | 7 | 70 (35,93) |
| < 35 | In 2nd+ salvage[b] | 150 | 21.6 | 27 | 18 (12, 25) | 40 | 21.2 | 17 | 43 (27, 59) |
| ≥ 35 | allo-SCT[a] | 41 | 5.9 | 11 | 27 (14, 43) | 24 | 12.7 | 14 | 58 (37, 78) |
| ≥ 35 | In 1st salvage[b] | 187 | 26.9 | 57 | 30 (24, 38) | 19 | 10.1 | 5 | 26 (9, 51) |
| ≥ 35 | In 2nd+ salvage[b] | 149 | 21.5 | 25 | 17 (11, 24) | 56 | 29.6 | 23 | 41 (28,55) |
| **Combined weighted estimate** | | **694** | **-** | **186** | **24 (20, 27)** | **189** | **-** | **81** | **43 (36, 50)** |

Reference: Gokbuget *et al.,* 2016[91]

[a] All patients with a history of allo-SCT (could be in 1st, 2nd or greater salvage)
[b] All patients without a history of allo-SCT
[c] Primary analysis data cut-off date (10 Oct 2013)

allo-SCT, allogeneic stem cell transplant, CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRsg, complete remission per study groups/sites.

**Table 4-28. Weighted analysis: comparison of OS from historical cohort and Study MT103-211**

| Stratum | | Historical cohort | | | | | Blinatumomab (Study MT103-211)[c] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age, years** | **Prior lines of treat-ment** | **N** | **Stratum %** | **Median OS, months (95% CI)** | **6 month survival, % (95% CI)** | **12 month survival, % (95% CI)** | **N** | **Stratum %** | **Median OS, months (95% CI)** | **6 month survival, % (95% CI)** | **12 month survival, % (95% CI)** |
| < 35 | allo-SCT[a] | 108 | 9.7 | 3.8 (2.9, 4.5) | 35 (26, 44) | 14 (8,21) | 40 | 21.2 | 7.6 (3.5, 9.4) | 59 (41, 73) | 28 (11, 47) |
| < 35 | In 1st salvage[b] | 258 | 23.2 | 5.7 (4.9, 6.3) | 46 (40, 52) | 25 (20, 30) | 10 | 5.3 | NE (4.1, NE) | 80 (41, 95) | 53 (17, 80) |
| < 35 | In 2nd+ salvage[b] | 161 | 14.5 | 2.9 (2.3,4.0) | 28 (21, 35) | 16 (11, 22) | 40 | 21.2 | 6.3 (3.7, 12.6) | 53 (36, 68) | 38 (22, 550 |
| ≥ 35 | allo-SCT[a] | 79 | 7.1 | 4.0 (2.8, 4.7) | 33 (23, 44) | 20 (12, 29) | 24 | 12.7 | 9.3 (3.3, NE) | 62 (40, 78) | 28 (6, 57) |
| ≥ 35 | In 1st salvage[b] | 341 | 30.7 | 3.7 (3.2, 4.4) | 34 (29, 39) | 15 (11, 19) | 19 | 10.1 | 5.1 (2.8, 7.0) | 30 (11, 53) | 0.0 (NE, NE) |
| ≥ 35 | In 2nd+ salvage[b] | 165 | 14.8 | 2.2 (1.7, 2.9) | 24 (17,30) | 13 (8, 19) | 56 | 29.6 | 3.7 (1.9, 6.5) | 39 (26, 51) | 19 (8, 32) |
| **Combined weighted estimate** | | **1112** | **-** | **3.3 (2.8, 3.6)** | **30 (27, 34)** | **15 (8,19)** | **189** | **-** | **6.1 (4.2, 7.5)** | **50 (43, 57)** | **28 (20, 36)** |

Reference: Gokbuget *et al.,* 2016[91]

[a] all patients with a history of allo-SCT (could be in 1st, 2nd or greater salvage)
[b] all patients without a history of allo-SCT
[c] Primary analysis data cut-off date (10 Oct 2013)

allo-SCT, allogeneic stem cell transplant; CI, confidence interval; NE,not estimable; OS, overalll survival.

Results from the propensity score analysis

The balance in baseline covariates between the historical cohort and Study MT103-211 was examined before and after making adjustments for the propensity score. Before adjustment, there were significant differences in six of the eight covariates assessed. In particular, the MT103-211 patients were more heavily pre-treated then the historical control patients (average line of salvage therapy 2.36 vs.1.52) and more were refractory to their last line of salvage (52% vs.23%). After adjustment, there were no significant differences in covariates, except for region (more European patients in the historical cohort). The covariate balance before and after adjustment in provided in Appendix V.

A comparison of CR rates and OS from the propensity score analysis is shown in Table 4-29. The predicted CR/CRh* rate in Study MT103-211 was higher than the CRsg rate in the historical cohort (49% vs. 26%) with the odds of achieving haematological remission more than doubled with blinatumomab (OR 2.68). The 6-month and 12-month OS rates were also higher in blinatumomab patients, and the OS HR (blinatumomab vs. historical control) was 0.54.

**Table 4-29. Propensity score analysis: comparison of CR and OS from historical cohort and Study MT103-211**

| | **Historical cohort** | **Blinatumomab (Study MT103-211)[b]** |
|---|---|---|
| CRsg (historical cohort) and CR/CRh* (MT103-211) predicted rate (95% CI) | 26% (23, 30) | 49% (33, 65) |
| CRsg vs. CR/CRh*, OR (95% CI)[a] | 2.68 (1.67, 4.31) | |
| OS, 6-month survival rate (95% CI) | 33% (31, 36) | 58% (55, 60) |
| OS, 12-month survival rate (95% CI) | 17% (15, 19) | 39% (36, 42) |
| OS, HR (95% CI) [a] | 0.54 (0.40, 0.73) | |

Reference: Gokbuget *et al.,* 2016[91]

[a] Estimate for Study MT103-211 versus historical cohort calculated using stabilised IPTW values
[b] Primary analysis data cut-off date (10 Oct 2013)

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRsg, complete remission per study groups/sites; HR, hazard ratio; IPTW, inverse probabilty of treatment weighting; OR, odds ratio; OS, overall survival.

## *4.12 Adverse reactions*

- Safety and tolerability data are presented from the safety analysis set of the TOWER RCT, including 267 patients who received at least one dose of blinatumomab and 109 patients who received at least one dose of SOC chemotherapy
- Blinatumomab was generally well tolerated relative to SOC chemotherapy, despite the substantially longer treatment exposure in the blinatumomab arm ([redacted] subject years vs. [redacted] subject years)
- The incidence of the most common TEAEs, including Grade 3 or higher AEs, such as neutropaenia, febrile neutropaenia, anaemia, thrombocytopaenia, and infections (e.g., pneumonia) was lower in the blinatumomab arm than in the SOC chemotherapy arm
- There was a higher incidence of CRS and neurologic AEs in the blinatumomab arm than in the SOC chemotherapy arm, consistent with the known safety profile of blinatumomab. Rates of ≥ Grade 3 neurologic AEs were similar across study arms, and CRS AEs led to treatment discontinuation in few patients. Specific safety warnings and corresponding management recommendations are detailed in the blinatumomab SmPC

The safety and tolerability data presented below are derived from TOWER, the only relevant RCT identified in the clinical efficacy/safety SLR (Section 4.1), and outcomes are based on the same primary analysis data cut-off date for which efficacy data are presented in Section 4.7 (4 January 2016). All presented safety and tolerability data are based on the safety analysis set (i.e., patients who received at least one dose of study drug).

### 4.12.1 Extent of exposure

#### *4.12.1.1 Exposure to study drug*

A total of 376 patients received at least one dose of study drug (267 patients in the blinatumomab arm and 109 patients in the SOC chemotherapy arm) and were included in the safety analysis set.

Table 4-30 summarises exposure to study drug in the blinatumomab arm. Most patients in the blinatumomab arm received one to two cycles of blinatumomab ([redacted]%), and a small proportion of patients received six or more cycles ([redacted] %). The mean number of cycles started was [redacted], and the mean number of cycles complete was [redacted]. The mean duration of treatment was [redacted] days, and the mean cumulative dose was [redacted].

**Table 4-30. Summary of exposure to study drug in the blinatumomab arm (TOWER, SAS)**

| | Blinatumomab (N = 267) |
|---|---|
| Total number of cycles started, n (%) | |
| 1 | [redacted] |
| 2 | [redacted] |
| 3 | [redacted] |
| 4 | [redacted] |
| 5 | [redacted] |
| 6 or more | [redacted] |
| Total number of cycles started | |
| Mean (SD) | [redacted] |
| Median (IQR) | 2.0 ([redacted]) |
| Total number of cycles completed | |
| Mean (SD) | [redacted] |
| Median (IQR) | [redacted] |
| Duration of treatment (days) | |
| Mean (SD) | [redacted] |
| Median (IQR) | [redacted] |
| Cumulative dose | |
| Mean (SD) | [redacted] |
| Median (IQR) | [redacted] |

References: TOWER primary analysis CSR (Table 12-1)[80]

Note: All exposure records with the start date before the data cut-off date were included. Exposure was recorded from the treatment start date until the last dose date plus 30 days or before the data cut-off date (4 January 2016), whichever came first.

[a] Cumulative dose was the sum of (duration of each infusion) × (dose of each infusion).

AE, adverse event; CSR, clinical study report; IQR, interquartile range; SAS, safety analysis set; SD, standard deviation.

Table 4-31 summarises exposure to study drug in the SOC chemotherapy arm. The most frequently used SOC chemotherapy was FLAG ± anthracycline which was given to 49 patients (45.0%). The vast majority of patients received one or two cycles of SOC chemotherapy (97.2%), and no patients received more than four cycles. The mean number of cycles was 1.3.

**Table 4-31. Summary of exposure to study drug in the SOC chemotherapy arm (TOWER, SAS)**

| | SOC Chemotherapy (N = 109) |
|---|---|
| Type of SOC chemotherapy, n (%) | |
| FLAG ± anthracycline based regimen | 49 (45.0) |
| HiDAC based regimen | 19 (17.4) |
| High-dose methotrexate based regimen | 22 (20.2) |
| Clofarabine or clofarabine based regimen | 19 (17.4) |
| Total number of cycles, n (%) | |
| 1 | [redacted] |
| 2 | [redacted] |
| 3 | [redacted] |
| 4 | [redacted] |
| Number of cycles | |
| Mean (SD) | [redacted] |
| Median (IQR) | 1.0 ([redacted]) |

References: TOWER primary analysis CSR (Table 12-2)[80]

Note: All exposure records with the start date before the data cut-off date were included. Exposure was recorded from the treatment start date until the last dose date plus 30 days or before the data cut-off date (4 January 2016), whichever came first.

AE, adverse event; CSR, clinical study report; FLAG, fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim); HiDAC, high-dose cytarabine; IQR, interquartile range; SAS, safety analysis set; SD, standard deviation; SOC, standard of care.

*4.12.1.2 Exposure to subsequent therapies*

There were no restrictions on subsequent anticancer therapies during the long-term follow-up phase of TOWER. A higher proportion of patients in the SOC chemotherapy arm received subsequent anticancer medications than patients in the blinatumomab arm ([redacted]%) including a higher proportion of innovative therapies (blinatumomab, inotuzumab, and CAR-T cells; [redacted] %; Table 4-32). A summary of anticancer medications received by > 2% of patients in either study arm during long-term follow-up is provided in Table 4-33.

**Table 4-32. Summary of innovative anticancer therapies received during long-term follow-up (TOWER, SAS)**

| | Blinatumomab (N = 267) | SOC Chemotherapy (N = 109) |
|---|---|---|
| Patients with innovative therapy use, n (%) | [redacted] | [redacted] |
| Blinatumomab | [redacted] | [redacted] |
| Inotuzumab[a] | [redacted] | [redacted] |
| CAR T-cell therapy[b] | [redacted] | [redacted] |

References: TOWER primary analysis CSR (Table 14-8.3)[80]

Note: Table incorrectly referred to as the full analysis set in the TOWER CSR.

[a] Recorded as inotuzumab or inotuzumab ozogamicin (CMC-544) on the long-term follow-up CRF
[b] Recorded as CAR T cells, CAR T 19, CAR T reinfusion, Day +8 post CD22 CAR T cells transplant or fludarabine+cytoxan+CAR T-cell infusion on the long-term follow-up CRF

CRF, case report form; CSR, clinical study report; SAS, safety analysis set; SOC, standard of care

**Table 4-33. Summary of anticancer medications received by > 2% of patients in either study arm during long-term follow-up (TOWER, SAS)**

| | Blinatumomab (N = 267) | SOC chemotherapy (N = 109) |
|---|---|---|
| Patients with concomitant medication use, n (%) | [redacted] | [redacted] |
| Clofarabine based combination regimen | [redacted] | [redacted] |
| Cyclophosphamide | [redacted] | [redacted] |
| Flag-IDA | [redacted] | [redacted] |
| Etoposide | [redacted] | [redacted] |
| Fludarabine | [redacted] | [redacted] |
| Blinatumomab | [redacted] | [redacted] |
| Dexamethasone | [redacted] | [redacted] |
| Inotuzumab ozogamicin (CMC-544) | [redacted] | [redacted] |
| Methotrexate | [redacted] | [redacted] |
| Purinethol | [redacted] | [redacted] |
| Vincristine | [redacted] | [redacted] |
| Mercaptopurine | [redacted] | [redacted] |
| 6-Mercaptopurine | [redacted] | [redacted] |
| Prednisone | [redacted] | [redacted] |

References: TOWER primary analysis CSR (Table 12-60)[80]

Note: Table incorrectly referred to as the full analysis set in the TOWER CSR.

CSR, clinical study report; FLAG-IDA, fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim), idarubicin; SAS, safety analysis set; SOC, standard of care.

### 4.12.2 Summary of adverse events

A summary of AEs that occurred after the first dose of study drug and up to 30 days after the last dose of study drug (i.e., treatment-emergent AEs [TEAEs]) is provided in Table 4-34.

As of the data cut-off date, 99.1% patients in the SOC chemotherapy arm and 98.5% of patients in the blinatumomab treatment arm had experienced at least one TEAE. A higher proportion of patients in the blinatumomab arm experienced some types of TEAE than in the SOC chemotherapy arm, including serious AEs (SAEs), and AEs leading to interruption and discontinuation of treatment. Rates of ≥ Grade 3 TEAEs and treatment-related AEs were lower in the blinatumomab arm than in the SOC chemotherapy arm, and rates of AEs of interest, life-threatening AEs, and fatal AEs were similar across study arms.

**Table 4-34. Summary of adverse events (TOWER, SAS)**

| | **Blinatumomab (N = 267) n (%)** | **SOC chemotherapy (N = 109) n (%)** |
|---|---|---|
| Treatment-emergent AEs | 263 (98.5) | 108 (99.1) |
| Grade ≥ 3 | 231 (86.5) | 100 (91.7) |
| Serious AE | 165 (61.8) | 49 (45.0) |
| Treatment-related AE | [redacted] | [redacted] |
| Led to interruption of investigational product | 86 (32.2) | 6 (5.5) |
| Led to discontinuation of investigational product | 33 (12.4) | 9 (8.3) |
| AE of interest | [redacted] | [redacted] |
| Life-threatening | [redacted] | [redacted] |
| Fatal | 51 (19.1) | 19 (17.4) |

References: TOWER primary analysis CSR (Tables 12-4 and 12-11)[80]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first.

AE, adverse event; CSR, clinical study report; SAS, safety analysis set; SOC, standard of care.

It is important to note that overall, patients in the blinatumomab arm had substantially longer treatment duration than patients in the SOC chemotherapy arm, and as such, the likelihood of observing AEs was not even between the two treatment arms. For events with constant or increasing HR over time, longer exposure to protocol-specified therapy often results in higher AE incidence rates compared with rates reported from shorter exposure durations. Crude rates not adjusted by exposure are therefore likely biased in favour of the SOC chemotherapy arm

The exposure-adjusted rates of TEAEs, SAEs, and AEs of interest are summarised in Table 4-35. The total exposure in patients treated with SOC chemotherapy was lower than for patients treated with blinatumomab ([redacted] subject years vs. [redacted] subject years). The exposure-adjusted incidence rates for all TEAEs, SAEs, and AEs of interest were substantially lower in the blinatumomab arm than in the SOC chemotherapy arm.

**Table 4-35. Summary of exposure-adjusted rates of treatment-emergent adverse events (TOWER, SAS)**

| | Blinatumomab (N = 267) n1 (n2)/r | SOC chemotherapy (N = 109) n1 (n2)/r |
|---|---|---|
| Exposure, subject years | [redacted] | [redacted] |
| Treatment-emergent AEs | [redacted] | [redacted] |
| Serious events | [redacted]/349.4 | [redacted] 641.9 |
| AEs of interest | [redacted] | [redacted] |

References: TOWER primary analysis CSR (Table 12-3)[80]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first.

CSR, clinical study report; n1, number of patients with an event; n2, number of events reported; r, exposure-adjusted event rate per 100 subject years (n2*100/total exposure); SAS, safety analysis set; SOC, standard of care.

### 4.12.3 Treatment-emergent adverse events

*4.12.3.1 All grades*

The overall patient incidence of TEAEs was balanced between the two study arms (blinatumomab 98.5%, SOC chemotherapy 99.1% (Table 4-34). Of the most common TEAEs (≥ 10% in either arm), there was a ≥ 5% difference between study arms in the patient incidence of pyrexia, cough and CRS (higher incidence in the blinatumomab arm), and anaemia, febrile neutropaenia, diarrhoea, neutropaenia, nausea, thrombocytopaenia, hypokalaemia, constipation, vomiting, hypomagnesaemia, decreased appetite, stomatitis, abdominal pain, platelet count decreased, pneumonia, hypoalbuminaemia, neutrophil count decreased and mucosal inflammation (higher incidence in the SOC chemotherapy arm). A detailed list of the most common TEAEs and patient incidence is provided in Appendix VI.

*4.12.3.2 Grade 3 or higher*

The patient incidence of ≥ Grade 3 TEAEs was 86.5% in the blinatumomab arm and 91.7% in the SOC chemotherapy arm (Table 4-36). The incidence of the majority of the most common ≥ Grade 3 TEAEs (≥ 5% in either arm) was higher in the SOC chemotherapy arm and at least 5% higher than in the blinatumomab arm for febrile neutropaenia, anaemia, neutropaenia, thrombocytopaenia, platelet count decreased, pneumonia, neutrophil count decreased and hypokalaemia. Grade 3 or higher pyrexia occurred more frequently in the blinatumomab arm ([redacted]%).

**Table 4-36. Summary of the most common ≥ Grade 3 treatment-emergent adverse events occurring in ≥ 5% of patients in either arm (TOWER, SAS)**

| | Blinatumomab (N = 267) n (%) | SOC chemotherapy (N = 109) n (%) |
|---|---|---|
| Number of patients with treatment-emergent ≥ Grade 3 AEs | 231 (86.5) | 100 (91.7) |
| Febrile neutropaenia | 57 (21.3) | 38 (34.9) |
| Anaemia | [redacted] | [redacted] |
| Neutropaenia | 47 (17.6) | 29 (26.6) |
| Thrombocytopaenia | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Alanine aminotransferase increased | 15 (5.6) | 9 (8.3) |
| Sepsis | 13 (4.9) | 7 (6.4) |
| White blood cell count decreased | [redacted] | [redacted] |
| Platelet count decreased | [redacted] | [redacted] |
| Pneumonia | 11 (4.1) | 11 (10.1) |
| Neutrophil count decreased | 10 (3.7) | 11 (10.1) |
| Hypokalaemia | [redacted] | [redacted] |
| Hyperglycaemia | [redacted] | [redacted] |
| Bacteraemia | 2 (0.7) | 6 (5.5) |

References: TOWER primary analysis CSR (Table 12-7)[80]

Note: Adverse events were coded according to MedDRA version 18.1.

AE, adverse event; CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; SOC, standard of care.

### 4.12.4 Treatment-related adverse events

The overall patient incidence of TEAEs deemed to be related to study drug by the investigator was slightly lower in the blinatumomab arm than the SOC chemotherapy arm ([redacted]) (Table 4-37). The incidence of ≥ Grade 3 treatment-related AEs was also lower in the blinatumomab arm ([redacted]%). Treatment-related AEs leading to discontinuation of treatment occurred at a similar incidence in each arm ([redacted]%), whereas treatment-related AEs leading to interruption of treatment occurred more frequently in the blinatumomab arm ([redacted]% vs. [redacted]%). Serious treatment-related AEs occurred in [redacted]% of patients in the blinatumomab arm and [redacted]% in the SOC chemotherapy arm. There were [redacted]%) fatal treatment-related AEs considered related to blinatumomab treatment and [redacted]%) considered related to SOC chemotherapy. These are discussed in more detail in Section 4.12.8.

**Table 4-37. Treatment-related adverse events (TOWER, SAS)**

| | Blinatumomab (N = 267) n (%) | SOC chemotherapy (N = 109) n (%) |
|---|---|---|
| Number of patients with treatment-related AEs | [redacted] | [redacted] |
| Grade ≥ 3 | [redacted] | [redacted] |
| Serious | [redacted] | [redacted] |
| Led to interruption of investigational product | [redacted] | [redacted] |
| Led to discontinuation of investigational product | [redacted] | [redacted] |
| Life-threatening | [redacted] | [redacted] |
| Fatal | [redacted] | [redacted] |

References: TOWER primary analysis CSR (Table12-4)[80]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first.

AE, adverse event; CSR, clinical study report; SAS, safety analysis set; SOC, standard of care.

### 4.12.5 Serious adverse events

Overall, there was a higher patient incidence of treatment-emergent SAEs in the blinatumomab arm than in the SOC chemotherapy arm (61.8% vs.45.0%) (Table 4-38). The most common SAE was neutropaenia in both arms (blinatumomab 8.6%, exposure-adjusted rate [redacted] per 100 subject years; SOC chemotherapy [redacted] %, exposure-adjusted rate [redacted] per 100 subject years). The patient incidence of pyrexia was higher in the blinatumomab arm than the SOC chemotherapy arm (6.0% vs.0.9%, exposure-adjusted rate per 100 subject years [redacted]). Cytokine release syndrome occurred in 2.6% of patients in the blinatumomab arm (exposure-adjusted rate [redacted] per 100 subject years).

**Table 4-38. Summary of the most common treatment-emergent serious adverse events occurring in ≥ 2% of patients in either arm, and corresponding exposure-adjusted rates (TOWER, SAS)**

| | Patient incidence rates | | Exposure-adjusted rates | |
|---|---|---|---|---|
| | Blin (N = 267) n (%) | SOC chemo (N = 109) n (%) | Blin (N = 267) n1 (n2)/r | SOC chemo (N = 109) n1 (n2)/r |
| Total exposure in years | N/A | N/A | [redacted] | [redacted] |
| Number of patients with treatment-emergent SAEs | 165 (61.8) | 49 (45.0) | [redacted] **349.4** | [redacted] **641.9** |
| Febrile neutropaenia | 23 (8.6) | 12 (11.0) | [redacted] | [redacted] |
| Pyrexia | 16 (6.0) | 1 (0.9) | [redacted] | [redacted] |
| Sepsis | 13 (4.9) | 7 (6.4) | [redacted] | [redacted] |
| Pneumonia | 10 (3.7) | 2 (1.8) | [redacted] | [redacted] |
| Overdose | 8 (3.0) | 0 | [redacted] | [redacted] |
| Septic shock | 8 (3.0) | 3 (2.8) | [redacted] | [redacted] |
| Cytokine release syndrome | 7 (2.6) | 0 | [redacted] | [redacted] |

| | Patient incidence rates | | Exposure-adjusted rates | |
|---|---|---|---|---|
| | Blin (N = 267) n (%) | SOC chemo (N = 109) n (%) | Blin (N = 267) n1 (n2)/r | SOC chemo (N = 109) n1 (n2)/r |
| Total exposure in years | N/A | N/A | [redacted] | [redacted] |
| Bacterial sepsis | 6 (2.2) | 2 (1.8) | [redacted] | [redacted] |
| Device related infection | 6 (2.2) | 1 (0.9) | [redacted] | [redacted] |
| Bacteraemia | 2 (0.7) | 3 (2.8) | [redacted] | [redacted] |

Reference: TOWER primary analysis CSR (Table 12-8)[80]

Note: AEs were coded according to MedDRA version 18.1.

Blin, blinatumomab; Chemo, chemotherapy; CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable; n1, number of patients with event; n2, number of events reported; r, exposure-adjusted event rate per 100 subject years (n2*100/total exposure); SAS, safety analysis set; SOC, standard of care.

### 4.12.6 Adverse events of interest

Table 4-39 summarises the patient incidence of TEAEs of interest by category. The patient incidence of neutropaenia, infections, cytopaenia, embolic and thrombotic events and elevated liver enzymes AEs of interest was lower in the blinatumomab arm than the SOC chemotherapy arm (overall and for ≥ Grade 3 events).

Consistent with the known safety profile of blinatumomab, neurologic AEs of interest (central neuropsychiatric events due to direct neurotoxicities) were more frequent in the blinatumomab arm than the SOC chemotherapy arm ([redacted] %), however ≥ Grade 3 events occurred at a similar frequency (9.4% vs.8.3%). Serious neurologic AEs of interest occurred in [redacted] of the blinatumomab arm and [redacted] % of the SOC chemotherapy arm.[80] Neurologic AEs of interest leading to treatment discontinuation were infrequent (blinatumomab 3.7%, SOC chemotherapy 0.9%). [redacted] [redacted] %) in the blinatumomab arm had a fatal neurologic AE of interest (preferred term: completed suicide).[80] Specific safety warnings and corresponding management recommendations are detailed in the blinatumomab SmPC.

Also consistent with the known safety profile of blinatumomab, CRS AEs of interest were reported in [redacted] % of patients in the blinatumomab arm (4.9% for ≥ Grade 3 events, [redacted] for serious events and 1.1% for events leading to treatment discontinuation).[80] No patients in the SOC chemotherapy arm experienced a CRS event. Similarly to neurologic events, specific safety warnings and corresponding management recommendations for CRS are detailed in the blinatumomab SmPC.

Infusion reaction considering duration AEs of interest were more commonly experienced in the blinatumomab arm than the SOC chemotherapy arm ([redacted] vs. [redacted] ≥ Grade 3: 3.4% vs.0.9%). These never led to treatment discontinuation.[80] The patient incidence of decreased immunoglobins AEs of interest was higher in the blinatumomab arm than the SOC chemotherapy arm ([redacted] % vs. [redacted] %; ≥ Grade 3: 2.6% vs. 0.0%). None of these events were serious or led to treatment discontinuation.[80] Tumour lysis syndrome AEs of interest were experienced by [redacted] % of patients in the blinatumomab arm compared with [redacted] % of patients

in the SOC chemotherapy arm (≥ Grade 3: 3.0% vs.0.9%). This led to treatment discontinuation for one patient in the blinatumomab arm (0.4%).[80]

**Table 4-39. Summary of treatment-emergent adverse events of interest (TOWER, SAS)**

| | Blinatumomab (N = 267) n (%) | SOC chemo-therapy (N = 109) n (%) |
|---|---|---|
| Patients with treatment-emergent AEs of interest | [redacted] | [redacted] |
| Central neuropsychiatric events[a] | [redacted] | [redacted] |
| Grade ≥ 3 | 25 (9.4) | 9 (8.3) |
| Cytokine release syndrome | [redacted] | [redacted] |
| Grade ≥ 3 | 13 (4.9) | 0 (0.0) |
| Infections | [redacted] | [redacted] |
| Grade ≥ 3 | 91 (34.1) | 57 (52.3) |
| Elevated liver enzymes | [redacted] | [redacted] |
| Grade ≥ 3 | 34 (12.7) | 16 (14.7) |
| Infusion reaction considering duration | [redacted] | [redacted] |
| Grade ≥ 3 | 9 (3.4) | 1 (0.9) |
| Tumour lysis syndrome | [redacted] | [redacted] |
| Grade ≥ 3 | 8 (3.0) | 1 (0.9) |
| Acute pancreatitis | [redacted] | [redacted] |
| Grade ≥ 3 | 1 (0.4) | 1 (0.9) |
| Embolic and thrombotic events | [redacted] | [redacted] |
| Grade ≥ 3 | 4 (1.5) | 2 (1.8) |
| Medication errors | [redacted] | [redacted] |
| Grade ≥ 3 | 4 (1.5) | 0 (0.0) |
| Cytopaenia | [redacted] | [redacted] |
| Grade ≥ 3 | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Grade ≥ 3 | 101 (37.8) | 63 (57.8) |
| Lymphopaenia | [redacted] | [redacted] |
| Grade ≥ 3 | 4 (1.5) | 4 (3.7) |
| Decreased immunoglobulins | [redacted] | [redacted] |
| Grade ≥ 3 | 7 (2.6) | 0 (0.0) |
| Progressive multifocal leukoencephalopathy | [redacted] | [redacted] |
| Grade ≥ 3 | 2 (0.7) | 0 (0.0) |

Reference: TOWER primary analysis CSR (Table 12-11)[80]

Note: AEs were coding according to MedDRA version 18.1. Severity graded was according to CTCAE v4.03.
[a] Due to direct neurotoxicities

AE, adverse event; CSR, clinical study report; CTCAE, Common Technical Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; SOC, standard of care.

### 4.12.7 Adverse events leading to treatment interruption or discontinuation

TEAEs leading to treatment interruption were reported in 32.2% of patients in the blinatumomab arm and 5.5% of patients in the SOC chemotherapy arm (Table 4-34). TEAEs leading to blinatumomab treatment interruption in at least four patients were CRS ([redacted] %), pyrexia ([redacted] %), neutropaenia ([redacted] %) and device-related infection ([redacted] %) (Appendix VI).

TEAEs leading to treatment discontinuation were reported in 12.4% of patients in the blinatumomab arm and 8.3% of patients in the SOC chemotherapy arm (Table 4-34). With the exception of [redacted] blinatumomab patients ([redacted] %) who experienced haematophagic histiocytosis, all other events leading to treatment discontinuation (in either treatment arm) occurred in no more than one patient (Appendix VI).

### 4.12.8 Fatal adverse events

As specified in the TOWER protocol, disease progression of the primary tumour was not considered to be an AE, therefore the number of fatal AEs is lower than the number of deaths reported in Section 4.7.

Fatal TEAEs were reported in 51 (19.1%) of patients in the blinatumomab arm and 19 (17.4%) of patients in the SOC chemotherapy arm (Table 4-34). The most frequently reported fatal AE in both treatment arms was sepsis (blinatumomab 3.0%, SOC chemotherapy 3.7%). (Appendix VI). Fatal AEs considered related to treatment were reported in eight patients (3.0%) in the blinatumomab arm and eight patients in the SOC chemotherapy arm (7.3%). In the blinatumomab arm, [redacted] fatal AEs were in the setting of severe infections and [redacted] fatal AE was reported as respiratory failure. Although the fatal AEs were deemed related to blinatumomab, infectious deaths occurring in the setting of active disease would not be unexpected in this patient population. Similarly, in the SOC chemotherapy arm [redacted] AEs were attributed to infections and occurred in the setting of active disease, with the remaining fatal AE reported as acute kidney injury.[80]

## *4.13 Interpretation of the clinical effectiveness and safety evidence.*

### 4.13.1 Summary of the principle findings of the clinical evidence base

*4.13.1.1 TOWER*

The phase 3 TOWER study is the first RCT in several decades to show a significant survival benefit for a new treatment versus SOC chemotherapy in R/R ALL. Blinatumomab was associated with a statistically significant improvement in OS compared with SOC chemotherapy (HR 0.71; p = 0.012); median OS was almost doubled from 4.0 months in the SOC chemotherapy arm to 7.7 months in the blinatumomab arm. This survival benefit was shown to be independent of whether or not patients received post-baseline allo-SCT. Significantly more patients treated with blinatumomab achieved a haematological remission than with SOC chemotherapy within 12 weeks of treatment initiation (CR: 33.6% vs. 15.7%, p < 0.001; CR/CRh*/CRi: 43.9% vs. 24.6%, p < 0.001). In addition:

- Haematological remission was more durable in patients treated with blinatumomab than with SOC chemotherapy (CR: [redacted] months; CR/CRh*/CRi: 7.3 months vs. 4.6 months)
- More CR/CRh*/CRi responders achieved MRD remission with blinatumomab than with SOC chemotherapy (76.3% vs. 48.5%; descriptive p [redacted]), underlining the high quality and depth of remissions associated with blinatumomab.
- Blinatumomab improved EFS compared with SOC chemotherapy (HR 0.55, descriptive p < 0.001)
- Blinatumomab was associated with delayed time to clinically-meaningful deterioration in HRQoL (10-point decrease in EORTC QLQ-C30 GHS/QoL) or EFS event (HR 0.67, descriptive p = 0.0051). Blinatumomab also improved EORTC QLQ-C30 scores from baseline relative to SOC chemotherapy (descriptive p [redacted] for overall treatment effect during Cycle 1 for the main GHS/QoL scale)

Subgroup analyses in the prior salvage therapy (yes vs. no) stratification factor subgroup suggest that the OS benefit is greater in patients who have not received prior salvage therapy than in patients who have. This is considered highly clinically plausible as treating patients earlier in the treatment pathway with a more effective therapy would be expected to improve both absolute and relative OS, and is pertinent to the decision problem as clinicians are likely to use blinatumomab early in the treatment pathway given the above. Subgroup analyses of OS were consistent in most other subgroups with a reasonable sample size.

Blinatumomab was generally well tolerated in TOWER relative to SOC chemotherapy, despite the substantially longer treatment exposure in the blinatumomab arm ([redacted] subject years vs. [redacted] subject years). The incidence of the most common TEAEs, including ≥ Grade 3 AEs, such as neutropaenia, febrile neutropaenia, anaemia, thrombocytopaenia, and infections (e.g., pneumonia) was lower in the blinatumomab arm than in the SOC chemotherapy arm. There was a higher incidence of CRS and neurologic AEs in the blinatumomab arm than in the SOC chemotherapy arm, consistent with the known safety profile of blinatumomab. Rates of ≥ Grade 3 neurologic AEs were similar across study arms, and CRS AEs led to treatment

discontinuation in few patients. Specific safety warnings and corresponding management recommendations are detailed in the blinatumomab SmPC.

Overall, blinatumomab demonstrated a favourable risk-benefit profile in the TOWER study.

*4.13.1.2 Study MT103-211*

The proportions of patients achieving a CR/CRh* and CR within the first two cycles (i.e., 12 weeks) of treatment in Study MT103-211 were 42.9% and 33.3%, respectively. This is consistent with the proportions of patients achieving a CR/CRh*/CRi (43.9%) and CR (33.6%) in the blinatumomab arm of the phase 3 TOWER RCT. Based on the most recent data cut-off date (15 July 2015), median OS was 6.5 months and median RFS in patients achieving CR/CRh* was 6.8 months. This median OS is similar to the 7.7 months seen in the blinatumomab arm of TOWER.

A comparison of blinatumomab data from Study MT103-211 with historical SOC chemotherapy control data, using different analytical methods to address imbalances in prognostic factors (weighted analysis and propensity score analysis), showed more favourable CR and OS outcomes with blinatumomab. The proportion of patients achieving a CR and median OS for blinatumomab in Study MT103-211 were approximately double those in the historical cohort, which is consistent with the relative treatment effects seen for blinatumomab versus SOC chemotherapy in TOWER.

### 4.13.2 Strengths and limitations of the clinical evidence base

The clinical evidence base for blinatumomab presented in this submission includes data from a large, international phase 3 RCT (TOWER) which represent the highest quality evidence for evaluating clinical efficacy. This in itself should be considered an important strength given the dearth of RCT evidence in the disease area. Results from key endpoints in TOWER (e.g., OS and haematological remission rates) were confirmed with a range of pre-specified sensitivity analyses. In addition, results from key endpoints in TOWER were consistently observed in most pre-specified patient subgroups with a reasonable sample size.

Important additional evidence presented in this submission comes from the key registrational single-arm phase 2 study (Study MT103-211), including a comparison of MT103-211 results with historical control data using statistical techniques to adjust the historical control data to the MT103-211 study population. Strengths of this analysis include the use of stringent inclusion criteria for the historical cohort and the use of statistical techniques to weight or adjust for known prognostic factors. In addition, the sample size of the historical cohort (N = 1139) is the largest ever assembled in the US and EU for adult patients with R/R Ph- B-precursor ALL.

The robustness of the clinical evidence base presented in this submission is further supported by a comparison of outcomes from TOWER with Study MT103-211; median OS and haematological remission rates in the blinatumomab arm of TOWER were highly consistent with Study MT103-211 (Table 4-40 and Table 4-41). Similarly, the relative efficacy (OS and haematological remission rates) for blinatumomab versus SOC chemotherapy seen in TOWER was consistent with a comparison of Study MT103-211 versus the historical comparator cohort, though the HR for OS was higher in TOWER. This could be a result of

potential confounding resulting from differences in approach to allo-SCT across study arms in TOWER and a higher rate of subsequent anticancer therapies (including innovative therapies) in the SOC chemotherapy arm in TOWER, as discussed later in this section.

**Table 4-40. Comparison of overall survival results from RCT and non-RCT evidence**

| Source | Outcome | Blinatumomab | SOC chemotherapy |
|---|---|---|---|
| TOWER | Median, months (95% CI) | 7.7 (5.6, 9.6) | 4.0 (2.9, 5.3) |
| | HR (95% CI) | 0.71 (0.55, 0.93) | |
| Study MT103-211 | Median, months (95% CI) [primary analysis] | 6.1 (4.2, 7.5) | N/A |
| | Median, months (95% CI) [additional ad-hoc analysis] | 6.5 (4.4, 7.7) | N/A |
| Historical SOC chemotherapy data (weighted to match MT103-211 population) | Median, months (95% CI) | N/A | 3.3 (2.8, 3.6) |
| Study MT103-211 vs. historical comparator (propensity score analysis) | HR (95% CI) | 0.54 (0.40, 0.73) | |

References: TOWER primary analysis CSR,[80] Topp *et al.,* 2015,[4] Gokbuget *et al.,* 2016,[91] Amgen data on file, 2015.[97]

CI, confidence interval; CSR, clinical study report; HR, hazard ratio; N/A, not applicable; OS, overall survival; SOC, standard of care.

**Table 4-41. Comparison of haematological remission results from RCT and non-RCT evidence**

| Source | Outcome | Blinatumomab | SOC chemotherapy |
|---|---|---|---|
| TOWER | CR, % (95% CI) | 34 (28, 40) | 16 (10, 23) |
| | CR/CRh*/CRi, % (95% CI) | 44 (38, 50) | 25 (18, 33) |
| MT103-211 | CR, % (95% CI) | 33 (27, 41) | N/A |
| | CR/CRh*, % (95% CI) | 43 (36, 50) | N/A |
| Historical SOC chemotherapy data (weighted to match MT103-211 population) | CRsg, % (95% CI) | N/A | 24 (20, 27) |
| Study MT103-211 vs. historical comparator: propensity score analysis | CR/CRh* ('211) and CRsg (historical cohort), % (95% CI) | 49 (33, 65) | 26 (23, 30) |

References: TOWER primary analysis CSR,[80] Topp *et al.,* 2015,[4] Gokbuget *et al.,* 2016, [91] Amgen data on file, 2015.[97]

CI, confidence interval, CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; CRsg, complete remission per study groups/sites; CSR, clinical study report; N/A, not applicable; SOC, standard of care.

Limitations of the clinical evidence base presented in this submission include:

- The open-label nature of TOWER meant that investigators and participants were not blinded to treatment. This likely led to more patients randomised to SOC chemotherapy deciding not to initiate treatment or withdrawing consent during the study than patients randomised to blinatumomab, as evidenced below. The complexity of combination SOC chemotherapy regimens means that it would have been extremely difficult and unethical to conduct a double-blind study of a single-agent intervention in this disease area
- There was a high number of drop-outs in TOWER, notably including a large imbalance of patients who dropped out before receiving their allocated study drug (18.7%, SOC chemotherapy; 1.5%, blinatumomab), most commonly due to patient choice (Section 4.5.1). This is unsurprising given the extremely poor prognosis associated with SOC chemotherapy, and unavoidable in an RCT of this nature. Most patients in the TOWER FAS who did not receive study drug continued to be followed-up for OS ([redacted] patients in the blinatumomab arm and [redacted] patients in the SOC chemotherapy arm).[85] The median duration of follow-up was [redacted] months in the SOC chemotherapy arm and was not estimable in the blinatumomab arm (as all [redacted] patients died). Any potential resulting bias is likely to be small as sensitivity analyses of OS and key secondary outcomes in the safety population (i.e., patients who received at least one dose of study drug) were consistent with the primary efficacy analyses. In addition, more patients in the SOC chemotherapy arm discontinued the study due to withdrawal of consent than patients in the blinatumomab arm (11.2% vs. 5.2%; Section 4.5.1), which could also have resulted in potential bias.
- The potential confounding effect of subsequent therapy in TOWER. Among patients who received study drug, more patients in the SOC chemotherapy arm received subsequent anticancer therapies ([redacted] %) than in the blinatumomab arm ([redacted] %) (Section 4.12.1.2). In addition, use of innovative anticancer therapies (blinatumomab, inotuzumab, and CAR-T) was more than double in the SOC chemotherapy arm than in the blinatumomab arm ([redacted] %). This could have biased the efficacy results in favour of the SOC chemotherapy arm. Use of subsequent therapies in an RCT in a life-threatening disease such as R/R Ph- B-precursor ALL is inevitable as it would be unethical to prevent patients with such a poor prognosis receiving additional therapies at the discretion of their treating clinician.
- The similar rates of SCT across study arms in TOWER could be indicative of outcome bias as clinicians may have been more likely to take a different approach to allo-SCT in patients receiving SOC chemotherapy than in patients receiving blinatumomab (Section 4.7.6). Therefore, a comparison of rates of allo-SCT in TOWER may not be directly indicative of the relative efficacy of blinatumomab versus SOC chemotherapy. This may also have biased OS results in favour of SOC chemotherapy.
- The early stopping of the TOWER study at the second interim analysis (based on DMC recommendations) and premature discontinuation of long-term follow-up means that there are limited long-term data on outcomes such as OS (median follow-up 11.7 months in the blinatumomab arm) and rates of allo-SCT from this study. Longer-term follow-up data is available from Study MT103-211 which had a median follow-up for OS of 27.8 months in the most recent analysis (‘additional ad-hoc analysis’, 15 July 2015 data cut-off date).

- The single-arm design of Study MT103-211, which has been addressed by a comparison of Study MT103-211 results with historical control data using appropriate statistical techniques to adjust the historical control data to the MT103-211 study population. Limitations of these analyses include potential heterogeneity around the definition of CR by the different study groups/sites in the historical control cohort and the difference in the timing of data collection.

Given the above mentioned limitations of the TOWER RCT, some of which may have confounded clinical effectiveness results, Study MT103-211 and the comparison with the historical comparator cohort (a robust non-randomised study and analysis with low risk of bias) should be considered an important additional source of clinical effectiveness evidence.

### 4.13.3 Relevance of the clinical evidence base to the decision problem

Patient population

The populations enrolled in the phase 3 TOWER RCT and Study MT103-211 (including the comparison with the historical cohort) are broadly consistent with the marketing authorisation for blinatumomab in adult patients with R/R Ph- B-precursor ALL. A notable exception is that TOWER and Study MT103-211 enrolled particularly difficult-to-treat patients as patients in late first relapse (first relapse after > 12 months in first remission), who have a better prognosis,[29] were not eligible for the studies. Blinatumomab should remain an option for these late first relapse patients because:

- There is no clear biologic difference between patients who relapse at 11.5 months compared with 12.5 months. The 12-month cut-off is not a clinical standard (late relapse has also been defined in the literature as > 18 and > 24 months).[25,49,99,100]
- The ability to achieve long-term remission and cure patients with ALL diminishes with each round of therapy due to increasing resistance of leukemic cells. For this reason, the best available therapeutic option should be used as early as possible.[29]
- As referenced in the blinatumomab EPAR (Appendix I), haematological remission rates in a small sample of 9 patients in late first relapse enrolled in the registrational studies and treated with blinatumomab were very high (CR/CRh* 88.9%, CR 77.7%), including a high proportion of patients achieving MRD remission (55.5%). Based on these data, the EMA concluded that efficacy can be 'considered established' in late first relapse patients; further efficacy data in the late first relapse population will be collected as part of a planned post-approval safety study.

That patients in late first relapse (who have a better prognosis)[29] were not eligible for TOWER or Study MT103-211 means that absolute outcomes from TOWER and Study MT103-211 are likely to represent a conservative estimate of the absolute efficacy of both blinatumomab and SOC chemotherapy. The relative efficacy in TOWER for blinatumomab versus SOC chemotherapy is expected to be at least as good as will be seen in clinical practice in a population including late first relapse patients.

In addition, patients with clinically-relevant CNS pathology were excluded from TOWER and Study MT103-211, though patients with clinically-relevant CNS pathology are eligible for treatment with blinatumomab per its marketing authorisation (subject to special warnings and precautions for use as outlined in the SmPC). This has limited impact on external

generalisability as patients with any CNS pathology are estimated to represent ≤ 10% of adult patients with R/R ALL seen in clinical practice,[25] and there is no clinical or biological reason why efficacy in patients with CNS pathology would be any different from patients without CNS pathology.

UK clinical experts consulted by Amgen confirmed that overall, the populations enrolled in TOWER and Study MT103-211 were broadly representative of patients seen in clinical practice in England and Wales. One noted potential difference was age, as patients seen in clinical practice are typically older than those enrolled in TOWER and Study MT103-211. This is commonly the case in oncology RCTs, and pre-specified subgroup analyses of TOWER suggest that efficacy of blinatumomab is consistent irrespective of age (< 35 years vs. ≥ 35 years) (Section 4.8).

Intervention

Blinatumomab was administered in TOWER and Study MT103-211 at a dose and on a dosing schedule consistent with its marketing authorisation and anticipated use in clinical practice in England and Wales during two induction and up to three additional consolidation cycles:

- Continuous IV infusion over 4 weeks (9 µg/day during Week 1 of Cycle 1 then 28 µg/day for the remainder of the cycle and during subsequent cycles) followed by a treatment-free interval of 2 weeks.

The criteria for consolidation therapy eligibility was slightly different in TOWER (bone marrow response [≤ 5% bone marrow blasts] or CR/CRh*/CRi) compared with the marketing authorisation for blinatumomab (CR/CRh*). This has limited impact on external generalisability as most patients with CR/CRh*/CRi in TOWER had a best response of CR or CRh* (93.4%),[80] and the majority of patients with ≤ 5% bone marrow blasts would be expected to have CR/CRh*/CRi. The criteria for consolidation therapy eligibility in Study MT103-211 were consistent with the marketing authorisation for blinatumomab.

In addition, patients in TOWER could receive up to 12 additional months of blinatumomab maintenance therapy if they continued to have a bone marrow response or CR/CRh*/CRi after three consolidation cycles, given as 12-week cycles (4 weeks continuous IV infusion at 28 µg/day followed by an 8-week treatment-free interval). Maintenance therapy is not included in the marketing authorisation for blinatumomab. Although the proportion of patients in the blinatumomab arm in whom six or more cycles of blinatumomab was initiated (i.e., more than the maximum five cycles permitted by the marketing authorisation) was small ([redacted] %), this should be considered a limitation of the clinical evidence from TOWER.

Comparators

The comparator in the TOWER study was SOC chemotherapy, selected from one of four investigator-chosen protocol-specified regimens. The most common intended SOC chemotherapy regimen at randomisation for patients randomised to the SOC chemotherapy was FLAG ± anthracycline ([redacted] %), which is pertinent given that the relevant comparator for this appraisal is FLAG-IDA (Section 3.5). This was also the most commonly used regimen in patients who received at least one dose of study drug in the SOC chemotherapy arm ([redacted] %).

In addition, available clinical guidelines, including the EWALL guidelines,[48] suggest that there is no clearly superior salvage chemotherapy regimen in R/R Ph- B-precursor ALL. UK clinical experts consulted by Amgen considered the outcomes in the SOC chemotherapy arm in TOWER to be broadly generalisable to the relevant comparator for this appraisal, FLAG-IDA.

Outcomes

The outcome data included in this submission, including OS, rates and duration of haematological remission (including CR/CRh*/CRi), rates of MRD remission, EFS, RFS, rates of allo-SCT, HRQoL, and AEs address all of the outcomes specified in the final scope for this appraisal.

OS, the primary endpoint in TOWER, represents arguably the most relevant endpoint for directly measuring patient benefit in medical oncology.

Rates of haematological remission are highly relevant to clinical practice as they are widely used to determine eligibility for allo-SCT (the only current potentially curative treatment option) and are predictive of clinical benefit.[40,67] The EMA has accepted the relevance of CR as an endpoint in R/R ALL, and has granted approval based on improvements in CR for clofarabine in paediatric patients.[101] Achieving a CR in acute leukaemia is clinically meaningful and has been established as a surrogate for clinical benefit in predicting longer life.[40] The criteria for CR used in TOWER and Study MT103-211 (≤ 5% blasts, no evidence of disease, platelets > 100,000/μL, and ANC > 1,000/μL) is a widely accepted definition that is routinely used in clinical practice. Inclusion of patients with CRh* and CRi in the assessment of efficacy is relevant and appropriate because the patient populations enrolled in TOWER and Study MT103-211 included some heavily pretreated patients (including some patients who had received allo-SCT) (Section 4.5.2 and 4.11.4.2). Bone marrow recovery was thus likely to be delayed because of poor marrow reserve and accumulation of chemotherapy-related toxicities. Further, in clinical practice, measures of CRh* or CRi may be used to inform treatment decisions because clinicians may not want to wait for a full recovery of peripheral blood counts, and patients achieving these levels of response may therefore be considered candidates for allo-SCT. Given additional time to recover, some patients may convert to a CR after achieving a CRh* or CRi.

Rates of MRD remission (defined as MRD < $1 \times 10^{-4}$) are also highly relevant as MRD is widely recognised as one of the most sensitive prognostic factors for relapse, regardless of treatment choice and risk classification in paediatric and adult patients with newly-diagnosed ALL.[50,102,103] The prognostic significance of MRD in paediatric patients following relapse is also

widely accepted.[104] In adults, the prognostic value of MRD in R/R patients is less well established, though evidence suggests that MRD remission in R/R patients both prior to and after allo-SCT is a significant predictor of improved OS and RFS.[105]

Measures of duration of response (e.g., duration of CR) and disease-free survival (i.e., RFS or EFS) can be considered relevant measures of patient benefit since prolonged response duration or disease-free survival can mean an improved chance of allo-SCT for eligible patients. RFS can be considered a more clinically relevant measure of efficacy than EFS, since analyses of EFS assign haematological non-responders an EFS duration of 1 day (an approach recommended by the EMA for acute leukaemia[86]), rendering estimates of median EFS in TOWER (0 months in both study arms) uninformative. In contrast, RFS is only assessed for patients who achieve a haematological remission.

Rates of allo-SCT can be considered a direct measure of patient benefit as allo-SCT is currently the only potential curative option for patients with R/R Ph- B-precursor ALL. However, data from TOWER suggest that clinicians may have adopted a different approach to allo-SCT in the different study arms (Section 4.7.6). Therefore, a comparison of rates of allo-SCT across study arms in TOWER may not be directly indicative of the relative efficacy of blinatumomab versus SOC chemotherapy.

HRQoL is also an important outcome in a disease where patients have an extremely poor prognosis and survival is measured in months. The main HRQoL measure in TOWER is EORTC-QLQ C30 which is one of the most widely used questionnaires in Europe for cancer patients.[106] For the reasons outlined above for EFS, assessment of change in EORTC-QLQ C30 QLQ-C30 GHS/QoL (and other EORTC QLQ-C30 scales/items) from baseline over time is likely to be more clinically informative than the pre-specified TOWER secondary endpoint of time to 10-point decrease in EORTC QLQ C30 GHS/QoL or EFS event.

### 4.13.4 Conclusion

The clinical evidence base presented in the submission adequately addresses the decision problem and is broadly generalisable to clinical practice in England and Wales. It provides compelling evidence to show that blinatumomab (a non-chemotherapeutic targeted immunotherapy), compared with SOC chemotherapy, is associated with a near-doubling of median OS, more than doubling of CR rates, fewer of the common toxicities seen with SOC chemotherapy, and improved HRQoL. Blinatumomab therefore offers adult R/R Ph- B-precursor ALL patients prolonged survival, and an improved likelihood of achieving haematological remission, thus giving them a better chance of being considered eligible for allo-SCT. As such, blinatumomab represents a step change in the management of patients with this devastating and highly aggressive disease that responds poorly to current salvage chemotherapy regimens and is associated with very poor survival.

## 4.14 End-of-life criteria

Blinatumomab for the treatment of adult patients with R/R Ph- B-precursor ALL meets the NICE end-of-life criteria (Table 4-42).

**Table 4-42. End-of-life criteria**

| | |
|---|---|
| **The treatment is indicated for patients with a short life expectancy, normally less than 24 months** | • Median OS with SOC chemotherapy in adult patients with R/R Ph- B-precursor ALL was 4.0 months in the phase 3 TOWER (Section 4.7.2)<br>• In a retrospective observational historical comparator international reference study, median OS with SOC chemotherapy in adult patients with R/R Ph- B-precursor ALL was 5.8 months for patients in first salvage, 3.9 months for patients in second salvage, and 2.9 months for patients in third or later salvage (Section 3.2.2)<br>• In both cases, median OS is substantially less than 24 months, though the estimates from the observational study may be considered more representative given that TOWER excluded patients in late first relapse (relapse after > 12 months remission) who have a better OS prognosis |
| **There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment** | • Blinatumomab was associated with a median OS of 7.7 months in the phase 3 TOWER study, a statistically significant 3.7-month improvement over SOC chemotherapy (Section 4.7.2) |
| ALL, acute lymphoblastic leukaemia; CI, confidence interval; OS, overall survival; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory; SOC, standard of care. | |

## 4.15 Ongoing studies

Additional data from a final analysis of TOWER, conducted after the 22 patients still on treatment with blinatumomab at the time of data cut-off for the primary analysis have stopped treatment with blinatumomab and completed their safety follow-up visit, are anticipated to become available by Q1 2017.

Similarly, additional data from a final analysis of Study MT103-211 after the 57 patients (42 in the PAS) still on study at the time of the secondary analysis have completed the study are anticipated to become available by Q3 2017.

# 5 Cost effectiveness

## 5.1 Published cost-effectiveness studies

An SLR was performed to identify publications reporting cost-effectiveness studies for therapies used for the management of adult R/R Ph- B-precursor ALL, resource use and treatment costs for the management of adult R/R Ph- B-precursor ALL, and studies reporting HRQoL or utilities relevant for adult R/R Ph- B-precursor ALL. The SLR was conducted in July 2015 and updated in November 2016. Searches were devised to identify relevant studies and were used to search Medline, EMBASE, the Cochrane library, EconLIT, and the NHS Economic Evaluation Database (EED). Supplementary searches of conference proceedings and grey literature sources were also carried out to identify additional relevant studies. Full details of the search strategies, inclusion/exclusion criteria, screening procedure, and quality assessment are provided in Appendix VII.

Three cost-effectiveness studies were identified, all of which assessed the cost-effectiveness of blinatumomab versus SOC chemotherapy.[13,107,108] The cost-effectiveness studies were all HTA appraisals (AWMSG, SMC, and the Canadian Agency for Drugs and Technologies in Health [CADTH]) and because they were not comprehensively reported, complete quality assessment was not feasible. Moreover, the cost-effectiveness analyses were based solely on non-randomised clinical study data, and are therefore not considered relevant to the *de novo* cost-effectiveness analysis which is mostly based on phase 3 RCT data from TOWER. Full details of the identified cost-effectiveness studies are provided in Appendix VII.

## 5.2 De novo analysis

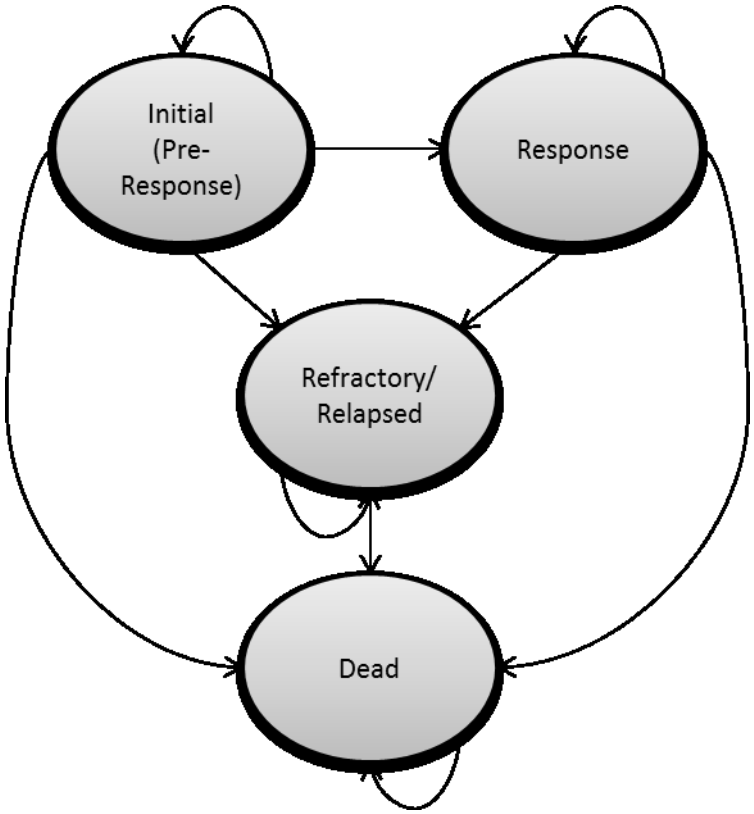
### 5.2.1 Patient population

Blinatumomab received a conditional marketing authorisation for the treatment of adult patients with R/R Ph- B-precursor ALL on 23 November 2015 (Section 2.2.1). The confirmatory phase 3 TOWER RCT and key registrational phase 2 study (Study MT103-211) enrolled adult R/R Ph- B-precursor ALL patient populations that are broadly consistent with the licensed indication for blinatumomab (Section 4.13.3). A notable exception is that TOWER and Study MT103-211 enrolled particularly difficult-to-treat patients, as patients in late first relapse (first relapse after > 12 months in first remission), who have a better prognosis,[29] were not eligible for the studies. The base-case model uses clinical data from TOWER and therefore assumes a patient population similar to that in the TOWER and broadly consistent with the licensed population.

### 5.2.2 Model structure

The evaluation uses a partitioned survival model with states defined on the basis of response to treatment, relapse, and death. A schematic of the model, which was programmed in Microsoft Excel, is presented in Figure 5-1. A weekly model cycle is used for estimating the proportion of patients in each health state over time. All patients enter the model in the "initial" state and remain in this state for 12 weeks (unless they die during that period), after which they may either enter the "refractory/relapsed" state or "response" state, depending on response to therapy. Patients entering the response state are at risk of relapse or death. Those who respond initially then relapse enter the relapsed/refractory state and are at risk of death.

**Figure 5-1. Schematic of the de novo model**




Clinical effectiveness inputs to inform health state probabilities for blinatumomab and the relevant comparator (FLAG-IDA) are based on data from the blinatumomab and SOC chemotherapy arms of the phase 3 TOWER RCT. The probabilities of response were estimated using data from TOWER on the proportion of patients achieving a haematological remission (CR/CRh*/CRi) within 12 weeks of treatment initiation. The proportion of patients in the refractory/relapsed state is based on the proportion non-responders remaining alive in the initial state at the end of 12 weeks, and the distribution of EFS among responders. The latter is calculated based on EFS data from TOWER, with time-to-event calculated from date of haematological remission among patients who achieved a haematological remission within 12 weeks of treatment initiation (hereafter referred to as "EFS among responders"). Distributions of EFS among responders and OS were estimated by fitting parametric survival distributions to individual patient failure time data from TOWER using Flexsurv, a package for fully-parametric modelling of survival data in the R programming environment.

Drug acquisition and administration costs for patients receiving blinatumomab and FLAG-IDA were modelled independently of response and were estimated by combining information on the percentage of patients initiating and completing each cycle of treatment in TOWER with estimates of the costs per cycle. Administration costs for blinatumomab include the costs of hospitalisation, outpatient visits for bag changes, and the pro-rated costs of infusion pump utilisation. Costs for FLAG-IDA include costs of hospitalisation and are informed from resource utilisation studies. Costs of allo-SCT are modelled independently of response; these were estimated by combining estimates of the proportion of patients receiving a post-baseline allo-SCT in TOWER with estimates of the lifetime healthcare costs of allo-SCT. Costs of subsequent salvage therapy are modelled as "one-off" costs at the time of entry into the refractory/relapsed state. Terminal care costs are modelled as one-off costs at the time of death.

### 5.2.3 Features and justification of the de novo analysis

A summary of the key features of the *de novo* analysis and their justification is provided in Table 5-1.

**Table 5-1. Features of the de novo analysis**

| Factor | Chosen values | Justification |
|---|---|---|
| Time horizon | 50 years | A 50-year time horizon corresponds to a lifetime projection for a typical patient in TOWER (median age [redacted] years, and [redacted] % patients aged 18 to < 35 years). The use of a lifetime projection is used to capture the long-term benefits and costs of blinatumomab treatment. In the model base case, 2% of blinatumomab and 1% of SOC chemotherapy patients are projected to be alive at 50 years. |
| Cycle length | Weekly | A weekly cycle length was used to permit accurate estimation of survival without the need for half-cycle correction |
| Were health effects measured in QALYs; if not, what was used? | QALY | Consistent with the NICE reference case[77] |
| Discount of 3.5% for utilities and costs (1.5% for health outcome only in sensitivity analysis) | 3.5% (1.5% in sensitivity analysis) | Consistent with the NICE reference case[77] |
| Perspective (NHS/PSS) | NHS/PSS | Consistent with the NICE reference case[77] |
| NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life-years; SOC, standard of care. | | |

### 5.2.4 Intervention technology and comparators

Blinatumomab was included in the model based on an administration, dose, and dosing schedule consistent with the phase 3 TOWER RCT and key registrational phase 2 study (Study MT103-211), its marketing authorisation, and anticipated use in clinical practice in England and Wales during two induction and up to three additional consolidation cycles:

- Continuous IV infusion over 4 weeks (9 µg/day during Week 1 of Cycle 1 then 28 µg/day for the remainder of the cycle and during subsequent cycles) followed by a treatment-free interval of 2 weeks.

Consistent with the phase 3 TOWER RCT, which is used to inform the base-case clinical effectiveness model inputs, a proportion of patients in the model base case received up to 12 additional months of blinatumomab maintenance therapy if they continued to have a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi after three consolidation cycles. However, maintenance therapy is not included in the marketing authorisation for blinatumomab. The proportion of patients in the blinatumomab arm of TOWER in whom six or more cycles of blinatumomab was initiated (i.e., more than the maximum five cycles permitted by the marketing authorisation) was small ([redacted] %).

FLAG-IDA is considered to represent the most relevant comparator for blinatumomab, given that FLAG-based regimens, particularly FLAG-IDA, are those most commonly used in clinical practice in England and Wales based on UK-specific data from a survey of haemato-oncologists and haematologists, as well as feedback from UK clinical experts consulted by Amgen (Section 3.4.4.2). Administration and dosing of FLAG- IDA was based on the FLAG-IDA protocol from the Royal Surrey NHS Foundation Trust (Section 5.5.3.2).[109] As a simplifying assumption, FLAG-IDA treatment duration in the model base case was based the SOC chemotherapy arm in the TOWER study.

## *5.3 Clinical parameters and variables*

### 5.3.1 Clinical data sources

All the clinical parameters used in the model base case were derived from the TOWER RCT (Section 4**Error! Reference source not found.**), and are summarised in Table 5-2. For the model base case, these clinical effectiveness estimates were based on data from the TOWER FAS (i.e., ITT population). Clinical outcomes for patients in the SOC chemotherapy arm in TOWER was assumed to be generalisable to patients receiving FLAG-IDA given that clinical guidelines, including the EWALL guidelines,[48] suggest that there is no clearly superior salvage chemotherapy regimen in R/R Ph- B-precursor ALL, and UK Clinical experts consulted by Amgen considered the outcomes in the SOC chemotherapy arm in TOWER to be broadly generalisable to FLAG-IDA (Section 4.13.3**Error! Reference source not found.**).

**Table 5-2. Clinical data sources for base-case analysis**

| | Response[a] | EFS among responders[a] | Overall survival |
|---|---|---|---|
| Blinatumomab | TOWER study blinatumomab arm (FAS) | TOWER study blinatumomab arm (FAS) | TOWER study blinatumomab arm (FAS) |
| FLAG-IDA | TOWER study SOC chemotherapy arm (FAS) | TOWER study SOC chemotherapy arm (FAS) | TOWER study SOC chemotherapy arm (FAS) |

[a] Response defined as haematological remission (CR/CRh*/CRi) within 12 weeks of treatment initiation

CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SOC, standard of care.

Scenario analyses were conducted on the TOWER SAS (i.e., patients who study drug) given the high proportion and imbalance of randomised patients who did not receive study drug (Section 4.13.2), and the pre-specified subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation given the relevant comparator for this appraisal is FLAG-IDA. As the OS HR for blinatumomab versus SOC chemotherapy was more favourable in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen (Section 4.8.2), this suggest the base-case approach (i.e. using the whole SOC chemotherapy arm) is potentially conservative. These scenario analyses are described in more detail in Section 5.8.3, and a list of the parameter values can be found in Appendix X.

Furthermore, a comprehensive subgroup analysis was conducted on the pre-specified stratification factor subgroup of patients in TOWER who had received no prior salvage therapy. This subgroup analysis is pertinent to the decision problem as clinicians are likely to use blinatumomab early in the treatment pathway (i.e., in patients who have not received prior salvage therapy) given that treating patients earlier in the treatment pathway (i.e., patients with a better prognosis) with a more effective therapy is likely to lead to improvements in both absolute and relative OS (Section 4.8.2). This subgroup analysis is described in more detail in Section 5.8.4, and a list of the parameter values can be found in Appendix XI.

The probabilities of response for patients receiving blinatumomab and SOC chemotherapy in the model base case were estimated based on the proportion of patients achieving a haematological remission (CR/CRh*/CRi) within 12 weeks of treatment initiation in the TOWER FAS (43.9% and 24.6% for blinatumomab and SOC chemotherapy respectively; Section 4.7.3).

In TOWER, EFS was defined as time since randomisation until the date of relapse after achieving a CR/CRh*/CRi or death, with subjects who did not achieve CR/CRh*/CRi within 12 weeks of treatment initiation being assigned an EFS duration of 1 day (Sections 4.3.3 and 4.4). This definition results in a large number (> 50%) of patients being assigned an event at Day 1, followed by a period of no event risk before response is assessed. In order to avoid convergence issues and erroneous projections resulting from this pattern, parametric curves were fitted to EFS only among responders (i.e., patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation) and from the date of response, rather than from the date of

randomisation. This eliminates the immediate drop on Day 1 as well as the period prior to response assessment during which there is no risk of an event.

Because survival distributions for EFS and OS in TOWER were incomplete, it was necessary to extrapolate survival distributions beyond the end of the trial to obtain unbiased estimates of the gains in life expectancy and QALYs with blinatumomab. Parametric distributions for EFS among responders and OS were estimated by fitting parametric survival distributions to individual patient failure time data from TOWER using Flexsurv.[110] A number of parametric distributions were fitted to data on EFS among responders and OS, including the exponential, Weibull, log-logistic, lognormal, Gompertz, gamma, and restricted cubic spline (RCS) distributions, and were selected based on fit statistics, as well as by visual inspection of survival distributions, hazard functions, time-dependent hazard ratios, diagnostic plots for treatment effects, and clinical plausibility (clinical expert opinion and observational data). The curves, fit statistics, and parameter values for the curves are reported in Appendix VIII.

The Bayesian information criterion (BIC) statistic was used as the primary fit statistic since it penalises overly complex models and its use mitigates the risk of overfitting statistical noise in the tails of the observed distributions. Diagnostic plots for the nature of treatment effects were produced using an extension of an approach proposed by Bagust and Beale and in accordance with recommendations from the NICE DSU Technical Support Document on survival analysis.[111] With this extended approach, an estimated treatment effect for each of four different treatment-effect assumptions (i.e., constant shift in survival time, accelerated failure time, proportional hazards, and proportional odds) was applied to failure times in the control group to obtain a counterfactual Kaplan–Meier survival distribution for the control group reflecting the expected outcome had those patients received study treatment with the specified treatment-effect assumption. The counterfactual control group survival distribution was then compared with the observed survival distribution for the group receiving study treatment. If the treatment-effect assumption is accurate, the two curves should overlap. This approach permits comparisons of different treatment-effect assumptions on the same (natural) scale.

For each time-to-event outcome (i.e., EFS among responders and OS) and distribution, models were estimated alternately (a) including a single indicator variable for treatment group in the model formulation (“restricted models”) and (b) including treatment-group interaction terms for every distributional parameter (“unrestricted models”). With both approaches, the distributions of survival for the treatment and control group are assumed to be of the same class (e.g., both are Weibull). However, with the first approach (restricted models), the effect of treatment is restricted to a single distributional parameter (e.g., the scale parameter of the Weibull distribution) and yields projections of survival that are consistent with either a proportional hazards and/or accelerated failure time treatment-effect model, depending on the distribution (e.g., the Gompertz is a proportional hazards model, the log-normal and log-logistic are accelerated failure time models, and the exponential and Weibull are both proportional hazards and accelerated failure time models). The second approach (unrestricted models) places no such restrictions on the distributional parameters or the assumed nature of treatment effect within the class. Estimating these restricted and unrestricted models in this way permits comparison of the BIC (and other fit statistics) for unrestricted and restricted models (which would not be possible if the unrestricted models were estimated as two separate regression equations—one for each arm of the trial). The assumption that the distributions of survival for the treatment and control group are of the same class is reasonable

because any differences in shapes between arms can generally be accommodated by the use of unrestricted forms of more flexible survival distributions (e.g., RCSs).

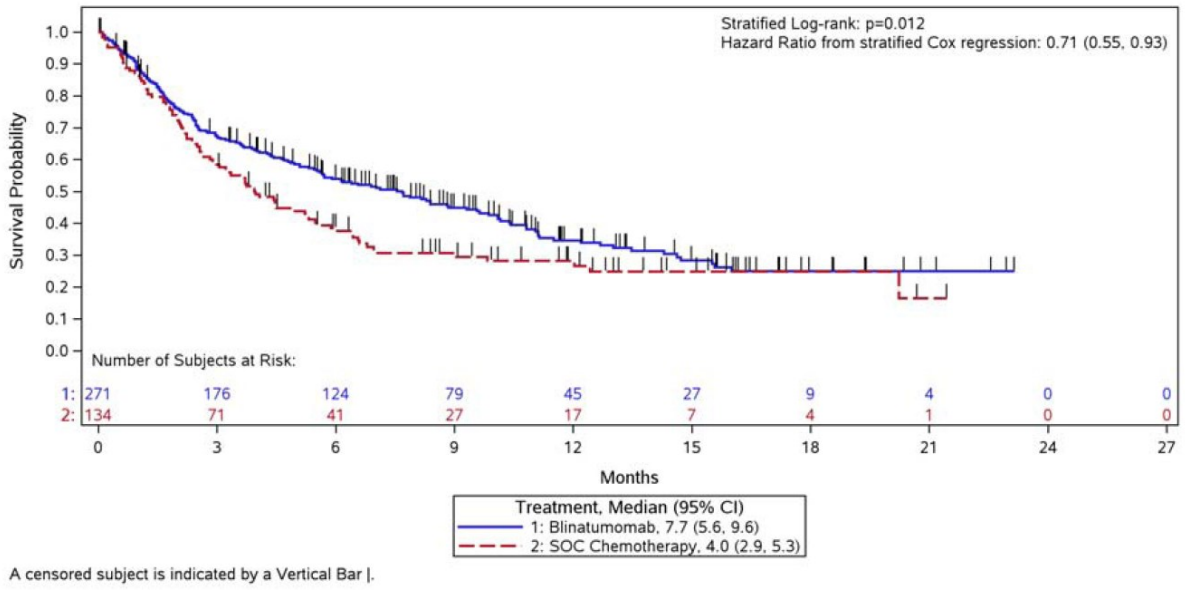
### 5.3.2 Overall survival

#### *5.3.2.1 Overall survival in TOWER*

Overall survival Kaplan–Meier curves and piecewise exponential hazard rates for patients in the TOWER FAS are shown in Figure 5-2 and Figure 5-3 below. Although the Kaplan–Meier plots clearly diverge within the first 3 months after randomisation and separation becomes more pronounced over time, the divergence appears to be limited to approximately 15 months. This should be interpreted in the context of the small patient numbers at risk at and beyond 15 months, the resulting highly limited statistical power to detect significant differences in treatment effects in later months of follow-up, and the potential confounding effects of allo-SCT and crossover to subsequent treatment (Section 4.7.1).

The hazard rates in both arms increased during the first 2 months, followed by decreasing hazards until the end of follow-up.

**Figure 5-2. Kaplan–Meier plot of overall survival (TOWER, FAS)**

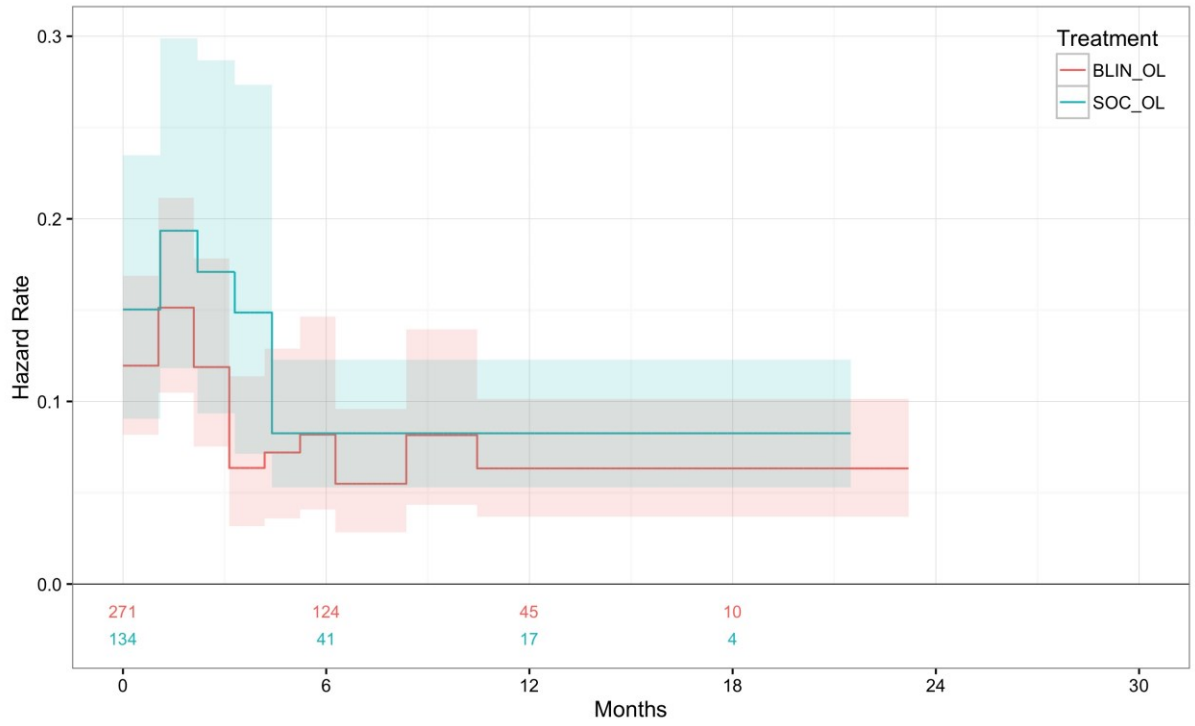



A censored subject is indicated by a Vertical Bar |.

Reference: TOWER primary analysis CSR (Figure 10-1)[80]

CI, confidence interval; FAS, full analysis set; SOC, standard of care.

**Figure 5-3. Piecewise exponential hazard rates for overall survival (TOWER, FAS)**




Note: Shaded areas represent 95% confidence intervals

Blin_OL, blinatumomab arm; SOC_OL, standard of care chemotherapy arm.

### *5.3.2.2 Overall survival curve selection*

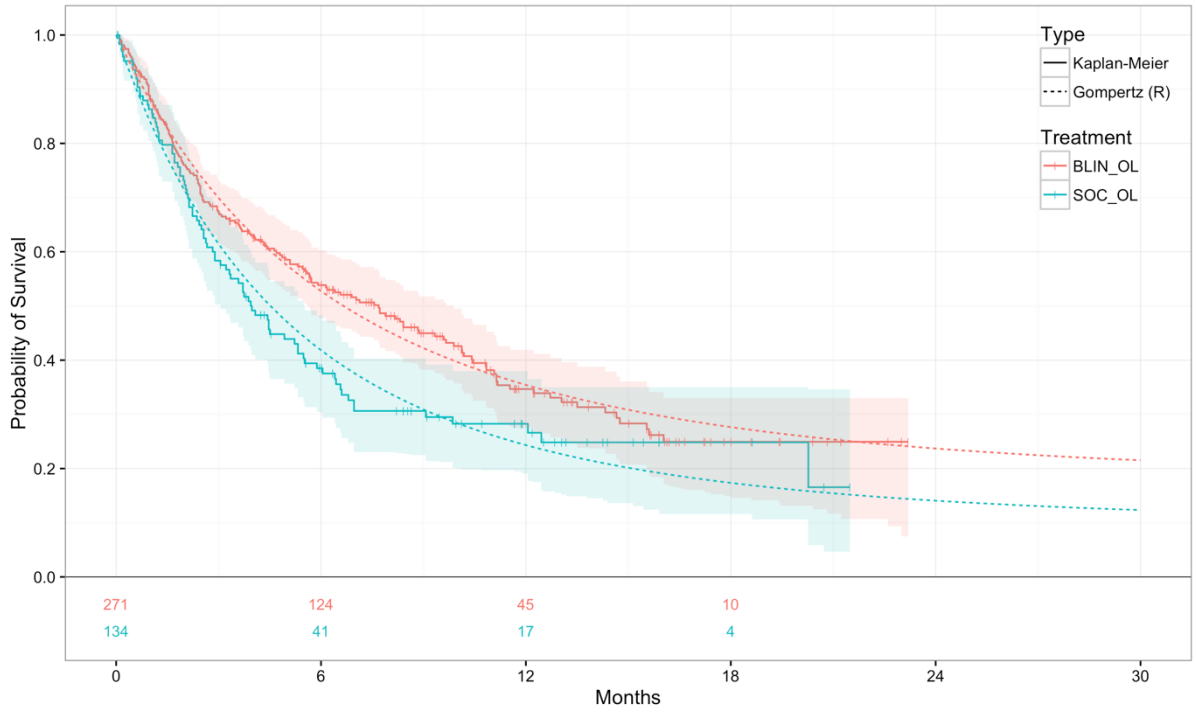
The criteria used for OS curve selection are described in Section 5.3.1, and are in accordance with the recommendations of the NICE DSU technical support document on survival analysis:[112]

- Visual inspection of goodness of fit
- Long term plausibility informed using historical data and expert opinion
- Statistical fit (BIC, Akaike information criterion [AIC])

Based on this framework, the restricted Gompertz was selected for modelling OS in the model base case. Additional details are provided below regarding the restricted Gompertz curve and curve selection process. Additional tables and figures relating to the curve-fitting process are shown in Appendix VIII.

The restricted Gompertz model OS curve and Kaplan–Meier OS curve for the TOWER FAS are compared in Figure 5-4. The visual fit of the chosen Gompertz model was excellent for the blinatumomab arm, showing no systematic under- or over-estimation. Fit to the SOC chemotherapy arm was less accurate, with survival overestimated from Months 3 to 10 and underestimated thereafter.

**Figure 5-4. Comparison of restricted Gompertz and Kaplan–Meier curves for overall survival among responders (TOWER, FAS)**

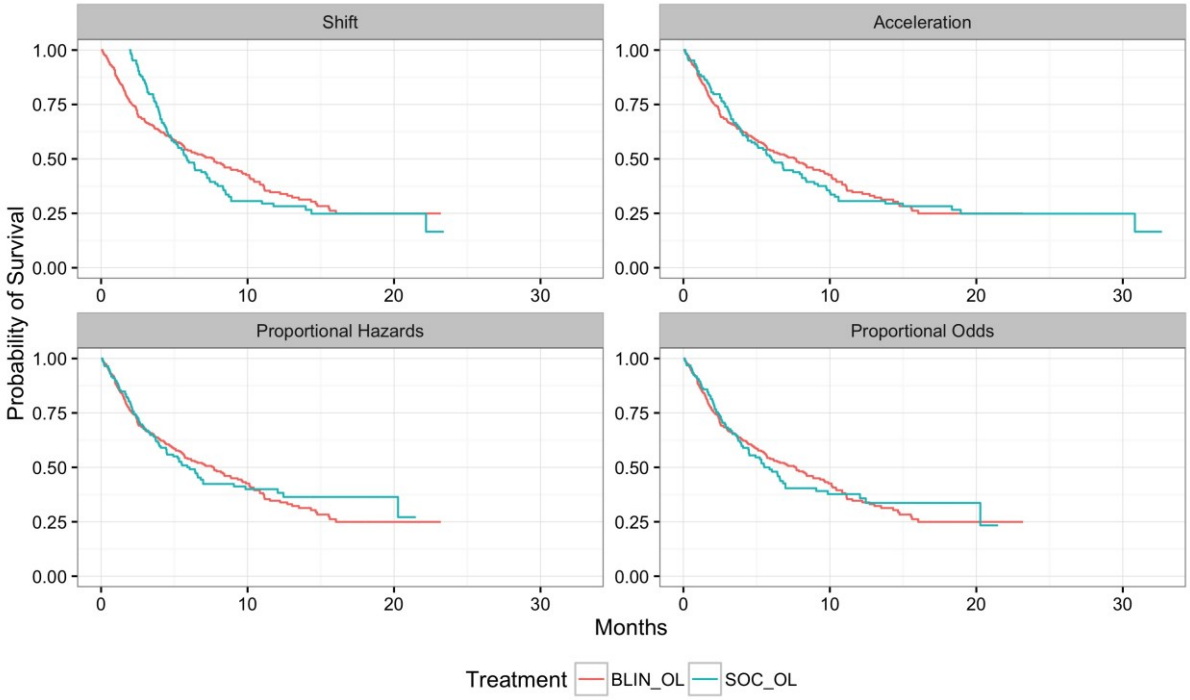



Note: Shaded areas represent 95% confidence intervals

(R), restricted; Blin_OL, blinatumomab arm; FAS, full analysis set; SOC_OL, standard of care chemotherapy arm.

Proportionality of hazards was evaluated using a combination of graphical methods and hypothesis testing. Counterfactual treatment-effect plots (Figure 5-5) showed a high degree of overlap between the blinatumomab and SOC chemotherapy arms for the proportional hazards model, providing supportive evidence in favour of models based on this treatment-effect assumption. No significant deviation from proportional hazards was identified in the Schoenfeld residuals (Figure 5-6).

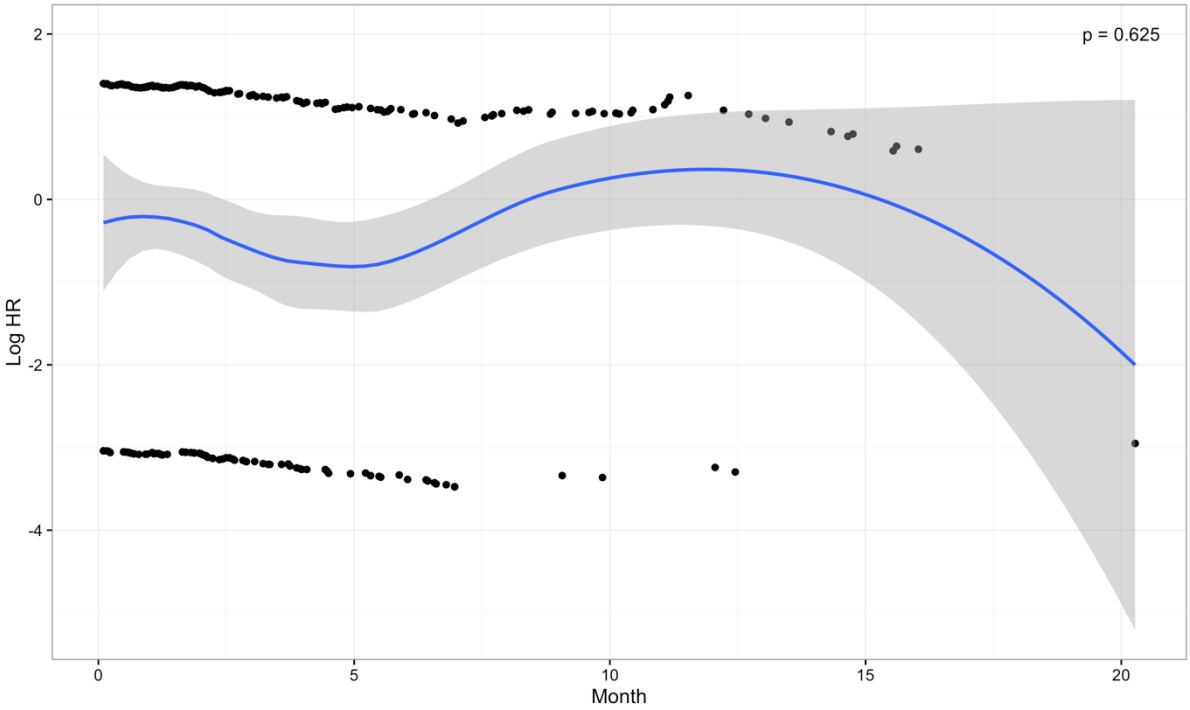
**Figure 5-5. Counterfactual survival plots for overall survival (TOWER, FAS)**




Note: Counterfactual SOC chemotherapy arm was calculated by applying to actual failure time date an estimate of the assumed treatment effect.

Blin_OL, blinatumomab arm; FAS, full analysis set; SOC_OL, standard of care chemotherapy arm.

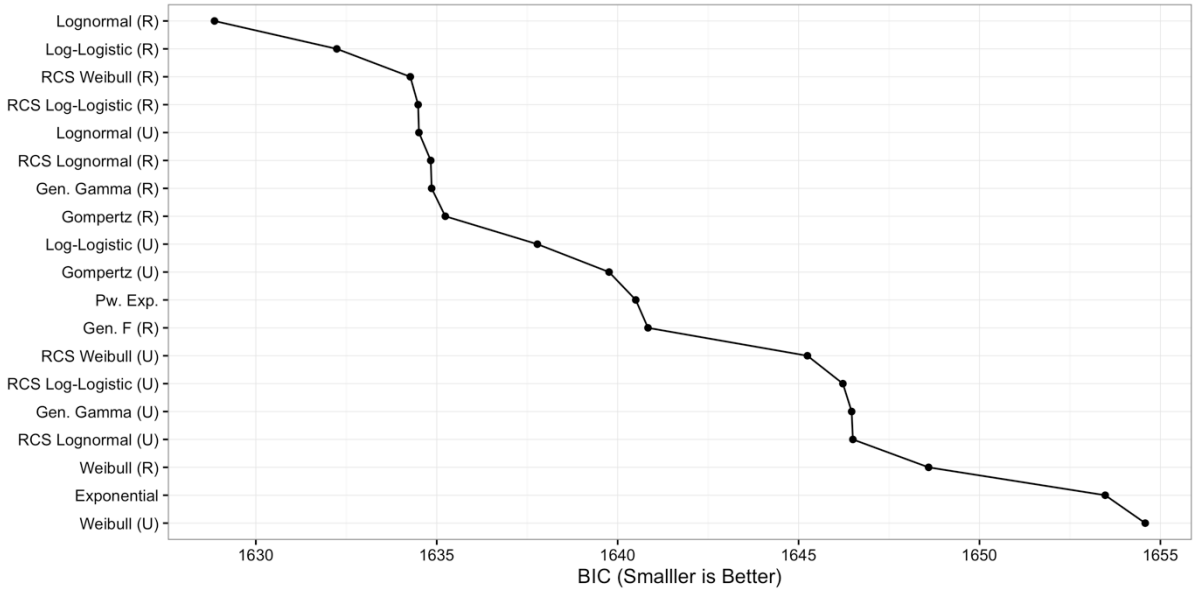
**Figure 5-6. Schoenfeld residuals for overall survival (TOWER, FAS)**




FAS, full analysis set; HR, hazard ratio

Statistical fit for all model distributions was assessed using the BIC and is shown in Figure 5-7. While the restricted Gompertz was ranked 8th in terms of statistical fit based on the BIC, its fit was not materially worse than that of the 3rd-ranked distribution (RCS Weibull).

**Figure 5-7. Fit statistics for overall survival (TOWER, FAS)**




(R), restricted; (U), unrestricted; BIC, Bayesian information criterion; F, F-distribution; FAS, full analysis set; Gen., generalised; PW. Exp., piecewise exponential; RCS, restricted cubic spline.

The plausibility of long-term projections of OS was assessed using data from a historical comparator cohort (Study 20120310). This historical comparator cohort represents the largest ever assembled cohort of R/R ALL patients, had a longer follow-up than TOWER, and was used by EMA to assess the relative effectiveness of blinatumomab for the treatment of adult patients with R/R Ph- B-precursor ALL.[12] In order to obtain a comparable set of patients from Study 20120310, only patients treated in or after the year 2000 were included. Consistent with the approach used to match patients in the historical cohort to patients in Study MT103-211 (Section 4.11.6.2), patients in the historical cohort were stratified by a combination of age (< 35 or ≥ 35 years) and prior lines of treatment (allo-SCT, in first salvage, in second or greater salvage), and weighted according to the distributions of these characteristics in the SOC chemotherapy arm of TOWER.

Kaplan–Meier curves of OS from TOWER and from matched patients from Study 20120310 are presented in Figure 5-8. Survival in the SOC chemotherapy arm of TOWER closely matched that of the historical cohort initially. Although survival in the historical comparator cohort is lower than that in the SOC chemotherapy arm of TOWER after 6 months, it is still within the 95% CI of the SOC chemotherapy arm. These differences might be a result of the [redacted] of dosed subjects in the SOC chemotherapy arm of TOWER who received subsequent treatment with innovative anticancer therapies (blinatumomab, inotuzumab, and CAR T cells; Section 4.12.1.2).

**Figure 5-8. Comparison Kaplan–Meier overall survival in TOWER (FAS) and matched patients from the historical cohort (Study 20120310)**

Note: Shaded areas represent 95% confidence intervals. 'Historical comparator' refers to matched patients from Study 20120310.

Blin_OL, blinatumomab arm; FAS, full analysis set; SOC_OL, standard of care chemotherapy arm.

The selected restricted Gompertz model OS curve and Kaplan–Meier OS curve from matched patients from Study 20120310 is shown in Figure 5-9. The Gompertz curves from TOWER exhibit a nearly identical shape as the historical comparator cohort, with a clear pattern of rapidly decreasing hazards. However, the Gompertz model projects survival for the TOWER SOC chemotherapy arm approximately 5% higher than that of the historical comparator cohort. This is likely a consequence of the improvement of survival outcomes for R/R ALL patients between 2000 and 2015 when TOWER was initiated,[29] and that patients recruited in large RCTs tend to have a better prognosis than patients treated in the real-world setting. The strong similarity of shape was confirmed by adjusting the historical comparator cohort curve by applying an arbitrary HR of 0.85. This "adjusted" historical comparator curve has a virtually identical shape to the Gompertz curve for the SOC chemotherapy arm of TOWER.

**Figure 5-9. Overall survival projections from TOWER (FAS) compared with Study 20120310**

Note: 'Historical comparator' refers to matched patients from Study 20120310.

Blin_OL, blinatumomab arm; FAS, full analysis set; HR, hazard ratio; SOC_OL, standard of care chemotherapy arm.

Because the hazard rates for OS based on the restricted Gompertz distribution asymptotically approach zero, these curves were assumed to reflect disease-specific mortality. Age- and sex-matched general population mortality rates were applied additively to the estimated Gompertz mortality in order to ensure that long-term survival projections reflected the aging patient cohort.[113] In calculating mortality rates the mean age and sex distribution of patients was based on the FAS distribution of TOWER (mean [redacted] years of age; 59% male; Section 4.5.2).

Whilst the estimated Gompertz model assumes a constant HR, it is not known how long the observed OS benefit of blinatumomab would last beyond the follow-up of TOWER. In the absence of evidence on the long-term survival benefit of blinatumomab, the hazard rate for the blinatumomab arm was assumed to be equal to that of SOC chemotherapy arm beyond 4 years in the base case. Based on feedback from UK clinical experts, patients remaining alive after 4 years are likely to be cured. If patients are cured then there should be no difference in mortality by treatment group.The distributions of OS used in the model base case are presented in Figure 5-10, along with the Kaplan–Meier OS curves from TOWER and matched patients from Study 20120310.

**Figure 5-10. Distributions of overall survival used in base-case analyses**

Note: 'Historical comparator' refers to matched patients from Study 20120310.

SOC, standard of care chemotherapy

The other fitted parametric curves and their performances according to selection criteria are summarised in Table 5-3. Distributions are sorted by statistical fit (best to worst). The RCS log-logistic distribution has similar statistical fit as the Gompertz. It also had satisfactory visual fit relative to the TOWER Kaplan–Meier curve and historical comparator cohort. It was not selected however, as long-term shape was different from that for the historical comparator cohort. Results using the RCS log-logistic as an alternative curve fit are explored in a scenario analysis (Section 5.8.3).

Additional details around all of the other fitted parametric curves are provided in Appendix VIII.

**Table 5-3. Selection criteria for parametric survival distributions for overall survival**

| Distribution | | | Treatment Effect | | Fit to TOWER | | Plausibility |
|---|---|---|---|---|---|---|---|
| Family | Restricted | Converged | Counter-factual Plot | Schoenfeld Residuals | Statistical Fit | Visual Fit | |
| Lognormal | Yes | ✔ | ✔ | N/A | 1st | ✔ | × |
| Log-Logistic | Yes | ✔ | ✔ | N/A | 2nd | ✔ | × |
| RCS Weibull | Yes | ✔ | ✔ | ✔ | 3rd | ✔ | × |
| RCS Log-Logistic | Yes | ✔ | ✔ | N/A | 4th | ✔ | × |
| Lognormal | No | ✔ | N/A | N/A | 5th | ✔ | × |
| RCS Lognormal | Yes | ✔ | N/A | N/A | 6th | ✔ | × |
| Gen. Gamma | Yes | ✔ | ✔ | N/A | 7th | ✔ | × |
| Res. Gompertz | Yes | ✔ | ✔ | ✔ | 8th | ✔ | ✔ |

| Distribution | | | Treatment Effect | | Fit to TOWER | | Plausibility |
|---|---|---|---|---|---|---|---|
| Family | Restricted | Converged | Counter-factual Plot | Schoenfeld Residuals | Statistical Fit | Visual Fit | |
| Log-Logistic | No | ✔ | N/A | N/A | 9th | ✔ | × |
| Gompertz | No | ✔ | N/A | N/A | 10th | ✔ | × |
| Piecewise Exponential | No | ✔ | N/A | N/A | 11th | × | × |
| Gen. F | Yes | ✔ | ✔ | N/A | 12th | ✔ | × |
| RCS Weibull | No | ✔ | N/A | N/A | 13th | ✔ | × |
| RCS Log-Logistic | No | ✔ | N/A | N/A | 14th | ✔ | × |
| Gen. Gamma | No | ✔ | N/A | N/A | 15th | ✔ | × |
| RCS Lognormal | No | ✔ | N/A | N/A | 16th | ✔ | × |
| Weibull | Yes | ✔ | ✔ | ✔ | 17th | × | × |
| Exponential | Yes | ✔ | ✔ | ✔ | 18th | × | × |
| Weibull | No | ✔ | N/A | N/A | 19th | × | × |
| Gen. F | No | × | N/A | N/A | n/a | n/a | × |

F, F-distribution; N/A, not applicable; RCS, restricted cubic spine; Res., restricted.

### 5.3.3 Event-free survival among responders

#### *5.3.3.1 Event-free survival among responders in TOWER*

This outcome is similar to the pre-specified TOWER secondary endpoint of duration of CR/CRh*/CRi reported in Section 4.7.3, but differs slightly in that for EFS, relapse dates were grouped into discrete intervals irrespective of where relapse occurred during the cycle to address potential bias relating to different cycle lengths between study arms (Sections 4.3.3 and 4.4). To address this potential bias, it was considered more appropriate to use EFS data among-responders (i.e., EFS in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation) to inform the model, rather than data on duration of CR/CRh*/CRi. Despite the differences in assignment of relapse dates (grouped for EFS vs. as observed for duration of CR/CRh*/CRi), median duration of CR/CRh*/CRi and median EFS among responders were similar (duration of response: median 4.6 and 7.3 months for blinatumomab and SOC chemotherapy, respectively [Section 4.7.3]; EFS among responders: median [redacted] and [redacted] months, respectively). As shown in Figure 5-11, the Kaplan–Meier distributions of duration of CR/CRh*/CRi and EFS among responders are similar.

**Figure 5-11 Comparison of Kaplan–Meier duration of CR/CRh*/CRi and event-free survival among repsonders (TOWER, FAS)**

Note: Shaded areas represent 95% confidence intervals. 'Responders' refers to patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation.

Blin_OL, blinatumomab arm; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; DOR, duration of response (CR/CRh*/CRi); EFS, event-free survival.

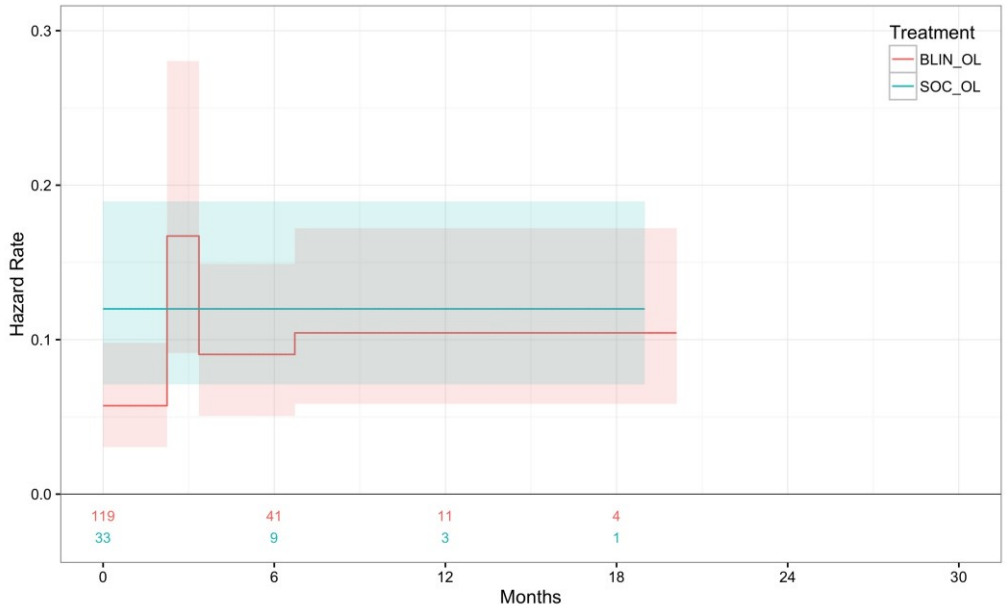
Kaplan–Meier survival curves and piecewise exponential hazards for EFS among responders from the date of response, are shown in Figure 5-12 and Figure 5-13, respectively. EFS among responders in the SOC chemotherapy arm was associated with substantial uncertainty due to the small number of patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation in this study arm (n = 33, 24.6%; Section 4.7.3). EFS among responders was generally higher for the blinatumomab arm during the first 11 months, with the SOC chemotherapy arm crossing above the blinatumomab arm from Months 11 to 19. No events were observed during the SOC chemotherapy arm from Months 9 to 19, which likely reflects the very small numbers of patients at risk. Hazards for blinatumomab initially increased, then were followed by lower rates in the later months of the trial. No pattern in the hazard rates of the SOC chemotherapy arm could be identified due to the extremely small number of events.

**Figure 5-12. Kaplan–Meier plot of event-free survival among responders (TOWER, FAS)**

Note: Shaded areas represent 95% confidence intervals. ‘Responders’ refers to patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation.

Blin_OL, blinatumomab arm; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; SOC_OL, standard of care chemotherapy arm.

**Figure 5-13. Piecewise exponential hazard rates for event-free survival among responders (TOWER, FAS)**




Note: Shaded areas represent 95% confidence intervals. ‘Responders’ refers to patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation.

Blin_OL, blinatumomab arm; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; SOC_OL, standard of care chemotherapy arm

#### *5.3.3.2 Event-free survival among responders curve selection*

The same approach described above for selecting the parametric survival distribution for OS (Section 5.3.2.2) was used to select the parametric survival distribution for EFS among responders. Based on this approach, the restricted generalised gamma distribution was selected for modelling EFS among responders in the model base case due to its combination of statistical fit, visual fit and the plausibility of its projections. It should be noted that unlike the restricted Gompertz model, which assumes proportionality of hazards, the restricted Gamma distribution is an accelerated failure time model. Accordingly, treatment is assumed to have a proportional effect on failure times rather than the hazard rate.

The restricted generalised gamma EFS among responders curve and Kaplan–Meier EFS among responders curve for the TOWER FAS are compared in Figure 5-14. A good visual fit was obtained for both study arms, with no clear pattern of bias.

**Figure 5-14. Visual fit of restricted generalised gamma distribution to event-free survival among responders (TOWER, FAS)**

Note: Shaded areas represent 95% confidence intervals. 'Responders' refers to patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation.

(R), restricted; Blin_OL, blinatumomab arm; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; FAS, full analysis set; SOC_OL, standard of care chemotherapy arm.

The plausibility of long-term projections was assessed based on two criteria. First, a pattern of decreasing hazards was expected. The OS data from Study 20120310 indicates a long-

term trend of decreasing hazard rates consistent with a subset of surviving patients being cured. Logically, this implies that a subset of patients achieve durable long-term remission and thus decreasing hazard rates for relapse would be expected as well. Distributions which did not yield projections of decreasing long-term hazard rates were therefore discarded from consideration. Second, the hazard rates for blinatumomab were assumed to not be greater than those for SOC chemotherapy at any time during the model timeframe. Evidence on the treatment effect of blinatumomab on EFS among responders is limited due to the small number of patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation in the SOC chemotherapy arm (n = 33, 24.6%; Section 4.7.3). Nevertheless, TOWER provides some evidence that blinatumomab may delay relapse among responders, and there is no reason to believe EFS among responders would ever be less for patients receiving blinatumomab than for patients receiving SOC chemotherapy. Accordingly, distributions that yielded projections in which that the hazard rate for EFS among responders would be greater in patients receiving blinatumomab than in patients receiving SOC chemotherapy were discarded.

The other fitted parametric curves and their performances according to selection criteria are summarised in Table 5-3. Distributions are sorted by statistical fit (best to worst). While all of the top three distributions in terms of statistical fit met both plausibility criteria, the restricted generalised gamma distribution was deemed most plausible due to its longer tail being more consistent with the results of Study 20120310. Detailed tables and figures used for the curve-selection process for EFS among responders are reported in Appendix VIII

**Table 5-4. Selection criteria for parametric survival distributions for event-free survival among responders**

| Distribution | | | Treatment Effect | | Fit to TOWER | | Plausibility | |
|---|---|---|---|---|---|---|---|---|
| Family | Restricted | Converged | Counter-factual Plot | Schoenfeld Residuals | Statistical Fit | Visual Fit | Decreasing Hazards | HR ≤ 1 |
| Lognormal | Yes | ✔ | ? | N/A | 1st | ✔ | ✔ | ✔ |
| Gen. Gamma | Yes | ✔ | ? | N/A | 2nd | ✔ | ✔ | ✔ |
| RCS Lognormal | Yes | ✔ | ? | N/A | 3rd | ✔ | ✔ | ✔ |
| Lognormal | No | ✔ | ? | N/A | 4th | ✔ | ✔ | × |
| Log-Logistic | Yes | ✔ | ? | N/A | 5th | ✔ | ✔ | ✔ |
| RCS Log-Logistic | Yes | ✔ | ? | N/A | 6th | ✔ | ✔ | ✔ |
| Gen. F | Yes | ✔ | ? | N/A | 7th | ✔ | ✔ | ✔ |
| RCS Weibull | Yes | ✔ | ? | × | 8th | ✔ | ✔ | ✔ |
| Log-Logistic | No | ✔ | ? | N/A | 9th | ✔ | ✔ | × |
| RCS Lognormal | No | ✔ | ? | N/A | 10th | ✔ | ✔ | × |
| Exponential | Yes | ✔ | ? | N/A | 11th | × | × | ✔ |
| RCS Log-Logistic | No | ✔ | ? | N/A | 12th | ✔ | ✔ | × |
| RCS Weibull | No | ✔ | ? | N/A | 13th | ✔ | ✔ | × |

| Distribution | | | Treatment Effect | | Fit to TOWER | | Plausibility | |
|---|---|---|---|---|---|---|---|---|
| **Family** | **Restricted** | **Converged** | **Counter-factual Plot** | **Schoenfeld Residuals** | **Statistical Fit** | **Visual Fit** | **Decreasing Hazards** | **HR ≤ 1** |
| Weibull | Yes | ✔ | ? | × | 14th | × | × | ✔ |
| Weibull | No | ✔ | ? | N/A | 15th | × | × | × |
| Gompertz | Yes | ✔ | ? | × | 16th | × | × | ✔ |
| Piecewise Exponential | No | ✔ | ? | N/A | 17th | × | × | × |
| Gompertz | No | ✔ | ? | N/A | 18th | × | × | × |
| Gen. F | No | × | N/A | N/A | N/A | N/A | N/A | N/A |
| Gen. Gamma | No | × | N/A | N/A | N/A | N/A | N/A | N/A |

Note: 'Responders' refers to patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation

CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; F, F-distribution; Gen., generalised; HR, hazard ratio; N/A, not applicable; RCS, restricted cubic spline.

The distributions of EFS among responders used in the base-case analysis are presented in Figure 5-15. Consistent with the approach for modelling OS, age- and sex-matched general population mortality rates were applied additively to EFS to accurately reflect rates of death in the later years of the model and to ensure that EFS and OS did not cross.

**Figure 5-15. Distributions of event-free survival among responders used in base-case analyses**

EFS, event-free survival; SOC, standard of care chemotherapy

### 5.3.4 Transition probabilities

As noted in Section 5.2.2, because the model does not use a Markov cohort structure, but rather a partitioned survival model approach, transition probabilities between all states are not calculated. Descriptions of the survival distributions used in the model are provided in Section 5.3.2 and Section 5.3.3. It should be noted that the distributions used in the model do reflect changing hazards of relapse and survival over time, as well as changing treatment effects on these outcomes, over time. In the model base case, it was assumed that the hazard rates for OS for blinatumomab would be the same as those for SOC chemotherapy after 48 months. That is, it was assumed that there would be no additional benefit of treatment on the hazards of death after this point. It was also assumed that the probabilities of death for all patients would be the sum of the probability of death from the parametric restricted Gompertz distribution fit to the OS data from TOWER and age- and sex-matched UK general population mortality. Hence, the probabilities of death for both SOC chemotherapy and blinatumomab were assumed to increase over time as a consequence of increasing general population mortality with age.

## *5.4 Measurement and valuation of health effects*

### 5.4.1 HRQoL data from clinical trials

As noted in Section 4.7.7, data on HRQoL for adult patients with R/R Ph- B-precursor ALL are available from the phase 3 TOWER RCT, which collected information on the EORTC QLQ-C30. Descriptive statistics for EORTC QLQ-C30 can be found in Appendix IX. The key registrational phase 2 study (Study MT103-211) did not include any assessment of HRQoL. Although there were no pre-specified analyses of preference-based measures of HRQoL (i.e., utility values) in TOWER, it is possible to calculate the EORTC-8D from the EORTC QLQ-C30 (see Appendix X for more details). The EORTC-8D is a condition-specific preference-based measure of HRQoL derived from the EORTC QLQ-C30 for use in patients with cancer.[114,115] Also, published algorithms to map from the EORTC QLQ-C30 to EQ-5D utility values are available.[116,117] The use of mapping from the EORTC QLQ-C30 to EQ-5D is consistent with the NICE reference case,[77] and was therefore used in the model base case.

### 5.4.2 Mapping

In the TOWER study, HRQoL was assessed using the EORTC QLQ-C30. Details regarding the methods and results of analyses of the EORTC QLQ-C30 in TOWER are reported in Section 4.7.7. Several published algorithms for mapping from the EORTC QLQ-C30 to EQ-5D are available.[116,117] The use of mapped values from the EORTC QLQ-C30 to EQ-5D is consistent with the NICE reference case.[77] An analysis was therefore conducted in which utility values were calculated based on mapping the EORTC QLQ-C30 data from TOWER to the EQ-5D. These values were used in the base case of the economic evaluation. Utility values based on the EORTC-8D also were generated and used in scenario analyses (Section 5.8.3 and Appendix X).

Several algorithms for mapping from the EORTC QLQ-C30 to EQ-5D are available and have been summarised in reviews by Doble & Lorgelly 2016[117] and Arnold *et al.,* 2015 [116]. Of the algorithms identified in these reviews, the algorithm developed by Longworth *et al.,* 2014[118] was selected for the model base case. This algorithm was developed using data from 771

patients enrolled in three studies of patients with breast cancer, lung cancer, and multiple myeloma. The studies of breast and lung cancer were conducted in Canada while the study of multiple myeloma was a multi-country study. Version 3.0 of the EORTC QLQ-30 was used. In estimating the algorithm, only responses from the screening visit were used. The algorithm was estimated using a response mapping approach in which each of the five dimensions of the EQ-5D was regressed on 15 EORTC QLQ-C30 scale scores using multi-nominal logistic regression. EORTC QLQ-C30 scales together with age and sex are used to estimate three levels of probabilities associated with each of the five domains of EQ-5D, and the estimated probabilities and tariffs are then used to derive EQ-5D utility levels. Both the Doble & Lorgelly *et al.,* 2016 and Arnold *et al.,* 2015 reviews identified the Longworth algorithm as being among the best-performing algorithms in terms of:

- Accurate prediction of the best and worst EORTC QLQ-C30 health states
- Predicted values within the appropriate country-specific EQ-5D tariff range
- Relatively small mean absolute errors (MAE) and root-mean squared errors (RMSE) between observed and predicted values
- Minimal differences between observed and predicted QALYs over time.

In addition, this algorithm was based on a large sample which included patients with haematological malignancies (who are potentially more similar to patients with ALL than those with solid tumours), used the same version of the EORTC QLQ-C30 employed in the TOWER study (v 3.0), and permits the use of UK tariffs for the EQ-5D.

Descriptive statistics on the EQ-5D values generated using patient level EORTC QLQ-C30 data from TOWER were calculated by treatment group and categories corresponding to model health states including:

- **Initial (pre-response)**: All post-baseline assessments prior to the week 12 assessment of response
- **Response**: For patients with response (based on CR/CRh*/CRi at 12 weeks), all assessment on or after the 12 week assessment of response but prior to relapse
- **Relapse/Refractory**
  - Relapse: For patients with response, all assessments on or after relapse
  - Refractory: for patients with no response, all assessment on or after the 12 week assessment of response

Descriptive statistics on baseline utility values also were calculated for each group.

UK tariffs were used in the calculation of utility values. Missing items on the EORTC-QLQ-C30 were imputed by carrying item values forward from prior assessments or backward from subsequent assessments if the prior assessments were also missing. Assessments for which imputation was not feasible were dropped from the analysis.

Descriptive statistics on the mapped EQ-5D utility values by treatment group and health state are shown in Table 5-5. Descriptive statistics on the dimensions of the EORTC QLQ-C30 used in the mapping algorithm by health states are reported in Appendix IX.

**Table 5-5. Descriptive statistics on EQ-5D utility values mapped from EORTC QLQ-C30 in TOWER (FAS)**

| Health States | Blinatumomab (N = 271) | | | | SOC chemotherapy (N = 134) | | | |
|---|---|---|---|---|---|---|---|---|
| | N Patients | N Assess-ments | Mean | (SD) | N Patients | N Assess-ments | Mean | (SD) |
| Baseline[a] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Initial (Pre-response) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Response | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Relapsed/refractory | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[a]Includes all baseline assessments, including those for patients without post-baseline assessments.

EQ-5D, EuroQol five dimensions; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30; FAS, full analysis set; SD, standard deviation; SOC, standard of care.

Mean utility values at baseline were numerically higher for the SOC chemotherapy arm compared with the blinatumomab arm. For post-baseline assessments, mean utility values were numerically higher for blinatumomab compared with SOC chemotherapy for all health states. For both arms, mean utility values were lowest for the relapsed/refractory states. Mean utility values were higher for the relapsed/refractory state (blinatumomab 0.607; SOC chemotherapy 0.547) compared with those in the refractory state (blinatumomab: 0.580; SOC chemotherapy 0.537), reflecting the relatively small number of post-relapse observations which tended to have relatively high utility values. For the purpose of the modelling, mean utility values for the relapsed/refractory states were calculated with post-relapse assessments excluded (i.e., using only assessments classified in the refractory state), as post-relapse assessments were generally captured relatively soon after relapse and were likely to be unrepresentative of utility values for all time in the relapsed/refractory state.

### 5.4.3 Published HRQoL studies

As described in Section 5.1, an SLR to identify publications reporting cost-effectiveness studies for therapies used for the management of adult R/R Ph- B-precursor ALL, resource use and treatment costs for the management of adult R/R Ph- B-precursor ALL, and studies reporting HRQoL or utilities relevant for adult R/R Ph- B-precursor ALL was conducted in July 2015 and updated in November 2016. Search strategies were devised to identify relevant studies and were used to search Medline, EMBASE, the Cochrane library, EconLIT, and the NHS EED. Supplementary searches of conference proceedings and grey literature sources were also carried out to identify additional relevant studies. Full details of the search strategies, inclusion/exclusion criteria, screening procedure, and quality assessment are provided in Appendix VII.

One study that reported HRQoL or utility data was identified, which described utility values of different health states in adult R/R Ph- B-precursor ALL in the UK (Aristides *et al.,* 2015)[119] In this study, health state descriptions (or "vignettes") were developed based on a recent clinical trial and were validated by clinicians and patients with experience in R/R B-precursor ALL. Preferences for health states were estimated in a sample of 123 persons in the UK general public using the time-trade off (TTO) method. Mean utility values for the five hypothetical

health states evaluated in this study are shown in Table 5-6 . Mean utility was highest for the complete remission health state and lowest for the progressive disease health state. Use of data from this study was explored in a scenario analysis as described in Section 5.8.3; in the base-case analysis, trial-based utility data from TOWER were preferred in line with the NICE reference case.[77]

**Table 5-6. Summary of relevant HRQoL studies identified in the systematic literature review**

| First author, year | Country, recruitment and study type | Intervention | Population tariff used | Respondent population and sample size | Absolute utility value | Events reported |
|---|---|---|---|---|---|---|
| Aristides *et. al.*, 2015[119] | Country<br>UK<br><br>Recruitment<br>Participants were recruited by a third party vendor from London, Newcastle and Edinburgh<br><br>Study type<br>Observational registry | Not an interventional study | TTO questionnaire in a moderated group session, based on the MVH protocol modelling of valuation tariffs (MVH Group. The measurement and valuation of health: final report on the modelling of valuation tariffs. University of York: Centre for Health Economics. 1995.) | Population<br>Consultant haematologists, clinical nurses and three patients with B-precursor ALL<br><br>Sample size<br>N = 123; all participants understood the health state descriptions and were able to score them using the TTO questionnaire. | Mean (SEM):<br>• Complete remission: 0.86 (0.01)<br>• Complete remission with partial haematological recovery: 0.75 (0.02)<br>• Aplastic bone marrow: 0.59 (0.02)<br>• Partial remission: 0.50 (0.03)<br>• Progressive disease: 0.30 (0.04) | N/A |

HRQoL, health-related quality of life; MVH, Measurement and Valuation of Health; N/A, not applicable; SEM, standard error of the mean; TTO, time trade-off.

### 5.4.4 Key differences between values derived from the literature and those reported in or mapped from the clinical trials

Because of the differences in the definitions of the health states, it is difficult to compare the mapped utility values obtained from TOWER (Section 5.4.2) with the utility values reported in Aristides *et al.,* 2015.[119] Nevertheless, some important differences can be identified. Most notably, the utility value for the progressive disease state (0.30) in Aristides *et al.,* 2015 is substantially lower than that for the mapped EQ-5D utility values for the refractory state for both treatment groups in TOWER ([redacted] for blinatumomab and [redacted] SOC chemotherapy in the FAS). The reasons for this difference are uncertain, but it may be due to failure of the health state descriptions to accurately portray this health state, lack of sensitivity of the mapped EQ-5D utilities to changes in HRQoL associated with lack of response, or limited numbers of assessments for the refractory health states in TOWER. Further information on the utility values used in Aristedes *et al.,* 2015 are provided in Appendix X.

### 5.4.5 Adverse reactions

The impact of AEs on utility values in TOWER was not explicitly evaluated as it is assumed that the effect of AEs on HRQoL are captured through the use of treatment-specific utility values derived from EORTC QLQ-C30. Since the crude incidence rates for the majority of the most common ≥ Grade 3 AEs were higher in the SOC chemotherapy arm than in the blinatumomab arm of TOWER (Section 4.12), it is therefore possible that this assumption is conservative.

### 5.4.6 HRQoL data used in cost-effectiveness analysis

Utility values in the model are assumed to be dependent on health state and treatment. In the base case, utility values were based on EQ-5D utility values derived from EORTC QLQ-C30 assessments in TOWER using the response mapping algorithm developed by Longworth *et al.,* 2014 and UK EQ-5D tariffs[116,118].

To obtain utility values for the model, mapped EQ-5D utility values from TOWER were analysed using generalised linear model (GLM)/generalised estimating equations (GEE) regression. In the GLM/GEE regression, utility values were the dependent variable and the following were included as independent variables:

- Blinatumomab baseline assessment (1 = yes, 0 = no)
- Blinatumomab pre-response assessment (1 = yes, 0 = no)
- Blinatumomab in response assessment (1 = yes, 0 = no)
- Blinatumomab refractory assessments (1 = yes, 0 = no)
- SOC baseline assessment (1 = yes, 0 = no)
- SOC pre-response assessments (1 = yes, 0 = no)
- SOC in response assessments (1 = yes, 0 = no)
- SOC refractory assessments (1 = yes, 0 = no)
- Time from death (1 = less than one month; 0 = 1 month or more)

The GLM/GEE approach was used to permit the calculation of standard errors (SEs) for predicted utility values which account for correlation of utility values within patients. The covariate coding above allows for different estimated utility values by treatment group and

health state, with a constant decrement in utility for the 1 month prior to death. The utility decrement for the month prior to death was included in the model to capture the well-established decline in HRQoL during the time period immediately prior to death and to avoid underestimating utility values for other health states. An identity link and normal error term distribution were used to ensure consistency with the assumed additive effect of death on HRQoL in the model (results were generally similar when log link functions and different error term distributions were used). Mean utility values for each health were calculated by taking the means of predicted values alternately setting the treatment group indicator covariates for blinatumomab to 1 or 0. For the purpose of the modelling, mean utility values for the relapsed/refractory states were calculated with post-relapse assessments excluded (i.e., using only assessments classified in the refractory state), as post-relapse assessments were generally captured relatively soon after relapse and were likely to be unrepresentative of utility values for all time in the relapsed/refractory state. A summary of the estimated mean EQ-5D utility values by health state from GLM/GEE regression of mapped EQ-5D utilities from TOWER is provided in Table 5-7

**Table 5-7. Estimated mean EQ-5D utility values by health state from GLM/GEE regression of mapped EQ-5D utilities from TOWER (FAS)**

| | Mean (SE) |
|---|---|
| Blinatumomab | |
| Initial | [redacted] |
| Response | [redacted] |
| Relapsed/refractory[a] | [redacted] |
| SOC chemotherapy | |
| Initial | [redacted] |
| Response | [redacted] |
| Relapsed/refractory[a] | [redacted] |
| Terminal Decrement | [redacted] |

[a] Utility based on refractory patients only as post-relapse assessments were generally captured relatively soon after relapse and were likely to be unrepresentative of utility values for all time in the relapsed/refractory state

EQ-5D, EuroQoL five dimension; GEE, generalised estimating equation; GLM, generalised linear model; FAS, full analysis set; SE, standard error; SOC, standard of care.

### 5.4.7 HRQoL over time

Because of the short follow-up in the TOWER study relative to the modelling time horizon, extrapolation of utility values derived from TOWER over the entire model projection is associated with substantial uncertainty and is potentially biased. In particular, it is uncertain how long the differences in utility values by treatment group observed in TOWER would be maintained beyond the end of follow-up in the trial. Also, if patients are considered cured after some point in time (e.g., 48 months), then it would be reasonable to use general population norm utility values rather than disease specific estimates. Furthermore, as patients grow older, HRQoL and utility values would be expected to decline. Accordingly, in the base case, utility values for patients surviving more than 4 years were based on age- and sex-matched UK general population norm values for the EQ-5D.[120] In scenario analyses in which some patients are assumed to be cured (Section 5.8.3), patients who are cured were also assigned utility values for the UK general population.

### 5.4.8 Comparison of baseline HRQoL and utility values for each health state

Utility values for patients entering the model (i.e., the initial state) are based on mapped EQ-5D utilities derived from EORTC QLC-C30 assessments during the 12 weeks prior to the assessment of response (baseline utility values were not included). For patients receiving blinatumomab, mean utility during this initial period was somewhat more favourable than mean baseline utility. Among patients receiving SOC chemotherapy, mean utility during the initial period was somewhat less favourable than mean baseline utility value. These findings might reflect a combination of improvements in HRQoL with blinatumomab due to an improved treatment response and toxicity profile compared to a combination of a relatively unfavourable treatment response and toxicity profile with SOC chemotherapy. The fact that utility values improved for blinatumomab and declined for SOC chemotherapy suggests that these changes reflect actual treatment effects and are not solely a consequence of regression to the mean. Mean utility values during the response state were higher than baseline utility values for both arms, while mean utility for patients with refractory disease was less than mean baseline utility for both arms.

### 5.4.9 Adjustment of utility values for cost-effectiveness analysis

Health state utility values used in the economic evaluation were not adjusted for difference in baseline utility values. As mean baseline utility values were slightly greater for patients receiving SOC chemotherapy, this approach is likely to be conservative (i.e., biased in favour of SOC chemotherapy).

### 5.4.10 Health effects found in the literature or clinical trials

Potential health effects of blinatumomab identified in prior clinical trials, including the MT103-211 and TOWER trials, include effects on OS, response, EFS, and adverse events. All these health effect were captured in the model. While the impact of adverse events on HRQoL was not modelled explicitly, any such effects would likely be captured in the EORTC QLQ-C30 assessments during TOWER that were used to derive the utility values.

### 5.4.11 Summary of chosen clinical utility values

Utility values in the model were assumed to be dependent on disease state and treatment and were estimated based on a mapping algorithm from the EORTC QLQ C30 to the EQ-5D using UK EQ-5D tariffs [116,121]. Utility values for patients surviving 4 years were based on age- and sex-matched UK general population norm values for the EQ-5D.[120] Utility values used in the model base case are summarised in Table 5-8.

**Table 5-8. Summary of utility values for cost-effectiveness analysis base case**

| | Utility value: mean (standard error) | 95% confidence interval | Reference in submission (section) | Justification |
|---|---|---|---|---|
| Mapped EQ-5D (TOWER, FAS) | | | Section 5.4.6 | Base case |
| Blinatumomab | | | | |
| Initial | [redacted] | [redacted] | | |
| Response | [redacted] | [redacted] | | |
| Relapsed/Refractory | [redacted] | [redacted] | | |
| SOC chemotherapy | | | | |
| Initial | [redacted] | [redacted] | | |
| Response | [redacted] | [redacted] | | |
| Relapsed/Refractory | [redacted] | [redacted] | | |
| Terminal Decrement | [redacted] | [redacted] | | |
| Survivors > 48 months, by age (years) | | | Section 5.4.7 | To reflect cured patients and decreasing average utility values with age |
| Male | | | | |
| < 25 | 0.94 | - | | |
| 25-34 | 0.93 | - | | |
| 35-44 | 0.91 | - | | |
| 45-54 | 0.84 | - | | |
| 55-64 | 0.78 | - | | |
| 65-74 | 0.78 | - | | |
| ≥ 75 | 0.75 | - | | |
| Female | | | | |
| < 25 | 0.94 | - | | |
| 25-34 | 0.93 | - | | |
| 35-44 | 0.91 | - | | |
| 45-54 | 0.85 | - | | |
| 55-64 | 0.81 | - | | |
| 65-74 | 0.78 | - | | |
| ≥ 75 | 0.71 | - | | |

Note: Confidence intervals for utility values are calculated using estimated standard error and assuming disutlity vs. perfect health is distributed as lognormal. Terminal decrement is assumed to be distributed as lognormal

EQ-5D, EuroQoL five dimension; FAS, full analysis set; SOC, standard of care.

## 5.5 Cost and healthcare resource use identification, measurement and valuation

### 5.5.1 Resource identification, measurement and valuation studies

As described in Section 5.1, an SLR to identify publications reporting cost-effectiveness studies for therapies used for the management of adult R/R Ph- B-precursor ALL, resource use and treatment costs for the management of adult R/R Ph- B-precursor ALL, and studies reporting HRQoL or utilities relevant for adult R/R Ph- B-precursor ALL was conducted in July 2015 and updated in November 2016. Search strategies were devised to identify relevant studies and were used to search Medline, EMBASE, the Cochrane library, EconLIT, and the NHS EED. Supplementary searches of conference proceedings and grey literature sources were also carried out to identify additional relevant studies. Full details of the search strategies, inclusion/exclusion criteria, screening procedure, and quality assessment are provided in Appendix VII.

Of the two identified cost/resource utilisation studies,[17,122] neither reported cost data from a UK perspective (one study was from the US and one was from France). These studies were therefore not considered to be relevant to the decision problem with respect to costs. However, data on duration of inpatient hospitalisation associated with chemotherapy from the French study by Dombret *et al.,* 2016[17] (a retrospective chart review of 33 adults with R/R Ph- B-precursor ALL treated during 2003–2014) was considered to be broadly generalisable to England and Wales and was used to inform the economic model in the absence of UK-specific resource utilisation data. This study showed that patients spent an average of 87 days in hospital during the chemotherapy treatment period, including a mean 2.2 inpatient admissions with a mean hospitalisation duration per inpatient admission of 16.8 days (Table 5-9). Full details of both identified cost/resource utilisation studies are provided in Appendix VII.

**Table 5-9. Summary of relevant cost/resource utilisation studies identified in the systematic literature review**

| First author, year | Country, date, and study type | Patient population | Applicability to clinical practice in England and Wales | Resource utilisation in the study | Resource utilisation used in the economic analysis | Technology costs |
|---|---|---|---|---|---|---|
| Dombret *et. al.*, 2016[17] | Country<br>France<br><br>Date<br>2003-2014<br><br>Study type<br>Retrospective chart review | Adult patients with R/R Ph-B-precursor ALL (N = 33) | Management of adult R/R Ph- B-precursor ALL is considered similar between European countries. The outputs of this study were presented to a UK clinician who estimated that the findings from this study were similar to what is observed in UK clinical practice. | Chemotherapy period (n = 32):<br>• Mean (SD) duration of days in hospital: 87 (35)<br>• Mean (SD) number of inpatient hospitalisations/day hospital stays/outpatient visits per patient: 2.2 (1.5)/2.1 (3.3)/0.2 (0.5)<br>• Mean (SD) duration of hospitalisation days per inpatient admission: 16.8 (14.8)<br>Index date to death excluding HSCT period (n = 33):<br>• Mean (SD) duration of days in hospital: NR<br>• Mean (SD) number of inpatient hospitalisations/day hospital stays/outpatient visits per patient: 3.7 (3.1)/4.3 (6.3)/0.7 (1.8)<br>• Mean (SD) duration of hospitalisation days per inpatient admission: 13.7 (13.5)<br>HSCT period (n = 7):<br>• Mean (SD) duration of days in hospital: NR<br>• Mean (SD) number of inpatient hospitalisations/day hospital stays/outpatient visits per patient: 2.6 (2.2)/2.9 (6.3)/11.3 (24.3)<br>• Mean (SD) duration of hospitalisation days per inpatient admission: 33.9 (38.0) | Chemotherapy period:<br>• Mean duration of hospitalisation per inpatient admission: 16.8 days | N/A |

ALL, acute lymphoblastic leukaemia; HSCT, haemapoietic stem cell transplant; N/A, not applicable; NR, not reported; Ph-, Philadelphia chromosome negative; R/R, relapsed or refractory; SD, standard deviation.

### 5.5.2 Unit cost identification and source

Blinatumomab and FLAG-IDA drug acquisition and administration costs were based on the dosing regimens in the TOWER trial and typical clinical practice. Drug acquisition costs for blinatumomab were based on its list price to the NHS. Drug acquisition costs for FLAG-IDA were based on prices from the British National Formulary (BNF, 2016)[123] and the NHS Generic Pharmaceuticals electronic Market Information Tool (eMit, 2015).[124] Unit costs of healthcare services relating to drug administration were based on 2014/15 NHS reference costs.[125] Costs of allo-SCT were based on a published study identified from a targeted review of the literature

### 5.5.3 Intervention and comparators' costs and resource use

#### *5.5.3.1 Blinatumomab*

Blinatumomab was included in the model based on an administration, dose, and dosing schedule consistent with the phase 3 TOWER RCT and key registrational phase 2 study (Study MT103-211), its marketing authorisation, and anticipated use in clinical practice in England and Wales during two induction and up to three additional consolidation cycles:

- Continuous IV infusion over 4 weeks (9 µg/day during Week 1 of Cycle 1 then 28 µg/day for the remainder of the cycle and during subsequent cycles) followed by a treatment-free interval of 2 weeks.

Consistent with the phase 3 TOWER RCT, which is used to inform the base-case clinical effectiveness model inputs, a proportion of patients in the model base case received up to 12 additional months of blinatumomab maintenance therapy if they continued to have a bone marrow response (≤ 5% bone marrow blasts) or CR/CRh*/CRi after three consolidation cycles. However, maintenance therapy is not included in the marketing authorisation for blinatumomab. The proportion of patients in the blinatumomab arm of TOWER in whom six or more cycles of blinatumomab was initiated (i.e., more than the maximum five cycles permitted by the marketing authorisation) was small ([redacted] %), and a scenario analysis assuming zero costs for maintenance treatment was conducted to quantify the potential impact of blinatumomab maintenance treatment costs (Section 5.8.3). Although maintenance treatment was administered in TOWER as 12-week cycles (4 weeks continuous IV infusion at 28 µg/day followed by an 8-week treatment-free interval), the model assumes for simplicity that all cycles are 6 weeks in duration (4 weeks of treatment followed by a 2 week treatment-free interval). Because costs during the treatment-free period of each cycle are assumed to be zero, this simplifying assumption has no impact on model results except as a consequence of discounting, with the discounted costs of blinatumomab being slightly overestimated.

Hospitalisation was implemented in accordance with the hospitalisation requirements specified in the SmPC, which recommends hospitalisation for initiation of therapy for a minimum of 9 days in Cycle 1 and 2 days in Cycle 2 (Section 2.3). In addition, the SmPC recommends 14 days hospitalisation during Cycle 1 for patients with a history or presence of clinically relevant CNS pathology. Patients with active CNS involvement were excluded from TOWER, and information on history of CNS pathology was not collected. In the model, it was assumed that patients without history of CNS involvement receiving blinatumomab would be hospitalised during the first 9 days of Cycle 1 and the first 2 days of the Cycle 2. It is estimated that 9% of R/R ALL patients in the UK will have CNS involvement,[25] and it was assumed that

these patients would require 14 days of hospitalisation during Cycle 1. Patients receiving blinatumomab were therefore assumed to require 10 days in hospital for the first cycle, on average (9% x 14 + 91% ≈ 10). It was assumed that all subsequent cycles would be received on an outpatient basis with IV bag changes every 4 days in an outpatient infusion centre.

For Cycle 1, during which a dose of 9 µg/day was used for the first 7 days, it was assumed that the contents of a single vial could be used over multiple days. Thus, a total of 6 vials would be used during the first hospitalisation as shown below (Table 5-10).

**Table 5-10. Calculation of numbers of vials of blinatumomab used during the initial hospital stay in Cycle 1**

| Day | Number of days | Daily dose (µg) | Total dose (µg) | Number of vials | Cumulative number of vials |
|---|---|---|---|---|---|
| 1–3 | 3 | 9 | 27 | 1 | 1 |
| 4–6 | 3 | 9 | 27 | 1 | 2 |
| 7–10 | 3 | 9 x 1<br>28 x 3 | 65 | 4 | 6 |

The percentage of patients starting and completing each cycle of blinatumomab was based on treatment exposure data from TOWER. To be consistent with the data on clinical outcomes, data for the FAS (ITT population) were used. The percentages of patients in the FAS of TOWER starting/completing each cycle are shown in Table 5-11.

**Table 5-11. Percentage of patients starting and completing each cycle of blinatumomab (TOWER, FAS)**

| | Patients starting cycle (%) | Patients completing cycle (%) |
|---|---|---|
| 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] |
| Cycle 10 | [redacted] | [redacted] |

FAS, full analysis set.

In calculating drug acquisition costs, inpatient and outpatient administration costs, and pump costs, patients who discontinued within a cycle were assumed to receive (i.e., use the applicable resources for) one half of that cycle.

The acquisition cost of blinatumomab was based on its list price to the NHS (£2017.00 per 38.5 µg vial [28 µg of useable contents]). The average cost per inpatient day for administration of blinatumomab was estimated to be £682.36, based on 2014/2015 National Schedule of Reference Costs for 2014–15 for NHS trusts and NHS foundation trusts for elective inpatients for the following HRG codes:

- SA24G - Acute Lymphoblastic Leukaemia with CC Score 5+;
- SA24H- Acute Lymphoblastic Leukaemia with CC Score 2-4; and
- SA24J-Acute Lymphoblastic Leukaemia with CC Score 0-1.

In calculating average daily costs, costs and days for excess bed days for these HRGs were included.

The cost of a visit to an outpatient infusion centre was estimated to be £204, based on the 2014–15 NHS Reference Cost for chemotherapy services for the HRG "*SB15Z-Deliver subsequent elements of a chemotherapy cycle*". In a scenario analysis in which it was assumed that outpatient bag changes for Cycles 3 and beyond could be managed by community nurse home visits (Section 5.8.3), the cost of such visit was estimated to be £66, based on the 2014–15 NHS Reference Cost for community health services for the HRG "*N10AF-Specialist Nursing, Cancer Related, Adult, Face to face*"

The pro-rated costs of the home infusion pump for outpatient administration of blinatumomab was estimated to be £107.59 per 28 days or £3.84 per day of use (Table 5-12). This cost was calculated based on input from UK oncology nurses considering the pump to be a BodyGuard 323™ Ambulatory Infusion Pump.

**Table 5-12. Calculation of home infusion pump costs**

| | Cost (£) | | |
|---|---|---|---|
| | **Total** | **Per day** | **Per 28 days** |
| Prorated pump cost assuming 5 years lifespan | 1,795 | 0.98 | 27.54 |
| Annual maintenance costs | 90 | 0.25 | 6.90 |
| Consumables, pack of 20, one every 4 days | 209 | 2.61 | 73.15 |
| Total | 2,094 | 3.84 | 107.59 |

#### *5.5.3.2 FLAG-IDA*

Drug acquisition costs are based on the salvage regimen FLAG-IDA, which includes the drugs cytarabine, fludarabine, idarubicin, and G-CSF. The dosage and treatment duration of the four chemotherapeutic agents in FLAG-IDA are based on the FLAG-IDA protocol from the Royal Surrey NHS Foundation Trust,[109] and are summarised in Table 5-13. The unit costs of the component in the FLAG-IDA regimen were based on the BNF (2016)[123] and the NHS Generic Pharmaceuticals eMit (2015).[124] Patients were assumed to receive treatment with FLAG-IDA in the inpatient setting. The cost per inpatient day for administration of FLAG-IDA was assumed to be the same as that for blinatumomab. The duration of hospitalisation per cycle for administration of FLAG-IDA was assumed to be 16.8 days, based on the mean duration of hospitalisation per inpatient admission among patients in the aforementioned retrospective chart review study adults with Ph- R/R B-cell precursor ALL in France (Section 5.5.1). The unit cost of filgrastim was based on the lowest cost 480 µg prefilled syringe of filgrastim listed on

the BNF (Zarzio®, £79.90).[123] The dosing of filgrastim was based on the recommended dosing in the SmPC, which recommends "*Daily dosing with filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukaemia, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days*."[126] The duration of treatment with filgrastim was assumed to be 9 days based on the median time of recovery of neutrophils in a trial of filgrastim versus pegfilgrastim in cancer patients receiving chemotherapy.[127]

**Table 5-13. FLAG-IDA dosage and cost**

| | Dose per day of treatment | Basis of dosing | Days treatment per cycle | Cost per item (£) | Mg per item | Daily dose (mg)[a] | Items per day | Cost per day (£) | Cost per cycle (£) |
|---|---|---|---|---|---|---|---|---|---|
| Filgrastim[123] | 0.005 | mg/kg | 9 | 79.90 | 0.48 | 0.368 | 1 | 79.90 | 719.10 |
| Fludarabine[124] | 30 | mg/m$^2$ | 5 | 35.64 | 50 | 55.271 | 2 | 71.28 | 356.40 |
| Cytarabine[124] | 2000 | mg/m$^2$ | 5 | 5.63 | 1000 | 3,684.745 | 4 | 22.52 | 112.60 |
| Idarubicin[123] | 8 | mg/m$^2$ | 3 | 87.36 | 5 | 14.739 | 3 | 262.08 | 786.24 |
| Total | | | | | | | | | 1,974.34 |

[a] Mean BSA ([redacted]) and weight ([redacted] kg) were based on the mean values for all patients with valid baseline values in the TOWER SAS. BSA was calculated from height and weight using the DuBois & DuBois formula (0.20247 x height [m]$^{0.725}$ x weight [kg]$^{0.425}$)

BSA, body surface area; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SAS, safety analysis set

*

The proportion of patients starting/completing each cycle of FLAG-IDA is based on exposure data for the SOC chemotherapy arm in the TOWER FAS (Table 5-14).

**Table 5-14. Proportion of patients starting and completing each cycle of SOC chemotherapy (TOWER, FAS)**

| | Patients starting cycle (%) | Patients completing cycle (%) |
|---|---|---|
| Cycle 1 | [redacted] | [redacted] |
| Cycle 2 | [redacted] | [redacted] |
| Cycle 3 | [redacted] | [redacted] |
| Cycle 4 | [redacted] | [redacted] |

FAS, full analysis set; SOC, standard of care.

#### *5.5.3.3 Comparative costs for blinatumomab versus FLAG-IDA*

A comparison of the estimated costs of treatment for blinatumomab and FLAG-IDA is shown in Table 5-15. The cost per cycle of blinatumomab (medication and administration) is £[redacted] for Cycle 1, £[redacted] for Cycle 2, and £[redacted] for subsequent cycles. The lower cost of Cycle 1 compared with other cycles is a consequence of the lower dose and therefore medication costs of blinatumomab during the first 7 days of treatment, which is only partly offset by the higher costs associated with longer inpatient stay. The higher cost of Cycle 2 versus subsequent cycles is due to the two inpatient days for administration in the second cycle. The cost of FLAG-IDA is £13,438 per cycle for all cycles. Most of this cost represents the cost of hospitalisation. When the estimated proportion of patients initiating and completing each cycle is taken into account, the total cost of blinatumomab treatment (medication and administration) over all cycles (not discounted) is £[redacted]. This compares with £14,240 (not discounted) for FLAG-IDA.

**Table 5-15. Comparison of costs of blinatumomab and FLAG-IDA**

| | | Cost per patient receiving cycle (£) | | | | | Percent receiving cycle | | Cost per patient entering model (£) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle | Medication | Inpatient | Out-patient | Pump | Total | Start | Com-plete | Medication | Inpatient | Out-patient | Pump | Total |
| Blinatum-omab | 1 | [redacted] | 6,824 | 1,020 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | 5,854 | 875 | 92 | [redacted] |
| | 2 | [redacted] | 1,365 | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | 723 | 756 | 57 | [redacted] |
| | 3 | [redacted] | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | -- | 427 | 32 | [redacted] |
| | 4 | [redacted] | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | -- | 303 | 23 | [redacted] |
| | 5 | [redacted] | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | -- | 200 | 15 | [redacted] |
| | 6 | [redacted] | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | -- | 140 | 11 | [redacted] |
| | 7 | [redacted] | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | -- | 87 | 7 | [redacted] |
| | 8 | [redacted] | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | -- | 29 | 2 | [redacted] |
| | 9 | [redacted] | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | [redacted] | -- | 21 | 2 | [redacted] |
| | 10 | -- | -- | 1,428 | 108 | [redacted] | [redacted] | [redacted] | -- | -- | -- | -- | -- |
| | **Total** | | | | | | | | [redacted] | **6,577** | **2,838** | **240** | [redacted] |
| FLAG-IDA | 1 | 1,974 | 11,464 | -- | -- | 13,438 | [redacted] | [redacted] | 1,606 | 9,325 | -- | -- | 10,931 |
| | 2 | 1,974 | 11,464 | -- | -- | 13,438 | [redacted] | [redacted] | 413 | 2,395 | -- | -- | 2,808 |
| | 3 | 1,974 | 11,464 | -- | -- | 13,438 | [redacted] | [redacted] | 44 | 257 | -- | -- | 301 |
| | 4 | 1,974 | 11,464 | -- | -- | 13,438 | [redacted] | [redacted] | 29 | 171 | -- | -- | 201 |
| | 5 | 1,974 | 11,464 | -- | -- | 13,438 | -- | -- | -- | -- | -- | -- | -- |
| | 6 | 1,974 | 11,464 | -- | -- | 13,438 | -- | -- | -- | -- | -- | -- | -- |
| | 7 | 1,974 | 11,464 | -- | -- | 13,438 | -- | -- | -- | -- | -- | -- | -- |
| | 8 | 1,974 | 11,464 | -- | -- | 13,438 | -- | -- | -- | -- | -- | -- | -- |
| | 9 | 1,974 | 11,464 | -- | -- | 13,438 | -- | -- | -- | -- | -- | -- | -- |
| | 10 | 1,974 | 11,464 | -- | -- | 13,438 | -- | -- | -- | -- | -- | -- | -- |
| | **Total** | | | | | | | | **2,092** | **12,148** | **--** | **--** | **14,240** |

Note: Numbers may not add due to rounding. Not discounted.

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin.

### 5.5.4 Health-state unit costs and resource use

Cost considered in the model included drug acquisition and administration costs for blinatumomab and FLAG-IDA, cost of allo-SCT, the costs of subsequent salvage therapy, and terminal care costs. These costs were calculated independently of the model states. Drug acquisition and administration costs for blinatumomab and FLAG-IDA are reported in Section 5.5.3. Cost of allo-SCT, subsequent salvage therapy, and terminal care are reported in Section 5.5.6.

### 5.5.5 Adverse reaction unit costs and resource use

The costs of AEs were not considered explicitly in the model but were assumed to be captured in the costs of inpatient and outpatient care for the administration of blinatumomab and FLAG-IDA.

### 5.5.6 Miscellaneous unit costs and resource use

In addition to the drug acquisition costs and the costs of inpatient and outpatient administration of blinatumomab and SOC chemotherapy, the model include the costs of allo-SCT, the costs of subsequent salvage therapy, and the costs of terminal care. Each of these cost components are described in detail below.

#### *5.5.6.1 Costs of allo-SCT.*

The proportions of patients receiving allo-SCT were estimated to be 24.35% for blinatumomab and 23.88% for FLAG-IDA based on the proportion of patients receiving allo-SCT in the blinatumomab and SOC chemotherapy arms in TOWER (Section 4.7.6).

The cost per patient receiving allo-SCT was assumed to be the same for patients receiving blinatumomab and FLAG-IDA, and was estimated based on an economic analysis conducted by the NHS Blood and Transplant service.[128] This study reported the costs of initial treatment, as well as short- and long-term follow-up costs (for 0 to 6 months, 7 to 12 months, and 13 to 24 months). The cost estimates in this report were based on a prior Dutch cost study,[129] but with unit costs for the UK provided by the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2013 database wherever possible. Where no equivalent unit costs were available, costs were converted to 2012/13 pounds using the Health and Social Care Pay & Prices index. Follow–up allo-SCT costs were adjusted based on post-transplant survival probabilities.[128] As cost values in the NHS Blood and Transplant service report were based on 2013 values, these were adjusted to 2014/15 values using the pay and prices index for healthcare and hospital services (HCHS) from PSSRU (Table 5-16).[130] The total undiscounted cost of allo-SCT was estimated to be approximately £104,000.

**Table 5-16. Estimated cost per patient of receiving allo-SCT (adjusted to 2014/2015 values)**

| | Value |
|---|---|
| Initial treatment cost (£) | 60,092.84 |
| Follow-up treatment, percent of patients receiving (%) | |
| 1-6 months | 90 |
| 7-12 months | 48 |
| 13-24 months | 31 |
| >24 months, cyclosporin | 20 |
| Cost | |
| 1-6 months cost (£) | 28,963 |
| 7-12 months (£) | 19,896 |
| 13-24 months (£) | 14,357 |
| >24 months, cyclosporin | |
| Mg per day | 100 |
| Cost per tab (£) | 0.85 |
| Mg per tab | 50.00 |
| Allo-SCT, allogenic stem cell transplant | |

*5.5.6.2 Costs of subsequent salvage therapy*

The model includes the expected costs of subsequent salvage therapy received by blinatumomab and FLAG-IDA patients based on the rates observed in TOWER. These were estimated based on the proportion of patients in TOWER SAS who received subsequent salvage therapy with innovative anticancer therapies, i.e., blinatumomab, inotuzumab, or CAR T ([redacted] % for blinatumomab and SOC chemotherapy, respectively), and other systemic anticancer therapies ([redacted] for blinatumomab and SOC chemotherapy, respectively). Data for the SAS rather than the FAS were used as information on subsequent salvage therapy was not routinely captured for patients in the FAS who did not receive study drug. The cost per course of subsequent salvage therapy with innovative anticancer therapies and other systemic anticancer therapies were assumed to be the same as those for initial salvage treatment with blinatumomab and FLAG-IDA, respectively (£[redacted] and £14,240).

*5.5.6.3 Costs of terminal care*

The cost for terminal care was applied as a one-off cost at death for patients who died within 48 months.

Terminal care costs per patient were estimated to be £8,602 based on an average length of stay in the hospital of 8 weeks as reported in a recent report by the King`s fund,[131] an average cost of £145 per day based on estimates from Marie Curie adjusted to 2014/15 values using the pay and prices index for HCHS from the PSSRU.[130,132]

## 5.6 *Summary of de novo analysis base-case inputs and assumptions*

### 5.6.1 *De novo* analysis base-case inputs

The inputs used in the base-case analysis are reported in Table 5-17.

**Table 5-17. Summary of variables used in the base-case analysis**

| | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Analytic variables | | | Section 5.2.3 |
| Timeframe | 50 | -- | |
| Annual discount rate for costs | 3.5% | -- | |
| Annual discount rate for effectiveness | 3.5% | -- | |
| Patient characteristics | | | |
| Starting age (years) | [redacted] | -- | Section 5.3.2 |
| Percent male | 59% | -- | |
| Mean BSA, $m^2$ | [redacted] | -- | Section 5.5.3.2 |
| Mean weight, kg | [redacted] | | |
| Efficacy | | | |
| Response rate | | | Section 5.3.1 |
| Blinatumomab | 43.9% | -- (Bootstrap) | |
| FLAG-IDA | 24.6% | -- (Bootstrap) | |
| EFS \| response distribution | Restricted Gamma | | Section 5.3.3 |
| OS distribution | Restricted Gompertz | | Section 5.3.2 |
| Duration of benefit (months) | 48 | -- | Section 5.3.2 |
| Costs | | | |
| Blinatumomab | | | Section 5.5.3.1 |
| Cost per vial | £2,017.00 | -- | |
| Days per bag change | 4 | -- | |
| Inpatient Costs | | | |
| Inpatient days per cycle received | | | |
| Cycle 1 | 10 | -- | |
| Cycle 2 | 2 | -- | |
| Cycle 3+ | 0 | -- | |
| Cost per inpatient day | £682.36 | £408.57 to £1,072.59 (Lognormal) | |
| Outpatient Costs | | | |
| Probability of receiving infusions in outpatient infusion center | | | |
| Cycle 1 | 1 | -- | |
| Cycle 2 | 1 | -- | |
| Cycle 3+ | 1 | -- | |
| Cost per visit to outpatient infusion center | £204.00 | £145.10 to £278.94 (Lognormal) | |
| Cost per nurse visit | £66.00 | £39.52 to £103.74 (Lognormal) | |
| Pump costs | | | |
| Cost per day of HIT | £3.84 | £1.61 to £7.78 (Lognormal) | |
| Duration of therapy | | | |
| % Starting cycle | | | |
| Cycle 1 | [redacted] | [redacted] to [redacted] (Beta) | |

| | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Cycle 2 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 3 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 4 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 5 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 6 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 7 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 8 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 9 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 10 | [redacted] | -- (Beta) | |
| % Completing cycle | | | |
| Cycle 1 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 2 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 3 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 4 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 5 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 6 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 7 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 8 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 9 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 10 | [redacted] | -- (Beta) | |
| FLAG-IDA | | | |
| Administration costs | | | |
| Inpatient days per cycle received | 16.8 | 12.3 to 22.4 (Lognormal) | |
| Cost per inpatient day | £682.36 | £408.57 to £1,072.59 (Lognormal) | |
| Duration of therapy | | | |
| % Starting cycle | | | |
| Cycle 1 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 2 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 3 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 4 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 5+ | [redacted] | -- (Beta) | |
| % Completing cycle | | | |
| Cycle 1 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 2 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 3 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 4 | [redacted] | [redacted] to [redacted] (Beta) | |
| Cycle 5+ | [redacted] | -- (Beta) | |
| Other Costs | | | |
| Allo-SCT | | | |
| Proportion of patients receiving allo-SCT | | | |
| Blinatumomab | 24.4% | 19.4% to 29.6% (Beta) | |
| FLAG-IDA | 23.9% | 17.1% to 31.5% (Beta) | |
| Cost | | | |
| Initial treatment | £60,092.84 | £35,981.13 to £94,458.64 (Lognormal) | |
| Follow-up | | | |
| Percent of patients receiving | | | |
| 0-6 months | 90.0% | -- | |
| 7-12 months | 48.0% | -- | |
| 13-24 months | 31.0% | -- | |
| >24 months, cyclosporin | 20.0% | -- | |
| Cost | | | |

Section 5.5.3.2

Section 5.5.6.1

| | Value | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| 0-6 months | £28,963.48 | £17,342.15 to £45,527.07 (Lognormal) | |
| 7-12 months | £19,895.94 | £11,912.87 to £31,274.00 (Lognormal) | |
| 13-24 months | £14,357.27 | £8,596.55 to £22,567.88 (Lognormal) | |
| Subsequent salvage Chemotherapy | | | Section 5.5.6.2 |
| Proportion receiving each treatment | | | |
| Blinatumomab patients | | | |
| Innovative therapies | [redacted] | 2.9% to 8.2% (Beta) | |
| Other systemic therapy | [redacted] | 19.7% to 30.1% (Beta) | |
| FLAG-IDA patients | | | |
| Innovative therapies | [redacted] | 5.9%% to 17.5%% (Beta) | |
| Other systemic therapy | [redacted] | 21.2% to 38.2% (Beta) | |
| Cost per Course | | | |
| Innovative therapies | £[redacted] | -- (0) | |
| Other systemic therapy | £14,240.26 | -- (0) | |
| Terminal care (for patients not cured) | £8,602 | £5139.65 to £15,468.67 (Lognormal) | Section 5.5.6.3 |
| Utility Inputs | | | Section 5.4.11 |
| Blinatumomab | | | |
| Initial | [redacted] | [redacted] | |
| Response | [redacted] | [redacted] | |
| Relapse/refractory | [redacted] | [redacted] | |
| SOC chemotherapy | | [redacted] | |
| Initial | [redacted] | [redacted] | |
| Response | [redacted] | [redacted] | |
| Relapse/refractory | [redacted] | [redacted] | |
| Terminal decrement | [redacted] | [redacted] | |

Note: Lognormal (Utility) refers to utility values sampled by sampling the disutility vs. perfect health (1 minus utility) as a lognormal variable

Allo-SCT, allogenic stem cell transplant; BSA, body surface area; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; HIT, home infusion treatment; OS, overall survival; SOC, standard of care.

### 5.6.2 *De novo* analysis assumptions

Key modelling assumptions and their justifications are listed below (Table 5-18).

**Table 5-18. Key modelling assumptions**

| Assumption | Justification |
|---|---|
| The whole SOC chemotherapy arm from TOWER is used to model costs and outcomes for FLAG-IDA | Available clinical guidelines, including the EWALL guidelines, suggest that there is no clearly superior salvage chemotherapy regimen in R/R Ph- B-precursor ALL. UK clinical experts consulted by Amgen considered the outcomes in the SOC chemotherapy arm in TOWER to be broadly generalisable to the relevant comparator for this appraisal, FLAG-IDA.<br><br>A scenario analysis has been conducted on the pre-specified subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation. As the OS HR for blinatumomab versus SOC chemotherapy was more favourable in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen, this suggest the base-case approach (i.e., using the whole SOC chemotherapy arm) is potentially conservative. |
| After 4 years, the hazard rates for OS are the same for blinatumomab and SOC chemotherapy | Based on UK clinical expert opinion, patients remaining alive after 4 years are likely to be cured. If patients are cured, then there should be no difference in mortality by treatment group. |
| Mortality after 4 years is equal to sum of that based on parametric distributions fit to trial data and UK general population mortality rates | Mortality rates will decline initially as patients who are not cured die, and then are expected to increase over time due to increasing non–disease-related mortality in cured patients. |
| Utility values after 4 years are the same for blinatumomab and FLAG-IDA and assumed to be equal to UK general population norms for EQ-5D | Patients surviving for 4 years are likely to be cured and to no longer suffer from disease-related decrements in HRQoL. As a consequence, utility values will be the same for patients receiving blinatumomab and FLAG-IDA. Over time, utility values will decrease due to age-related reductions in HRQoL. |
| Patients without history of CNS involvement receiving blinatumomab will be hospitalised for the first 9 days of Cycle 1. Those with active CNS pathology or history of CNS involvement will be hospitalised for 14 days of the Cycle 1. All patients will be hospitalised for the first 2 days of Cycle 2. | Consistent with the minimum hospitalisation requirements described in the blinatumomab SmPC |
| Costs of AEs are captured in costs of inpatient and outpatient administration of medications | Since blinatumomab is administered initially in hospital, the treatment of AEs is likely to be provided during the hospital stay and therefore |

| Assumption | Justification |
|---|---|
| | included in the hospitalisation cost. As patients are assumed to visit outpatient infusion centres every 4 days when receiving the drug out of hospital, it is likely AEs could be managed during these scheduled visits. For FLAG-IDA, patients are assumed to be hospitalised for 16.8 days each cycle. As with blinatumomab, the treatment of AEs is likely to be provided during the hospital stay. |
| Only the costs of subsequent salvage observed during the TOWER trial were included in the model | Given the relatively small proportion of patients receiving subsequent salvage during the TOWER trial, projections of utilisation beyond the end of the trial would be associated with substantial uncertainty. Since utilisation of innovative therapies such as blinatumomab, inotuzomab, and CAR T was greater in the SOC chemotherapy arm than the blinatumomab arm, the use of trial results only may be conservative. |
| AE, adverse event; ALL, acute lymphoblastic leukaemia; CNS, central nervous system; EWALL, European Working Group for adult ALL; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HRQoL, health-related quality of life; Ph-, Philadelphia chromosome negative, R/R, relapsed or refractory; SmPC, summary of product characteristics; SOC, standard of care. | |

## *5.7 Base-case results*

Results of the cost-effectiveness analyses presented in this submission are based on the list price of blinatumomab. Amgen has proposed a simple PAS which has been approved by the DoH; analyses incorporating the PAS are included in the PAS addendum to this submission.

### 5.7.1 Base-case incremental cost effectiveness analysis results

Base-case results for the cost-effectiveness of blinatumomab versus FLAG-IDA in adult patients with R/R Ph- B-precursor ALL are reported in Table 5-19. Blinatumomab was projected to yield 1.78 more discounted life-years (LYs) and 1.45 more discounted QALYs than FLAG-IDA. Total costs were estimated to be £[redacted] higher with blinatumomab than with FLAG-IDA. The ICER for blinatumomab versus FLAG-IDA was estimated to be £[redacted] per QALY gained.

**Table 5-19. Base-case results**

| | Total cost (£) | Total LYs (discounted) | Total QALYs (discounted) | Incremental costs (£) | Incremental LYs (discounted) | Incremental QALYs (discounted) | ICER (£) |
|---|---|---|---|---|---|---|---|
| Blinatumomab | [redacted] | 4.38 | 3.35 | [redacted] | 1.78 | 1.45 | [redacted] |
| FLAG-IDA | 64,165 | 2.61 | 1.90 | | | | |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life-years.

Incremental costs and QALYs with blinatumomab versus FLAG-IDA are plotted on the cost-effectiveness plane in Figure 5-16. Also shown on the figure is the line representing a willingness-to-pay threshold of £50,000 per QALY gained.

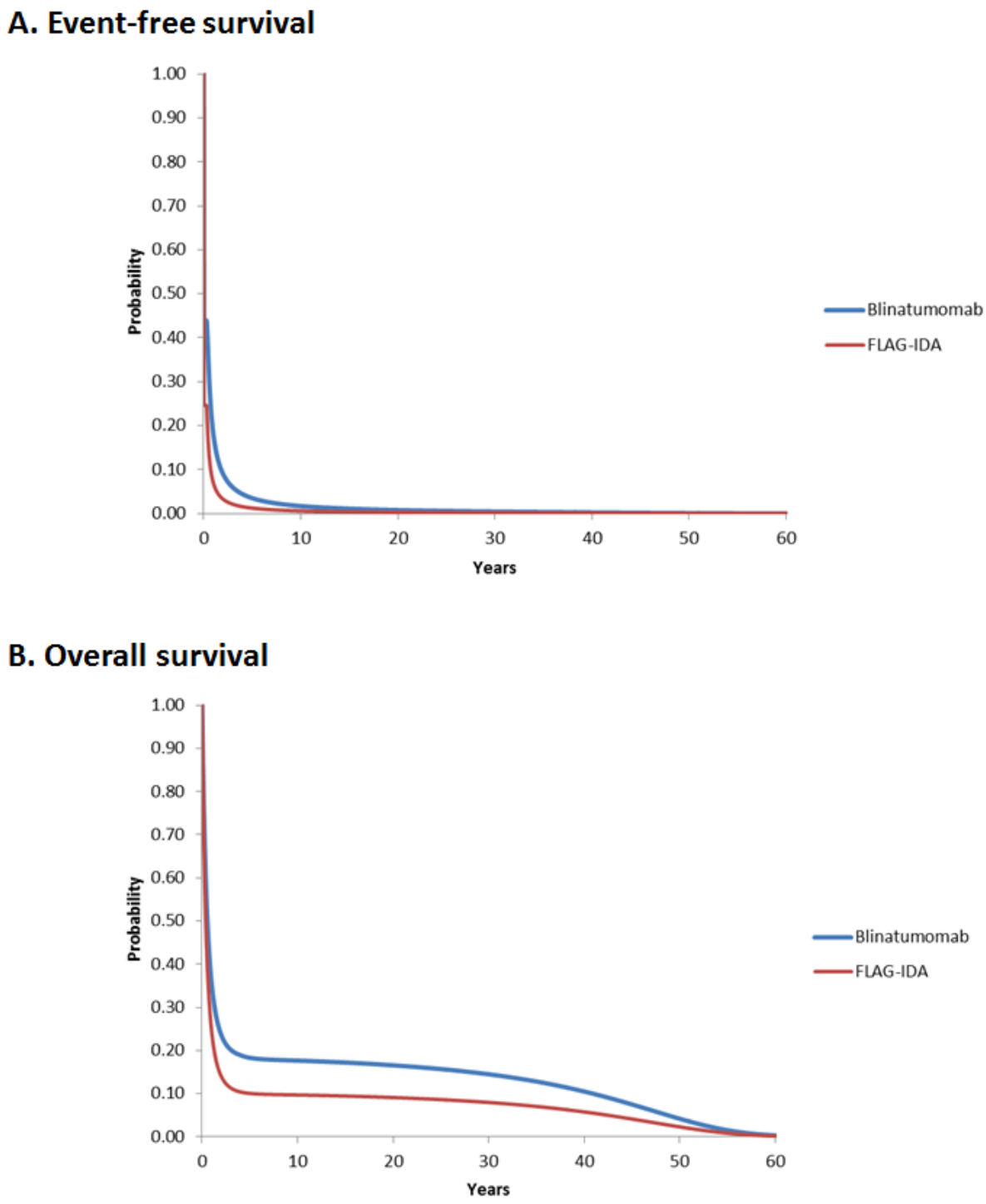
**Figure 5-16. Incremental costs and QALYs with blinatumomab versus FLAG-IDA**

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; WTP, willingness to pay

### 5.7.2 Clinical outcomes from the model

The main clinical outcomes generated by the model are OS and EFS. Estimates of EFS and OS from the model are shown in Figure 5-17.

**Figure 5-17. Event-free survival and overall survival in the model**




Note: Model time horizon is 50 years in base case. 'Responders' refers to patients achieving a CR/CRh*/CRi within 12 weeks of treatment initiation.

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin.

Estimates of the probabilities of OS from the model are compared with Kaplan-Meier estimates of OS from TOWER in Table 5-20. At 21.5 months (the last observed failure or censoring time for SOC chemotherapy in TOWER), the model projections very closely approximate the Kaplan Meier survival probabilities for both blinatumomab and SOC chemotherapy.

**Table 5-20. Comparison of probabilities of survival in the model and in TOWER at selected landmarks**

| Month | Blinatumomab | | SOC chemotherapy[a] | |
|---|---|---|---|---|
| | TOWER | Model | TOWER | Model |
| 6 | 53.9% | 52.3% | 38.5% | 41.3% |
| 12 | 34.7% | 35.2% | 28.3% | 24.1% |
| 21.5[b] | 24.9% | 25.0% | 16.6% | 15.1% |

[a] Used as a proxy for FLAG-IDA
[b] Maximum failure or censor time for the SOC chemotherapy arm in TOWER

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SOC, standard of care

Because patients without a response (i.e. patients who did not achieve a CR/CRh*/CRi within 12 weeks of treatment initiation) were assigned an EFS duration of 1 day, and less than 50% of patients in both arms did not achieve response, median EFS was one day for both arms in TOWER. Estimates of the probabilities of EFS from the model are compared with Kaplan-Meier estimates of EFS from TOWER in Table 5-21**Error! Reference source not found.**. Although the model predicts EFS less well than it does OS, this reflects the smaller number of patients available to estimate the distribution of EFS and thus the high degree of instability in the Kaplan Meier estimates.

**Table 5-21. Comparison of probabilities of event-free survival from TOWER and the model at selected landmarks**

| Month | Blinatumomab | | SOC chemotherapy[a] | |
|---|---|---|---|---|
| | TOWER | Model | TOWER | Model |
| 6 | 29.7% | 32.7% | 11.4% | 14.3% |
| 12 | 12.4% | 17.6% | 8.2% | 6.8% |
| 20.3[b] | 9.1% | 10.5% | 0.0% | 3.9% |

[a] Used as a proxy for FLAG-IDA
[b] Maximum failure or censor time for the SOC chemotherapy arm in TOWER

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SOC, standard of care

### 5.7.3 Disaggregated results of the base-case incremental cost-effectiveness analysis

Life years and QALYs by health state are shown in Table 5-22. Since the base-case analysis does not make any explicit assumptions regarding cure, the expected LYs and QALYs in the cured state is zero for both treatments. The gain in time in the relapsed/refractory state accounts for 75% of the gain in LYs and QALYs with blinatumomab versus FLAG-IDA.

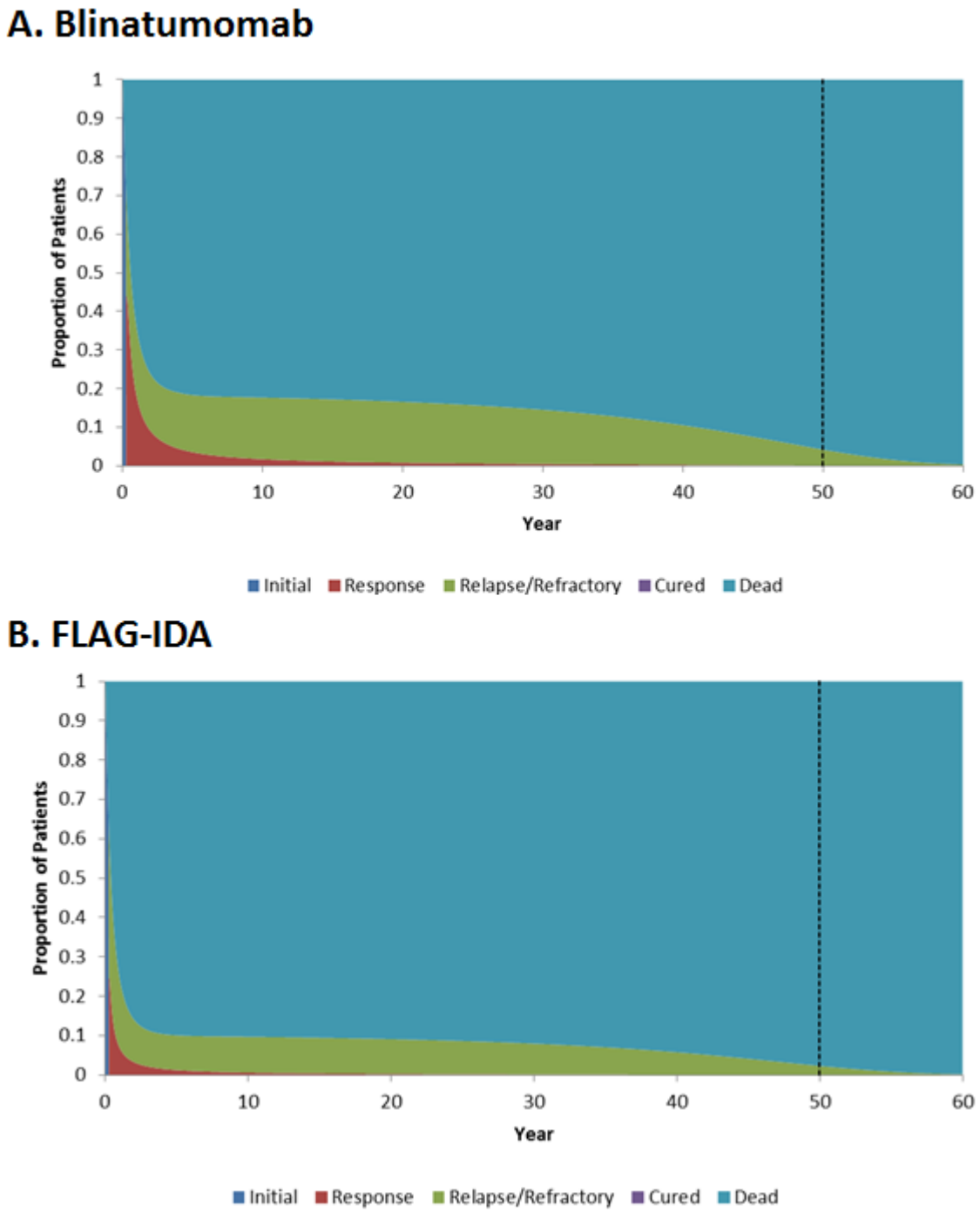
**Table 5-22. Summary of LYs and QALY gain by health state**

| Effectiveness, discounted | Blinatumomab | FLAG-IDA | Incremental | Absolute Incremental | Absolute Incremental % |
|---|---|---|---|---|---|
| LYs | | | | | |
| Initial | 0.20 | 0.19 | 0.01 | 0.01 | 0.6 |
| Response | 0.70 | 0.27 | 0.43 | 0.43 | 24.2 |
| Relapse/refractory | 3.48 | 2.15 | 1.34 | 1.34 | 75.3 |
| Total | 4.38 | 2.61 | 1.78 | 1.78 | 100.00 |
| QALYs | | | | | |
| Initial | 0.13 | 0.11 | 0.02 | 0.02 | 1.7 |
| Response | 0.53 | 0.20 | 0.34 | 0.34 | 23.3 |
| Relapse/refractory | 2.68 | 1.59 | 1.09 | 1.09 | 75.0 |
| Total | 3.35 | 1.90 | 1.45 | 1.45 | 100.00 |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; LYs, life-years; QALY, quality-adjusted life-year.

The proportion of patients in each state over time (“survival trace”) is presented in Figure 5-18.

**Figure 5-18. Proportion of patients in each state over time**




Note: Dashed line indicates model time horizon.

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin

Costs are not calculated by health state. Costs by category of service are presented in Table 5-23. Medication costs represent over 90% of the absolute incremental costs.

**Table 5-23. Summary of predicted resource use by category of cost**

| | Blinatumo-mab (£) | FLAG-IDA (£) | Incremental (£) | Absolute incremental (£) | Absolute incremental % |
|---|---|---|---|---|---|
| Salvage therapy | | | | | |
| Medication | [redacted] | 2,092 | [redacted] | [redacted] | [redacted] |
| Administration | | | | | |
| Inpatient | 6,577 | 12,148 | -5,571 | 5,571 | [redacted] |
| Outpatient visits | 2,837 | 0 | 2837 | 2837 | [redacted] |
| Pump | 240 | 0 | 240 | 240 | [redacted] |
| Total administration | 9,654 | 12,148 | -2,494 | 2,494 | [redacted] |
| Total salvage therapy | [redacted] | 14,240 | [redacted] | [redacted] | [redacted] |
| Allo-SCT | 24,154 | 24,359 | -205 | 205 | [redacted] |
| Subsequent salvage therapy | [redacted] | [redacted] | -8,184 | 8,184 | [redacted] |
| Terminal Care | [redacted] | 7,425 | [redacted] | [redacted] | [redacted] |
| **Total** | [redacted] | **64,165** | [redacted] | [redacted] | [redacted] |

Allo-SCT, allogenic stem cell transplant; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin.

## 5.8 Sensitivity analyses

### 5.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted by simultaneously sampling from estimated probability distributions of model parameters to obtain 1000 sets of model input estimates. Distributional assumptions for the model parameters are summarised below:

- Response rates and parameters of EFS among responders and OS distributions were sampled based on bootstrapping. EFS among responders and OS curves were estimated using a set of 1000 pseudo-samples generated from the individual patient data from TOWER via sampling with replacement. Parameters of survival distributions used in the model were then sampled by selecting at random from the bootstrapped parameters. In order to ensure appropriate correlations, all parameters for a comparator were selected from the same bootstrap sample.
- Utility values were sampled by first transforming the utility to a disutility vs. perfect health and then using a log-normal distribution for the disutility.
- Drug acquisition costs were taken as given and not sampled. All other cost parameters were sampled assuming a log-normal distribution and a standard error of 25% of the base-case value.
- Probabilities for which standard errors were available were sampled using beta distributions.

For each simulation, expected costs and QALYs were calculated for each comparator, along with the incremental costs and QALYs. Ninety-five percent credible intervals (CrIs) for these measures were calculated based on the 2.5 and 97.5 percentiles of these simulations. Simulation results were plotted on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) were constructed for blinatumomab and FLAG-IDA.

Descriptive statistics on the results of the PSA are reported in Table 5-24. Mean costs from the PSA were similar to mean costs in the base-case analyses. Mean QALYs for blinatumomab were approximately 3% less in the PSA than the base-case estimates. This discrepancy reflects truncation of the survival distribution for OS at 50 years, which impacts extreme values of the sampled survival distribution parameters.

**Table 5-24. Descriptive statistics on results of probabilistic sensitivity analyses**

| Outcome | Blinatumomab | FLAG-IDA | Incremental |
|---|---|---|---|
| LYs (not discounted) | | | |
| Mean | 7.45 | 4.38 | 3.07 |
| SD | 1.93 | 1.64 | 1.40 |
| Median | 7.50 | 4.22 | 3.07 |
| 95% LCL | 3.63 | 1.46 | 0.31 |
| 95% UCL | 11.27 | 8.04 | 5.90 |
| QALYs (discounted) | | | |
| Mean | 3.27 | 1.89 | 1.38 |
| SD | 0.78 | 0.67 | 0.58 |
| Median | 3.29 | 1.83 | 1.38 |
| 95% LCL | 1.73 | 0.71 | 0.22 |
| 95% UCL | 4.82 | 3.39 | 2.55 |
| Cost (discounted) (£) | | | |
| Mean | [redacted] | 63,973 | [redacted] |
| SD | [redacted] | 8,238 | [redacted] |
| Median | [redacted] | 63,404 | [redacted] |
| 95% LCL | [redacted] | 48,845 | [redacted] |
| 95% UCL | [redacted] | 81,368 | [redacted] |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; LCL, lower confidence limit; LYs, life-years; QALYs, quality-adjusted life-years; SD, standard deviation; UCL, upper confidence limit.

Results of the PSA are plotted on the cost-effectiveness plane using a willingness-to-pay threshold of £50,000 per QALY gained in Figure 5-19. There is little to no correlation of incremental costs and QALYs. This result is consistent with expectations, as costs are modelled independently of QALYs.

**Figure 5-19. Scatter plot of incremental costs and QALYs from probabilistic sensitivity analyses**

Note: ICER shown is from the base-case analysis

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

In 98.3% percent of simulations, blinatumomab was projected to yield more QALYs than FLAG-IDA chemotherapy with higher costs.

Cost-effectiveness acceptability curves for blinatumomab and FLAG-IDA are shown in Figure 5-20. At a threshold value of £50,000 per QALY gained, the probability that blinatumomab is cost-effective is estimated to be 10.7%.

**Figure 5-20. Cost-effectiveness acceptability curves for blinatumomab and FLAG-IDA chemotherapy**

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay

### 5.8.2 Deterministic sensitivity analysis

Results from deterministic sensitivity analyses on model parameters are reported in the form of a tornado diagram in **Error! Reference source not found.**Figure 5-21. The model was most sensitive to the HR for OS for blinatumomab vs. FLAG-IDA derived from the restricted Gompertz distribution. The model was relatively insensitive to all the other parameters examined.

**Figure 5-21. Tornado diagram on ICER for blinatumomab vs. FLAG-IDA**

AF, accelerated failure; allo-SCT, allogenic stem cell transplant; Blin, blinatumomab; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; R/R, relapsed/refractory

Because of the relatively large impact on the ICER of the OS treatment effect for blinatumomab, it is difficult to visualize the impact of other parameters in the tornado diagrameabove. Sensitivity analyses on model parameters excluding the sensitivity analyses on blinatumomab treatment effect on OS are shown in Figure 5-22.

**Figure 5-22. Tornado diagram on ICER for blinatumomab vs. FLAG-IDA (excluding OS treatment effect)**

AF, accelerated failure; allo-SCT, allogenic stem cell transplant; Blin, blinatumomab; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; R/R, relapsed/refractory

### 5.8.3 Scenario analyses

#### *5.8.3.1 Description of the scenario analyses*

An overview of the scenario analyses is provided in Table 5-25.

**Table 5-25. Description of scenario analyses**

| No. | Description | Base-case setting | Scenario setting | Justification |
|---|---|---|---|---|
| 1 | TOWER SAS | TOWER FAS | Response rates, EFS among responders, OS, treatment exposure, and rates of allo-SCT are based on the SAS. | To investigate the impact of the high proportion and imbalance in drop-outs across study arms in TOWER following randomisation. |
| 2 | Subgroup of patients who were intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm | All patients | Response rates, EFS among responders, OS, treatment exposure, rates of allo-SCT, rates of subsequent salvage therapy are based on the subgroup of patients intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm. | To examine outcomes among patients who were intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm in TOWER, given that FLAG-IDA is the relevant comparator for this appraisal.<br><br>As the OS HR for blinatumomab versus SOC chemotherapy was more favourable in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation, this suggest the base-case approach (i.e., using the whole SOC chemotherapy arm) is potentially conservative. |
| 3 | OS based on RCS log-logistic | OS based on restricted Gompertz from TOWER | OS for blinatumomab and FLAG-IDA are based on restricted RSC log-logistic distribution. Details regarding this distribution are provided in Appendix VIII. | The RSC log-logistics was the second-best fitting distribution for OS based on the fit criteria used for distribution selection. |
| 4 | Survivors cured - 36 months | OS based on restricted Gompertz from TOWER, no assumption of cure | In these scenarios, all patients remaining alive at 36, 48 and 60 months, respectively, are assumed to be cured. Patients are assumed to begin entering the cured state at 23 months. Patients who are | To investigate the impact of the assumption that survivors after 36–60 months are cured. |
| 5 | Survivors cured - 48 months | | | |
| 6 | Survivors cured - 60 months | | | |

| No. | Description | Base-case setting | Scenario setting | Justification |
|---|---|---|---|---|
| | | | cured are assumed to have UK general population mortality rates and utility values. Details regarding the structure and assumptions used in the models assuming survivors are cured are provided in Appendix X. | |
| 7 | EFS among responders based on Lognormal | EFS among responders based on restricted gamma | EFS among responders for blinatumomab and FLAG-IDA are based on restricted RSC lognormal distribution. Details regarding this distribution are provided in Appendix VIII. | The lognormal distribution was the second best fitting distribution for EFS among responders based on the fit criteria used for distribution selection. |
| 8 | 36-month duration of benefit | OS for blinatumomab and FLAG-DA is based on restricted Gompertz from TOWER. After 48 months the hazards for death for blinatumomab are the same as those for FLAG-IDAC | OS for blinatumomab and FLAG-IDA are based on restricted Gompertz from TOWER. After 36 and 60 months, respectively, the hazards for death for blinatumomab are the same as those for FLAG-IDA. | To investigate the impact of different assumption regarding the duration of benefit with blinatumomab. |
| 9 | 60-month duration of benefit | | | |
| 10 | 10-year model timeframe | 50-year model timeframe | Model timeframe set to 10, 20, and 60 years, respectively. | To investigate the impact of different time horizons on the results of the analysis. |
| 11 | 20-year model timeframe | | | |
| 12 | 60-year model timeframe | | | |
| 13 | 1.5% discount rate | 3.5% discount rate for costs and QALYs | Discount rate for costs and QALYs are set to 1.5%. | As outlined in the NICE guide to the methods of the technology appraisal (2013) when considering treatment effects that are both substantial in restoring health and sustained over a very long period (normally at least 30 years). |

| No. | Description | Base-case setting | Scenario setting | Justification |
|---|---|---|---|---|
| 14 | 10 inpatient days for blinatumomab for all cycles | 10 days for Cycle 1, 2 days for Cycle 2, and 0 days for subsequent cycles | Days for inpatient administration of blinatumomab are set to 10 days for all cycles. | To investigate the sensitivity of the model to assumptions regarding the frequency and duration of hospitalisation for administration of blinatumomab. |
| 15 | Zero cost for blinatumomab Cycle 6+ | Utilisation of blinatumomab as in TOWER | Drug acquisition and administration costs for blinatumomab after cycle five are set to zero. | In TOWER, patients could receive up to 12 months of maintenance therapy. However, the SmPC for blinatumomab does not include maintenance treatment. This scenario investigates the impact of assuming no costs for blinatumomab maintenance. This scenario may be biased in favour of blinatumomab as it does not adjust for the potentially beneficial effects of maintenance therapy. |
| 16 | HIT Cycle 3+ | Bag changes at outpatient infusion centre | Blinatumomab infusion bag changes are assumed to be administered at home by a community nurse. | To estimate the impact of different assumptions regarding the setting of blinatumomab infusion bag changes. |
| 17 | Clofarabine costs included in SOC chemotherapy | All patients receiving FLAG-IDA | In this scenario, [redacted] of patients in the SOC chemotherapy arm are assumed to receive treatment with clofarabine (40 mg/m$^2$/day IV for 5 days each 28 day cycle) based on the proportion of SOC chemotherapy arm patients in TOWER who received clofarabine or clofarabine based regimens in Cycle 1 (Table 4-31). | To investigate the sensitivity of the model to the assumed treatment regimen for patients in the FLAG-IDA arm. |
| 18 | Rate of allo-SCT from Study MT103-211 and the matched/weighted historical | Rates of allo-SCT from TOWER (24.35% for blinatumomab and 23.88% for SOC chemotherapy) | Rates of allo-SCT are based on the proportion of patients receiving allo-SCT after salvage therapy (irrespective of response) observed in Study MT103-211 | To investigate the impact of differential rates of allo-SCT on model results. |

| No. | Description | Base-case setting | Scenario setting | Justification |
|---|---|---|---|---|
| | control cohort in Study 20120310 | | and the matched/weighted historical control cohort in Study 20120310 (25% and 18%, respectively; Section 4.11.6.2). | |
| 19 | EORTC-8D utilities | Mapped EQ-5D utilities from TOWER | Utility values to 48 months were based on EORTC-8D utility values from TOWER. Descriptive statistics on the EORTC-8D utility values by treatment group and health state, as well as GLM/GEE regression estimates of the utility values used in the model are reported in Appendix X. | To investigate the impact on model results of alternative sources of utility values. |
| 20 | TTO utilities from Aristides *et al.,* 2015 vignettes study | Mapped EQ-5D utilities from TOWER | Utility values to 48 months were based on TTO utility values from the vignettes study by Aristides *et al.,* 2015. Details regarding the calculation of the TTO utility values are reported in Appendix X. | To investigate the impact on model results of alternative sources of utility values |
| Allo-SCT, allogenic stem cell transplant; EFS, event-free survival; EORTC-8D, European Organisation for Research and Treatment of Cancer eight dimension; EQ-5D, EuroQoL five dimensions; FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HIT, home infusion treatment; HR, hazard ratio; OS, overall survival; SAS, safety analysis set; SmPC, summary of product characteristics; SOC, standard of care; TTO, time trade off; | | | | |

*5.8.3.2 Scenario analysis results*

Results of scenario analyses are provided in Table 5-26. Most of the scenario analyses do not have large impact on the ICER. However, it is pertinent to note that in Scenario 2, restricting the analysis to the subgroup of patients who were intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm in TOWER results in a significantly lower ICER, £[redacted]. As explained above, to maximise the use of the data from TOWER and based on feedback from UK clinical experts we assumed that the effectiveness of the whole SOC chemotherapy arm of TOWER would constitute a valuable and acceptable proxy for the effectiveness of FLAG-IDA, which is the most relevant comparator in England and Wales. Results from this scenario analysis suggest this assumption could be conservative.

Another notable exception is for Scenario 3; when the RCS log-logistic survival function is used instead of the RCS Gompertz to predict long-term OS, the ICER increases to £[redacted], which highlights the limitations of this curve in predicting long-term survival for R/R ALL patients. Indeed, as discussed in Section 5.3.2.2, the long-term OS of patients with R/R ALL displays a clear decrease in hazard over time as a consequence of a proportion of patients achieving a cure. The RCS log-logistic curve, although displaying close fit to the initial part of the OS curves from the TOWER trial, did not satisfy long-term OS plausibility and failed to reflect the proportion of cured patients. This limitation can be addressed when combining the use of this curve with a cured-model framework which allows R/R patients to be considered cured at different time points (Scenarios 4 to 6). Based on feedback from UK clinical experts and the shape of the long-term OS curves from the historical comparator cohort in Study 20120310, this can be considered between 3 and 5 years depending on the patient's characteristics and responses.

In addition, when the time horizon for the analysis is reduced (Scenarios 10 and 11), the ICERs increase significantly, which is not surprising as most of the incremental cost linked to utilisation of blinatumomab will occur early, whereas the benefits are accumulated over the lifetime of patients benefiting from treatment with blinatumomab. Indeed, since adult R/R ALL patients are typically young (median age at diagnosis of 39) it is appropriate to use a 50-year time horizon. Furthermore, as recommended in the NICE guide to the methods of technology appraisal (2013),[77] since meaningful health benefits are accrued over more than 30 years, it is appropriate to also evaluate a lower discount rate (1.5%), and this scenario (Scenario 13) results in a meaningfully decreased ICER of £[redacted].

**Table 5-26. Results of the scenario analyses**

| # | Scenario | Blinatumomab | | | FLAG-IDA | | | Blinatumomab vs. FLAG-IDA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cost (£) | LYs | QALYs | Cost (£) | LYs | QALYs | Cost (£) | LYs | QALYs | ICER(£) |
| | Base Case (All patients, TOWER FAS) | [redacted] | 4.38 | 3.35 | 64,165 | 2.61 | 1.90 | [redacted] | 1.78 | 1.45 | [redacted] |
| 1 | TOWER SAS | [redacted] | 3.94 | 3.00 | 73,315 | 2.29 | 1.66 | [redacted] | 1.65 | 1.34 | [redacted] |
| 2 | Subgroup of patients who were intended to receive a FLAG ± anthracycline based regimen if randomised to the SOC chemotherapy arm | [redacted] | 4.41 | 3.40 | 61,377 | 1.36 | 0.98 | [redacted] | 3.04 | 2.42 | [redacted] |
| 3 | OS based on RCS log-logistic | [redacted] | 1.95 | 1.42 | 64,298 | 1.42 | 0.95 | [redacted] | 0.53 | 0.47 | [redacted] |
| 4 | Survivors cured - 36 months | [redacted] | 4.57 | 3.58 | 65,910 | 3.23 | 1.77 | [redacted] | 1.34 | 1.81 | [redacted] |
| 5 | Survivors cured - 48 months | [redacted] | 4.12 | 3.19 | 65,673 | 2.90 | 1.59 | [redacted] | 1.22 | 1.60 | [redacted] |
| 6 | Survivors cured - 60 months | [redacted] | 3.80 | 2.92 | 65,512 | 2.67 | 1.47 | [redacted] | 1.13 | 1.45 | [redacted] |
| 7 | EFS among responders based on lognormal | [redacted] | 4.38 | 3.34 | 64,288 | 2.61 | 1.89 | [redacted] | 1.78 | 1.45 | [redacted] |
| 8 | 36-Month duration of benefit | [redacted] | 4.31 | 3.29 | 64,165 | 2.61 | 1.90 | [redacted] | 1.71 | 1.39 | [redacted] |
| 9 | 60-month duration of benefit | [redacted] | 4.41 | 3.37 | 64,165 | 2.61 | 1.90 | [redacted] | 1.80 | 1.47 | [redacted] |
| 10 | 10-year model timeframe | [redacted] | 2.10 | 1.54 | 64,244 | 1.35 | 0.91 | [redacted] | 0.75 | 0.63 | [redacted] |
| 11 | 20-year model timeframe | [redacted] | 3.15 | 2.39 | 64,209 | 1.93 | 1.37 | [redacted] | 1.22 | 1.02 | [redacted] |
| 12 | 60-year model timeframe | [redacted] | 4.41 | 3.37 | 64,160 | 2.62 | 1.91 | [redacted] | 1.79 | 1.46 | [redacted] |
| 13 | 1.5% discount rate | [redacted] | 5.86 | 4.50 | 64,594 | 3.42 | 2.53 | [redacted] | 2.44 | 1.97 | [redacted] |
| 14 | 10 inpatient days for blinatumomab administration for all cycles | [redacted] | 4.38 | 3.35 | 65,046 | 2.61 | 1.90 | [redacted] | 1.78 | 1.45 | [redacted] |
| 15 | Zero cost for blinatumomab Cycle 6+ | [redacted] | 4.38 | 3.35 | 62,946 | 2.61 | 1.90 | [redacted] | 1.78 | 1.45 | [redacted] |
| 16 | Blinatumomab HIT for Cycle 3+ | [redacted] | 4.38 | 3.35 | 64,077 | 2.61 | 1.90 | [redacted] | 1.78 | 1.45 | [redacted] |
| 17 | Clofarabine costs Included in SOC chemotherapy | [redacted] | 4.38 | 3.35 | 69,372 | 2.61 | 1.90 | [redacted] | 1.78 | 1.45 | [redacted] |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | Rate of allo-SCT from Study MT103-211 and matched/weighted historical control cohort in Study 20120310 | [redacted] | 4.38 | 3.35 | 58,167 | 2.61 | 1.90 | [redacted] | 1.78 | 1.45 | [redacted] |
| 19 | EORTC-8D Utilities | [redacted] | 4.38 | 3.49 | 64,165 | 2.61 | 2.00 | [redacted] | 1.78 | 1.49 | [redacted] |
| 20 | TTO utilities from Aristides *et al.,* 2015 vignettes study | [redacted] | 4.38 | 3.18 | 64,165 | 2.61 | 1.78 | [redacted] | 1.78 | 1.40 | [redacted] |

allo-SCT, allogenic stem cell transplant; EFS, event-free survival; EORTC-8D, European Organisation for Research and Treatment of Cancer eight dimension; FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HIT, home infusion treatment; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYs, life years; OS, overall survival; QALYs, quality-adjusted life-years; RCS, restricted cubic spline; SAS, safety analysis set; SOC, standard of care; TTO, time trade off;

### 5.8.4 Subgroup analysis

A subgroup analysis was conducted for patients who have not received prior salvage therapy. Results from a pre-specified stratification factor subgroup analysis of OS by prior salvage therapy (yes vs. no) suggest that patients who have not received prior salvage therapy are likely to benefit more from treatment with blinatumomab than patients who have received prior salvage therapy (HR [redacted]) (Section 4.8.2). Median OS in patients who had not received prior salvage therapy was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months). For patients who had received prior salvage therapy, median OS was [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (treatment difference: [redacted] months). Clinical experts consulted by Amgen consider this to be highly clinically plausible, given that treating patients earlier in the treatment pathway (i.e., patients with a better prognosis) with a more effective therapy is likely to lead to improvements in both absolute and relative OS. This subgroup analysis is pertinent to the decision problem as clinicians are likely to use blinatumomab early in the treatment pathway (i.e., in patients who have not received prior salvage therapy) given the above.

In the cost-effectiveness analysis of this subgroup, patient characteristics, responses rates, EFS among responders, OS, probabilities of initiation and completion of each cycle, probabilities of allo-SCT, utilisation of subsequent salvage therapy, and utility values were calculated for both blinatumomab and SOC chemotherapy arms of TOWER using data for patients in this subgroup. For the subgroup of patients with no prior salvage therapy, the restricted Gompertz was used for OS and the restricted gamma was used for EFS among responders (Figure 5-24 and Figure 5-23, respectively) consistent with the base-case analysis. Details regarding the curve-fitting analysis and survival parameters for this subgroup are provided in Appendix VIII.

**Figure 5-23. Distributions of overall survival used in base-case analyses (TOWER, patients with no prior salvage therapy)**

(R), restricted; BLIN_OL, blinatumomab arm; SOC_OL, standard of care chemotherapy arm.

**Figure 5-24. Distributions of event-free survival among responders used in base-case analyses (TOWER, patients with no prior salvage therapy)**

(R), restricted; BLIN_OL, blinatumomab arm; SOC_OL, standard of care chemotherapy arm.

Model parameter inputs used in the base-case analysis of the subgroup of patients with no prior salvage therapy are reported Appendix XI.

#### *5.8.4.1 Base-case results for subgroup analysis of patients with no prior salvage therapy*

Base-case results as well as results from deterministic sensitivity analyses, scenario analyses, and PSAs are provided below in Table 5-27 through Table 5-31 and Figure 5-25 through Figure 5-29.

Blinatumomab was projected to yield 2.40 more discounted LYs and 1.98 more discounted QALYs than FLAG-IDA. Total costs were estimated to be £[redacted] higher with blinatumomab than with FLAG-IDA. The ICER for blinatumomab versus FLAG-IDA was estimated to be £ [redacted] per QALY gained.

**Table 5-27. Base-case results, patients with no prior salvage therapy**

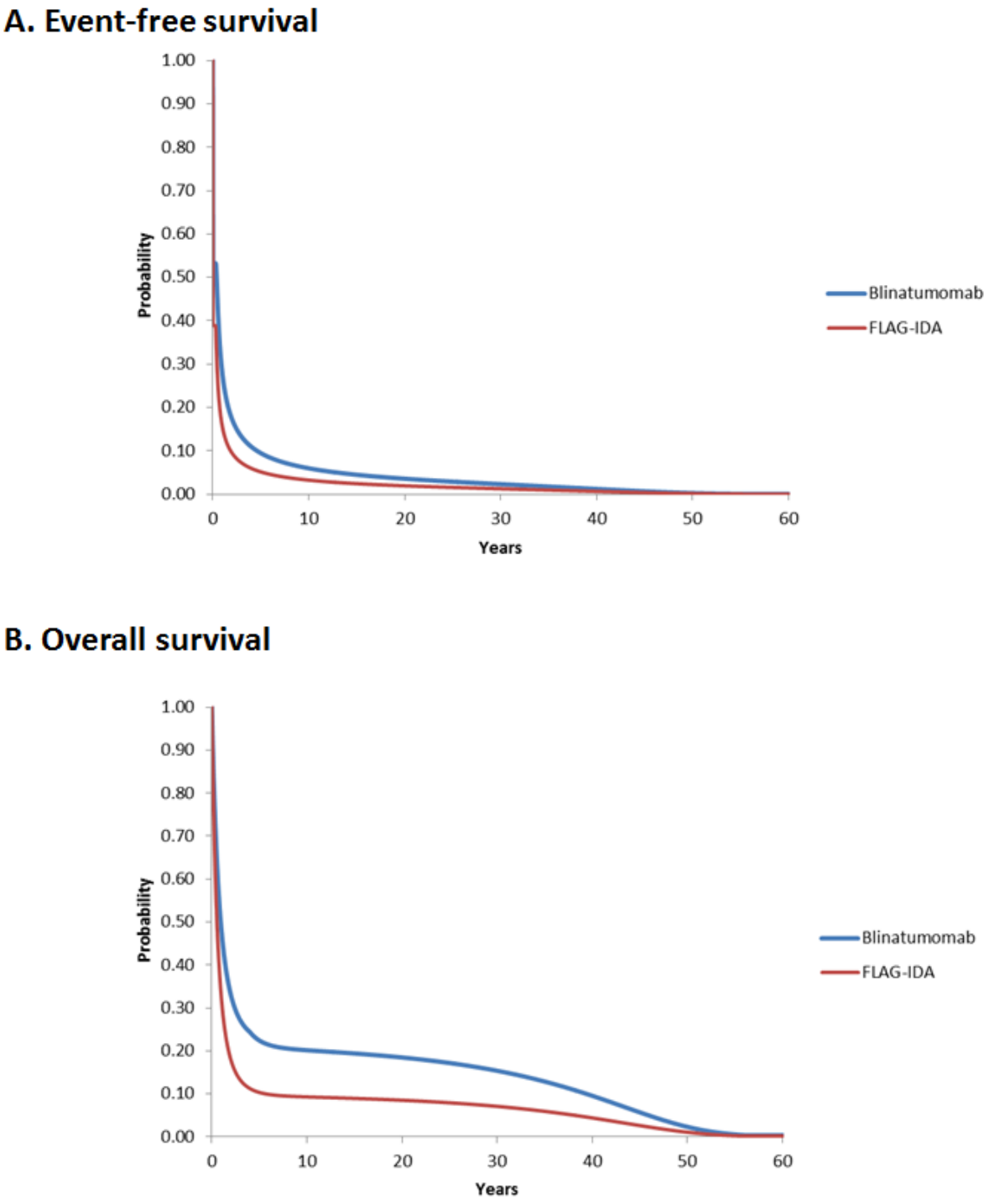
| Treatment | Total cost (£) | Total LYs (discounted) | Total QALYs (discounted) | Incremental costs (£) | Incremental LYs (discounted) | Incremental QALYs (discounted) | ICER |
|---|---|---|---|---|---|---|---|
| Blinatumomab | [redacted] | 5.06 | 3.91 | [redacted] | 2.40 | 1.98 | [redacted] |
| FLAG-IDA | 74,703 | 2.65 | 1.94 | | | | |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.

**Figure 5-25. Incremental costs and QALYs for blinatumomab versus FLAG-IDA chemotherapy, patients with no prior salvage therapy**

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; WTP, willingness to pay.

**Figure 5-26. Event-free survival and overall survival in the model, patients with no prior salvage therapy**




Note: Model time horizon is 50 years in base case.

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SOC, standard of care.

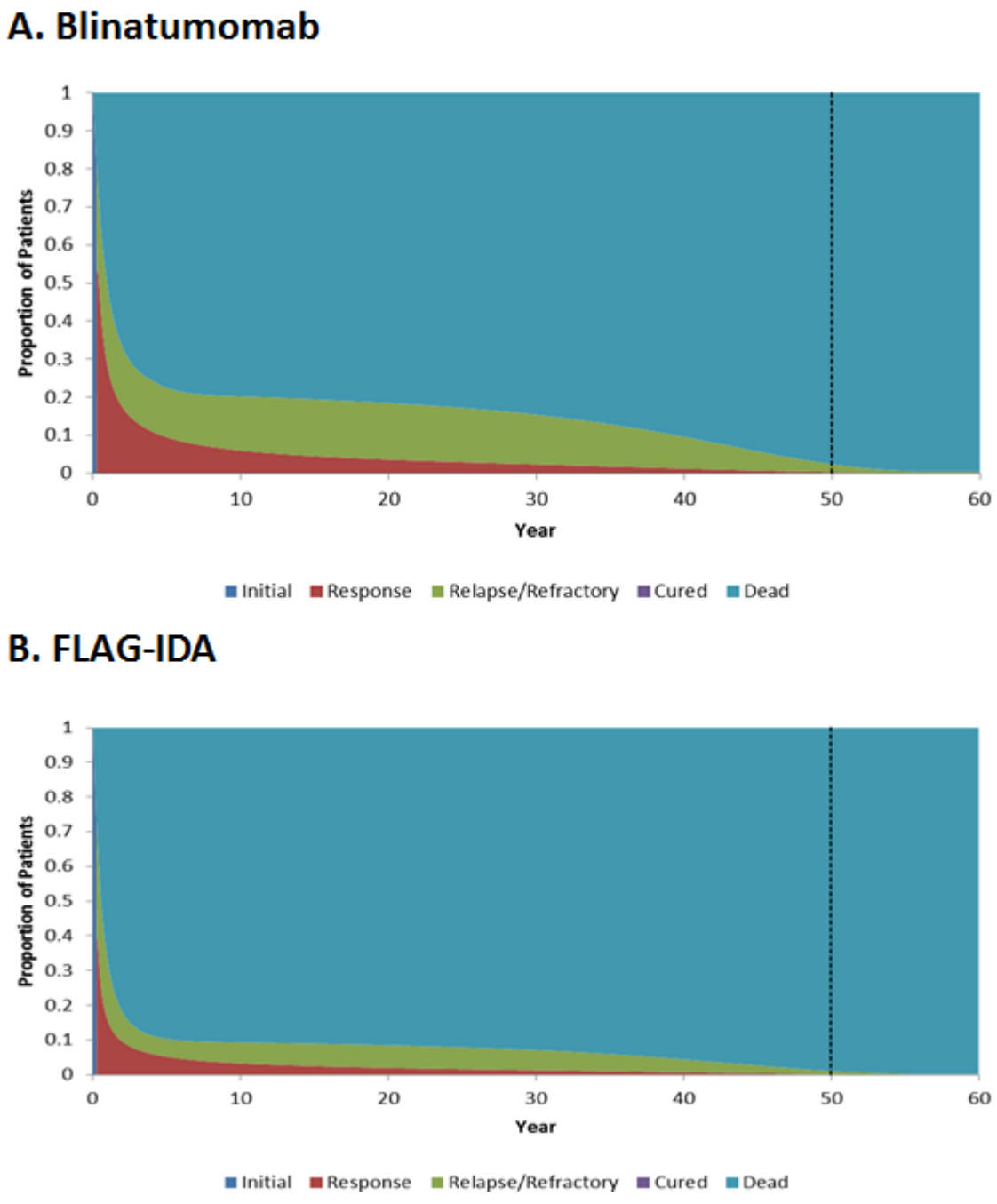
**Table 5-28. Summary of LYs and QALY gain by health state, patients with no prior salvage therapy**

| Effectiveness, discounted | Blinatumomab | FLAG-IDA | Incremental | Absolute incremental | Absolute incremental % |
|---|---|---|---|---|---|
| LYs | | | | | |
| Initial | 0.21 | 0.20 | 0.01 | 0.01 | 0.4 |
| Response | 1.63 | 0.91 | 0.72 | 0.72 | 29.9 |
| Relapse/refractory | 3.22 | 1.54 | 1.67 | 1.67 | 69.7 |
| Total | 5.06 | 2.65 | 2.40 | 2.40 | 100.0 |
| QALYs | | | | | |
| Initial | 0.15 | 0.12 | 0.02 | 0.02 | 1.3 |
| Response | 1.29 | 0.69 | 0.60 | 0.60 | 30.4 |
| Relapse/refractory | 2.48 | 1.13 | 1.35 | 1.35 | 68.4 |
| Total | 3.91 | 1.94 | 1.98 | 1.98 | 100.0 |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; LYs, life-years; QALY, quality-adjusted life-year

The proportion of patients in each state over time ("survival trace") is shown in Figure 5-27.

**Figure 5-27. Proportion of patients in each state over time, patients with no prior salvage therapy**




Note: Dashed line indicates model time horizon.

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin.

Costs by category of service are presented in Table 5-29. Medication costs represent over 90% of the absolute incremental costs.

**Table 5-29. Summary of predicted resource use by category of cost, patients with no prior salvage therapy**

| | Blinatumomab (£) | FLAG-IDA (£) | Incremental (£) | Absolute incremental (£) | Absolute Incremental % |
|---|---|---|---|---|---|
| Salvage therapy | | | | | |
| Medications | [redacted] | 2,377 | [redacted] | [redacted] | [redacted] |
| Administration | | | | | |
| Inpatient | 6,919 | 13,799 | -6,880 | 6,880 | [redacted] |
| Outpatient visits | 3,436 | 0 | 3,436 | 3,436 | [redacted] |
| Pump | 286 | 0 | 286 | 286 | [redacted] |
| Total administration | 10,641 | 13,799 | -3,158 | 3,158 | [redacted] |
| Total salvage therapy | [redacted] | 16,175 | [redacted] | [redacted] | [redacted] |
| allo-SCT | 28,694 | 33,956 | [redacted] | [redacted] | [redacted] |
| Subsequent salvage therapy | [redacted] | [redacted] | -3,918 | 3,918 | [redacted] |
| Terminal care | 6,286 | 7,373 | -1,087 | 1,087 | [redacted] |
| **Total** | [redacted] | **74,703** | [redacted] | [redacted] | [redacted] |

allo-SCT, allogenic stem cell transplant; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin.

*5.8.4.2 Probabilistic sensitivity analysis*

Descriptive statistics on the results of the PSA for patients who have not received prior salvage therapy are reported in Table 5-30.

**Table 5-30. Descriptive statistics on results of probabilistic sensitivity analyses, patients with no prior salvage therapy**

| Outcome | Blinatumomab | FLAG-IDA | Incremental |
|---|---|---|---|
| LYs (not discounted) | | | |
| Mean | 7.56 | 4.07 | 3.49 |
| SD | 4.00 | 2.77 | 2.37 |
| Median | 7.51 | 3.43 | 3.23 |
| 95% LCL | 1.34 | 0.71 | -0.08 |
| 95% UCL | 15.35 | 10.95 | 8.30 |
| QALYs (discounted) | | | |
| Mean | 3.57 | 1.88 | 1.69 |
| SD | 1.66 | 1.16 | 1.01 |
| Median | 3.57 | 1.63 | 1.59 |
| 95% LCL | 0.96 | 0.44 | 0.08 |
| 95% UCL | 6.86 | 4.78 | 3.75 |
| Cost (discounted) (£) | | | |
| Mean | [redacted] | 74,933 | [redacted] |
| SD | [redacted] | 12,307 | [redacted] |
| Median | [redacted] | 74,033 | [redacted] |
| 95% LCL | [redacted] | 53,013 | [redacted] |
| 95% UCL | [redacted] | 101,934 | [redacted] |

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; LCL, lower confidence limit; LYs, life-years; QALYs, quality-adjusted life-years; SD, standard deviation; UCL, upper confidence limit.

Results of the PSA are plotted on the cost-effectiveness plane in Figure 5-28.

**Figure 5-28. Scatter plot of incremental costs and QALYs from probabilistic sensitivity analyses, patients with no prior salvage therapy**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; WTP, willingness to pay.

In 98.0% percent of simulations, blinatumomab was projected to yield more QALYs than FLAG-IDA for higher costs.

Cost-effectiveness acceptability curves for blinatumomab and FLAG-IDA chemotherapy in the subgroup of patients with no prior salvage therapy are shown in Figure 5-29. At a willingness-to-pay threshold of £50,000 per QALY gained, the probability that blinatumomab is cost-effective is estimated to be 21.3%.

**Figure 5-29. Cost-effectiveness acceptability curves for blinatumomab and FLAG-IDA, patients with no prior salvage therapy**

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

#### *5.8.4.3 Deterministic sensitivity analysis*

Deterministic sensitivity analyses on selected model parameters for the no prior salvage therapy subgroup of TOWER are reported in Figure 5-30 and Figure 5-31. As with the analyses of the total population of TOWER, the model was most sensitive to the HR for OS for blinatumomab vs. FLAG-IDA derived from the restricted Gompertz distribution, and was relatively insensitive to all the other parameters examined.

**Figure 5-30. Tornado diagram on ICER for blinatumomab vs. FLAG-IDA, no prior salvage subgroup**

AF, accelerated failure; allo-SCT, allogenic stem cell transplant; Blin, blinatumomab; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; R/R, relapsed/refractory

**Figure 5-31. Tornado diagram on ICER for blinatumomab vs. FLAG-IDA, no prior salvage subgroup (excluding OS treatment effect)**

AF, accelerated failure; allo-SCT, allogenic stem cell transplant; Blin, blinatumomab; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; R/R, relapsed/refractory

#### *5.8.4.4 Scenario analyses*

Deterministic sensitivity analyses on selected model parameters for the no prior salvage therapy subgroup of TOWER are reported in Table 5-31.

**Table 5-31. Results of scenario and deterministic sensitivity analyses, patients with no prior salvage therapy**

| # | Scenario | Blinatumomab | | | FLAG-IDA | | | Blinatumomab vs. FLAG-IDA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cost (£) | LYs | QALYs | Cost (£) | LYs | QALYs | Cost (£) | LYs | QALYs | ICER (£) |
| | Base case (no prior salvage subgroup, TOWER FAS) | [redacted] | 5.06 | 3.91 | 74,703 | 2.65 | 1.94 | [redacted] | 2.40 | 1.98 | [redacted] |
| 1 | TOWER SAS (No prior salvage subgroup) | [redacted] | 4.55 | 3.51 | 84,175 | 2.68 | 1.96 | [redacted] | 1.87 | 1.56 | [redacted] |
| 2 | OS based on RCS log-logistic | [redacted] | 2.54 | 1.94 | 74,825 | 1.65 | 1.15 | [redacted] | 0.89 | 0.79 | [redacted] |
| 3 | Survivors cured - 36 months | [redacted] | 6.08 | 4.78 | 77,178 | 3.81 | 2.19 | [redacted] | 2.27 | 2.59 | [redacted] |
| 4 | Survivors cured - 48 months | [redacted] | 5.50 | 4.30 | 76,845 | 3.42 | 1.98 | [redacted] | 2.08 | 2.32 | [redacted] |
| 5 | Survivors cured - 60 months | [redacted] | 5.06 | 3.94 | 76,613 | 3.13 | 1.82 | [redacted] | 1.93 | 2.12 | [redacted] |
| 6 | EFS among responders based on lognormal | [redacted] | 5.06 | 3.90 | 75,216 | 2.65 | 1.92 | [redacted] | 2.40 | 1.98 | [redacted] |
| 7 | 36-month duration of benefit | [redacted] | 4.86 | 3.76 | 74,703 | 2.65 | 1.94 | [redacted] | 2.21 | 1.82 | [redacted] |
| 8 | 60-month duration of benefit | [redacted] | 5.16 | 3.99 | 74,703 | 2.65 | 1.94 | [redacted] | 2.50 | 2.05 | [redacted] |
| 9 | 10-year model timeframe | [redacted] | 2.60 | 2.01 | 75,148 | 1.52 | 1.06 | [redacted] | 1.08 | 0.95 | [redacted] |
| 10 | 20-year model timeframe | [redacted] | 3.79 | 2.95 | 74,986 | 2.07 | 1.49 | [redacted] | 1.72 | 1.46 | [redacted] |
| 11 | 60-year model timeframe | [redacted] | 5.07 | 3.92 | 74,680 | 2.66 | 1.94 | [redacted] | 2.41 | 1.98 | [redacted] |
| 12 | 1.5% discount rate | [redacted] | 6.59 | 5.10 | 75,469 | 3.36 | 2.48 | [redacted] | 3.23 | 2.61 | [redacted] |
| 13 | 10 inpatient days for blinatumomab administration for all cycles | [redacted] | 5.06 | 3.91 | 75,580 | 2.65 | 1.94 | [redacted] | 2.40 | 1.98 | [redacted] |
| 14 | Zero cost for blinatumomab Cycle 6+ | [redacted] | 5.06 | 3.91 | 73,150 | 2.65 | 1.94 | [redacted] | 2.40 | 1.98 | [redacted] |
| 15 | Blinatumomab HIT for Cycle 3+ | [redacted] | 5.06 | 3.91 | 74,607 | 2.65 | 1.94 | [redacted] | 2.40 | 1.98 | [redacted] |
| 16 | Clofarabine costs Included in SOC chemotherapy | [redacted] | 5.06 | 3.91 | 80,529 | 2.65 | 1.94 | [redacted] | 2.40 | 1.98 | [redacted] |
| 17 | Rate of allo-SCT from Study MT103-211 and matched/weighted historical control cohort in Study 20120310 | [redacted] | 5.06 | 3.91 | 59,083 | 2.65 | 1.94 | [redacted] | 2.40 | 1.98 | [redacted] |
| 18 | EORTC-8D Utilities | [redacted] | 5.06 | 4.05 | 74,703 | 2.65 | 2.02 | [redacted] | 2.40 | 2.03 | [redacted] |
| 19 | TTO utilities from Aristides *et al.,* 2015 vignettes study | [redacted] | 5.06 | 3.67 | 74,703 | 2.65 | 1.86 | [redacted] | 2.40 | 1.81 | [redacted] |

| # | Scenario | Blinatumomab | | | FLAG-IDA | | | Blinatumomab vs. FLAG-IDA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cost (£) | LYs | QALYs | Cost (£) | LYs | QALYs | Cost (£) | LYs | QALYs | ICER (£) |

allo-SCT, allogenic stem cell transplant; EFS, event-free survival; EORTC-8D, European Organisation for Research and Treatment of Cancer eight dimension; FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HIT, home infusion treatment; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYs, life-years; OS, overall survival; QALYs, quality-adjusted life-years; RCS, restricted cubic spline; SAS, safety analysis set; SOC, standard of care; TTO, time trade off.

## 5.9 Validation

### 5.9.1 Validation of de novo cost-effectiveness analysis

The model calculations were validated by entering the model inputs into a generalised partitioned survival model which has been used in numerous prior economic evaluations of oncology therapies for submissions to UK reimbursement authorities and which has been previously validated by external analysts. Results from the validation model were not materially different from those of the model used in this evaluation and could be explained by minor differences in implementation of the model calculations.

Given the paucity of data on long-term outcomes and costs for adult patients with R/R Ph- B-precursor ALL, it is difficult to assess the external validity of longer-term projections of survival. Model projections of OS for FLAG-IDA were similar to long-term survival data from the historical comparator cohort in Study 20120310.

## 5.10 Interpretation and conclusions of economic evidence

### 5.10.1 Comparison with published economic literature

To our knowledge, this is the first economic evaluation comparing blinatumomab versus FLAG-IDA in adult patients with R/R Ph- B-precursor ALL based on the phase 3 TOWER RCT; therefore, a comparison of cost-effectiveness results with published literature is not possible.

### 5.10.2 Relevance of the economic evaluation to all patients who could potentially use the technology as identified in the decision problem

The base-case analysis presented the comparison of blinatumomab versus FLAG-IDA, using the SOC chemotherapy arm in TOWER as a proxy for the efficacy of FLAG-IDA, is based on randomised head-to-head phase 3 RCT evidence and is therefore considered a robust comparison. Furthermore, FLAG-IDA constitutes the most relevant comparator currently used in clinical practice in England and Wales in the licensed population for blinatumomab. A relevant scenario analysis using data for the pre-specified subgroup of patients intended to receive a FLAG ± anthracycline-based regimen if randomised to the SOC chemotherapy arm of TOWER was also presented.

Furthermore, the cost-effectiveness of blinatumomab was considered in the pre-specified stratification factor subgroup of patients from TOWER who did not receive prior salvage therapy. This subgroup analysis is highly pertinent to the decision problem as clinicians are likely to use blinatumomab early in the treatment pathway (i.e., in patients who have not received prior salvage therapy).

### 5.10.3 Strengths and generalisability of the economic evaluation

A key strength of the economic evaluation is that the model has been developed to use patient-level data from the phase 3 TOWER RCT extensively. In addition, the most clinically plausible extrapolation of OS data was selected for the base-case analyses based on extensive historical comparator cohort long-term OS data.

The analysis is relevant and generalisable to clinical practice in England and Wales. Almost all the model inputs (effectiveness, HRQoL, drug doses) are based on patient-level data from the TOWER RCT, which included a total of 265 (65.4%) patients from Europe, including 21 (5.2%) patients from the UK. Furthermore, the comparators in the SOC chemotherapy arm of TOWER can be considered generalisable to the treatments used in current clinical practice for adult patients with R/R Ph- B-precursor ALL. The results of this trial are therefore expected to be generalisable to England and Wales (Section 4.13.3).

The populations enrolled in the phase 3 TOWER RCT and Study MT103-211 (including the comparison with the historical cohort) are broadly consistent with the marketing authorisation for blinatumomab in adult patients with R/R Ph- B-precursor ALL. A notable exception is that TOWER and Study MT103-211 enrolled particularly difficult-to-treat patients, as patients in late first relapse (first relapse after > 12 months in first remission), who have a better prognosis,[29] were not eligible for the studies. This means that absolute outcomes from TOWER and Study MT103-211 are likely to represent a conservative estimate of the absolute efficacy of both blinatumomab and SOC chemotherapy. Therefore, the relative efficacy in TOWER for blinatumomab versus SOC chemotherapy is expected to be at least as good as will be seen in clinical practice in a population including late first relapse patients, and the analysis excluding those patients could be considered conservative.

The TOWER RCT compared blinatumomab with SOC chemotherapy, selected from one of four investigator-chosen protocol-specified regimens with the most common intended SOC chemotherapy regimen at randomisation being FLAG ± anthracycline ([redacted]%), which is pertinent given that FLAG-IDA is considered as the most relevant comparator for this appraisal (Section 3.5). In addition, available clinical guidelines, including the EWALL guidelines,[48] suggest that there is no clearly superior salvage chemotherapy regimen in R/R Ph- B-precursor ALL. UK Clinical experts consulted by Amgen considered the outcomes in the SOC chemotherapy arm in TOWER to be broadly generalisable to the relevant comparator for this appraisal, FLAG-IDA.

### 5.10.4 Limitations of the economic evaluation

A key limitation of the analysis is that OS data had to be extrapolated as data were incomplete. The TOWER study was designed to measure the impact of blinatumomab on OS, and was stopped early for efficacy and long-term follow-up discontinued after a significant survival benefit for blinatumomab was demonstrated. Despite this, by extrapolating OS based on the observed data in the TOWER study the best available evidence has been taken into account, and efforts were made to account for the uncertainty arising from the incomplete data observed in the clinical trials through the use of pertinent external evidence (historical comparator cohort data) and input from UK clinical experts. The most clinically plausible extrapolations of OS data were selected for the base-case analyses and exhaustive scenario analyses were presented.

Other limitations of the analysis include:

- Data on utilities were not directly collected in TOWER; however, data on an oncology-specific HRQoL measure, the EORTC QLQ-C30, were collected and mapped to EQ-5D.
- In the TOWER study, contrary to the marketing authorisation, patients could receive blinatumomab maintenance therapy if they continued to have a bone marrow response or CR/CRh*/CRi after five cycles of treatment. This concerns a small proportion of patients ([redacted]%) and is unlikely to have a meaningful net impact on the resulting ICERs.
- Upon relapse or failure to achieve haematological remission, patients in TOWER received subsequent salvage therapies which will have an impact on the OS for both study arms. Given the short follow-up and early stopping of the TOWER study, there is insufficient data to conduct a robust adjustment of the impact of those salvage therapies on the OS benefit of blinatumomab over SOC chemotherapy This is likely biased against the true benefit of blinatumomab, as more SOC chemotherapy patients were salvaged with innovative anticancer therapies ([redacted]%, respectively, among patients who received study drug).

### 5.10.5 Conclusions

Blinatumomab, which has demonstrated meaningful and consistent efficacy in adult patients with R/R Ph- B-precursor ALL, in both TOWER and Study MT103-211 (including a comparison with a historical control), represents a major therapeutic innovation and a step change in the management of patients with this devastating and highly aggressive disease that responds poorly to current salvage chemotherapy regimens and is associated with very poor survival.

Based on a simple and robust model using data derived largely from the TOWER RCT, the base-case ICER for blinatumomab versus FLAG-IDA is £[redacted] per QALY in the TOWER FAS population, corresponding to a 1.45 QALY gain for an incremental cost of £[redacted]. An informative scenario analysis was conducted on the pre-specified subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation, the resulting ICER was reduced to £[redacted], suggesting that the base-case approach is potentially conservative. In addition, a key subgroup analysis was also presented where the cost effectiveness of blinatumomab was assessed for patients who had not received prior salvage therapy (a stratification subgroup in TOWER). UK clinical experts consulted by Amgen consider the more favourable survival outcomes in this subgroup to be highly clinically plausible, given that treating patients earlier in the treatment pathway (i.e., patients with a better prognosis) with a more effective therapy is likely to lead to improvements in both absolute and relative OS. The resulting ICER for this subgroup is £[redacted] per QALY, and is lower than the base case ICER. Finally, when using an alternative discount rate of 1.5% for health outcome as recommended in the NICE guide to the methods of technology appraisal (2013) when considering treatment effects that are both substantial in restoring health and sustained over a very long period (normally at least 30 years),[77] the ICERs for the TOWER FAS population and no prior salvage subgroup are reduced to £[redacted] and £[redacted] respectively.

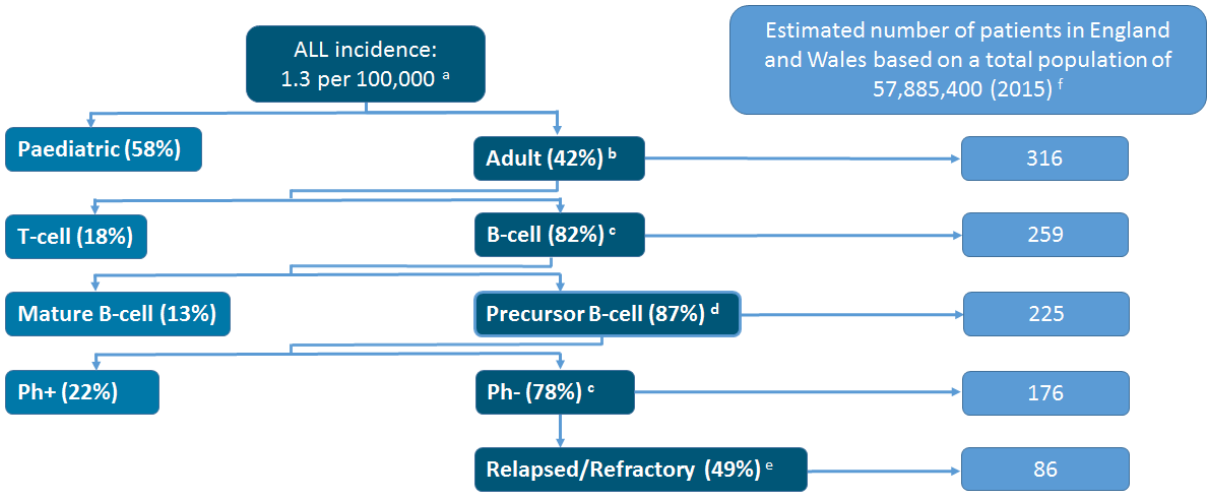
The cost-effectiveness analyses presented in this submission are based on the list price of blinatumomab. Amgen has proposed a simple PAS which has been approved by the DoH; analyses incorporating the PAS are included in the PAS addendum to this submission. Using

current NICE methodology, demonstrating cost effectiveness of blinatumomab is challenging for this extremely rare disease, even with the application of end-of-life criteria (and corresponding willingness-to-pay threshold) and a simple PAS. Additional benefits associated with blinatumomab are unlikely to be captured within the standard NICE incremental cost-utility framework, specifically, the benefits to patients and their families of minimising hospitalisation requirements and to wider society of treating a younger patient population (median age at diagnosis 34–39 years) with an effective treatment option that may lead to more patients achieving long-term remission and survival. Given that blinatumomab is indicated for a rare condition in a very small number of patients (86 per year) who have a huge unmet medical need and who stand to gain substantially from access to blinatumomab, this therapy meets many of the criteria for appraisal under the HST framework. Consequently, blinatumomab should be evaluated taking into account a wider range of criteria about the benefits and costs, as NICE does for HST appraisals. Applying the standard approach to evaluating medicines for this very small group of patients is likely to be unfairly biased against blinatumomab. Given the huge unmet need and the significant clinical benefit including additional benefit not captured by the QALY, blinatumomab is proposed for use in England and Wales for the full licensed population (i.e., in all adult patients with R/R Ph- B-precursor ALL).

# 6 Assessment of factors relevant to the NHS and other parties

As detailed in Section 3, adult R/R Ph- B-precursor ALL is an extremely rare disease; and based on available ALL incidence data it is estimated that 86 patients who will become eligible for treatment with blinatumomab were diagnosed in England and Wales in 2015 (Figure 6-1).

**Figure 6-1. Estimated incidence of adult R/R Ph- B-precursor ALL in England and Wales**




[a] Cancer Research UK (2013 estimate)[27]
[b] Calculated from UK age-specific ALL incidence data reported by Cancer Research UK (2011-2013 estimate).[26] Since data were only provided for 5-year age groups, the 15–19 year age group was split such that 60% of the population projection for this age group was considered 15–17, and the remaining 40% were considered 18–19 and included in the estimate for adult patients.
[c] Weighted average of data from (i) a UK cytogenetic population-based study of 349 patients (> 15 years of age) with ALL diagnosed between 1983 and 2001 (Moorman *et al.,* 2010);[23] and (ii) an analysis of cytogenetic data from 1522 patients (15–65 years of age) with ALL enrolled on the MRC UKALLXII/ECOG 2993 study (Moorman *et al.,* 2007).[24] Data on T- and B-cell lineage from Moorman *et al.,* 2007 were calculated using separately reported proportions of patients with T-cell lineage in subsets of patients with Ph+ ALL and Ph- ALL.
[d] Based on UK data from a cytogenetic population-based study of 349 patients (> 15 years of age) with ALL diagnosed between 1983 and 2001 (Moorman *et al.,* 2010).[23]
[e] Based on data from 1508 newly diagnosed patients (15–60 years of age) with ALL enrolled in the MRC UKALLXII/ECOG 2993 study, of whom 136 died or failed to achieve remission in induction (refractory) and 609 relapsed after achieving a remission (Fielding *et al.,* 2007).[25]
[f] Office of National Statistics (2015 estimate).[28]

Based on market research, it is expected that blinatumomab will achieve the following market shares in the population of adult R/R Ph- B-precursor ALL patients (Table 6-1).

**Table 6-1. Estimated number of eligible patients treated with blinatumomab per year (2017–2021)**

| Year | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|
| **Number of patients** | 86 | 86 | 86 | 86 | 86 |
| **Expected patient share** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **R/R ALL patients treated with blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Using the costs for treatment acquisition and administration calculated within the economic models for Years 1–5 under the base-case assumptions, the estimated annual budget impact was calculated as shown in Table 6-2.

**Table 6-2 Estimated NHS annualised budgetary impact of using blinatumomab**

| Year | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|
| **New patients treated with blinatumomab each year** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total cost** | £2,603,482 | £ 5,206,964 | £5,206,964 | £5,206,964 | £5,206,964 |
| **Cumulative cost** | £ 2,603,482 | £7,810,446 | £13,017,410 | £18,224,374 | £23,431,338 |

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

## Blinatumomab for previously treated B-precursor acute lymphoblastic leukaemia

## Patient access scheme submission

**Prepared by:**

AMGEN

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| | 1.0 | Yes – redacted | |

# 1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

# 2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

# 3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Technology: Blinatumomab (Blincyto®)

Disease area: Adult relapsed or refractory Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia (R/R Ph- B-precursor ALL).

3.2 Please outline the rationale for developing the patient access scheme.

The rationale behind the patient access scheme (PAS) is to mitigate any uncertainty associated with analysis of cost effectiveness presented in company submission of evidence to NICE.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The proposed PAS is a simple scheme (confidential discount of the NHS list price of blinatumomab). The proposed confidential discount is [redacted]. The scheme is expected to be implemented at the time of positive (or draft positive) NICE guidance, expected in June 2017

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS applies to the whole population for which blinatumomab is licensed, i.e. for the treatment of Adult relapsed or refractory Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia (R/R Ph- B-precursor ALL)

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent on any additional criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Not applicable.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The price (including the PAS confidential discount) will be demonstrated to NHS organisations on the original invoice.

No additional information will need to be collected.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

See above.

3.10 Please provide details of the duration of the scheme.

The PAS will remain in place until NICE next reviews the product under the technology appraisals programme and any final decision has been published by NICE (as per the declaration signed by Amgen in the PAS proposal template).

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The PAS does not require completion of any forms or other administrative process.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

# 4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The PAS applies to the entire licensed population for blinatumomab, which covers the populations presented in the main submission of evidence.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

No changes relating to assumptions have been made to the model.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been incorporated into the economic model by utilising the discounted price per vial of blinatumomab that would apply in the context of a simple discount. The NHS list price of blinatumomab is £2,017.00 per vial (38.5 µg). The PAS is a fixed price of [redacted] per 38.5 µg vial, and has been implemented in the economic model [redacted]

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data for blinatumomab come from the phase 3, randomised, controlled trial (TOWER) presented in the main evidence submission. Blinatumomab cost (list price and PAS price) was included in the model based on an administration, dose, and dosing schedule consistent with the phase 3 TOWER RCT, its marketing authorisation, and anticipated use in clinical practice in England and Wales during two induction and up to three additional consolidation cycles:

- Continuous IV infusion over 4 weeks (9 µg/day during Week 1 of Cycle 1 then 28 µg/day for the remainder of the cycle and during subsequent cycles) followed by a treatment-free interval of 2 weeks.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence

There will be no costs associated with the implementation and operation of the proposed PAS as this scheme involves a simple confidential discount of [redacted] applied at the point of order.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Implementation of the PAS will not incur additional treatment-related costs.

## *Summary results*

### Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

In our original submission, the base-case comparison is Blinatumomab positioned as an alternative treatment option to FLAG-IDA in adult relapsed or refractory Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia (R/R Ph- B-precursor ALL) based on the TOWER FAS (i.e. intent-to-treat [ITT] population).

In addition a comprehensive subgroup analysis comparing blinatumomab to FLAG-IDA was also performed using TOWER data for the pre-specified stratification factor subgroup of patients who had not received prior salvage therapy, as this subgroup represent a clinically relevant subgroup of patients likely to benefit even further from receiving blinatumomab

The base case cost-effectiveness results for blinatumomab versus FLAG-IDA in all R/R Ph- B-precursor ALL patients with the list and PAS price for blinatumomab are presented in Table 1 and Table 2, respectively.

The base case cost-effectiveness results for blinatumomab versus FLAG-IDA in R/R Ph- B-precursor ALL patients with no prior salvage therapy with both list and PAS price for blinatumomab are presented in Table 3 and Table 4, respectively.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

**Table 1 Base-case cost-effectiveness results Blinatumomab vs. FLAG-IDA for all patients – blinatumomab list price**

| | Blinatumomab | FLAG-IDA |
|---|---|---|
| Intervention cost (£) | [redacted] | 2,092 |
| Other costs (£) | [redacted] | 62,073 |
| Total costs (£) | [redacted] | 64,165 |
| Difference in total costs (£) | | [redacted] |
| LYG | 4.38 | 2.61 |
| LYG difference | | 1.78 |
| QALYs | 3.35 | 1.90 |
| QALY difference | | 1.45 |
| ICER (£) | | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYG, life-year gained; N/A, not applicable QALY, quality-adjusted life-year; | | |

**Table 2 Base-case cost-effectiveness results Blinatumomab vs. FLAG-IDA for all patient – blinatumomab PAS price**

| | Blinatumomab | FLAG-IDA |
|---|---|---|
| Intervention cost (£) | [redacted] | 2,092 |
| Other costs (£) | [redacted] | 62,073 |
| Total costs (£) | 144,611 | 64,165 |
| Difference in total costs (£) | | 80,446 |
| LYG | 4.38 | 2.61 |
| LYG difference | | 1.78 |
| QALYs | 3.35 | 1.90 |
| QALY difference | | 1.45 |
| ICER (£) | | 55,501 |
| ICER, incremental cost-effectiveness ratio; LYG, life-year gained; N/A, not applicable; QALY, quality-adjusted life-year; | | |

**Table 3 Base-case cost-effectiveness results Blinatumomab vs. FLAG-IDA in patients with no prior salvage therapy - list price**

| | Blinatumomab | FLAG-IDA |
|---|---|---|
| Intervention cost (£) | [redacted] | 2,377 |
| Other costs (£) | [redacted] | 72,326 |
| Total costs (£) | [redacted] | 74,703 |
| Difference in total costs (£) | | [redacted] |
| LYG | 5.06 | 2.65 |
| LYG difference | | 2.40 |
| QALYs | 3.91 | 1.94 |
| QALY difference | | 1.98 |
| ICER (£) | | [redacted] |
| ICER, incremental cost-effectiveness ratio; LYG, life-year gained; N/A, not applicable; QALY, quality-adjusted life-year; | | |

**Table 4 Base-case cost-effectiveness results Blinatumomab vs. FLAG-IDA in patients with no prior salvage therapy - PAS price**

| | Blinatumomab | FLAG-IDA |
|---|---|---|
| Blinatumomab cost (£) | [redacted] | 2,377 |
| Other costs (£) | [redacted] | 72,326 |
| Total costs (£) | 171,879 | 74,703 |
| Difference in total costs (£) | | 97,176 |
| LYG | 5.06 | 2.65 |
| LYG difference | | 2.40 |
| QALYs | 3.91 | 1.94 |
| QALY difference | | 1.98 |
| ICER (£) | | 49,190 |
| ICER, incremental cost-effectiveness ratio; LYG, life-year gained; N/A, not applicable; QALY, quality-adjusted life-year; | | |

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

The base incremental case cost-effectiveness results for blinatumomab vs. FLAG-IDA in all R/R Ph- B-precursor ALL patients with the list and PAS price for blinatumomab are presented in Table 5 and Table 6, respectively.

The base incremental case cost-effectiveness results for blinatumomab vs. FLAG-IDA in R/R Ph- B-precursor ALL patients with no prior salvage therapy with both list and PAS price for blinatumomab are presented in Table 7 and Table 8, respectively.

**Table 5 Base-case incremental results Blinatumomab vs. FLAG-IDA in all patients – blinatumomab list price**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|
| Blinatumomab | [redacted] | 4.38 | 3.35 | [redacted] | 1.78 | 1.45 | [redacted] |
| FLAG-IDA | 64,165 | 2.61 | 1.90 | | | | |

**Table 6 Base-case incremental results Blinatumomab vs. FLAG-IDA in all patients – blinatumomab PAS price**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|
| Blinatumomab | 144,611 | 4.38 | 3.35 | 80,446 | 1.78 | 1.45 | 55,501 |
| FLAG-IDA | 64,165 | 2.61 | 1.90 | | | | |

**Table 7 Base-case incremental results Blinatumomab vs. FLAG-IDA in patients with no prior salvage therapy – blinatumomab list price**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|
| Blinatumomab | [redacted] | 5.06 | 3.91 | [redacted] | 2.40 | 1.98 | [redacted] |
| FLAG-IDA | 74,703 | 2.65 | 1.94 | | | | |

**Table 8 Base-case incremental results Blinatumomab vs. FLAG-IDA in patients with no prior salvage therapy – blinatumomab PAS price**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|
| Blinatumomab | 171,879 | 5.06 | 3.91 | 97,176 | 2.40 | 1.98 | 49,190 |
| FLAG-IDA | 74,703 | 2.65 | 1.94 | | | | |

**Sensitivity analyses**

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analyses for blinatumomab versus FLAG-IDA in all R/R Ph- B-precursor ALL patients with the list and PAS price for blinatumomab are presented in **Error! Reference source not found.** and Figure 1, respectively.

Deterministic sensitivity analyses for FLAG-IDA in R/R Ph- B-precursor ALL patients with no prior salvage therapy with both list and PAS price for blinatumomab are presented in

and **Figure 2**, respectively.

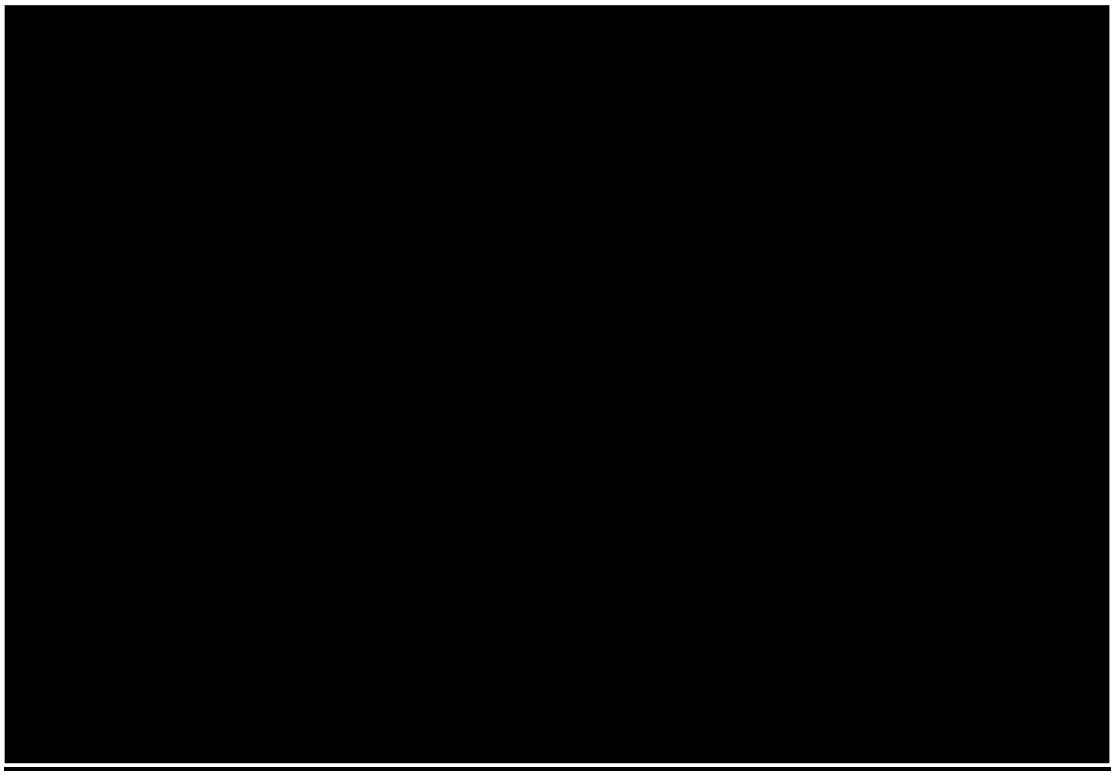
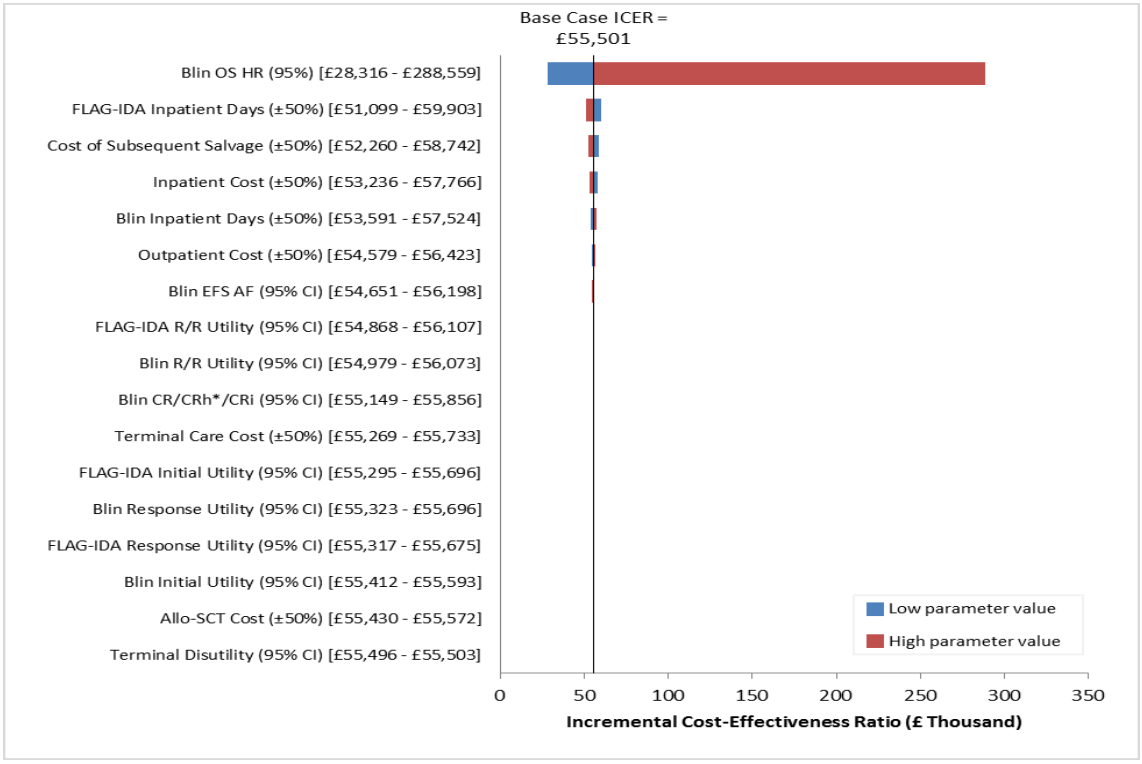
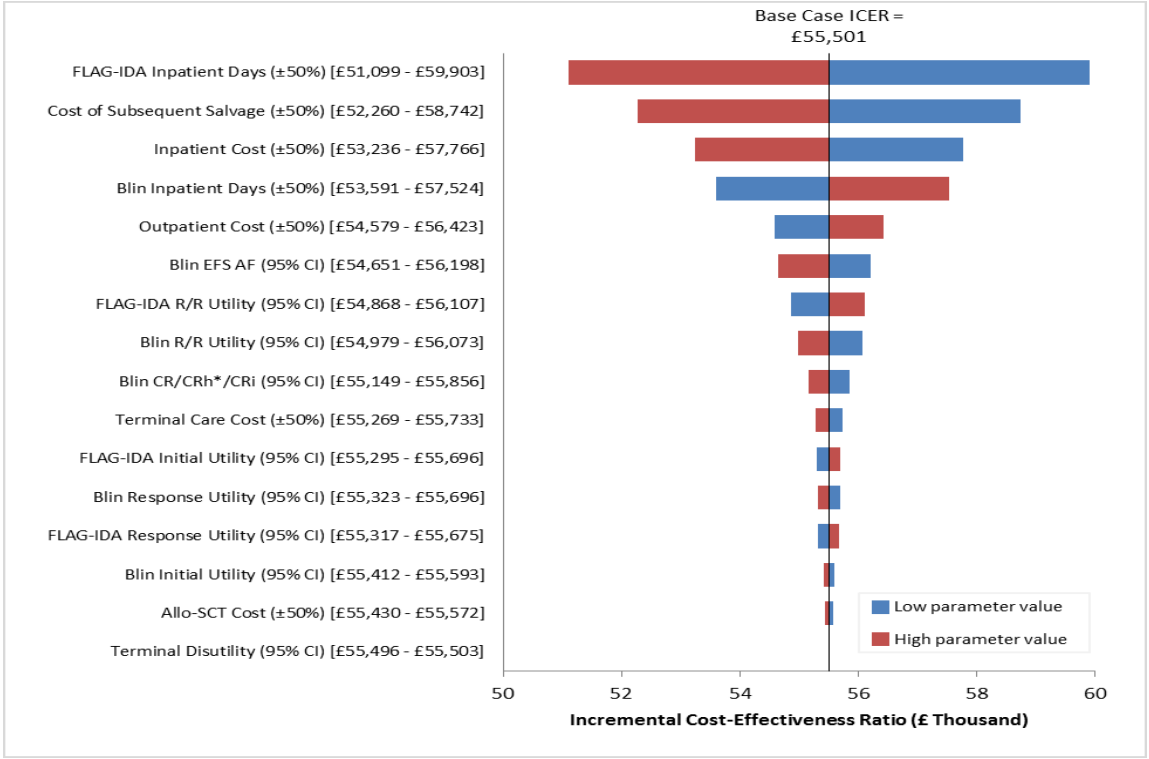


**Figure 1 Tornado diagram blinatumomab versus FLAG-IDA - blinatumomab PAS price**

## A. All parameters

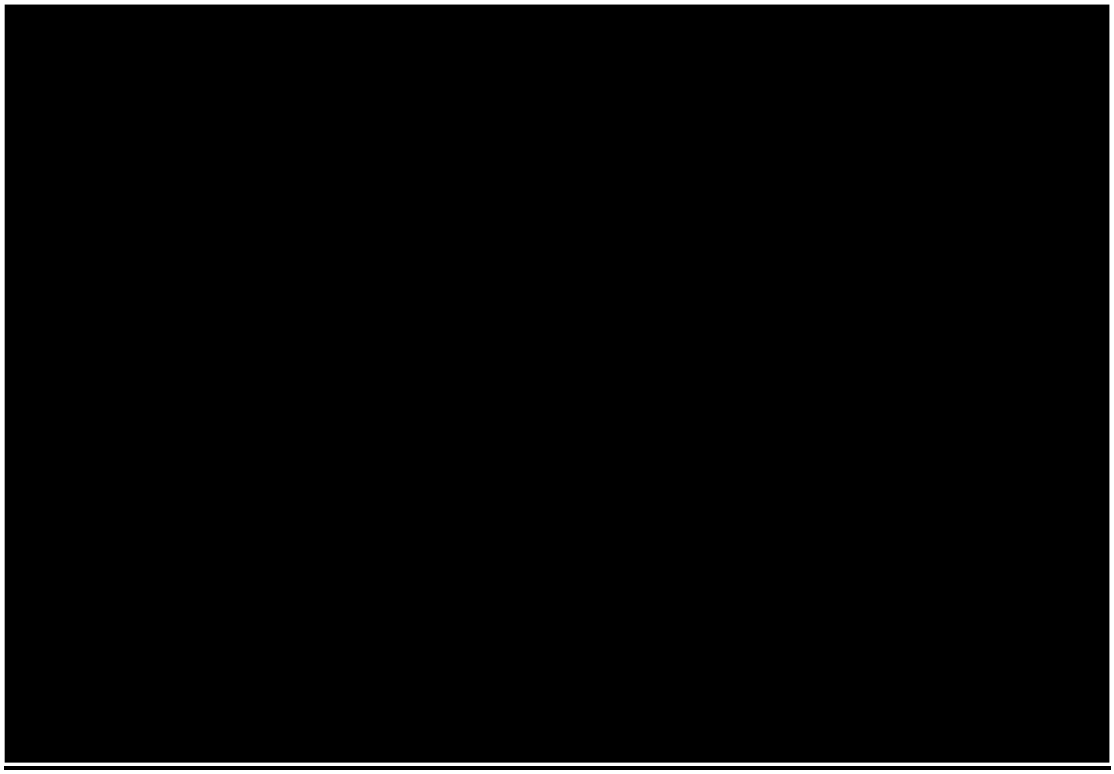



## B. Excluding SA on OS



[redacted]

[redacted]



[redacted]

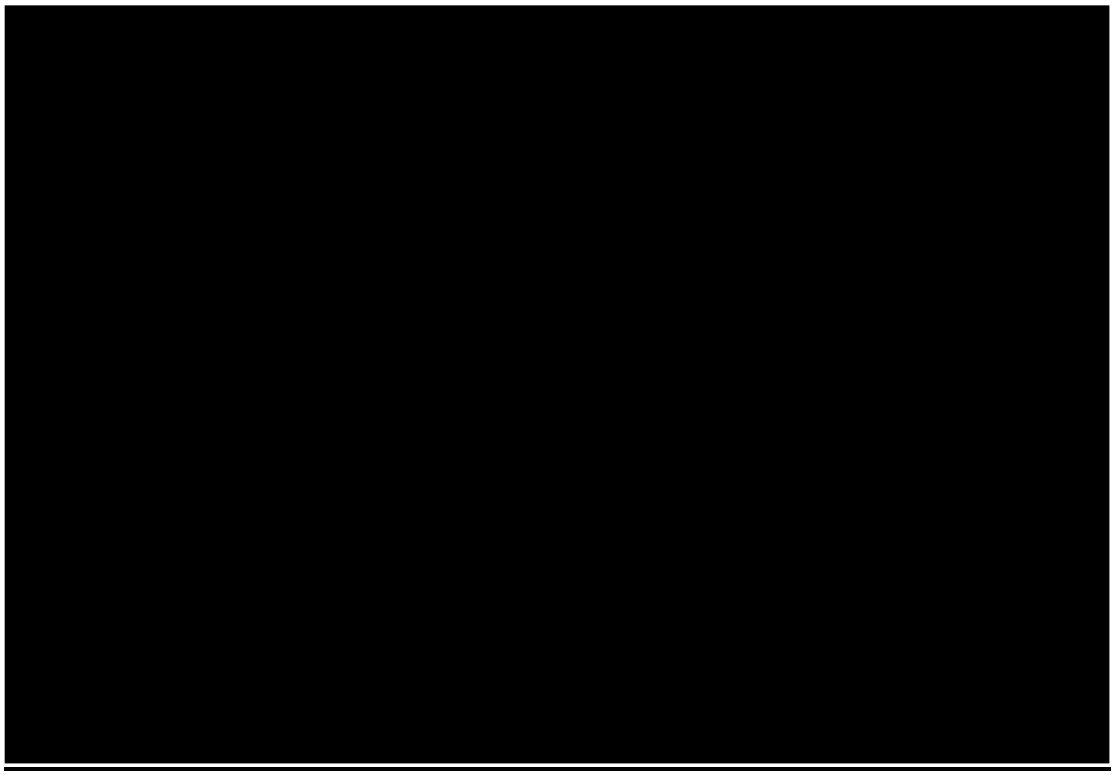
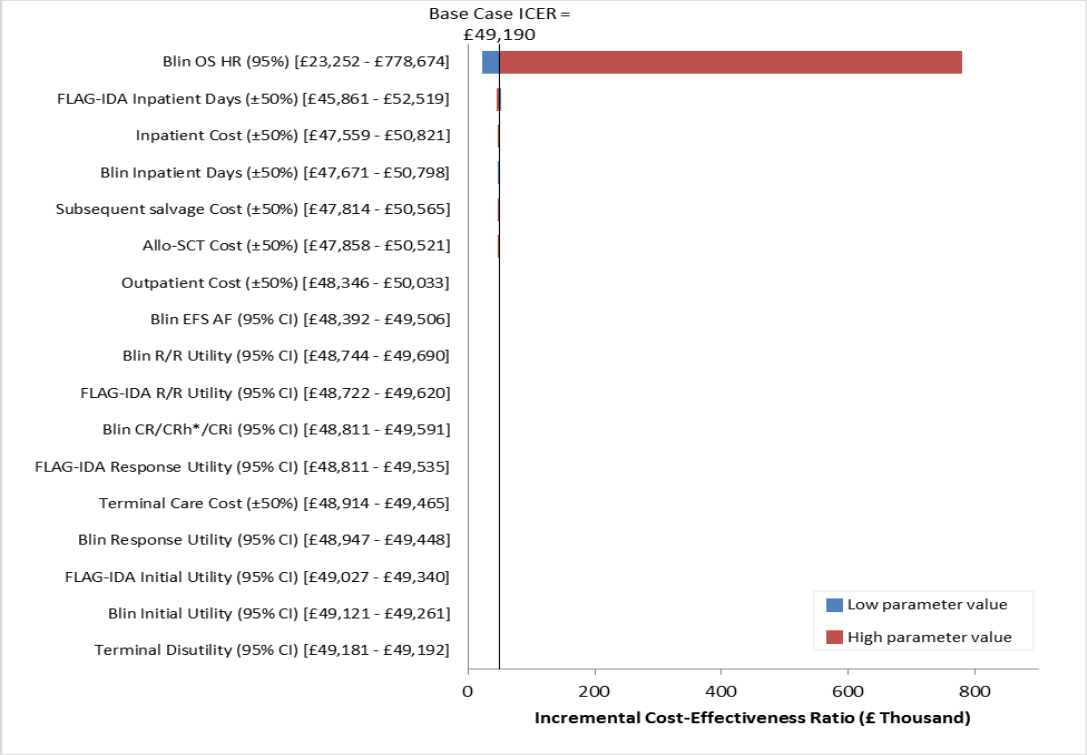
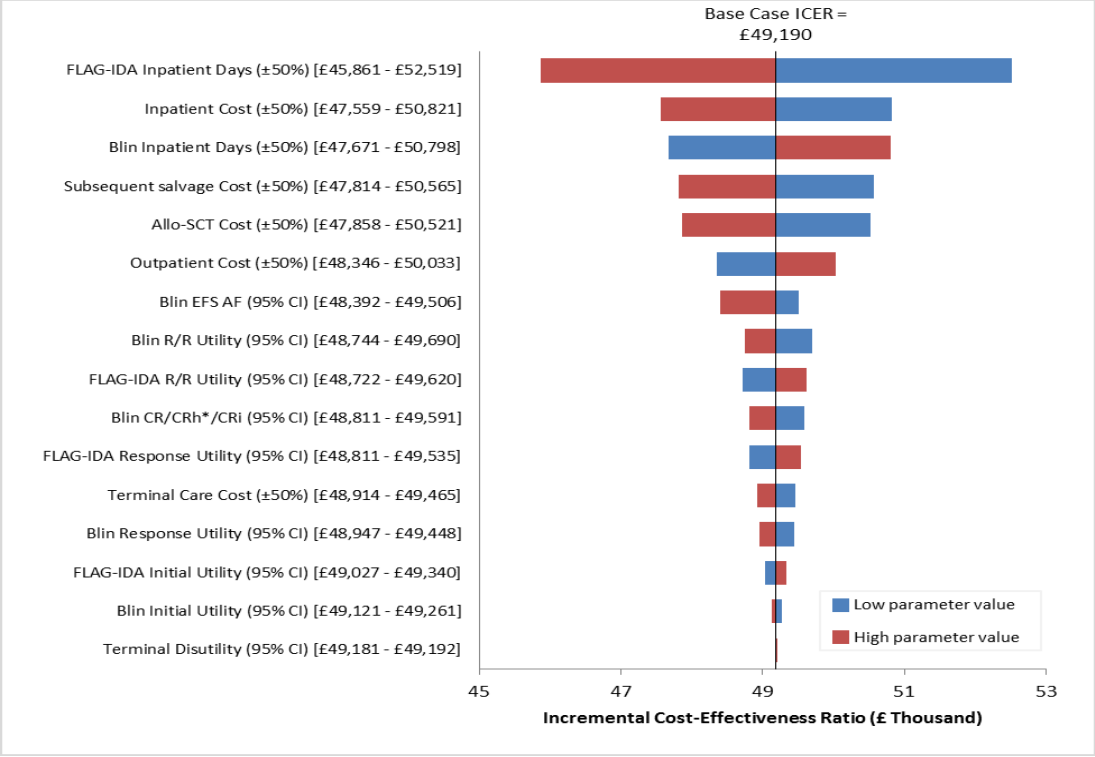


**Figure 2 Tornado diagram: blinatumomab versus FLAG-IDA in patient with no prior salvage therapy – blinatumomab PAS price**

## A. All parameters




## B. Excluding SA on OS



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis results for blinatumomab versus FLAG-IDA in all R/R Ph- B-precursor ALL patients with the list and PAS price for blinatumomab are presented in Table 9 and Table 10, respectively. Scatter plots are presented in

and Figure 3, and cost-effectiveness acceptability curves are presented in and **Error! Reference source not found.**.

**Table 9 Blinatumomab versus FLAG-IDA in all patientss – Probabilistic ICER – blinatumomab list price**

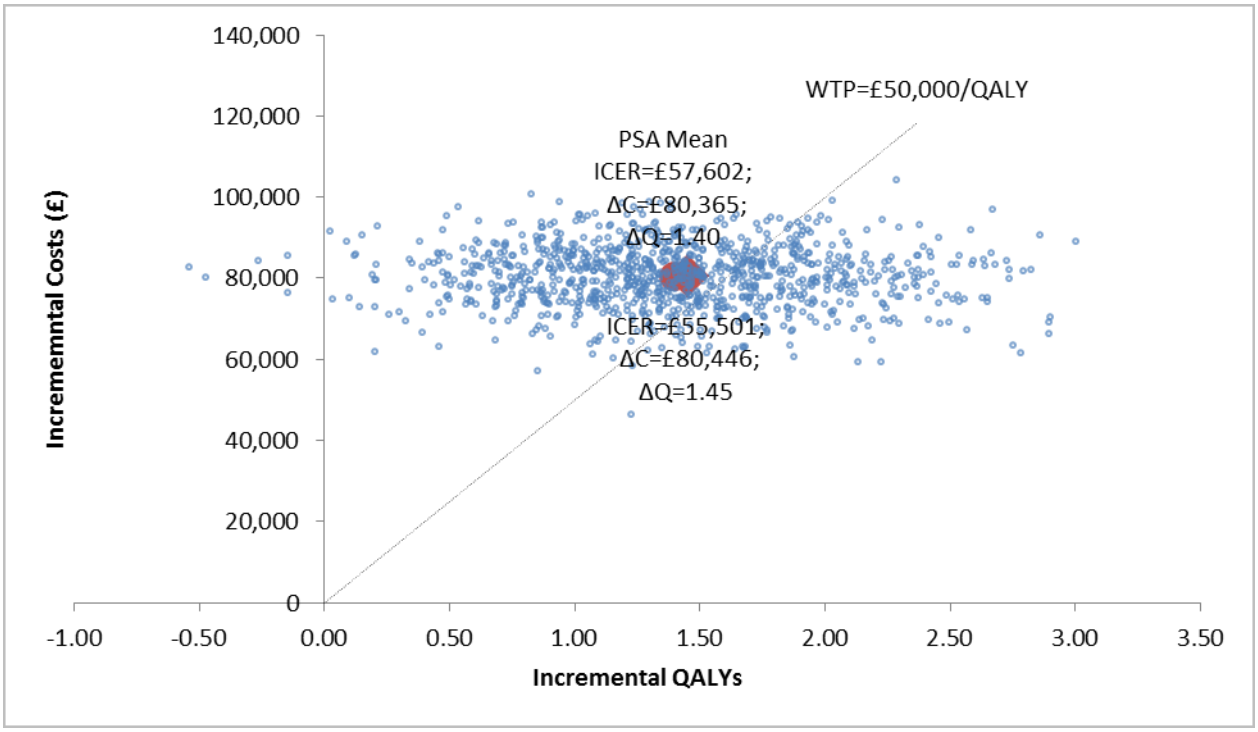
| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Blinatumomab | [redacted] | 3.28 | [redacted] | 1.38 | [redacted] |
| FLAG-IDA | 64,074 | 1.90 | | | |
| ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; | | | | | |

**Table 10 Blinatumomab versus FLAG-IDA in all patients – Probabilistic ICER – blinatumomab PAS price**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Blinatumomab | 144,692 | 3.30 | 80,365 | 1.40 | 57,602 |
| FLAG-IDA | 64,327 | 1.91 | | | |
| ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; | | | | | |

[redacted]

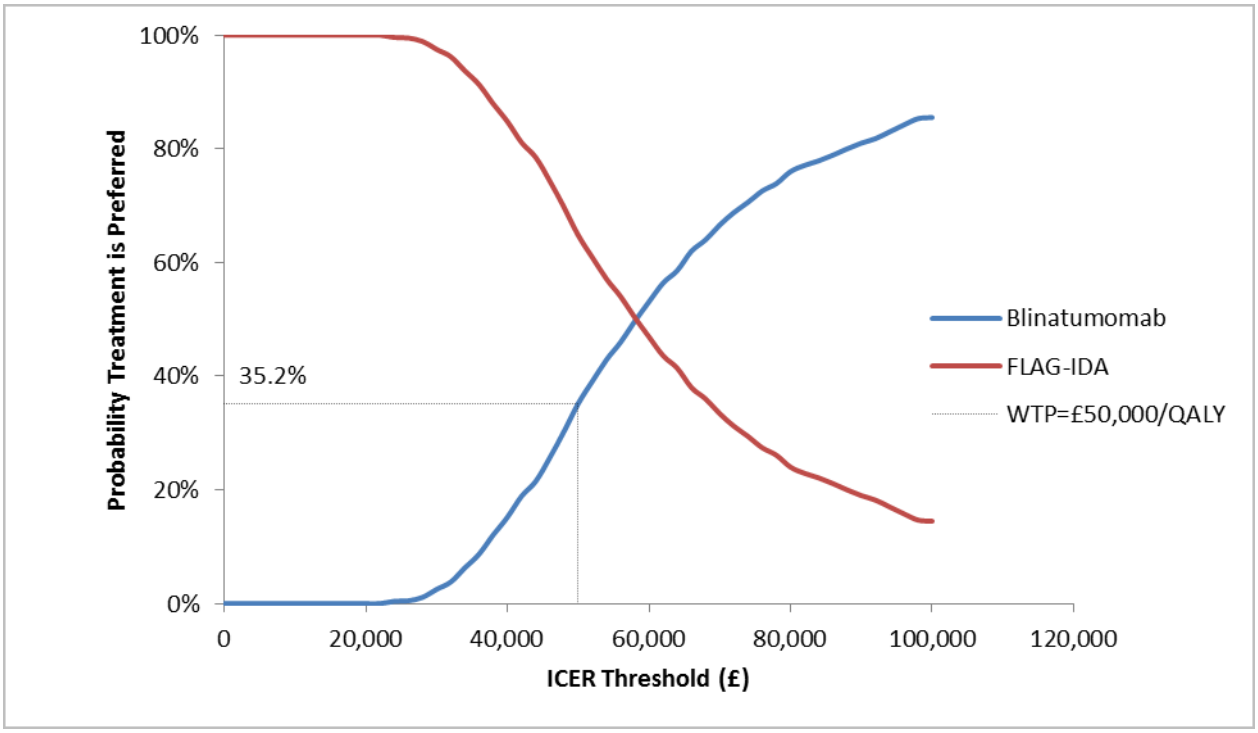
**Figure 3 Scatter plot of incremental cost and QALYs – blinatumomab versus FLAG-IDA – blinatumomab PAS price**



[redacted]

[redacted]

**Figure 8 Cost-effectiveness acceptability curve – blinatumomab versus FLAG-IDA - blinatumomab PAS price**



Probabilistic sensitivity analysis results for blinatumomab versus FLAG-IDA in R/R Ph- B-precursor ALL patients with no prior salvage therapy with the list and PAS price for blinatumomab are presented in Table 9 and Table 10, respectively. Scatter plots are presented in

and Figure 3, and cost-effectiveness acceptability curves are presented in and **Error! Reference source not found.**.

**Table 11 Blinatumomab versus FLAG-IDA in patients with no prior salvage therapy – Probabilistic ICER – blinatumomab list price**

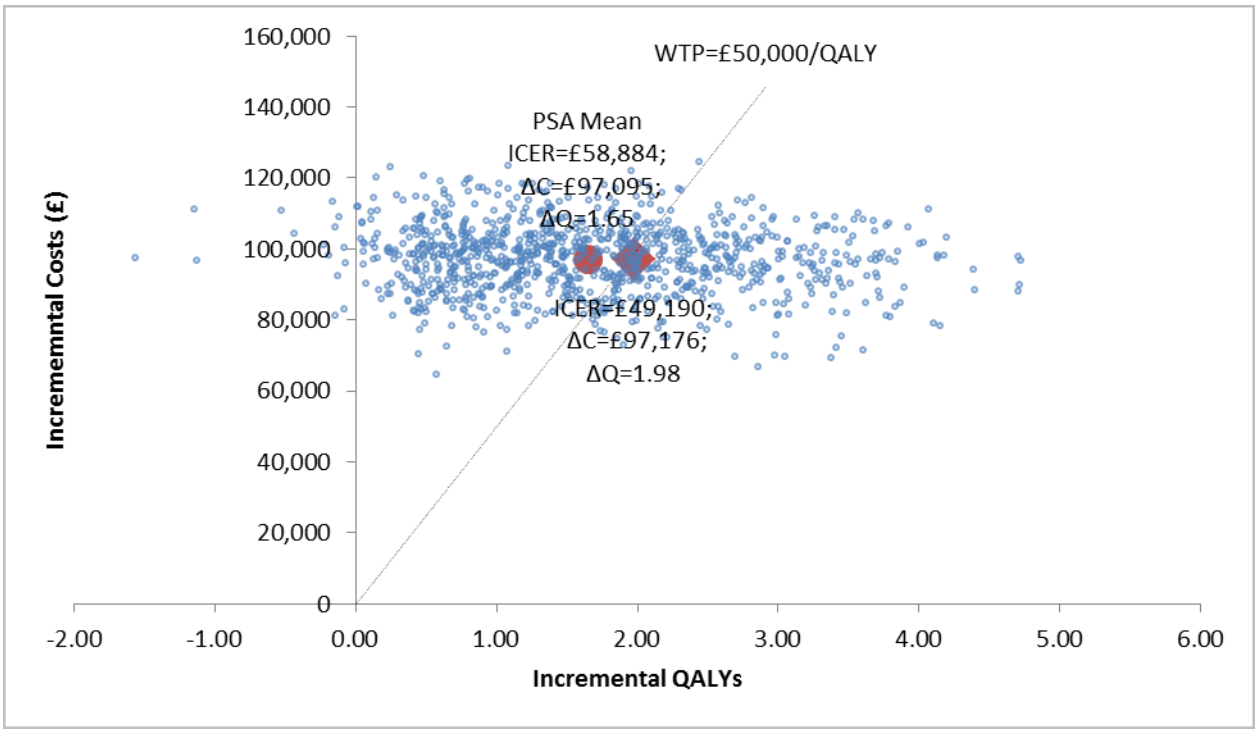
| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Blinatumomab | [redacted] | 3.57 | [redacted] | 1.69 | [redacted] |
| FLAG-IDA | 74,933 | 1.88 | | | |
| ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; | | | | | |

**Table 12 Blinatumomab versus FLAG-IDA in patients with no prior salvage therapy – Probabilistic ICER – blinatumomab PAS price**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Blinatumomab | 172,220 | 3.59 | 97,095 | 1.65 | 58,884 |
| FLAG-IDA | 75,125 | 1.94 | | | |
| ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; | | | | | |

[redacted]

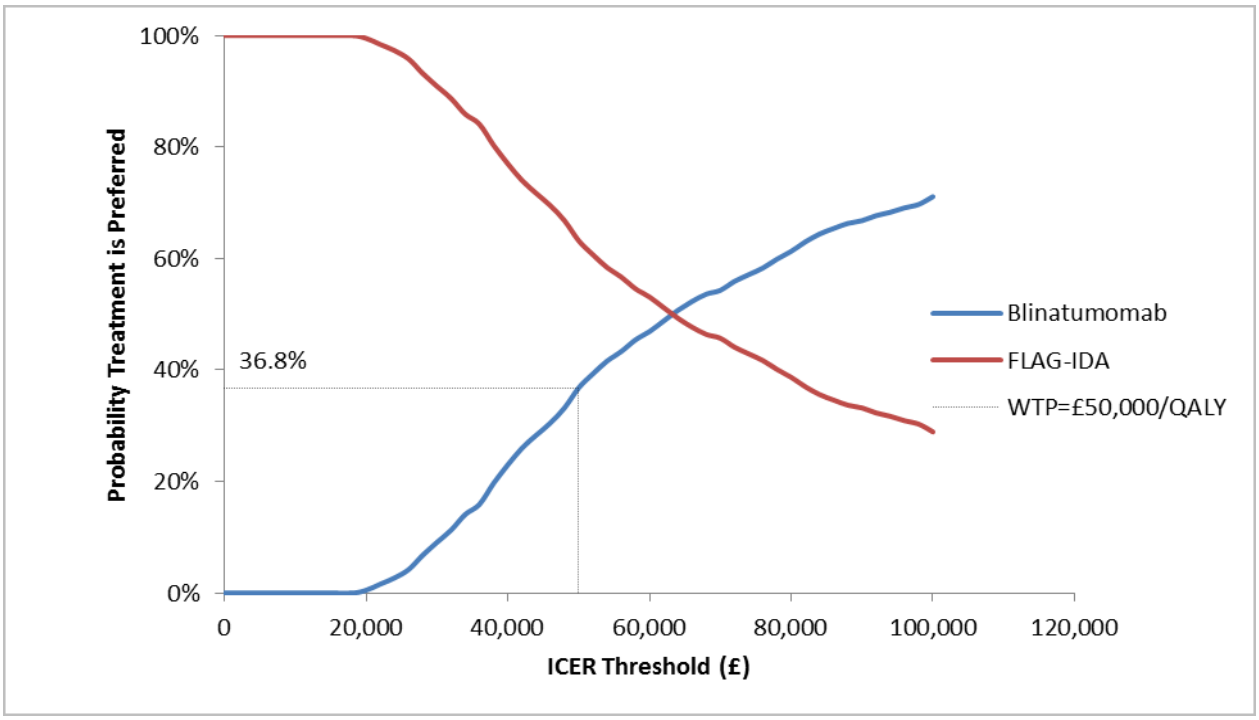
**Figure 10 Scatter plot of incremental cost and QALYs – blinatumomab versus FLAG-IDA in patients with no prior salvage therapy –PAS price**



[redacted]

[redacted]

**Figure 4 Cost-effectiveness acceptability curve – blinatumomab versus FLAG-IDA with no prior salvage therapy – blinatumomab PAS price**



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

A list and justification of the key scenario analysis for the comparisons of blinatumomab versus FLAG-IDA in both the ITT and no-prior salvage therapy subgroup is presented in the main submission of evidence (Table 5-25, page 185), the resulting ICERs with the blinatumomab list price and PAS price are presented in Table 13 and Table 14 for the ITT population and Table 15 and Table 16 for the no-prior salvage therapy, respectively.

**Table 13 Scenario analysis results – Blinatumomab vs. FLAG-IDA all patients– blinatumomab list price**

| Scenario number | Scenario | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|
| | Base Case (All Patients ITT ) | [redacted] | 1.45 | [redacted] |
| 1 | Safety analysis set | [redacted] | 1.34 | [redacted] |
| 2 | Subgroup of patients that were intended to receive a FLAG-IDA SOC therapy regimen at randomization | [redacted] | 2.42 | [redacted] |
| 3 | OS Based on RCS Log-Logistic | [redacted] | 0.47 | [redacted] |
| 4 | Survivors Cured - 36 Months | [redacted] | 1.81 | [redacted] |
| 5 | Survivors Cured - 48 Months | [redacted] | 1.60 | [redacted] |
| 6 | Survivors Cured - 60 Months | [redacted] | 1.45 | [redacted] |
| 7 | EFS Based on Lognormal | [redacted] | 1.45 | [redacted] |
| 8 | 36-Month Duration of Benefit | [redacted] | 1.39 | [redacted] |
| 9 | 60-Month Duration of Benefit | [redacted] | 1.47 | [redacted] |
| 10 | 10-Year Model Timeframe | [redacted] | 0.63 | [redacted] |
| 11 | 20-Year Model Timeframe | [redacted] | 1.02 | [redacted] |
| 12 | 60-Year Model Timeframe | [redacted] | 1.46 | [redacted] |
| 13 | 1.5% Discount Rate | [redacted] | 1.97 | [redacted] |
| 14 | 10 Inpatient Days Blinatumomab All Cycles | [redacted] | 1.45 | [redacted] |
| 15 | Zero cost for Blinatumomab Cycle 6+ | [redacted] | 1.45 | [redacted] |
| 16 | Blinatumomab home IV bag changes for Cycle 3+ | [redacted] | 1.45 | [redacted] |
| 17 | Clofarabine Included in FLAG-IDA | [redacted] | 1.45 | [redacted] |
| 18 | Rate of allo-SCT from MT103-211 | [redacted] | 1.45 | [redacted] |
| 19 | EORTC-8D Utilities | [redacted] | 1.49 | [redacted] |
| 20 | TTO Utilties from Vignette Study | [redacted] | 1.40 | [redacted] |

**Table 14 Scenario analysis results – Blinatumomab vs. FLAG-IDA All patients – blinatumomab PAS price**

| Scenario number | Scenario | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|
| | Base Case (All Patients ITT) | 80,446 | 1.45 | 55,501 |
| 1 | Safety analysis set | 74,256 | 1.34 | 55,314 |
| 2 | Subgroup of patients that were intended to receive a FLAG-IDA SOC therapy regimen at randomization | 78,459 | 2.42 | 32,371 |
| 3 | OS Based on RCS Log-Logistic | 80,824 | 0.47 | 171,487 |
| 4 | Survivors Cured - 36 Months | 78,866 | 1.81 | 43,527 |
| 5 | Survivors Cured - 48 Months | 79,280 | 1.60 | 49,485 |
| 6 | Survivors Cured - 60 Months | 79,572 | 1.45 | 55,017 |
| 7 | EFS Based on Lognormal | 80,461 | 1.45 | 55,659 |
| 8 | 36-Month Duration of Benefit | 80,446 | 1.39 | 57,754 |
| 9 | 60-Month Duration of Benefit | 80,444 | 1.47 | 54,696 |
| 10 | 10-Year Model Timeframe | 80,466 | 0.63 | 126,896 |
| 11 | 20-Year Model Timeframe | 80,455 | 1.02 | 78,878 |
| 12 | 60-Year Model Timeframe | 80,444 | 1.46 | 55,135 |
| 13 | 1.5% Discount Rate | 80,852 | 1.97 | 41,081 |
| 14 | 10 Inpatient Days Blinatumomab All Cycles | 88,069 | 1.45 | 60,760 |
| 15 | Zero cost for Blinatumomab Cycle 6+ | 72,179 | 1.45 | 49,798 |
| 16 | Blinatumomab home IV bag changes for Cycle 3+ | 79,677 | 1.45 | 54,971 |
| 17 | Clofarabine Included in FLAG-IDA | 76,206 | 1.45 | 52,576 |
| 18 | Rate of allo-SCT from MT103-211 | 87,085 | 1.45 | 60,081 |
| 19 | EORTC-8D Utilities | 80,446 | 1.49 | 53,910 |
| 20 | TTO Utilties from Vignette Study | 80,446 | 1.40 | 57,438 |

**Table 15 Scenario analysis results – Blinatumomab vs. FLAG-IDA in patients with no prior salvage therapy – blinatumomab list price**

| Scenario number | Scenario | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|
| | Base Case (No Prior Salvage) | [redacted] | 1.98 | [redacted] |
| 1 | Safety analysis set (No Prior Salvage) | [redacted] | 1.58 | [redacted] |
| 2 | OS Based on RCS Log-Logistic | [redacted] | 0.79 | [redacted] |
| 3 | Survivors Cured - 36 Months | [redacted] | 2.59 | [redacted] |
| 4 | Survivors Cured - 48 Months | [redacted] | 2.32 | [redacted] |
| 5 | Survivors Cured - 60 Months | [redacted] | 2.12 | [redacted] |
| 6 | EFS Based on Lognormal | [redacted] | 1.98 | [redacted] |
| 7 | 36-Month Duration of Benefit | [redacted] | 1.82 | [redacted] |
| 8 | 60-Month Duration of Benefit | [redacted] | 2.05 | [redacted] |
| 9 | 10-Year Model Timeframe | [redacted] | 0.95 | [redacted] |
| 10 | 20-Year Model Timeframe | [redacted] | 1.46 | [redacted] |
| 11 | 60-Year Model Timeframe | [redacted] | 1.98 | [redacted] |
| 12 | 1.5% Discount Rate | [redacted] | 2.61 | [redacted] |
| 13 | 10 Inpatient Days Blinatumomab All Cycles | [redacted] | 1.98 | [redacted] |
| 14 | Zero cost for Blinatumomab Cycle 6+ | [redacted] | 1.98 | [redacted] |
| 15 | Blinatumomab home IV bag changes for Cycle 3+ | [redacted] | 1.98 | [redacted] |
| 16 | Clofarabine Included in FLAG-IDA | [redacted] | 1.98 | [redacted] |
| 17 | Rate of allo-SCT from MT103-211 | [redacted] | 1.98 | [redacted] |
| 18 | EORTC-8D Utilities | [redacted] | 2.03 | [redacted] |
| 19 | TTO Utilties from Vignette Study | [redacted] | 1.81 | [redacted] |

**Table 16 Scenario analysis results – Blinatumomab vs. FLAG-IDA in patients with no prior salvage therapy – blinatumomab PAS price**

| Scenario number | Scenario | Incremental costs (£) | Incremental QALYs | ICER (£) |
|---|---|---|---|---|
| | Base Case (No Prior Salvage) | 97,176 | 1.98 | 49,190 |
| 1 | Safety analysis set (No Prior Salvage) | 74,070 | 1.58 | 46,821 |
| 2 | OS Based on RCS Log-Logistic | 97,624 | 0.79 | 123,824 |
| 3 | Survivors Cured - 36 Months | 95,114 | 2.59 | 36,761 |
| 4 | Survivors Cured - 48 Months | 95,678 | 2.32 | 41,211 |
| 5 | Survivors Cured - 60 Months | 96,078 | 2.12 | 45,339 |
| 6 | EFS Based on Lognormal | 97,140 | 1.98 | 49,114 |
| 7 | 36-Month Duration of Benefit | 97,166 | 1.82 | 53,389 |
| 8 | 60-Month Duration of Benefit | 97,177 | 2.05 | 47,291 |
| 9 | 10-Year Model Timeframe | 97,214 | 0.95 | 102,439 |
| 10 | 20-Year Model Timeframe | 97,206 | 1.46 | 66,788 |
| 11 | 60-Year Model Timeframe | 97,174 | 1.98 | 49,055 |
| 12 | 1.5% Discount Rate | 97,621 | 2.61 | 37,336 |
| 13 | 10 Inpatient Days Blinatumomab All Cycles | 107,383 | 1.98 | 54,356 |
| 14 | Zero cost for Blinatumomab Cycle 6+ | 82,931 | 1.98 | 41,979 |
| 15 | Blinatumomab home IV bag changes for Cycle 3+ | 96,070 | 1.98 | 48,630 |
| 16 | Clofarabine Included in FLAG-IDA | 92,806 | 1.98 | 46,978 |
| 17 | Rate of allo-SCT from MT103-211 | 108,862 | 1.98 | 55,105 |
| 18 | EORTC-8D Utilities | 97,176 | 2.03 | 47,881 |
| 19 | TTO Utilties from Vignette Study | 97,176 | 1.81 | 53,680 |

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

**Impact of patient access scheme on ICERs**

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

The cost-effectiveness results for the base case and scenario analyses with and without the proposed blinatumomab PAS are provided in

- Table 17 for blinatumomab versus FLAG-IDA in all R/R Ph- B-precursor ALL patients and in
- Table 18 for blinatumomab vs. FLAG-IDA in patients who have received no prior salvage therapy.

**Table 17 Results showing the impact of PAS on ICERs for blinatumomab vs. FLAG-IDA in all patients**

| No. | Scenario | ICER (£) | |
|---|---|---|---|
| | | No PAS | With PAS |
| | Base Case (All Patients ITT) | [redacted] | 55,501 |
| 1 | Safety analysis set | [redacted] | 55,314 |
| 2 | Subgroup of patients that were intended to receive a FLAG-IDA SOC therapy regimen at randomization | [redacted] | 32,371 |
| 3 | OS Based on RCS Log-Logistic | [redacted] | 171,487 |
| 4 | Survivors Cured - 36 Months | [redacted] | 43,527 |
| 5 | Survivors Cured - 48 Months | [redacted] | 49,485 |
| 6 | Survivors Cured - 60 Months | [redacted] | 55,017 |
| 7 | EFS Based on Lognormal | [redacted] | 55,659 |
| 8 | 36-Month Duration of Benefit | [redacted] | 57,754 |
| 9 | 60-Month Duration of Benefit | [redacted] | 54,696 |
| 10 | 10-Year Model Timeframe | [redacted] | 126,896 |
| 11 | 20-Year Model Timeframe | [redacted] | 78,878 |
| 12 | 60-Year Model Timeframe | [redacted] | 55,135 |
| 13 | 1.5% Discount Rate | [redacted] | 41,081 |
| 14 | 10 Inpatient Days Blinatumomab All Cycles | [redacted] | 60,760 |
| 15 | Zero cost for Blinatumomab Cycle 6+ | [redacted] | 49,798 |
| 16 | Blinatumomab home IV bag changes for Cycle 3+ | [redacted] | 54,971 |
| 17 | Clofarabine Included in FLAG-IDA | [redacted] | 52,576 |

| | | | |
|---|---|---|---|
| 18 | Rate of allo-SCT from MT103-211 | [redacted] | 60,081 |
| 19 | EORTC-8D Utilities | [redacted] | 53,910 |
| 20 | TTO Utilties from Vignette Study | [redacted] | 57,438 |

**Table 18 Results showing the impact of PAS on ICERs for blinatumomab vs. FLAG-IDA in patients with no prior salvage therapy**

| No. | Scenario | ICER (£) | |
|---|---|---|---|
| | | No PAS | With PAS |
| | Base Case (No Prior Salvage) | [redacted] | 49,190 |
| 1 | Safety analysis set (No Prior Salvage) | [redacted] | 46,821 |
| 2 | OS Based on RCS Log-Logistic | [redacted] | 123,824 |
| 3 | Survivors Cured - 36 Months | [redacted] | 36,761 |
| 4 | Survivors Cured - 48 Months | [redacted] | 41,211 |
| 5 | Survivors Cured - 60 Months | [redacted] | 45,339 |
| 6 | EFS Based on Lognormal | [redacted] | 49,114 |
| 7 | 36-Month Duration of Benefit | [redacted] | 53,389 |
| 8 | 60-Month Duration of Benefit | [redacted] | 47,291 |
| 9 | 10-Year Model Timeframe | [redacted] | 102,439 |
| 10 | 20-Year Model Timeframe | [redacted] | 66,788 |
| 11 | 60-Year Model Timeframe | [redacted] | 49,055 |
| 12 | 1.5% Discount Rate | [redacted] | 37,336 |
| 13 | 10 Inpatient Days Blinatumomab All Cycles | [redacted] | 54,356 |
| 14 | Zero cost for Blinatumomab Cycle 6+ | [redacted] | 41,979 |
| 15 | Blinatumomab home IV bag changes for Cycle 3+ | [redacted] | 48,630 |
| 16 | Clofarabine Included in FLAG-IDA | [redacted] | 46,978 |
| 17 | Rate of allo-SCT from MT103-211 | [redacted] | 55,105 |
| 18 | EORTC-8D Utilities | [redacted] | 47,881 |
| 19 | TTO Utilties from Vignette Study | [redacted] | 53,680 |

# Appendices

## *4.14 Appendix A: Additional documents*

4.14.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable.

## *4.15 Appendix B: Details of outcome-based schemes*

4.15.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

4.15.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

4.15.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable.

4.15.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

4.15.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

4.15.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the

patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

4.15.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

4.15.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

Not applicable.

4.15.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable.

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**Single technology appraisal**

**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

Dear Kawitha

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 25th November, 2016 from Amgen. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **9 January 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/22604.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Boglarka Mikudina, Technical Lead (Boglarka.Mikudina@nice.org.uk). Any procedural questions should be addressed to Project Managers, Marcia Miller or Liv Gualda at TACommA@nice.org.uk .

Yours sincerely

Eleanor Donegan

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Technical Advisor – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

## Section A: Clarification on effectiveness data

### Decision problem / background

A1. **Priority question:** It is stated in table 1-1 of the company submission, that all outcomes listed in the scope are included in the submission. However it is not clear what is the connection between the different outcomes included in the submission and the different outcomes listed in the scope. More specifically which outcome captures relapse-free survival? If relapse-free survival is not presented, please give an explanation why it was not included.

A2. When exactly is, and what types of, laboratory monitoring are expected to take place throughout a course of treatment with blinatumomab? How does this compare to SOC chemotherapy?

A3. Under which circumstances do patients receive only one cycle of blinatumomab?

### Systematic review

A4. Please clarify which platform was used to simultaneously search EMBASE, Medline and CENTRAL in the clinical efficacy/safety systematic review and Embase, Medline, CENTRAL, EconLIT and NHS EED in the economic, cost and resource use SLR.

A5. **Priority question:** In the systematic review, the company applied one set of inclusion and exclusion criteria and subsequently applied another set of inclusion and exclusion criteria to arrive at the final set of included papers.

a. Why were studies with less than 50 patients excluded, especially given the relative rarity of the disease of interest?

b. Why were studies not directly examining blinatumomab excluded, as this would have precluded a network meta-analysis?

c. Why were all scoped outcomes not included as inclusion criteria, and would this have altered the ability to estimate indirect treatment comparisons?

### Included studies

A6. **Priority question:** Clofarabine was a comparator in the scope and recent updates from NICE suggest that it will be considered for commissioning through alternative means. Appendix IV contains subgroup analyses for OS, EFS, CR and

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CR/CRh*/CRi. Please present subgroup analyses across all remaining outcomes that were included in the scope for clofarabine and 'clofarabine-eligible' patients in TOWER, as well as for FLAG and 'FLAG-eligible' patients?

A7. **Priority question:** According to expert clinicians, patients who do not benefit from one cycle are unlikely to benefit from two. The company submission includes outcomes for CR, and for CR/CRh*/CRi, after 12 weeks of treatment. Please provide these outcomes after six weeks of treatment (i.e. after one cycle) for the TOWER trial?

A8. Please present statistical significance tests for the demographic characteristics of patients on the different arms of TOWER trial in the intent to treat population?

A9. Were the trial arms of TOWER trial balanced in terms of time from initial diagnosis or time from relapse?

A10. Given the imbalanced dropout rates between the trial arms in the TOWER trial, please present demographic data for patients in the safety analysis set, and present whether there were statistically significant differences between the trial arms?

A11. **Priority question:** Please clarify, why the 'long-term follow-up discontinued' in TOWER trial and how it was implemented.

A12. Why were patients with untreated first relapse with first remission duration of more than 12 months excluded from TOWER trial?

A13. **Priority question:** To what degree did the analyses in TOWER account for treatment switching, both in terms of switching from the control arm to the blinatumomab arm and also to novel anti-cancer therapies after the trial period?

A14. Please present statistical significance tests for absolute probability of minimal residual disease in each arm of the TOWER trial?

A15. Please present statistical significance tests for time to allo-SCT and risk of mortality after allo-SCT in TOWER, and also present associated Kaplan-Meier curves?

A16. Please present statistical significance tests for differences in response (CR, CR/CRh*/CRi) duration in TOWER, and present associated Kaplan-Meier curves?

A17. In TOWER, what was the extent of the difference in time to clinically meaningful deterioration in HRQoL?

A18. In the CSR for TOWER, results for exposure-response analyses, ALL-specific symptoms, tumour DNA/anti-blinatumomab antibody formation/resistance, vital signs, laboratory parameters and pharmacokinetics are not reported. Please provide these results or justify why these results were not presented in the CSR.

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A19. Please present demographic data to establish adequate balance between the treatment cohort and the natural history cohort for the propensity score matching in the comparative cohort analysis using data from MT103-211. ?

A20. Please provide statistical significance tests for the outcomes presented in Tables 3 and 5 in Appendix III of the Company Submission.

**Section B: Clarification on cost-effectiveness data**

B1. The ERG understands that people with active central nervous system (CNS) involvement were excluded from the TOWER trial. However, information on the history of CNS pathology was not collected. Please justify why this information was not collected.

B2. **Priority question:** The main source of treatment effect on overall survival was based on the TOWER tria'sl results. However, it is unclear how the treatment effect has been applied to the natural history comparator. Please clarify this by explaining which one of the suggestions below describe the analyses.

a. The treatment effect was derived from the Kaplan-Meier plots for overall survival and applied to the adjusted historical comparator cohort data

b. The treatment effect was based on parametric models, fitted to the Kaplan-Meier plots for overall survival and applied to the adjusted historical comparator cohort

c. The treatment effect was based on parametric models fitted to the Kaplan-Meier plots for overall survival, then the historical comparator cohort had been used to extrapolate beyond the trial time horizon

B3. **Priority question:** The ERG understands that various parametric curves have been fitted to the overall survival curve from matched patients from Study 20120310, and the restricted Gompertz model fitted to these data. Additionally, a Gompertz model was fitted to the overall survival for the TOWER SOC chemotherapy arm. Figure 5-9 shows the overall survival projections from the TOWER SOC chemotherapy arm is higher than the survival in the natural history arm. Please can you clarify how the adjusted hazard ratio of 0.85 was applied to the overall survival curve for the historical comparator cohort?

B4. **Priority question:** Please clarify why there is a difference between the overall survival as seen in the TOWER trial (figure 5-2) compared to the overall survival in the economic model (fig 5-17).

B5. The company has undertaken extensive survival analyses; namely extrapolation of overall survival and event free survival curves beyond the observed trial data to a

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lifetime horizon. In the absence of long-term data, this will introduce some uncertainty, especially if, based on expert opinion, it is assumed that patients who are alive after 4 years of treatment are likely to be cured from the disease. Please present the results of a sensitivity analysis which is based on the time horizon of the trial.

B6. **Priority question:** Table 5-12 presents cost for home infusion pump. These costs were based on pro-rated pump costs assuming 5 years lifespan. Please clarify what prorated means. Does this assume that these pumps are transferable from one patient to another? If pumps are not reusable, this would suggest that the cost and hence projected costs would have been underestimated.

B7. **Priority question:** For people who received SOC chemotherapy, the mean utility value in the initial health state was lower than on the blinatumomab arm. Please clarify if this difference was statistically significant. Additionally, please provide explanation and supporting evidence why this difference occurred.

**Section C: Textual clarifications and additional points**

C1. Clinical outcomes for patients' on the SOC chemotherapy arm in the TOWER trial were assumed to be generalisable to patients receiving FLAG-IDA. Please provide justification for this assumption, and how the differences between treatments were taken into account.

C2. **Priority question:** Mean EQ-5D utility values along with their standard errors are presented in Table 5-7. In Table 5-17 these utility values are presented along with confidence intervals, which appear at a glance to be in reverse order. Based on our calculations, the standard errors and confidence intervals do not equate. Please clarify which are the correct values to be used, and whether the presented standard errors in Table 5-7 are applied to the log utility values.

C3. **Priority question:** The company suggested that adverse events were not modelled explicitly as they would have been captured in the EORTC QLQ-C30, and costs for adverse events were assumed to be captured in inpatient and outpatient care. Please state the frequency of grade 3 or higher adverse events occurring in post-treatment follow-up.

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

# Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia

## Response to clarification questions

## Prepared by:


## January 2017

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| | 1.0 | Yes<br>AIC highlighted | 09 January 2017 |

# Acronyms and abbreviations

| | |
|---|---|
| AE | adverse event |
| Allo-SCT | allogenic stem cell transplant |
| ALL | acute lymphoblastic leukaemia |
| ALLSS | acute lymphoblastic leukaemia symptom scale |
| ANC | absolute neutrophil count |
| ALP | alkaline phosphase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| $C_{ss}$ | steady state concentration |
| CDF | Cancer Drugs Fund |
| CI | confidence interval |
| CNS | central nervous system |
| CR | complete remission |
| CRF | case report form |
| CRh* | complete remission with partial haematological recovery |
| CRi | complete remission with incomplete haematological recovery |
| CRS | cytokine release syndrome |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| EFS | event-free survival |
| eGFR | estimated glomerular filtration rate |
| ERG | Evidence Review Group |
| EMA | European Medicines Agency |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EORTC QLQ-C30 GHS/QoL | European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 global health status/quality of life scale |
| EPAR | European Public Assessment Report |
| EQ-5D | EuroQoL five dimensions |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FLAG | fludarabine, cytarabine, granulocyte colony stimulating factor |
| FLAG-IDA | fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin |
| GEE | generalised estimating equations |
| GGT | gamma-glutamyl transferase |
| GLM | generalised linear model |
| HiDAC | high-dose cytarabine |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ICER | incremental cost-effectiveness ratio |
| IP | investigational product |
| IPTW | inverse probability of treatment weighting |
| IQR | interquartile range |

| | |
|---|---|
| IVRS | interactive voice response system |
| MRD | minimal residual disease |
| N/A | not applicable |
| NE | not estimable |
| NICE | National Institute for Health and Care Excellence |
| NMA | network meta-analysis |
| ONS | Office for National Statistics |
| OS | overall survival |
| PAS | patient access scheme |
| QALY | quality-adjusted life year |
| RCT | randomised controlled trial |
| RFS | relapse-free survival |
| R/R Ph- B-precursor ALL | relapsed or refractory Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia |
| SAP | statistical analysis plan |
| SAS | safety analysis set |
| SE | standard error |
| SLR | systematic literature review |
| SmPC | summary of product characteristics |
| SOC | standard of care |
| STA | single technology appraisal |
| WBC | white blood cell |

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# Introduction

Thank you for the opportunity to respond to questions from the Evidence Review Group (ERG) and to clarify key aspects of the company submission. Detailed responses to the ERG questions are provided in:

- Section A (clarification on clinical effectiveness data).
- Section B (clarification on cost-effectiveness data).
- Section C (textual clarification and additional points).

# A: Clarification on clinical-effectiveness data

**A1 (PRIORITY QUESTION): It is stated in table 1-1 of the company submission, that all outcomes listed in the scope are included in the submission. However it is not clear what is the connection between the different outcomes included in the submission and the different outcomes listed in the scope. More specifically which outcome captures relapse-free survival? If relapse-free survival is not presented, please give an explanation why it was not included.**

A summary of the individual outcomes included in the National Institute of Health and Care Excellence (NICE) scope for this appraisal and clarification on what outcome data are presented in the company submission, as well as where these data are presented, is provided in Table A-1 for the two relevant studies included in the company submission:

- TOWER: phase 3 randomised controlled trial (RCT).
- Study MT103-211: key registrational phase 2 single-arm study.

With respect to the ERG's specific uncertainty on relapse-free survival (RFS), this was a prespecified endpoint in Study MT103-211 (results presented in Section 4.11.6.1 of the company submission), but was not explicitly defined as an endpoint in the TOWER study. However, the prespecified TOWER secondary endpoints of duration of complete remission (CR) and duration of complete remission/complete remission with partial haematological recovery/complete remission with incomplete haematological recovery (CR/CRh*/CRi), results for which were presented the company submission (Section 4.7.3), can be considered broadly synonymous with RFS. These duration of response endpoints were defined in a virtually identical way to RFS in Study MT103-211 i.e. time from achievement of haematological remission until relapse or death, whichever occurred first (Table A-2).

**Table A-1 Summary of NICE scope outcomes and data presented in the company submission**

| NICE scope outcome | TOWER data presented in the company submission[a] | Study MT103-211 data presented in the company submission[a] |
|---|---|---|
| Overall survival | Yes, see Section 4.7.2 for OS results. | Yes, see Section 4.11.6.1 for OS results and Section 4.11.6.2 for comparison with a historical cohort. |
| Event-free survival | Yes, see Section 4.7.4 for EFS results. | Yes, see Section 4.11.6.1 for EFS results. |
| Relapse-free survival | RFS was not explicitly defined as a TOWER endpoint, but the secondary endpoints of duration of CR and CR/CRh*/CRi (see company submission Section 4.7.3 for results) can be considered broadly synonymous with RFS. | Yes, see Section 4.11.6.1 for RFS results. |
| Treatment response rates (including MRD | Yes (haematologic response rates), see Section 4.7.3 for rates of CR and CR/CRh*/CRi within 12 weeks of treatment initiation. | Yes (haematologic response rates), see Section 4.11.6.1 for rates of CR/CRh*, CR, CRh*, partial |

| NICE scope outcome | TOWER data presented in the company submission[a] | Study MT103-211 data presented in the company submission[a] |
|---|---|---|
| and haematologic responses) | Yes (MRD response rates), see Section 4.7.5 for rates of MRD remission within 12 weeks of treatment initiation. | remission, and aplastic bone marrow response within two cycles (i.e. 12 weeks) of treatment initiation. See company submission Section 4.11.6.2 for comparison of CR/CRh* with a historical cohort.<br>Yes, (MRD response rates), see Section 4.11.6.1 for rates of MRD remission within two cycles of treatment initiation. |
| Time to and duration of response | No (time to response), data on time to response were not collected in TOWER.<br>Yes (duration of response), see Section 4.7.3 for duration of CR and CR/CRh*/CRi results. | Yes (time to response), see Section 4.11.6.1 for time to response results.<br>Yes (duration of response), see Section 4.11.6.1 for time to haematological relapse results. |
| Rates of stem cell transplant | Yes, see Section 4.7.6 for rates of allo-SCT. | Yes, see Section 4.11.6.1 for rates of allo-SCT and Section 4.11.6.2 for comparison with a historical cohort. |
| AEs of treatment | Yes, see Section 4.12 for a comprensive overview of results for a range of safety and tolerability outcomes. | No, safety data from Study MT103-211 were not presented for brevity given the lack of control arm and availability of RCT evidence from TOWER. |
| HRQoL | Yes, see Section 4.7.71 for time to 10-point decrease time to 10-point decrease in EORTC-QLQ C30 GHS/QoL or EFS event results. See Section 4.7.7.2 for change from baseline in all EORTC QLQ-C30 scales and single items results[b] | No, data on HRQoL were not collected in Study MT103-211. |

[a] Prespecified outcomes unless otherwise specified.
[b] Not a prespecified outcome.

AE, adverse event; allo-SCT, allogenic stem cell transplant; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; EORTC QLC-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 global health status/quality of life scale; HRQoL, health-related quality of life; MRD, minimal residual disease; OS, overall survival; RCT, randomised controlled trial; RFS, relapse-free survival.

**Table A-2 Comparison of definitions of RFS in Study MT103-211 and durations of haematological remission (CR and CR/CRh*/CRi) in the TOWER study**

| Study | Endpoint(s) | Definition as described in the statistical analysis plan |
|---|---|---|
| Study MT103-211 | RFS | • The analysis of RFS will be restricted to patients who experienced CR or CRh* during the core study.[a]<br>• RFS will be calculated relative to the date of bone marrow aspiration when CR or CRh* was detected for the first time in this study. The date of bone marrow aspiration at which hematological relapse or progressive disease was first detected or the date of diagnosis on which the hematological or extra medullary relapse was documented or the date of death due to any cause will be used as the event date for RFS, whichever is earlier. |
| TOWER | • Duration of CR<br>• Duration of CR/CRh*/CRi | Calculated only for subjects who achieve a CR or CR/CRh*/CRi, the duration will be calculated from the date a CR or CR/CRh*/CRi is first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. |

References: TOWER SAP[1] and Study MT103-211 SAP[2]

[a] A screening period of up to 3 weeks followed by a treatment period of up to 30 weeks, followed by an end of core study visit 30 days after the end of the last cycle.

CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; RFS, relapse-free survival; SAP, statistical analysis plan.

**A2: When exactly is, and what types of, laboratory monitoring are expected to take place throughout a course of treatment with blinatumomab? How does this compare to SOC chemotherapy?**

As outlined in the company submission (Section 2.2.3), the following recommended laboratory monitoring steps for blinatumomab are specified in the blinatumomab summary of product characteristics (SmPC):

- Laboratory evaluation of renal function in the first 48 hours after the first infusion (monitoring for signs and symptoms of tumour lysis syndrome).
- Laboratory evaluation of serum amylase and serum lipase (monitoring for signs and symptoms of pancreatitis).
- Laboratory evaluation of parameters related to neutropaenia and febrile neutropaenia, including (but not limited to) white blood cell count and absolute neutrophil count.
- Laboratory evaluation of parameters related to elevated liver enzymes i.e. alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during treatment especially during the first 48 hours of the first two cycles.

Further details based on UK clinical expert feedback on how these laboratory monitoring recommendations (as well as other types of routine laboratory monitoring anticipated to occur during treatment) are likely to be implemented in clinical practice, including timings of such assessments and any differences versus standard of care (SOC) chemotherapy, are provided in Table A-3.

Based on this UK clinical expert feedback, it is not anticipated that any additional laboratory monitoring steps will occur during treatment with blinatumomab compared with SOC chemotherapy in clinical practice in England and Wales. Furthermore, laboratory monitoring is anticipated to occur less frequently with blinatumomab than with SOC chemotherapy in clinical practice.

**Table A-3 Details of anticipated laboratory monitoring for blinatumomab in clinical practice and differences versus SOC chemotherapy based on UK clinical expert feedback**

| | Blinatumomab SmPC recommendation | Details of anticipated laboratory evaluation | Anticipated frequency/timing[a] | Anticipated differences vs. SOC |
|---|---|---|---|---|
| Renal function | Laboratory evaluation of renal function in the first 48 hours after the first infusion. | Parameters: Creatinine (eGFR) and urea/electrolytes<br>Method: Standard blood tests | Ongoing, twice-weekly at bag changes. | For SOC chemotherapy, some centres monitor daily, some 3 times per week. |
| Signs and symptoms of pancreatitis | Laboratory evaluation of serum amylase and serum lipase. | N/A - Evaluation is not anticipated to be routinely conducted in clinical practice | N/A | None. |
| Parameters related to neutropaenia and febrile neutropaenia | Laboratory evaluation of parameters related to neutropaenia and febrile neutropaenia, including (but not limited to) WBC count and ANC. | Parameters: WBC count and ANC (per SmPC) plus haemoglobin and platelets<br>Method: Standard blood tests | Ongoing, twice-weekly at bag changes | For SOC chemotherapy, some centres monitor daily, some 3 times per week. |
| Parameters related to liver enzymes | Laboratory evaluation of parameters related to elevated liver enzymes i.e. ALT, AST, GGT, and total blood bilirubin prior to the start of and during treatment especially during the first 48 hours of the first two cycles. | Parameters: ALT, AST, GGT, and total blood bilirubin (per SmPC) plus ALP<br>Method: Standard blood tests | Ongoing, twice-weekly at bag changes. | For SOC chemotherapy, some centres monitor daily, some 3 times per week. |
| Other anticipated laboratory monitoring | N/A – not explicitly recommended in the blinatumomab SmPC. | Parameters: Bone marrow blasts<br>Method: Bone marrow aspiration | End of Cycle 1 and Cycle 2 of treatment. | None. |

[a] Assuming treatment in the outpatient setting. Based on UK clinical expert feedback, it is expected that most blinatumomab-treated patients will be treated in this setting in clinical practice.

ALT, alanine aminotransferase; ALP, alkaline phosphase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GCT, gamma-glutamyl transferase; N/A, not applicable; SmPC, summary of product characteristics; SOC, standard of care; WBC, white blood cell.

**A3: Under which circumstances do patients receive only one cycle of blinatumomab?**

The SmPC for blinatumomab states that patients may receive two 28-day cycles of initial treatment separated by a 2-week treatment-free interval. There is no early stopping rule for blinatumomab included in the SmPC,[3] though the SmPC states that consideration to temporarily or permanently discontinue of treatment should be made in the case of the following Grade 3 or Grade 4 adverse events (AEs):

- Cytokine release syndrome (CRS).
- Tumour lysis syndrome.
- Neurological toxicity.
- Elevated liver enzymes.
- Any other clinically relevant toxicities.

If any treatment interruption due to toxicity takes more than 14 days to resolve, treatment should be generally be permanently discontinued, unless described differently in the detailed recommendations around dose-adjustments for specific toxicities provided in Section 4.2 of the SmPC. In addition, temporary or permanent treatment discontinuation may be necessary to manage signs and symptoms of infections, infusion reactions, and pancreatitis.

Based on UK clinical expert feedback, it is anticipated that some patients may discontinue treatment after one cycle or less in clinical practice due to the following:

- Toxicities.
- Failure to achieve a haematological remission or relapse after haematological remission.
- Death.
- Decision to treat with allogenic stem cell transplant (allo-SCT) or other therapy.
- Patient choice.

This is supported by Cycle 1 patient disposition data from TOWER, which show that the reasons for discontinuing treatment with blinatumomab by the end of Cycle 1 were consistent with those anticipated to occur in clinical practice as described above (Table A-4).

**Table A-4 Patient disposition in Cycle 1 (TOWER, FAS)**

| | **Blinatumomab (N = 271)** | **SOC chemotherapy (N = 134)** | **Total (N = 405)** |
|---|---|---|---|
| Received IP in Cycle 1 | 267 (98.5) | 109 (81.3) | 376 (92.8) |
| Continued to receive IP at end of Cycle 1 | [redacted] | [redacted] | [redacted] |
| Discontinued IP by end of Cycle 1 | [redacted] | [redacted] | [redacted] |
| AE | [redacted] | [redacted] | [redacted] |
| Subject request | [redacted] | [redacted] | [redacted] |
| Death | [redacted] | [redacted] | [redacted] |

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | Total (N = 405) |
|---|---|---|---|
| Protocol-specified criteria | [redacted] | [redacted] | [redacted] |
| Premature end of induction due to progression without prior CR/CRh*/CRi | [redacted] | [redacted] | [redacted] |
| Failure to achieve CR/CRh*/CRi | [redacted] | [redacted] | [redacted] |
| Relapse subsequent to CR/CRh*/CRi on treatment | [redacted] | [redacted] | [redacted] |
| Intention to receive allo-SCT | [redacted] | [redacted] | [redacted] |
| Intention to receive additional therapy other than allo-SCT | [redacted] | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

AE, adverse event; allo-SCT, allogeneic stem cell transplant; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; IP, investigational product; SOC, standard of care.

**A4: Please clarify which platform was used to simultaneously search EMBASE, Medline and CENTRAL in the clinical efficacy/safety systematic review and Embase, Medline, CENTRAL, EconLIT and NHS EED in the economic, cost and resource use SLR.**

The Ovid platform was used to conduct the cross-database searches for each of the systematic literature reviews (SLRs). The database searches were carried out in line with the NICE guide to the methods of technology appraisal.[5]

**A5 (PRIORITY QUESTION): In the systematic review, the company applied one set of inclusion and exclusion criteria and subsequently applied another set of inclusion and exclusion criteria to arrive at the final set of included papers.**

**a. Why were studies with less than 50 patients excluded, especially given the relative rarity of the disease of interest?**

As outlined in the company submission (Section 4.1), a comprehensive and broad systematic literature review (SLR) was initially conducted to identify RCT and observational studies reporting the efficacy and safety of current treatments for adult patients with relapsed or refractory Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia (R/R Ph- B-precursor ALL). The additional exclusion criterion to remove studies including < 50 patients was subsequently applied to the studies identified in the broad SLR in order to exclude less robust evidence with low patient numbers, which would provide highly limited information for decision-making.

No RCT studies and only two non-randomised studies (reported in four publications) that met the eligibility criteria for the broad SLR were subsequently excluded because they assessed < 50 patients, details of which are summarised in Table A-5. These were small observational studies assessing blinatumomab (including 21 and 36 patients, respectively) with similar

populations to the substantially larger studies ultimately included in the company submission (i.e. TOWER [N = 405] and Study MT103-211 [N = 189]). These studies were therefore considered to provide limited additional information that would be useful to inform decision-making in the context of the current appraisal.

**Table A-5 Summary of studies excluded from the clinical efficacy/safety SLR because they included < 50 patients**

| Study number (acronym) and references | Population | Intervention | Comparator |
|---|---|---|---|
| NCT01209286<br>(MT103-206)<br><br>Topp *et al.,* 2014[6] (primary study reference)<br>Schuab *et al.,* 2013[7] (abstract)<br>Zugmaier *et al.,* 2015[8] (long-term outcomes in patients who achieved an MRD response) | Adult patients with relapsed or refractory B-precursor ALL (N=36) | Blinatumomab | N/A – single arm study |
| NCT00560794<br><br>Topp *et al.,* 2011[9] | Adult patients with chemotherapy-refractory or relapsed MRD in B-precursor ALL (N=21) | Blinatumomab | N/A – single arm study |
| ALL, acute lymphoblastic leukaemia; MRD, minimal residual disease; N/A, not applicable | | | |

**b. Why were studies not directly examining blinatumomab excluded, as this would have precluded a network meta-analysis?**

As outlined in the company submission (Section 4.1), a comprehensive and broad SLR was initially conducted to identify RCT and observational studies reporting the efficacy and safety of current treatments for adult patients with R/R Ph- B-precursor ALL. The additional exclusion criterion to remove studies not assessing blinatumomab was subsequently applied to the studies identified in the broad SLR for the following reasons:

- Define the list of relevant RCTs for inclusion in the company submission as specified in Section 4.2 of the NICE single technology appraisal (STA) submission template ('List of relevant randomised controlled trials'): 'Provide details of the randomised controlled trials (RCTs) that provide evidence on the clinical benefits of the technology at its licensed dosage within the indication being appraised.'[10]
- Identify additional relevant non-randomised evidence for inclusion in the company submission which also evaluated blinatumomab and could be used to supplement evidence from the relevant RCT.

Only three RCT studies (reported in four publications) that met the eligibility criteria for the broad SLR were subsequently excluded because they did not assess blinatumomab, details of which are summarised in Table A-6. In order to address the ERG's concerns, we have further considered the feasibility of including these studies in a network meta-analysis (NMA) with the only RCT that was ultimately included in the company submission (i.e. TOWER), and the relevance of any such NMA to the decision problem:

- Two of the three RCTs (Solary *et al.,* 1996[11] and Bertrand *et al.,* 2015[12]) that met the eligibility criteria for the broad SLR and were subsequently excluded because they did not assess blinatumomab shared no common interventions or comparators with any of the other RCTs identified in the broad SLR (including TOWER). Furthermore, the interventions and comparators assessed in these studies were not included in the NICE scope for this appraisal, and these studies are therefore not considered relevant to the decision problem
- The remaining RCT (INO-VATE, Kantarjian *et al.,* 2016)[13] that met the eligibility criteria for the broad SLR and was subsequently excluded because it did not assess blinatumomab shared a common comparator with TOWER (SOC chemotherapy). However, the intervention (inotuzumab) was not included in the NICE scope for this appraisal, and is therefore not considered relevant to the decision problem.

In summary, the exclusion in the company submission of RCTs that did not assess blinatumomab has not resulted in the exclusion of studies that would have been useful in informing an NMA to provide additional relevant information on the comparative effectiveness of blinatumomab relative to comparators included in the NICE scope.

**Table A-6 Summary of RCT studies excluded from the clinical efficacy/safety SLR because they did not assess blinatumomab**

| Study number (acronym) and references | Population | Intervention | Comparator |
|---|---|---|---|
| Solary *et al.,* 1996[11] | Patients aged 15-65 years with a bone marrow diagnosis of acute non-lymphoblastic leukaemia or ALL as defined by the French-American-British classification system. | Mitoxantrone + cytarabine + quinine | Mitoxantrone + cytarabine |
| Bertrand *et al.,* 2015[12] | Patients with relapsed ALL | Erythrocyte encapsulated L-asparaginase | Native L-asparaginase |

| Study number (acronym) and references | Population | Intervention | Comparator |
|---|---|---|---|
| NCT01564784<br>(INO-VATE)<br><br>Kantarjian *et al.,* 2016[13] (primary study reference)<br>D'Angelo *et al.,* 2015[14] (abstract) | Patients aged > 18 years of with relapsed or refractory (≥ 5% bone marrow blasts on local morphologic analysis), CD22-positive, Ph-positive or Ph-negative ALL and scheduled to receive their first or second salvage treatment. | Inotuzumab ozogamicin | Investigator choice of SOC chemotherapy:<br>• FLAG<br>• Mitroxantrone + cytarabine<br>• HiDAC |
| ALL, acute lymphoblastic leukaemia; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; Ph, Philadelphia chromosome; RCT, randomised controlled trial; SLR, systematic literature review; SOC, standard of care. | | | |

**c. Why were all scoped outcomes not included as inclusion criteria, and would this have altered the ability to estimate indirect treatment comparisons?**

The clinical efficacy and safety SLR protocol was developed, and the initial SLR conducted (October 2015), prior to availability of the draft and final NICE scope. As noted by the ERG, the outcomes specified in the SLR inclusion criteria were consequently not fully aligned with outcomes of interest in the NICE scope for this appraisal.

However, the SLR reviewers were instructed not to exclude studies on the basis of outcomes at the initial screening stage. and a comprehensive overview of outcome data for the studies included in the company submission (i.e. TOWER and Study MT106-211) including those outcomes included in the NICE scope but not specified in the SLR inclusion criteria were reported.

Only two RCT studies (reported in two publications) were excluded at the full-text screening stage because they did not assess an outcome specified in the SLR inclusion criteria (Freireich *et al.,* 2013[15] and Lu *et al.,* 2009[16]). In order to address the ERG's concerns, we have further considered the feasibility of including these studies in an NMA with the only RCT that was ultimately included in the company submission (i.e. TOWER) as well as RCT studies identified in the broad SLR but excluded because they did not assess blinatumomab (Question A5b), and the relevance of any such NMA to the decision problem. These two RCTs shared no common interventions or comparators with TOWER or any of the other RCTs identified in the broad SLR. Furthermore, the interventions and comparators assessed these studies were not included in the NICE scope for this appraisal, and these studies are therefore not considered relevant to the decision problem.

In summary, the exclusion in the company submission of RCTs that did not include an outcome specified in the SLR inclusion criteria has not resulted in the exclusion of studies that would have been useful in informing an NMA to provide additional relevant information on the comparative effectiveness of blinatumomab relative to comparators included in the NICE scope.

**A6 (PRIORITY QUESTION): Clofarabine was a comparator in the scope and recent updates from NICE suggest that it will be considered for commissioning through alternative means. Appendix IV contains subgroup analyses for OS, EFS, CR and CR/CRh*/CRi. Please present subgroup analyses across all remaining outcomes that were included in the scope for clofarabine and 'clofarabine-eligible' patients in TOWER, as well as for FLAG and 'FLAG-eligible' patients?**

As outlined in the company submission (Section 3.5), although clofarabine-based combination chemotherapy is included in the NICE scope, we do not believe that it represents a relevant comparator because it is licensed specifically as a monotherapy for paediatric use in patients who have received at least two prior regimens, and where there is no other treatment option anticipated to result in a durable response[17] It is also most commonly used for paediatric patients in UK clinical practice.[18] In addition, although the ERG have highlighted recent updates from NICE on the ongoing funding of clofarabine in adult patients since the expiration of the previous Cancer Drugs Fund (CDF),[19] interim transitioning funding remains subject to a future commissioning decision to be taken by the CDF 'off-label process,' and its future routine availability therefore remains subject to substantial uncertainty.

Nevertheless, to address the ERG's question, additional subgroup analyses based on the prespecified TOWER subgroups of patients by intended SOC regimen at randomisation (including both FLAG ± anthracycline based regimen and clofarabine or clofarabine based regimen) are provided for the following additional outcomes included in the NICE scope, as described in further detail in Table A-7:

- Duration of response.
- Rates of minimal residual disease (MRD) response.
- Rates of SCT.
- Health-related quality of life (HRQoL).
- AEs of treatment.

The only other outcomes included in the NICE scope for which subgroup data by intended SOC regimen at randomisation were not already provided in the company submission or submission appendices are RFS and time to response.

As outlined in the response to Question A1, RFS was not explicitly defined as an endpoint in TOWER. However, the prespecified TOWER endpoints of duration of CR and duration of CR/CRh*/CRi can be considered broadly synonymous with RFS given that they are defined in a virtually identical way to RFS in Study MT103-211 (i.e. time from haematological remission until relapse or death, whichever occurs first). As outlined in the company submission (Sections 4.3.3 and 4.11), time to response was not a prespecified TOWER endpoint, and information on time to response was not collected in the study. Consequently, it is not possible to provide subgroup analyses for this outcome.

It should be noted that TOWER was not primarily designed to detect significant treatment effects within baseline covariate subgroups, and consequently lacked power to detect significant treatment-covariate interactions. Patient numbers in subgroups according to intended SOC regimen at randomisation are highly limited in some subgroups, particularly in the SOC chemotherapy arm given the 2:1 randomisation of patients in the study. For example, in the subgroup of patients intended to receive clofarabine or a clofarabine based regimen at randomisation, there are just [redacted] patients in the SOC chemotherapy arm.[20] In addition, as intended SOC regimen at randomisation was not a stratification factor in TOWER, there might be differences in prognostic baseline characteristics across study arms in these subgroups that confound any subgroup-specific treatment effect estimates. Based on the above, estimated treatment effects for individual subgroups according to intended SOC regimen at randomisation, and any comparisons of treatment effects across these subgroups, should be interpreted with a high degree of caution. As discussed in response to Question C1, these limitations form part of the rationale for why we strongly believe that it is not appropriate to utilise TOWER subgroup data by intended SOC regimen at randomisation to inform the base case cost-effectiveness analyses.

**Table A-7 Summary of additional TOWER subgroup data by intended SOC regimen at randomisation presented in the response**

| Additional NICE scope outcome | Additional TOWER subgroup outcome data presented and reference to the relevant tables in the response | Additional notes/justification |
|---|---|---|
| Duration of response | Duration of CR among patients in the TOWER FAS who achieved a CR within 12 weeks of treatment initiation (Table A-8).<br>Duration of CR/CRh*/CRi among patients in the TOWER FAS who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation (Table A-9). | As discussed in response to Question A1, the prespecified duration of CR and CR/CRh*/CRi endpoints in TOWER were defined in virtually the same way as RFS in Study MT103-211 i.e. time from achievement of haematological remission until relapse or death, whichever occurs first. |
| Rate of MRD response | MRD remission rates within 12 weeks of treatment initiation among patients in the TOWER FAS who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation and had a post-baseline MRD assessment (Table A-10).<br>MRD remission rates within 12 weeks of treatment initiation among patients in the TOWER FAS (Table A-11). | • As discussed in the company submission (Section 4.7.5), although the prespecified primary statistical analyses were to be conducted on the FAS, it is considered more clinically meaningful to assess the proportion of patients with MRD remission amongst those who achieved a CR/CRh*/CRi and had a post-baseline MRD assessment.<br>• This is because MRD remission represents a deeper response than CR/CRh*/CRi, and therefore patients achieving an MRD remission represent a subset of patients who have achieved a CR/CRh*/CRi. |
| Rate of stem cell transplant | Subject incidence of post-baseline allo-SCT among patients in the TOWER FAS (Table A-12). | None. |
| HRQoL | Summary of EORTC QLQ-C30 GHS/QoL baseline scores and scores and change from baseline at each scheduled visit during Cycle 1 among patients in the TOWER EORTC analysis set (Table A-13). | • As highlighted in the company submission, the prespecified TOWER HRQoL secondary endpoint of time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event was not considered informative since analyses of EFS assign haematological non-responders an EFS duration of 1 day, leading to a median EFS estimate in TOWER of 0 months in both study arms. Data for the prespecified TOWER HRQoL exploratory endpoint of changes in ALLSS scores over time were not |

| Additional NICE scope outcome | Additional TOWER subgroup outcome data presented and reference to the relevant tables in the response | Additional notes/justification |
|---|---|---|
| | | included in the expedited primary analysis CSR or available at the time of the company submission.<br>• Only data for the main EORTC QLQ-C30 scale (the GHS/QoL scale) are presented for brevity given that the EORTC QLQ-C30 comprises a total of 15 different scales/single items.<br>• Only data for Cycle 1 are presented as small patient numbers in the SOC chemotherapy arm beyond Cycle 1 preclude any meaningful comparisons across study arms. As highlighted in the company submission, for the whole EORTC analysis set (i.e. not divided by subgroup) this was [redacted] patients in the SOC chemotherapy arm; patient numbers are even smaller when analysed by intended SOC regimen subgroup (e.g. n = [redacted] for FLAG ± anthracycline based regimen and n = [redacted] for clofarabine or clofarabine based regimen). |
| AEs of treatment | Top line overview of treatment-emergent AEs by category among patients in the TOWER SAS (Table A-14). | • Only data for the subgroups of patients intended to receive (i) a FLAG ± anthracycline based regimen or (ii) clofarabine or a clofarabine based regimen at randomisation are presented for brevity, given that these are the most relevant intended SOC chemotherapy regimen subgroups for this ERG question.<br>• A top line overview of treatment-emergent AEs and a summary of the most common ≥ Grade 3 treatment-emergent AEs are reported in the |
| | Summary of the most common ≥ Grade 3 treatment-emergent AEs (≥ 5% in either arm) among patients in the TOWER SAS (Table A-15 and Table A-16). | |

| Additional NICE scope outcome | Additional TOWER subgroup outcome data presented and reference to the relevant tables in the response | Additional notes/justification |
|---|---|---|
| | Additional safety outcome summary data reported in Appendix A:<br>• Most common treatment-emergent AEs (≥ 10% in either arm) among patients in the TOWER SAS (Table Appendix A-1 and Table Appendix A-2).<br>• Most common serious treatment-emergent AEs (≥ 2% in either arm) among patients in the TOWER SAS (Table Appendix A-3 and Table Appendix A-4).<br>• Most common treatment-emergent AEs related to IP (≥ 2% in either arm) among patients in the TOWER SAS (Table Appendix A-5 and Table Appendix A-6).<br>• Treatment-emergent AEs leading to treatment discontinuation among patients in the TOWER SAS (Table Appendix A-7 and Table Appendix A-8).<br>• Fatal treatment-emergent AEs among patients in the TOWER SAS (Table Appendix A-9 and Table Appendix A-10). | main response; the remaining safety outcomes are reported in Appendix A given the large volume of data.<br>• As highlighted in the company submission, it is important to note that overall, patients in the blinatumomab arm had a substantially longer treatment duration than patients in the SOC chemotherapy arm, and as such, the likelihood of observing AEs was not even between the two treatment arms. For events with a constant or increasing HR over time, longer exposure to protocol-specified therapy often results in higher AE incidence rates compared with rates reported from shorter exposure durations. The presented crude rates not adjusted by exposure are therefore likely biased in favour of the SOC chemotherapy arm. |

Note: The FAS included all randomised subjects, the SAS included all randomised subject who received at least one dose of study drug, and the EORTC analysis set included all randomised subjects who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item.

AE, adverse event; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; CSR, clinical study report; EFS, event-free survival; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status/Quality of Life; ERG, Evidence Review Group; FAS, full analysis set; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; HR, hazard ratio; IP, investigational product; MRD, minimal residual disease; RFS, relapse-free survival; SAS, safety analysis set; SOC, standard of care.

**Table A-8 Subgroup analyses of duration of CR by intended SOC regimen at randomisation in patients who achieved a CR within 12 weeks of treatment initiation (TOWER, FAS)**

| | Blinatumomab events/ subjects (%) | SOC chemotherapy events/ subjects (%) | Hazard ratio blinatumomab:SOC chemotherapy (95% CI) | Interaction p-value[a] |
|---|---|---|---|---|
| Intended SOC chemotherapy regimen | | | | [redacted] |
| Clofarabine or clofarabine based regimen | [redacted] | [redacted] | [redacted] | |
| FLAG with or without anthracycline based regimen | [redacted] | [redacted] | [redacted] | |
| HiDAC based regimen | [redacted] | [redacted] | [redacted] | |
| High-dose methotrexate based regimen | [redacted] | [redacted] | [redacted] | |

Reference: Amgen data on file, 2017[4]

[a] The p-value is from a test of the interaction term in an unstratified logistic model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model.

CI, confidence interval; CR, complete remission; FAS, full analysis set; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; SOC, standard of care.

**Table A-9 Subgroup analyses of duration of CR/CRh*/CRi by intended SOC regimen at randomisation in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation (TOWER, FAS)**

| | Blinatumomab events/ subjects (%) | SOC chemotherapy events/ subjects (%) | Hazard ratio blinatumomab:SOC chemotherapy (95% CI) | Interaction p-value[a] |
|---|---|---|---|---|
| Intended SOC chemotherapy regimen | | | | [redacted] |
| Clofarabine or clofarabine based regimen | [redacted] | [redacted] | [redacted] | |
| FLAG with or without anthracycline based regimen | [redacted] | [redacted] | [redacted] | |
| HiDAC based regimen | [redacted] | [redacted] | [redacted] | |
| High-dose methotrexate based regimen | [redacted] | [redacted] | [redacted] | |

Reference: Amgen data on file, 2017[4]

[a] The p-value is from a test of the interaction term in an unstratified logistic model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model.

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; SOC, standard of care.

**Table A-10 Subgroup analyses of MRD remission within 12 weeks of treatment initiation by intended SOC regimen at randomisation in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation and had a post-baseline MRD evaluation (TOWER, FAS)**

| | Blinatumomab events/ subjects (%) | SOC chemotherapy events/ subjects (%) | Odds ratio blinatumomab:SOC chemotherapy (95% CI)[a] | Interaction p-value[b] |
|---|---|---|---|---|
| Intended SOC chemotherapy regimen | | | | [redacted] |
| Clofarabine or clofarabine based regimen | [redacted] | [redacted] | [redacted] | |
| FLAG with or without anthracycline based regimen | [redacted] | [redacted] | [redacted] | |
| HiDAC based regimen | [redacted] | [redacted] | [redacted] | |
| High-dose methotrexate based regimen | [redacted] | [redacted] | [redacted] | |

Reference: Amgen data on file, 2017[4]

[a] To enable the estimation of an odds ratio when subgroups with zero events within a treatment group occurred, a continuity correction of 0.33 and 0.67 was added to the SOC chemotherapy arm and blinatumomab arm, respectively, which reflects the 2:1 randomisation of patients in TOWER.
[b] The p-value is from a test of the interaction term in an unstratified logistic model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model.

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; MRD, minimal residual disease; SOC, standard of care.

**Table A-11 Subgroup analyses of MRD remission within 12 weeks of treatment initiation by intended SOC regimen at randomisation (TOWER, FAS)**

| | Blinatumomab events/ subjects (%) | SOC chemotherapy events/ subjects (%) | Odds ratio blinatumomab:SOC chemotherapy (95% CI)[a] | Interaction p-value[b] |
|---|---|---|---|---|
| Intended SOC chemotherapy regimen | | | | [redacted] |
| Clofarabine or clofarabine based regimen | [redacted] | [redacted] | [redacted] | |
| FLAG with or without anthracycline based regimen | [redacted] | [redacted] | [redacted] | |
| HiDAC based regimen | [redacted] | [redacted] | [redacted] | |
| High-dose methotrexate based regimen | [redacted] | [redacted] | [redacted] | |

Reference: Amgen data on file, 2017[4]

[a] To enable the estimation of an odds ratio when subgroups with zero events within a treatment group occurred, a continuity correction of 0.33 and 0.67 was added to the SOC chemotherapy arm and blinatumomab arm, respectively, which reflects the 2:1 randomisation of patients in TOWER.
[b] The p-value is from a test of the interaction term in an unstratified logistic model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model.

CI, confidence interval; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; MRD, minimal residual disease; SOC, standard of care.

**Table A-12 Subgroup analyses of subject incidence of post-baseline allo-SCT by intended SOC regimen at randomisation (TOWER, FAS)**

| | Blinatumomab events/ subjects (%) | SOC chemotherapy events/ subjects (%) | Odds ratio blinatumomab:SOC chemotherapy (95% CI)[a] | Interaction p-value[b] |
|---|---|---|---|---|
| Intended SOC chemotherapy regimen | | | | [redacted] |
| Clofarabine or clofarabine based regimen | [redacted] | [redacted] | [redacted] | |
| FLAG with or without anthracycline based regimen | [redacted] | [redacted] | [redacted] | |
| HiDAC based regimen | [redacted] | [redacted] | [redacted] | |
| High-dose methotrexate based regimen | [redacted] | [redacted] | [redacted] | |

Reference: Amgen data on file, 2016[21]

[a] To enable the estimation of an odds ratio when subgroups with zero events within a treatment group occurred, a continuity correction of 0.33 and 0.67 was added to the SOC chemotherapy arm and blinatumomab arm, respectively, which reflects the 2:1 randomisation of patients in TOWER.
[b] The p-value is from a test of the interaction term in an unstratified logistic model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model.

Allo-SCT, allogenic stem cell transplant; CI, confidence interval; FAS, full analysis set; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; SOC, standard of care.

**Table A-13 Subgroup analyses of EORTC QLQ-C30 GHS/QoL mean scores at baseline and mean scores and change from baseline at each scheduled visit during Cycle 1 by intended SOC regimen at randomisation (TOWER, EORTC analysis set)**

| | FLAG with or without anthracycline based regimen | | HiDAC based regimen | | High-dose methotrexate based regimen | | Clofarabine or clofarabine based regimen | |
|---|---|---|---|---|---|---|---|---|
| | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) |
| Baseline | | | | | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cycle 1, Day 8 | | | | | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline | | | | | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cycle 1, Day 15 | | | | | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| | FLAG with or without anthracycline based regimen | | HiDAC based regimen | | High-dose methotrexate based regimen | | Clofarabine or clofarabine based regimen | |
|---|---|---|---|---|---|---|---|---|
| | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) | SOC chemotherapy (N = [redacted]) | Blinatumomab (N = [redacted]) |
| Change from baseline | | | | | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Cycle 1, Day 29 | | | | | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Change from baseline | | | | | | | | |
| n | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SD | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

References: Amgen data on file, 2017[4]

Note: The EORTC analysis set included patients who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item.

CI, confidence interval; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status/Quality of Life; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; SD standard deviation; SOC, standard of care.

**Table A-14 Top line overview of treatment-emergent AEs by category in the subgroups of patients intended to receive a FLAG ± anthracycline based regimen and clofarabine or clofarabine based regimen at randomisation (TOWER, SAS)**

| | FLAG with or without anthracycline based regimen | | Clofarabine or clofarabine based regimen | |
|---|---|---|---|---|
| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = [redacted]) n (%) | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = [redacted]) n (%) |
| Any treatment-emergent AE | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥ Grade 3 | [redacted] | [redacted] | [redacted] | [redacted] |
| Any treatment-emergent serious AE | [redacted] | [redacted] | [redacted] | [redacted] |
| Any treatment-emergent AE related to IP[a] | [redacted] | [redacted] | [redacted] | [redacted] |
| Any treatment-emergent AE leading to treatment discontinuation | [redacted] | [redacted] | [redacted] | [redacted] |
| Any fatal treatment-emergent AE | [redacted] | [redacted] | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

[a] As deemed by the study investigator

AE, adverse event; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; SAS, safety analysis set; SOC, standard of care.

**Table A-15 Summary of the most common ≥ Grade 3 treatment-emergent adverse events (≥ 5% in either arm) in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Any ≥ Grade 3 treatment-emergent AE | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Febrile neutropaenia | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Device related infection | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |
| Neutrophil count decreased | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Platelet count decreased | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] |
| Bacteraemia | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; SAS, safety analysis set; SOC, standard of care.

**Table A-16 Summary of the most common ≥ Grade 3 treatment-emergent adverse events (≥ 5% in either arm) in the subgroup of patients intended to receive clofarabine or a clofarabine based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Any ≥ Grade 3 treatment-emergent AE | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |
| Febrile neutropaenia | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Alanine aminotransferase increased | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Bronchopulmonary aspergillosis | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Pneumonia | [redacted] | [redacted] |
| White blood cell count decreased | [redacted] | [redacted] |
| Aspartate aminotransferase increased | [redacted] | [redacted] |
| Hyperglycaemia | [redacted] | [redacted] |
| Hyperkalaemia | [redacted] | [redacted] |
| Hypertension | [redacted] | [redacted] |
| Hypophosphataemia | [redacted] | [redacted] |
| Pancytopaenia | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] |
| Blood bilirubin increased | [redacted] | [redacted] |
| Decreased appetite | [redacted] | [redacted] |
| Gamma-glutamyltransferase increased | [redacted] | [redacted] |
| Hyponatraemia | [redacted] | [redacted] |
| Leukopaenia | [redacted] | [redacted] |
| Neutrophil count decreased | [redacted] | [redacted] |
| Platelet count decreased | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] |
| Catheter site infection | [redacted] | [redacted] |
| Device related infection | [redacted] | [redacted] |
| Dyspnoea | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| Lymphocyte count decreased | [redacted] | [redacted] |
| Mouth haemorrhage | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Abscess fungal | [redacted] | [redacted] |
| Acute hepatic failure | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Agitation | [redacted] | [redacted] |
| Amylase increased | [redacted] | [redacted] |
| Cytomegalovirus infection | [redacted] | [redacted] |
| Haemorrhage intracranial | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] |
| Hepatocellular injury | [redacted] | [redacted] |
| Hypermagnesaemia | [redacted] | [redacted] |
| Lipase increased | [redacted] | [redacted] |
| Liver function test abnormal | [redacted] | [redacted] |
| Metabolic acidosis | [redacted] | [redacted] |
| Mucosal inflammation | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Multi-organ failure | [redacted] | [redacted] |
| Pancreatitis | [redacted] | [redacted] |
| Peripheral artery thrombosis | [redacted] | [redacted] |
| Pneumonia fungal | [redacted] | [redacted] |
| Pulmonary pain | [redacted] | [redacted] |
| Seizure | [redacted] | [redacted] |
| Shock | [redacted] | [redacted] |
| Sleep disorder due to general medical condition, hypersomnia type | [redacted] | [redacted] |
| Staphylococcal sepsis | [redacted] | [redacted] |
| Stomatitis | [redacted] | [redacted] |
| Streptococcal bacteraemia | [redacted] | [redacted] |
| Subarachnoid haemorrhage | [redacted] | [redacted] |
| Supraventricular tachycardia | [redacted] | [redacted] |
| White blood cell count | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; SAS, safety analysis set; SOC, standard of care.

**A7 (PRIORITY QUESTION): According to expert clinicians, patients who do not benefit from one cycle are unlikely to benefit from two. The company submission includes outcomes for CR, and for CR/CRh*/CRi, after 12 weeks of treatment. Please provide these outcomes after six weeks of treatment (i.e. after one cycle) for the TOWER trial?**

A summary of rates of CR and CR/CRh*/CRi within 6 weeks of treatment initiation (i.e. after one cycle of treatment) is provided in Table A-17. A higher proportion of patients in the blinatumomab arm achieved a CR or CR/CRh*/CRi within 6 weeks of treatment initiation than patients in the SOC chemotherapy arm (CR: [redacted]% vs. [redacted]%, descriptive p = [redacted]; CR/CRh*/CRi: [redacted]% vs. [redacted]%, descriptive p = [redacted]).

**Table A-17 Rates of CR and CR/CRh*/CRi within 6 weeks of treatment initiation (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| CR, n (%) | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] |
| p-value[a] | [redacted] | |
| CR/CRh*/CRi, n (%) | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] |
| p-value[a] | [redacted] | |

References: Amgen data on file, 2016[21]

[a] Descriptive p-value from Cochran-Mantel-Haenszel test after adjusting for stratification factors of age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no), and prior allo-SCT (yes vs.no).

Allo-SCT, allogenic stem cell transplant; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological response; CRi, complete remission with incomplete haematological response; CSR, clinical study report; FAS, full analysis set; SOC, standard of care.

In contrast to the clinical expert opinion feedback solicited by the ERG, data from TOWER (as well as from Study MT103-211) suggest that there is a substantial proportion of patients who do not achieve a haematological remission after one cycle of treatment with blinatumomab, but go on to achieve a haematological remission after treatment with a second cycle. In TOWER, [redacted] of the [redacted] patients in the blinatumomab arm did not achieve a CR/CRh*/CRi within six weeks of treatment initiation (i.e. within one cycle) (Table A-17). Of these patients, [redacted] continued to receive treatment with blinatumomab in Cycle 2, among whom [redacted] ([redacted]%) went on to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation (i.e. within two cycles).[4] Similarly in Study MT103-211, 125 of the 189 patients treated with blinatumomab did not achieve a CR/CRh* within 6 weeks of treatment initiation.[22] Of these patients, 39 continued to receive treatment with blinatumomab in Cycle 2, among whom 17 (43.9%) went on to achieve a CR/CRh* within 12 weeks of treatment initiation.[4]

**A8: Please present statistical significance tests for the demographic characteristics of patients on the different arms of TOWER trial in the intent to treat population?**

Statistical tests to assess differences in patient characteristics across study arms are not commonly conducted or reported:

- Randomisation is intended to ensure that baseline characteristics are well balanced across study arms.
- Because of the high number of baseline characterises for which data are typically collected and reported in clinical studies, there is likelihood of observing results suggestive of a significant difference by chance.

However, to address the ERG's question, the summary table of baseline demographic, disease, and prior treatment history characteristics originally reported in the company submission (Section 4.5.2) for the TOWER full analysis set (FAS) is replicated below in Table A-18, with the addition of the requested statistical tests for differences across study arms.

**Table A-18 Summary of demographic, disease-related, and prior treatment characteristics (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | p-value[a] |
|---|---|---|---|
| Sex, n (%) | | | [redacted] |
| Men | 162 (59.8) | 77 (57.5) | |
| Women | 109 (40.2) | 57 (42.5) | |
| Age | | | [redacted][b] |
| Median (IQR), years | 37.0 (25.0, 54.0) | 37.0 (26.0, 58.0) | |
| Mean (SD), years[c] | [redacted] | [redacted] | |
| < 35 years, n (%) | [redacted] | [redacted] | |
| 35 to 54 years, n (%) | [redacted] | [redacted] | |
| 55 to 64 years, n (%) | [redacted] | [redacted] | |
| ≥ 65 years, n (%) | [redacted] | [redacted] | |
| Maximum of central/local bone marrow blasts, n (%) | | | [redacted][d] |
| < 50% | 69 (25.4) | 30 (22.4) | |
| ≥ 50% | 201 (74.2) | 104 (77.6) | |
| Unknown | 1 (0.4) | 0 (0) | |
| Key ALL entry criterion, n (%) | | | [redacted][e] |
| Refractory to primary or salvage therapy | 115 (42.4) | 54 (40.3) | |
| In 1st relapse with 1st remission < 12 months | 76 (28.0) | 37 (27.6) | |
| In untreated 2nd or greater relapse | 32 (11.8) | 16 (11.9) | |
| Relapse after allo-SCT | 46 (17.0) | 27 (20.1) | |
| No criteria met | 2 (0.7) | 0 (0) | |
| Prior salvage therapy (per randomised strata), n (%) | | | [redacted] |
| Yes | [redacted] | [redacted] | |
| No[e] | [redacted] | [redacted] | |
| Number of prior salvage regimens, n (%) | | | [redacted] |
| 0[f] | 114 (42.1) | 65 (48.5) | |
| 1 | 91 (33.6) | 43 (32.1) | |
| 2 | 45 (16.6) | 16 (11.9) | |

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | p-value[a] |
|---|---|---|---|
| 3 | 14 (5.2) | 5 (3.7) | |
| > 3 | 7 (2.6) | 5 (3.7) | |
| Prior allo-SCT, n (%) | 94 (34.7) | 46 (34.3) | [redacted] |
| Intended SOC chemotherapy regimen at randomisation | | | [redacted] |
| FLAG ± anthracycline based regimen | [redacted] | [redacted] | |
| High-dose methotrexate based regimen | [redacted] | [redacted] | |
| Clofarabine or clofarabine based regimen | [redacted] | [redacted] | |
| HiDAC based regimen | [redacted] | [redacted] | |

References: TOWER primary analysis CSR (10 November 2014 data cut-off date) Tables 9-7, 14-2.3, and 14-4.4.5)[20] and Amgen data on file, 2017[4]

[a] Descriptive p-value from Cochran-Mantel Haenszel test.
[b] The statistical test was performed on age group.
[c] Incorrectly reported as 'mean (IQR)' in the company submission with IQR values for the median.
[d] The statistical test excluded the 'unknown' category given that few patients (n = [redacted]) were categorised as such.
[e] The statistical test excluded the 'no criteria met' category given that few patients (n = [redacted]) were categorised as such.
[f] Numbers are not the same as data for prior salvage yes vs. no (stratification factor) is based on the IVRS and data on the number of lines of prior salvage regimens is based on the CRFs.

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; CRF, case report form; CSR, clinical study report; FAS, full analysis set; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; HiDAC, high-dose cytarabine; IVRS, interactive voice/response system; IQR, interquartile range; SOC chemotherapy; WBC, white blood cell.

**A9: Were the trial arms of TOWER trial balanced in terms of time from initial diagnosis or time from relapse?**

A summary of time from diagnosis at randomisation and time from last relapse at randomisation in TOWER is provided in Table A-19. These data show that both time from diagnosis and time from last relapse were balanced across study arms at randomisation.

**Table A-19 Summary of time from diagnosis and time from last relapse at randomisation (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | p-value[a] |
|---|---|---|---|
| Time from initial diagnosis to randomisation, months | | | [redacted] |
| n | [redacted] | [redacted] | |
| Mean (SD) | [redacted] | [redacted] | |
| Median (IQR) | [redacted] | [redacted] | |
| Time from last relapse to randomisation, months | | | [redacted] |
| n | [redacted] | [redacted] | |
| Mean (SD) | [redacted] | [redacted] | |
| Median (IQR) | [redacted] | [redacted] | |

Reference: Amgen data on file, 2017[4]

[a] Descriptive p-value from Wilcoxon rank sum test

FAS, full analysis set; IQR, interquartile range; SD, standard deviation; SOC, standard of care.

**A10: Given the imbalanced dropout rates between the trial arms in the TOWER trial, please present demographic data for patients in the safety analysis set, and present whether there were statistically significant differences between the trial arms?**

Detailed tables of baseline demographic, disease, and prior treatment history characteristics in the TOWER safety analysis set (SAS) are reported in the TOWER primary analysis clinical study report (CSR; Tables 14-2.2 and 14-2.4).[20]

Statistical tests to assess differences in patient characteristics across study arms are not commonly conducted or reported:

- Randomisation is intended to ensure that baseline characteristics are well balanced across study arms.
- Because of the high number of characterises for which data are typically collected and reported in clinical studies, there is likelihood of observing results suggestive of a significant difference by chance.

However, to address the ERG's question, the summary table of baseline demographic, disease, and treatment history characteristics originally reported in the company submission for the TOWER FAS (Section 4.5.2) is replicated below in Table A-20 for the TOWER SAS, with the addition of the requested statistical tests for differences across study arms.

**Table A-20 Summary of demographic, disease-related, and prior treatment characteristics (TOWER, SAS)**

| | Blinatumomab (N = 267) | SOC chemotherapy (N = 109) | p-value[a] |
|---|---|---|---|
| Sex, n (%) | | | [redacted] |
| Men | [redacted] | [redacted] | |
| Women | [redacted] | [redacted] | |
| Age | [redacted] | [redacted] | [redacted][b] |
| Median (IQR), years | [redacted] | [redacted] | |
| Mean (SD), years[c] | [redacted] | [redacted] | |
| < 35 years, n (%) | [redacted] | [redacted] | |
| 35 to 54 years, n (%) | [redacted] | [redacted] | |
| 55 to 64 years, n (%) | [redacted] | [redacted] | |
| ≥ 65 years, n (%) | [redacted] | [redacted] | |
| Maximum of central/local bone marrow blasts, n (%) | | | [redacted][d] |
| < 50% | 69 (25.8) | 23 (21.1) | |
| ≥ 50% | 198 (74.2) | 86 (78.9) | |
| Unknown | 0 (0) | 0 (0) | |
| Key ALL entry criterion, n (%) | | | [redacted][e] |
| Refractory to primary or salvage therapy | 112 (41.9) | 43 (39.4) | |
| In 1st relapse with 1st remission < 12 months | 76 (28.5) | 30 (27.5) | |
| In untreated 2nd or greater relapse | 31 (11.6) | 14 (12.8) | |
| Relapse after allo-SCT | 46 (17.2) | 22 (20.2) | |
| No criteria met | 2 (0.7) | 0 (0.0) | |
| Prior salvage therapy (per randomised strata), n (%) | | | [redacted] |
| Yes | [redacted] | [redacted] | |
| No[f] | [redacted] | [redacted] | |
| Number of prior salvage regimens, n (%) | | | [redacted] |
| 0[f] | 112 (41.9) | 55 (50.5) | |
| 1 | 91 (34.1) | 34 (31.2) | |
| 2 | 43 (16.1) | 12 (11.0) | |
| 3 | 14 (5.2) | 5 (4.6) | |
| > 3 | 7 (2.6) | 3 (2.8) | |
| Prior allo-SCT, n (%) | 93 (34.8) | 35 (32.1) | [redacted] |

| | Blinatumomab (N = 267) | SOC chemotherapy (N = 109) | p-value[a] |
|---|---|---|---|
| Intended SOC chemotherapy regimen at randomisation | | | [redacted] |
| FLAG ± anthracycline based regimen | [redacted] | 49 (45.0) | |
| High-dose methotrexate based regimen | [redacted] | 22 (20.2) | |
| Clofarabine or clofarabine based regimen | [redacted] | 19 (17.4) | |
| HiDAC based regimen | [redacted] | 19 (17.4) | |

Reference: TOWER primary analysis CSR (Tables 14-2.2, 14-2.4, and 14-4.4.2) [20]

[a] Descriptive p-value from Cochran-Mantel Haenszel test.
[b] The statistical test was performed on age group.
[c] Incorrectly reported as mean (IQR) for the TOWER FAS in the company submission with IQR values for the median.
[d] The statistical test excluded the 'unknown' category given that [redacted] patients were categorised as such.
[e] The statistical test excluded the 'no criteria met' category given that few patients (n = [redacted]) were categorised as such.
[f] Numbers are not the same as data for prior salvage yes vs. no (stratification factor) is based on the IVRS and data on the number of lines of prior salvage regimens is based on the CRFs.

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplant; CRF, case report form; CSR, clinical study report; FAS, full analysis set; FLAG, fludarabine, cytarabine, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; IVRS, interactive voice/response system; IQR, interquartile range; SAS, safety analysis set; SOC chemotherapy.

**A11 (PRIORITY QUESTION): Please clarify, why the 'long-term follow-up discontinued' in TOWER trial and how it was implemented.**

As outlined in the company submission (Section 4.2) and the TOWER primary analysis CSR, the long-term follow-up period of the study was discontinued prematurely since the primary study endpoint had been met (i.e. a significant OS benefit for blinatumomab had been observed). More specifically, once patients had stopped study treatment, they could receive commercially-available blinatumomab (or other anti-cancer therapies or allo-SCT) off-study. At the time of data cut-off for the primary analysis (4 January 2016), 22 patients randomised to the blinatumomab arm and no patients randomised to the SOC chemotherapy arm were still receiving study treatment, as outlined in the company submission (Section 4.15). It was anticipated that a substantial proportion of patients remaining alive and not on study treatment would move on to off-study treatment with blinatumomab (or other anti-cancer therapies or allo-SCT). As this would have substantially limited the interpretability of any additional long-term follow-up data, particularly for comparisons across the two study arms, the long-term follow-up period of the study was discontinued. Additional data from a final analysis of TOWER after the 22 patients still receiving study treatment with blinatumomab at the time of data cut-off for the primary analysis have stopped treatment and completed their safety follow-up visit are anticipated to become available by Q1 2017.

In terms of implementation, the long-term follow up period of the study was discontinued on 4 February 2016 (first notification to a regulatory authority), and no further data for patients in long-term follow-up were collected after this date.

**A12: Why were patients with untreated first relapse with first remission duration of more than 12 months excluded from TOWER trial?**

The TOWER study was a confirmatory RCT conducted based on a European Medicines Agency (EMA) request to confirm the outcomes observed in the key phase 2 single-arm registrational study (Study MT103-211). As Study MT103-211 excluded patients in untreated first relapse with a first remission duration of > 12 months ('late first relapse patients'), similar eligibility criteria were employed in TOWER to ensure enrolment of a similar study population.

Late first relapse patients were excluded from Study MT103-211 since duration of first remission is a well-established prognostic variable,[23] and the intent at the time of design of this study was to enrol a more homogenous high-risk adult R/R Ph- B-cell precursor ALL population where there is a particularly high unmet medical need.

As outlined in the company submission (Section 4.13.3), the exclusion of late first relapse patients from TOWER and Study MT103-211 means that the populations enrolled in these studies represent particularly difficult-to-treat patients. However, blinatumomab should remain an option for these late first relapse patients because:

- There is no clear biologic difference between patients who relapse at 11.5 months compared with 12.5 months. The 12-month cut-off is not a clinical standard (late relapse has also been defined in the literature as > 18 and > 24 months).[24-27]
- The ability to achieve long-term remission and cure patients with ALL diminishes with each round of therapy due to increasing resistance of leukaemic cells. For this reason, the best available therapeutic option should be used as early as possible.[23]
- As referenced in the blinatumomab European Public Assessment Report (EPAR; provided in Appendix I to the company submission), haematological remission rates in a small sample of 9 patients in late first relapse enrolled in the registrational studies and treated with blinatumomab were very high (CR/CRh* 88.9%, CR 77.7%), including a high proportion of patients achieving MRD remission (55.5%). Based on these data, the EMA concluded that efficacy can be 'considered established' in late first relapse patients; further efficacy data in the late first relapse population will be collected as part of a planned post-approval safety study.

That late first relapse patients (who have a better prognosis)[23] were not eligible for TOWER or Study MT103-211 means that absolute outcomes from TOWER and Study MT103-211 are likely to represent a conservative estimate of the absolute efficacy of both blinatumomab and SOC chemotherapy. The relative efficacy in TOWER for blinatumomab versus SOC chemotherapy is expected to be at least as good as will be seen in clinical practice in a population including late first relapse patients.

**A13 (PRIORITY QUESTION): To what degree did the analyses in TOWER account for treatment switching, both in terms of switching from the control arm to the blinatumomab arm and also to novel anti-cancer therapies after the trial period?**

Although not reported in the company submission, the following additional prespecified analyses to explore the effect on overall survival (OS) of blinatumomab drop-in from the SOC chemotherapy arm during long-term follow-up were conducted (results of which are reported in the TOWER primary analysis CSR):[1,20]

- The number and percentage of patients in the SOC chemotherapy arm who received blinatumomab during long-term follow-up were summarised, along with summary statistics for the timing of drop-in (Table A-21). A higher percentage of patients in the SOC chemotherapy arm (n = [redacted]; [redacted] %) received blinatumomab during long-term follow-up than patients in the blinatumomab arm (n = [redacted]; [redacted]%).
- A treatment effect was estimated as if no patients in the SOC chemotherapy arm dropped-in to receive blinatumomab treatment during long-term follow-up (Table A-22). This was formulated using an iterative parameter estimation method that uses a Weibull accelerated failure time model adjusting for the stratification errors; the variance of the treatment effect estimate was obtained using bootstrapping (Branson and Whitehead, 2002[28]). This analysis yielded an OS hazard ratio (HR) for blinatumomab versus SOC chemotherapy of [redacted], which is virtually identical to the HR from the primary OS analysis reported in the company submission ([redacted]).
- A stratified Gehan-Wilcoxon test was performed which gives less weight to treatment differences at later times when drop-in is most likely to occur (Table A-23). This yielded a p-value ([redacted]) which is slightly larger than the p-value from the primary OS analysis stratified log-rank test reported in the company submission ([redacted]), likely as a result of the higher weight given to events occurring early during treatment before the OS curves separated.

In conclusion, the difference in blinatumomab use across study arms during long-term follow-up could have potentially resulted in confounding of OS data over the duration of follow-up in TOWER. However, these analyses suggest that the extent of crossover may not have been high enough to have had a meaningful impact on results.

**Table A-21 Blinatumomab use during long-term follow-up (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| Subjects using blinatumomab, n (%) | [redacted] | [redacted] |
| Time to blinatumomab use from randomisation, n (%) | | |
| ≤ 1 month | [redacted] | [redacted] |
| > 1 to < 3 months | [redacted] | [redacted] |
| 3 to < 6 months | [redacted] | [redacted] |
| 6 to < 9 months | [redacted] | [redacted] |
| 9 to < 12 months | [redacted] | [redacted] |
| 12 to < 18 months | [redacted] | [redacted] |
| ≥ 18 months | [redacted] | [redacted] |
| Unknown | [redacted] | [redacted] |
| Time to blinatumomab use from randomisation, months | | |
| Mean (SD) | [redacted] | [redacted] |
| Median (IQR) | [redacted] | [redacted] |

Reference: TOWER primary analysis CSR (Table 14-4.12)[20]

Allo-SCT, allogenic stem cell transplant; CI, confidence interval; FAS, full analysis set; IQR, interquartile range; SD, standard deviation; SOC, standard of care.

**Table A-22 Estimated latent treatment effect on OS without subsequent blinatumomab drop-in from the SOC chemotherapy arm (TOWER, FAS)**

| | n-subjects / events[a] | Hazard ratio (95% CI) | p-value |
|---|---|---|---|
| n-subjects / events | [redacted] | N/A | N/A |
| Treatment (blinatumomab vs. SOC chemotherapy) | N/A | [redacted] | [redacted] |
| Age (< 35 years vs. ≥ 35 years) | N/A | [redacted] | [redacted] |
| Prior salvage therapy (yes vs. no) | N/A | [redacted] | [redacted] |
| Prior allo-SCT (yes vs. no) | N/A | [redacted] | [redacted] |

Reference: TOWER primary analysis CSR (Table 14-4.11)[20]

Note: This method assumes a Weibull accelerated failure time model and a time-invariant treatment benefit at time of subsequent therapy that is the same as the blinatumomab treatment effect at randomisation (Branson and Whitehead, 2002[28]).

[a] Number of subjects and events in the parametric model.

Allo-SCT, allogenic stem cell transplant; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; N/A, not applicable; OS, overall survival; SOC, standard of care.

**Table A-23 OS using the Gehan-Wilcoxon test (TOWER, FAS)**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| Died, n (%) | [redacted] | [redacted] |
| Censored, n (%) | [redacted] | [redacted] |
| OS duration, median months (95% CI) | [redacted] | [redacted] |
| Median follow-up for OS, months (IQR) | [redacted] | [redacted] |
| Stratified Gehan-Wilcoxon test[a] | | |
| Normal score[b] | [redacted] | |
| p-value | [redacted] | |

Reference: TOWER primary analysis CSR (Table 14-4.5.5)[20]

[a] Stratified by age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no) and prior allo-SCT (yes vs.no).
[b] A normal score < 0 indicates fewer than expected events for blinatumomab relative to SOC chemotherapy and therefore a longer survival time.

CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IQR, interquartile range; OS, overall survival; SOC, standard of care.

Analyses adjusting for crossover to other innovative anticancer therapies during long-term follow-up (e.g. inotuzumab and CAR-T cells) were not included in the prespecified TOWER statistical analyses for the following reasons:

- It would have been impossible to know in advance of the study what other innovative anticancer therapies patients would have received, and consequently it would have been impossible to define a comprehensive list of other innovative anticancer therapies that would need to be included in any such adjustment.
- There was limited evidence at the time the study was designed on the effectiveness of inotuzumab and CAR-T cells.

Consequently, the TOWER analyses reported in the TOWER primary analysis CSR and company submission do not include any adjustments for crossover to subsequent treatment with other innovative anticancer therapies (e.g. inotuzumab and CAR-T cells) during long-term follow-up. However, the proportion of patients receiving subsequent treatment with inotuzumab and CAR-T cells was similar across study arms in the TOWER SAS (SOC chemotherapy: [redacted]%; blinatumomab: [redacted]%), as reported in Section 4.12.1.2 of the company submission. Crossover to subsequent treatment with other innovative anticancer therapies is therefore considered to be unlikely to have had any meaningful impact on OS results over the duration of follow-up in TOWER.

**A14: Please present statistical significance tests for absolute probability of minimal residual disease in each arm of the TOWER trial?**

Based on the prespecified statistical testing strategy, formal inferential testing was not conducted for the prespecified TOWER secondary endpoint of MRD remission within 12 weeks of treatment initiation. Furthermore, descriptive p-values for the comparison across study arms of the absolute probability of achieving MRD remission within 12 weeks of treatment initiation were already reported in the company submission and submission appendices:

- For patients in the TOWER FAS who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation and had a post-baseline MRD assessment, the absolute probabilities of achieving an MRD remission within 12 weeks of treatment initiation were 76.3% in the blinatumomab arm and 48.5% in the SOC chemotherapy arm (descriptive p = [redacted] for comparison) (company submission Section 4.7.5). Although the prespecified primary statistical analyses were to be conducted on the FAS, it is considered more clinically meaningful to assess the proportion of patients with MRD remission amongst those who achieved a CR/CRh*/CRi and had a post-baseline MRD assessment. This is because MRD remission represents a deeper response than CR/CRh*/CRi, and therefore patients achieving an MRD remission represent a subset of patients who have achieved a CR/CRh*/CRi.
- When the total number of patients in the TOWER FAS was used as the denominator per the prespecified primary statistical analyses, the absolute probabilities of achieving an MRD remission within 12 weeks of treatment initiation were [redacted]% in the blinatumomab arm and [redacted]% in the SOC chemotherapy arm (descriptive p < [redacted] for comparison) (Appendix III to the company submission, Section 1.3.2).

**A15: Please present statistical significance tests for time to allo-SCT and risk of mortality after allo-SCT in TOWER, and also present associated Kaplan-Meier curves?**

Time to allo-SCT was not a prespecified endpoint in TOWER, and formal inferential testing for differences across study arms was therefore not conducted based on the prespecified statistical testing strategy. However, to address the ERG's question, Kaplan-Meier plots of time to allo-SCT and descriptive p-values for comparisons across study arms are provided below for:

- Patients in the TOWER FAS who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation (time from first occurrence of CR/CRh*/CRi) (Figure A-1). This population is considered particularly relevant since achievement of haematological remission is commonly used to assess patient eligibility for allo-SCT.
- All patients in the TOWER FAS (time from randomisation) (Figure A-2).

**Figure A-1 Kaplan-Meier plot of time from first occurrence of CR/CRh*/CRi to allo-SCT in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation (TOWER, FAS)**

Reference: Amgen data on file, 2017[4]

Note: Descriptive p-value from unstratified log-rank test. Vertical bars indicate censoring. 'Survival probability' refers to probability of allo-SCT.

Allo-SCT, allogenic stem cell transplant; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; NE, not estimable; SOC, standard of care.

**Figure A-2 Kaplan-Meier plot of time from randomisation to allo-SCT (TOWER, FAS)**

Reference: Amgen data on file, 2017[4]

Note: Descriptive p-value from unstratified log-rank test. Vertical bars indicate censoring. 'Survival probability' refers to probability of allo-SCT.

Allo-SCT, allogenic stem cell transplant; FAS, full analysis set; NE, not estimable; SOC, standard of care.

As discussed in the company submission (Section 4.7.6), that patients in the SOC chemotherapy arm were transplanted earlier than patients in the blinatumomab arm suggests that for patients randomised to blinatumomab, clinicians may have been more inclined to adopt a 'watch and wait' approach. This is potentially because of the risk associated with the allo-SCT procedure, availability of protocol-permitted maintenance treatment with blinatumomab and potential for long-term remission with blinatumomab, and the favourable tolerability profile of blinatumomab compared with SOC chemotherapy. This assertion is supported by feedback from a UK clinical expert (a TOWER investigator).

Risk of mortality following allo-SCT for the duration of follow-up was also not a prespecified endpoint in TOWER (100-day mortality rates following allo-SCT was a secondary safety endpoint). However, to address the ERG's question, Kaplan-Meier plots for risk of mortality following post-baseline allo-SCT for the duration of follow-up and descriptive p-values for comparisons across study arms are provided below for:

- Patients in the TOWER FAS who received a post-baseline allo-SCT, achieved a CR/CRh*/CRi within 12 weeks of treatment initiation, and did not receive additional anticancer therapy prior to the allo-SCT (Figure A-3). As discussed in the analysis of 100-day mortality following post-baseline allo-SCT reported in the company submission (Section 4.7.6), given the influence of a range of clinician-driven considerations and substantial potential confounding, focussing on this population was considered appropriate to reduce the impact of such potential confounding.
- All patients in the TOWER FAS who received a post-baseline allo-SCT (Figure A-4).

**Figure A-3 Kaplan-Meier plot of risk of mortality following post-baseline allo-SCT in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation and did not receive other anticancer therapy prior to the allo-SCT (TOWER, FAS)**

Reference: Amgen data on file, 2017[4]

Note: Descriptive p-value from unstratified log-rank test. Vertical bars indicate censoring.

Allo-SCT, allogenic stem cell transplant; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; NE, not estimable; SOC, standard of care.

**Figure A-4 Kaplan-Meier plot of risk of mortality following post-baseline allo-SCT (TOWER, FAS)**

Reference: Amgen data on file, 2017[4]

Note: Descriptive p-value from unstratified log-rank test. Vertical bars indicate censoring.

Allo-SCT, allogenic stem cell transplant; FAS, full analysis set; NE, not estimable; SOC, standard of care.

**A16: Please present statistical significance tests for differences in response (CR, CR/CRh*/CRi) duration in TOWER, and present associated Kaplan-Meier curves?**

Kaplan-Meier plots for the prespecified TOWER secondary endpoints of duration of CR and duration of CR/CRh*/CRi are provided below in Figure A-5 and Figure A-6, respectively. Based on the prespecified statistical testing strategy, formal inferential testing was not conducted for these endpoints. However, to address the ERG's question, descriptive p-values for comparisons across study arms have been included within these Kaplan-Meier plots.

**Figure A-5 Kaplan-Meier plot of duration of CR in patients who achieved a CR within 12 weeks of treatment initiation (TOWER, FAS)**

Reference: Amgen data on file, 2017[4]

Note: Descriptive p-value from unstratified log-rank test. Vertical bars indicate censoring.

CI, confidence interval; CR, complete remission; FAS, full analysis set; SOC, standard of care.

**Figure A-6 Kaplan-Meier plot of duration of CR/CRh*/CRi in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation (TOWER, FAS)**

Reference: Amgen data on file, 2017[4]

Note: Descriptive p-value from unstratified log-rank test. Vertical bars indicate censoring.

CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; SOC, standard of care.

### A17: In TOWER, what was the extent of the difference in time to clinically meaningful deterioration in HRQoL?

The following HRQoL endpoints were prespecified for TOWER:

- Time to 10-point decrease in European Organisation for Research and Treatment of Cancer Quality of Life questionnaire Core 30 global health status/quality of life scale (EORTC QLQ-C30 GHS/QoL) or event-free survival (EFS) event (secondary endpoint).
- Acute lymphoblastic leukaemia symptom scale (ALLSS) scores measured at selected time points (exploratory endpoint).

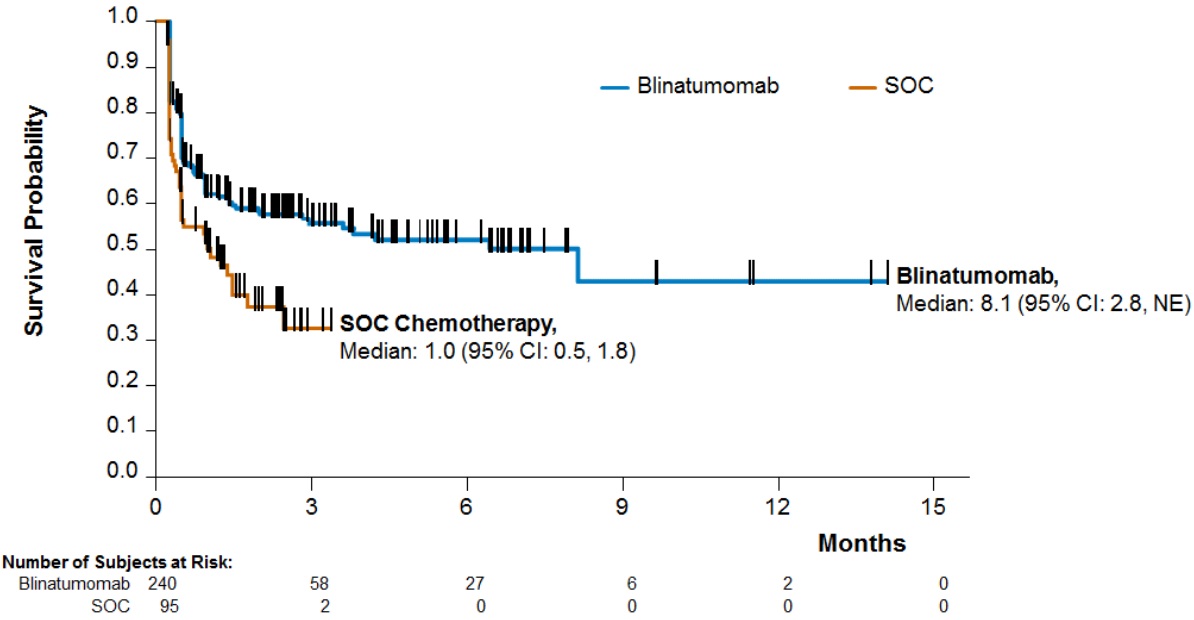
Information on the time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event endpoint was presented in the company submission (Section 4.7.7), along with data from an exploratory post-hoc analysis of EORTC QLQ-C30 scales and single items over time as EORTC QLQ-C30 data from TOWER were used inform the cost-effectiveness analysis. Results from the exploratory HRQoL endpoint of ALLSS score over time were not available for analysis at the time of this appraisal and were therefore not reported in the company submission.

As discussed in the company submission (Section 4.7.7), changes of between 5 and 10 points on the EORTC QLQ-C30 scales can be considered clinically meaningful.[29-31] However, as acknowledged in the company submission (Section 4.13.3), the prespecified time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event endpoint has limited clinical relevance as haematological non-responders were assigned an EFS duration of 1 day (an approach

recommended by the EMA for acute leukaemia[32]). This resulted in more than > 50% of patients in both study arms being assigned an EFS duration of 1 day, and renders estimates of median time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event in TOWER (0 months in both study arms) uninformative.

An additional post-hoc exploratory analysis of time to 10-point decrease in EORTC QLQ-C30 GHS/QoL alone (i.e. not including EFS in the outcome measure) suggests that blinatumomab delays time to clinically-meaningful deterioration in HRQoL compared with SOC chemotherapy (Figure A-7 and Table A-24). The median time to 10-point decrease in EORTC QLQ-C30 GHS/QoL was 8.1 months in the blinatumomab arm and 1.0 months in the SOC chemotherapy arm (descriptive p = [redacted]).

**Figure A-7 Kaplan-Meier plot of time to 10-point decrease in EORTC QLQ-C30 GHS/QOL (TOWER, EORTC analysis set)**




Reference: Amgen data on file, 2016[21]

Note: The EORTC analysis set included patients who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item. Vertical bars indicate censoring.

CI, confidence interval; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 global health status/quality of life scale; NE, not estimable; SOC, standard of care

**Table A-24 Summary of time to 10-point deterioration in EORTC QLQ-C30 GHS/QOL (TOWER, EORTC analysis set)**

| | Blinatumomab (N = 247) | SOC chemotherapy (N = 95) |
|---|---|---|
| Number of patients | 240 | 95 |
| Events, n (%) | [redacted] | [redacted] |
| Censored, n (%) | [redacted] | [redacted] |
| Time to event, months | | |
| Median (95% CI) | 8.1 (2.8, NE) | 1.0 (0.5, 1.8 |
| IQR | [redacted] | [redacted] |
| p-value[a] | [redacted] | |

Reference: Amgen data on file, 2016[21]

Note: The EORTC analysis set included patients who had a non-missing baseline assessment and at least one post-baseline assessment of any EORTC QLQ-C30 scale/item.

[a] Descriptive p-value from log-rank test after adjusting for stratification factors of age (< 35 years vs. ≥ 35 years), prior salvage therapy (yes vs. no), and prior allo-SCT (yes vs.no).

CI, confidence interval; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 global health status/quality of life scale; NE, not estimable; SOC, standard of care.

**A18: In the CSR for TOWER, results for exposure-response analyses, ALL-specific symptoms, tumour DNA/anti-blinatumomab antibody formation/resistance, vital signs, laboratory parameters and pharmacokinetics are not reported. Please provide these results or justify why these results were not presented in the CSR.**

Information on the following requested analyses are reported in the TOWER primary analysis CSR:

- Pharmacokinetics (CSR Section 11.1).
- Laboratory parameters (CSR Section 12.7).
- Vital signs (CSR Section 12.8).
- Anti-blinatumomab antibody formation (CSR Section 11.2).

Exposure-response analyses and ALL-specific symptoms are discussed below.

Exposure-response analyses

Exposure-response analyses have not been conducted for TOWER alone or submitted as part of the TOWER data package to the EMA. However, exposure-response analyses based on pooled data from TOWER, Study MT103-211, and Study MT103-216 (another registrational single-arm phase 2 study) have been conducted and will be submitted as part of the TOWER

data package to the Food and Drug Administration (FDA), based on a specific request from the FDA for these pooled analyses.

These pooled exposure-efficacy analyses were conducted for probability of CR and duration of OS, and exposure-safety analyses were conducted for probability of CRS; only assessed for blinatumomab as CRS events did not occur in the SOC chemotherapy arm) and neurologic events.[21] A range of selected baseline covariates were evaluated in the analyses, and the effect of blinatumomab was assessed by including treatment (blinatumomab vs. SOC chemotherapy) and blinatumomab exposure (dose-dependent blinatumomab steady state concentration [$C_{ss}$]). The following blinatumomab $C_{ss}$ values were used in the analyses:

- For events that occurred in Cycle 1 Week 1, the blinatumomab $C_{ss}$ during Cycle 1 Week 1 (9 µg/day dose) was used (exposure-safety analyses only).
- For events that occurred in subsequent weeks of Cycle 1, the blinatumomab $C_{ss}$ during Cycle 1 Week 2 (28 µg/day dose) was used.
- For events that occurred in Cycle 2 or later, the blinatumomab $C_{ss}$ during Cycle 2 (28 µg/day dose) was used unless blinatumomab $C_{ss}$ during Cycle 2 was not available, in which case Cycle 1 Week 2 data were used instead.

For each endpoint, the effect of the selected covariates on the exposure-efficacy/safety relationship was investigated in univariate and multivariate stepwise analysis models. The multivariate analyses included only those covariates identified as being associated with outcome in the univariate analyses, as well as treatment and blinatumomab exposure. Effects were considered significant in the if they resulted in a p-value < 0.1 (univariate analyses) or < 0.05 (multivariate analyses). P-values were not adjusted for multiplicity, and results should therefore be interpreted with caution.

Of the [redacted] patients in the pooled exposure-response analyses, [redacted] received blinatumomab and [redacted] received SOC chemotherapy. Data on blinatumomab $C_{ss}$ was available for [redacted] patients receiving the 9 µg/day dose in Cycle 1 Week 1, for [redacted] patients receiving the 28 µg/day dose in Cycle 1 Week 2, and for [redacted] patients receiving the 28 µg/day dose in Cycle 2. For probability of CR, treatment with blinatumomab and higher blinatumomab $C_{ss}$ were associated with greater probability of CR ($p < 0.05$) in the multivariate analysis. When the analysis was updated to exclude patients receiving SOC chemotherapy in order to confirm the effect of blinatumomab $C_{ss}$ in patients receiving blinatumomab (i.e. accounting for treatment effect), blinatumomab $C_{ss}$ was no longer associated with greater probability of CR ($p =$ [redacted]). For OS, higher blinatumomab $C_{ss}$ was associated with a lower OS hazard in the multivariate analysis before ($p <$ [redacted]) and after ($p <$ [redacted]) accounting for treatment effect. The exposure-safety analyses showed that blinatumomab $C_{ss}$ following the 9 µg/day dosing or 28 µg/day dosing was not associated with probability of CRS events in the multivariate analysis. This suggests that any risk of higher blinatumomab $C_{ss}$ levels triggering a higher frequency of CRS events during initial treatment with blinatumomab is successfully mitigated by use of a lower dose in Cycle 1 Week 1. Similarly, the exposure-safety analyses showed that blinatumomab $C_{ss}$ following the 9 µg/day dosing or 28 µg/day dosing was not associated with probability of neurologic events, after accounting for treatment effect.

If further details around the methods or results of these exposure-response analyses are required by the ERG, these can be made available on request when the exposure-response analysis report is finalised (anticipated to be late-January 2017).

ALL-specific symptoms

ALL-specific symptoms were not explicitly grouped in the reporting of AEs in the TOWER primary analysis CSR or company submission given this was not part of the prespecified analysis strategy. Rates of ALL-specific symptoms are captured within tables included in the TOWER CSR and company submission that report the incidence of AEs of different categories (e.g. most common treatment-emergent AEs, treatment-related AEs, serious AEs, AEs of interest, etc.).

**A19: Please present demographic data to establish adequate balance between the treatment cohort and the natural history cohort for the propensity score matching in the comparative cohort analysis using data from MT103-211?**

For clarification, the propensity score analysis that provided comparative data on outcomes observed in Study MT103-211 and the historical comparator cohort involved a propensity score 'adjustment' (using inverse probability of treatment weighting [IPTW] methodology) rather than propensity score 'matching'.

A summary of the propensity score adjustment methodology and adjustment results was provided in the company submission (Section 4.11.6), and a detailed table of covariates before and after propensity score adjustment was provided in Appendix V to the company submission (Section 1.3). This information is repeated below:

- A propensity score analysis was performed to balance measured patient characteristics in the historical cohort and Study MT103-211.[33] Available covariates included age, sex, duration between initial diagnosis and salvage therapy, region (US, Europe), prior allo-SCT, prior number of salvage therapies, primary refractory and in first salvage (yes, no) and refractory to last salvage therapy (yes, no). An estimated propensity score (the predicted probability of participating in Study MT103-211 if it were being conducted during the period of the historical comparator study) was assigned to each patient based on their set of covariates. Regression modelling and standardised differences were used to assess the balance of covariates. When estimating treatment effects, the propensity scores were used to adjust for patient differences between the historical cohort and Study MT103-211 using IPTW methodology.
- The balance in baseline covariates between the historical cohort and Study MT103-211 was examined before and after making adjustments for the propensity score. Before adjustment, there were significant differences in six of the eight covariates assessed. In particular, the MT103-211 patients were more heavily pre-treated then the historical control patients (average number of prior salvage therapies 2.36 vs.1.52) and a higher proportion were refractory to their last line of salvage (52% vs. 23%). After adjustment, there were no significant differences in covariates, except for region (more European patients in the historical cohort).

- The balance in baseline covariates between Study MT103-211 and the historical cohort (Study 20120310) before and after propensity score adjustments is summarised in Table A-25.

In addition to the above information already provided in the company submission and submission appendices, we would like to take this opportunity to clarify/acknowledge in response to the ERG's question that the propensity score adjustment was carried out only for the eight covariates reported across both data sets. As highlighted by the authors of the primary study publication for the analysis, 'nearly all known important prognostic factors were adjusted for' in the propensity score analysis and the weighted analysis that was conducted in parallel (also reported in the company submission).[33] Nonetheless, it is possible that unknown imbalances across other prognostically relevant covariates not reported across both datasets and consequently not included in the propensity score adjustment have may have resulted in residual confounding; this represents a limitation of propensity score modelling using IPTW methodology in general.

**Table A-25 Study MT103-211 versus historical cohort: covariate balance before and after propensity score adjustments**

| Covariate | Before adjustments | | | | After adjustments | | | |
|---|---|---|---|---|---|---|---|---|
| | Blinatumomab trial (Study MT103-211) (N = 189) | Historical dataset (Study 20120310) (N = 1131) | Standardised difference | p-value | Blinatumomab trial (Study MT103-211) (N = 189) | Historical dataset (Study 20120310) (N = 1131) | Standardised difference | p-value[a] |
| Age, years Mean (SD) | 41.1 (17.3) | 37.4 (14.2) | 0.233 | 0.0014 | 36.9 (15.7) | 38.1 (14.5) | -0.078 | 0.4694 |
| Female, n (%) | 70 (37) | 477 (42) | -0.105 | 0.1850 | 68 (36) | 475 (42) | -0.122 | 0.2913 |
| Duration since initial diagnosis in months, mean (SD) | 28.1 (36.5) | 12.2 (12.3) | 0.585 | <0.0001 | 15.6 (18.0) | 13.8 (15.1) | 0.106 | 0.1740 |
| Region Europe, n (%) | 95 (50) | 822 (73) | -0.473 | <0.0001 | 89 (47) | 780 (69) | -0.452 | 0.0001 |
| Prior allo-SCT, n (%) | 64 (34) | 209 (18) | 0.355 | <0.0001 | 38 (20) | 238 (21) | -0.019 | 0.8475 |
| Number of prior salvage therapies, mean (SD) [b] | 2.36 (0.99) | 1.52 (0.82) | 0.924 | <0.0001 | 1.69 (0.87) | 1.64 (0.89) | 0.061 | 0.5334 |
| Primary refractory and in | 4 (2) | 62 (5) | -0.177 | 0.0587 | 19 (10) | 57 (5) | 0.194 | 0.1882 |

| Covariate | Before adjustments | | | | After adjustments | | | |
|---|---|---|---|---|---|---|---|---|
| | **Blinatumomab trial (Study MT103-211) (N = 189)** | **Historical dataset (Study 20120310) (N = 1131)** | **Standardised difference** | **p-value** | **Blinatumomab trial (Study MT103-211) (N = 189)** | **Historical dataset (Study 20120310) (N = 1131)** | **Standardised difference** | **p-value[a]** |
| 1st salvage, n (%) | | | | | | | | |
| Refractory to preceding salvage, n (%) | 98 (52) | 259 (23) | 0.627 | <0.0001 | 51 (27) | 305 (27) | -0.002 | 0.9833 |

Reference: Gokbuget et al., 2016 (Supplemental Table 5)[33]

[a] P-value is from a logistic regression model for the binary variables and a linear regression for the continuous variables
[b] Includes the last line of treatment, which is blinatumomab for blinatumomab patients

Note: Based on the primary analysis set for Study MT103-211 and the survival data analysis set for the historical cohort (i.e. all patients with survival data)

allo-SCT, allogeneic stem cell transplant; SD, standard deviation.

**A20: Please provide statistical significance tests for the outcomes presented in Tables 3 and 5 in Appendix III of the Company Submission.**

P-values were already reported for all analyses included in Table 3 of Appendix III to the company submission, which presented a summary of results from the primary and sensitivity analyses of the prespecified TOWER secondary endpoints of rates of CR and CR/CRh*/CRi within 12 weeks of treatment initiation.

Table 5 of Appendix III to the company submission includes results from the primary and sensitivity analyses of the prespecified TOWER secondary endpoints of duration of CR and duration of CR/CRh*/CRi in patients who achieved a CR or CR/CRh*/CRi within 12 weeks of treatment initiation. Based on the prespecified statistical testing strategy, formal inferential testing was not conducted for these endpoints. However, to address the ERG's question, Table 5 of Appendix III is replicated below, with the addition of descriptive p-values (Table A-26).

**Table A-26 Duration of best haematological response (CR or CR/CRh*/CRi) (primary and sensitivity analyses)**

| | Blinatumomab (N = 271) | | SOC chemotherapy (N = 134) |
|---|---|---|---|
| Primary analysis 1: Duration of CR (FAS) | | | |
| Events, n (%) | [redacted] | | [redacted] |
| Median, months (95% CI)[a] | [redacted] | | [redacted] |
| p-value[b] | | [redacted] | |
| Sensitivity analysis 1: Duration of CR (FAS; censoring at time of allo-SCT) | | | |
| Events, n (%) | [redacted] | | [redacted] |
| Median, months (95% CI)[a] | [redacted] | | [redacted] |
| p-value[b] | | [redacted] | |
| Primary analysis 2: Duration of CR/CRh*/CRi (FAS) | | | |
| Events, n (%) | [redacted] | | [redacted] |
| Median, months (95% CI)[a] | 7.3 (5.8, 9.9) | | 4.6 (1.8, 19.0) |
| p-value[b] | | [redacted] | |
| Sensitivity analysis 2: Duration of CR/CRh*/CRi (FAS; censoring at time of allo-SCT) | | | |
| Events, n (%) | [redacted] | | [redacted] |
| Median, months (95% CI)[a] | [redacted] | | [redacted] |
| p-value[b] | | [redacted] | |

Reference: TOWER primary analysis CSR (Table 10-8, Table 14-4.8.2, and Table 14-4.9.2)[20] and Amgen data on file, 2017[4]

[a] Months are calculated as days from randomisation date to event/censor date, divided by 30.5.
[b] Descriptive p-value from unstratified log-rank test.

Allo-SCT, allogenic stem cell transplantation; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; FAS, full analysis set; SOC, standard of care.

# B: Clarification on cost-effectiveness data

**B1: The ERG understands that people with active central nervous system (CNS) involvement were excluded from the TOWER trial. However, information on the history of CNS pathology was not collected. Please justify why this information was not collected.**

For clarification, as well as patients with active central nervous system (CNS) involvement, patients with history or presence of clinically-relevant CNS pathology were also excluded from TOWER, as outlined in the company submission (Section 4.3.1). As stated in Section 4.2 of the TOWER protocol, patients were excluded from TOWER for the following reasons relating to CNS pathology:[34]

- 'Active ALL in the CNS (confirmed by cerebrospinal fluid [CSF] analysis).'
- 'History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis. With the exception of history of CNS leukaemia that is controlled with intrathecal therapy.'

We apologise for incorrectly stating in the company submission that no data on history of CNS pathology were collected in TOWER. A comprehensive overview of baseline medical history is reported in the TOWER primary analysis CSR (Table 14-2.5) by system organ class and high level term, though data on history of CNS pathology are not explicitly grouped.

**B2 (PRIORITY QUESTION): The main source of treatment effect on overall survival was based on the TOWER tria'sl results. However, it is unclear how the treatment effect has been applied to the natural history comparator. Please clarify this by explaining which one of the suggestions below describe the analyses.**

**a. The treatment effect was derived from the Kaplan-Meier plots for overall survival and applied to the adjusted historical comparator cohort data**

**b. The treatment effect was based on parametric models, fitted to the Kaplan-Meier plots for overall survival and applied to the adjusted historical comparator cohort**

**c. The treatment effect was based on parametric models fitted to the Kaplan-Meier plots for overall survival, then the historical comparator cohort had been used to extrapolate beyond the trial time horizon**

The adjusted OS curve for the matched historical comparator cohort was not used explicitly in the model. Rather, it was used to assess the plausibility of the model projections based on the Gompertz distribution and general population mortality.

As outlined in the company submission (Section 5.3.2), the approach used for modelling OS was:

- A proportional hazards Gompertz model was fitted to the TOWER OS data, and was used to represent disease-specific mortality from ALL for patients treated with FLAG-IDA (using the TOWER SOC chemotherapy arm as a proxy) or blinatumomab.

- Age- and gender-matched general population mortality rates were estimated based on the mean age in TOWER, the proportion of TOWER patients who were male, and Office for National Statistics (ONS) life tables to represent non-diseases-specific mortality.
- Survival probabilities by week for FLAG-IDA were calculated by multiplying the probability of survival in the previous period by the conditional probability of survival from the FLAG-IDA arm of the fitted Gompertz model and by the conditional probability of survival based on general-population mortality.
- Survival probabilities by week for blinatumomab were estimated as follows:
  - Years 1-4: Calculated by multiplying the probability of survival in the previous period by the conditional probability of survival from the blinatumomab arm of the fitted Gompertz model and by the conditional probability of survival based on general population rates.
  - Year 5+: Calculated by multiplying the probability of survival in the previous period by the conditional probability of survival from the FLAG-IDA arm of the fitted Gompertz model and by the conditional probability of survival based on general population rates.

**B3 (PRIORITY QUESTION): The ERG understands that various parametric curves have been fitted to the overall survival curve from matched patients from Study 20120310, and the restricted Gompertz model fitted to these data. Additionally, a Gompertz model was fitted to the overall survival for the TOWER SOC chemotherapy arm. Figure 5-9 shows the overall survival projections from the TOWER SOC chemotherapy arm is higher than the survival in the natural history arm. Please can you clarify how the adjusted hazard ratio of 0.85 was applied to the overall survival curve for the historical comparator cohort?**

As described above in response to Question B3, the adjusted OS curve for the matched historical comparator cohort was not used explicitly in the model. Rather, it was used to assess the plausibility of the model projections based on the Gompertz distribution and general population mortality.

The adjusted OS curve for the matched historical comparator was calculated using the formula below:

$$S_A[t] = S[t]^{HR}$$

Where

$S_A[t]$ = Adjusted Kaplan-Meier survival distribution for matched historical comparator

$S[t]$ = Unadjusted Kaplan-Meier survival distribution for matched historical comparator

HR = Hazard ratio for adjusted vs. unadjusted Kaplan-Meier survival distribution for the matched historical comparator

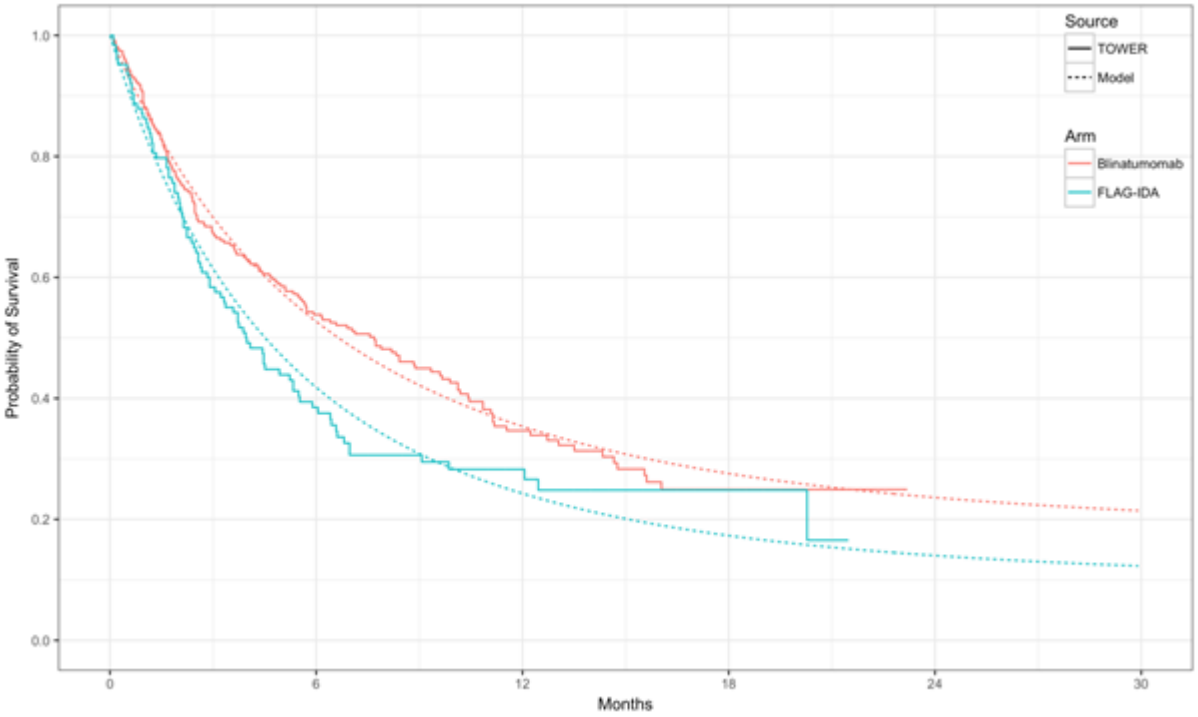
The HR for the adjusted versus unadjusted Kaplan-Meier survival distribution (0.85) was obtained using trial and error and visual inspection.

**<u>B4 (PRIORITY QUESTION):</u>Please clarify why there is a difference between the overall survival as seen in the TOWER trial (figure 5-2) compared to the overall survival in the economic model (fig 5-17).**

Figure 5-2 in the company submission presented the TOWER OS Kaplan-Meier curves for blinatumomab and SOC chemotherapy (used as a proxy for FLAG-IDA in the model) on a scale extending to 27 months. In contrast, Figure 5-17 (B) in the company submission presented the modelled OS curves for blinatumomab and FLAG-IDA on a scale extending to 60 years (720 months). Because of the difference in scales, it is difficult to compare the survival curves across the two figures.

So that these curves can be more easily visually compared, a comparison of the TOWER OS Kaplan-Meier curves and modelled OS over the TOWER trial duration is provided in Figure B-1. This shows that the TOWER Kaplan-Meier curves for blinatumomab and SOC chemotherapy are broadly similar to the modelled OS curves for blinatumomab and FLAG-IDA over the duration of follow-up in TOWER.

**Figure B-1 Comparison of TOWER OS Kaplan-Meier curves and modelled OS curves over the TOWER trial duration (TOWER, FAS)**




Note: The TOWER Kaplan-Meier curve for FLAG-IDA is the TOWER SOC chemotherapy arm, which was used as a proxy for FLAG-IDA in the model

FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; OS, overall survival; SOC, standard of care

Furthermore, as highlighted in Table 5-20 of the company submission (replicated below in Table B-1), the model projections very closely approximate the Kaplan-Meier survival probabilities from TOWER for both blinatumomab and SOC chemotherapy at selected

landmarks including the last observed failure or censoring time for SOC chemotherapy in TOWER (21.5 months).

**Table B-1 Comparison of probabilities of survival in the model and in TOWER at selected landmarks**

| Month | Blinatumomab | | SOC chemotherapy[a] | |
|---|---|---|---|---|
| | TOWER | Model | TOWER | Model |
| 6 | 53.9% | 52.3% | 38.5% | 41.3% |
| 12 | 34.7% | 35.2% | 28.3% | 24.1% |
| 21.5[b] | 24.9% | 25.0% | 16.6% | 15.1% |

[a] Used as a proxy for FLAG-IDA in the model
[b] Maximum failure or censor time for the SOC chemotherapy arm in TOWER

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SOC, standard of care

**B5: The company has undertaken extensive survival analyses; namely extrapolation of overall survival and event free survival curves beyond the observed trial data to a lifetime horizon. In the absence of long-term data, this will introduce some uncertainty, especially if, based on expert opinion, it is assumed that patients who are alive after 4 years of treatment are likely to be cured from the disease. Please present the results of a sensitivity analysis which is based on the time horizon of the trial.**

In order to address the ERG's question, an additional scenario analysis was conducted in which the model time horizon was limited to 2 years (the maximum follow-up time in TOWER, 23.7 months, rounded to the nearest month). Results of this additional scenario analysis in the overall TOWER trial population with the blinatumomab simple patient access scheme (PAS) discount incorporated are presented in Table B-2. The incremental cost-effectiveness ratio (ICER) from this scenario analyses (£432,478 per quality-adjusted life year [QALY] gained) is, as expected, substantially less favourable than the base case ICER (£55,501 per QALY gained).

Arbitrarily limiting the time horizon to 2-years based on the maximum follow-up in TOWER (itself arbitrarily limited by the prespecified second interim analysis triggered when 75% of OS events had occurred and subsequent discontinuation of long-term follow-up) is inappropriate and represents a clinically implausible scenario. As seen in TOWER, blinatumomab's innovative and targeted mechanism of action results in compelling efficacy, including more than doubling of rates of CR and almost doubling of OS relative to SOC chemotherapy. In TOWER, 24.9% and 16.6% of patients in the blinatumomab and SOC chemotherapy arms, respectively, were alive at 21.5 months (the last observed failure or censoring time for SOC chemotherapy) as outlined in the company submission (Section 5.7.2) and the response to Question B4. In the key registrational phase 2 single-arm study (Study MT103-211), the proportions of patients alive at both 2-years and 3-years based on the most recent data cut-off date were around 20% as shown by the OS Kaplan-Meier curves reported in the company submission (Section 4.11.6.1). As stated in the NICE reference case, 'analyses that limit the time horizon to periods shorter than the expected impact of treatment do not usually provide the best estimates of benefits and costs.'[5]

**Table B-2 Results of the additional scenario analysis with a 2-year model time horizon (TOWER, FAS) (base case ICER: £55,501) – with blinatumomab PAS**

| Technology (and comparators) | Total costs (£) | Total life years | Total QALYs | Incremental costs (£) | Incremental life years | Incremental QALYs | ICER versus baseline (£) |
|---|---|---|---|---|---|---|---|
| FLAG-IDA | 63,678 | 0.66 | 0.38 | - | - | - | - |
| Blinatumomab | 144,120 | 0.86 | 0.57 | 80,442 | 0.19 | 0.19 | 432,478 |

FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life-years.

**B6 (PRIORITY QUESTION): Table 5-12 presents cost for home infusion pump. These costs were based on pro-rated pump costs assuming 5 years lifespan. Please clarify what prorated means. Does this assume that these pumps are transferable from one patient to another? If pumps are not reusable, this would suggest that the cost and hence projected costs would have been underestimated.**

With respect to the calculation of infusion pump costs, 'prorated' means that the total costs of the pump were distributed over the estimated useful life of the pump. Assuming a total cost of £1,795, and a useful life of 5 years, the daily cost of the pump was estimated to be £0.98 (i.e. £1,795 total cost ÷ [365 days x 5 years] = £0.98 per day). Additionally, there was an annual maintenance cost of £90, or £0.25/day and cost for consumables of £2.61 a day, so initially the daily cost of the pump was £3.84.

This calculation assumes that the pumps are transferable from one patient to another, which was based on feedback from UK clinical experts who suggested that pumps are routinely reused in clinical practice in England and Wales. To assess the impact of this assumption on the cost-effectiveness analyses, an additional scenario analysis was conducted in which it was assumed that the pumps are not reusable (i.e. each individual patient is assigned the full cost of the pump). Results of this scenario analysis in the overall TOWER trial population with the blinatumomab simple PAS discount incorporated are presented in Table B-3. The ICER from this scenario analysis (£56,627 per QALY gained) is very similar to the base case ICER (£55,501 per QALY gained), showing that the assumption on pump resuability does not materially impact the cost-effectiveness results.

**Table B-3 Results of the additional scenario analysis assuming that infusion pumps are not reusable (TOWER, FAS) (base case ICER: £55,501) - with blinatumomab PAS**

| Technology (and comparators) | Total costs (£) | Total life years | Total QALYs | Incremental costs (£) | Incremental life years | Incremental QALYs | ICER versus baseline (£) |
|---|---|---|---|---|---|---|---|
| FLAG-IDA | 64,354 | 2.61 | 1.90 | - | - | - | - |
| Blinatumomab | 146,432 | 4.38 | 3.35 | 82,079 | 1.78 | 1.45 | 56,627 |

FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life-years.

**B7 (PRIORITY QUESTION): For people who received SOC chemotherapy, the mean utility value in the initial health state was lower than on the blinatumomab arm. Please clarify if this difference was statistically significant. Additionally, please provide explanation and supporting evidence why this difference occurred.**

Analyses of mean utility values by health state and study arm in TOWER were descriptive only. The generalised linear model(GLM)/generalised estimating equations (GEE) regression model was not coded to explicitly examine the treatment effect on utilities by health state. However, to address the ERG's question, we used the model coefficients and variance-covariance matrix from the GLM/GEE regression to calculate a descriptive p-value for the difference in the mean EuroQoL five dimensions (EQ-5D) utility values between study arms within the initial health state (assuming a normal distribution) in the overall TOWER trial population. The difference in mean utility between study arms was 0.094 (standard error [SE], 0.038), and based on this statistical analysis the p-value was estimated to be 0.013.

No analyses were conducted to explicitly evaluate the factors contributing to any differences in utility values by treatment within health states. However, descriptive analyses of the dimensions of the EORTC QLQ-C30 used in the mapping algorithm to generate utility values show that the mean values for all but one of the functional scales and symptom scales/single items during the initial health state were more favourable for blinatumomab than for SOC chemotherapy (reported in Appendix IX to the company submission). The exception was the financial difficulties single item, which was slightly less numerically favourable for blinatumomab than for SOC chemotherapy. These differences in utility during the initial health state could reflect the better toxicity profile and improved efficacy with blinatumomab relative to SOC chemotherapy over the course of 12 weeks of treatment (i.e. the time period spent by patients in the initial health state). As shown in the response to Question A17, the median time to clinically meaningful 10-point decrease in EORTC QLQ-C30 GHS/QoL was just 1.0 months in the SOC chemotherapy arm (compared with 8.1 months in the blinatumomab arm).

To assess the impact of the different initial health state utility values on the cost-effectiveness analyses, an additional scenario analysis was conducted in which it was assumed that the utility values during the initial health state would be the same for patients receiving FLAG-IDA and blinatumomab. In this analysis, both treatments were assigned a weighted average of the treatment-group specific initial health state utility values (0.646). Results of this scenario analysis in the overall TOWER population with the blinatumomab simple PAS discount incorporated are presented in Table B-4. The ICER from this scenario analysis (£56,195 per QALY gained) is very similar to the base case ICER (£55,501 per QALY gained), showing that the difference in initial health state utilities across treatments does not materially impact the cost-effectiveness results.

**Table B-4 Results of the additional scenario analysis assuming that initial health state utility is the same for blinatumomab and FLAG-IDA (TOWER, FAS) (base case ICER: £55,501) – with blinatumomab PAS**

| Technology (and comparators) | Total costs (£) | Total life years | Total QALYs | Incremental costs (£) | Incremental life years | Incremental QALYs | ICER versus baseline (£) |
|---|---|---|---|---|---|---|---|
| FLAG-IDA | 64,165 | 2.61 | 1.91 | - | - | - | - |
| Blinatumomab | 144,611 | 4.38 | 3.34 | 80,446 | 1.78 | 1.43 | 56,195 |

FAS, full analysis set; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life-years.

# C: Textual clarification and additional points

**C1: Clinical outcomes for patients' on the SOC chemotherapy arm in the TOWER trial were assumed to be generalisable to patients receiving FLAG-IDA. Please provide justification for this assumption, and how the differences between treatments were taken into account.**

As outlined in the company submission (Section 4.13.3), the most common intended SOC chemotherapy regimen at randomisation for patients randomised to the SOC chemotherapy arm was a FLAG ± anthracycline based regimen ([redacted]%), and this was also the most commonly used regimen in patients who received at least one dose of study drug in the SOC chemotherapy arm (45.0%). In addition, available clinical guidelines, including the European Working Group for Acute Lymphoblastic Leukaemia (EWALL) guidelines,[35] suggest that there is no clearly superior salvage chemotherapy regimen in R/R Ph- B-precursor ALL. UK clinical experts consulted by Amgen considered the clinical outcomes in the SOC chemotherapy arm in TOWER to be broadly generalisable to FLAG-IDA. We acknowledge that there may be some minor differences in clinical outcomes across different SOC chemotherapy regimens, most likely with respect to the safety/tolerability profiles of the different agents in these regimens.

In the base case cost-effectiveness analysis, it was assumed that there are no differences between SOC chemotherapy regimens in TOWER in terms of clinical outcomes, and the whole SOC chemotherapy arm was used as a proxy for FLAG-IDA clinical outcomes as a simplifying assumption. In the absence of a head-to-head study of blinatumomab versus FLAG-IDA and the dearth of RCT evidence in this disease area precluding any indirect comparison, this approach was considered to be the most robust way in which to estimate relative clinical outcomes for blinatumomab versus FLAG-IDA. An alternative approach to modelling the cost-effectiveness of blinatumomab versus FLAG-IDA would have been to use data from the prespecified subgroup of patients in TOWER intended to receive a FLAG ± anthracycline based regimen at randomisation, which was explored in a scenario analysis (Section 5.8.3 of the company submission). Using these subgroup data in the base case analysis was not considered appropriate because this approach results in a substantially smaller sample size, and patients in TOWER were not stratified by intended SOC chemotherapy regimen resulting in potential imbalances across study arms in prognostic variables. Furthermore, as highlighted

in the company submission (Secton 4.8.2), in the prespecified subgroup analyses of OS (a key driver of the cost-effectiveness model), the HR in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation ([redacted]) was lower than in any of the other SOC chemotherapy regimen subgroups, and than in the primary OS analysis in the ITT population. Use of treatment effect estimates from the whole SOC chemotherapy arm in the base-case cost-effectiveness analysis therefore represents a potentially more conservative approach than using treatment effect estimates from the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation.

**C2 (PRIORITY QUESTION): Mean EQ-5D utility values along with their standard errors are presented in Table 5-7. In Table 5-17 these utility values are presented along with confidence intervals, which appear at a glance to be in reverse order. Based on our calculations, the standard errors and confidence intervals do not equate. Please clarify which are the correct values to be used, and whether the presented standard errors in Table 5-7 are applied to the log utility values.**

We would like to thank the ERG for flagging this error in the company submission. The ERG is correct that the upper and lower bounds of the 95% confidence intervals (CIs) for the utility values reported in Table 5-17 of the company submission are in reverse order, and that these 95% CI values were calculated incorrectly.

We have corrected these 95% CIs for the utility values, as reported in Table C-1 below. These corrected 95% CIs were calculated using the means and SEs for the predicted utility values from the GLM/GEE model (as reported in Table 5-7 of the company submission), and assuming lognormal distributions for the disutilities versus perfect health to ensure that utility values greater than 1.0 are not sampled in the probabilistic sensitivity analyses. The corrected 95% CIs are wider than those originally reported in the company submission.

**Table C-1 Corrected 95% CIs for utility values used in the model**

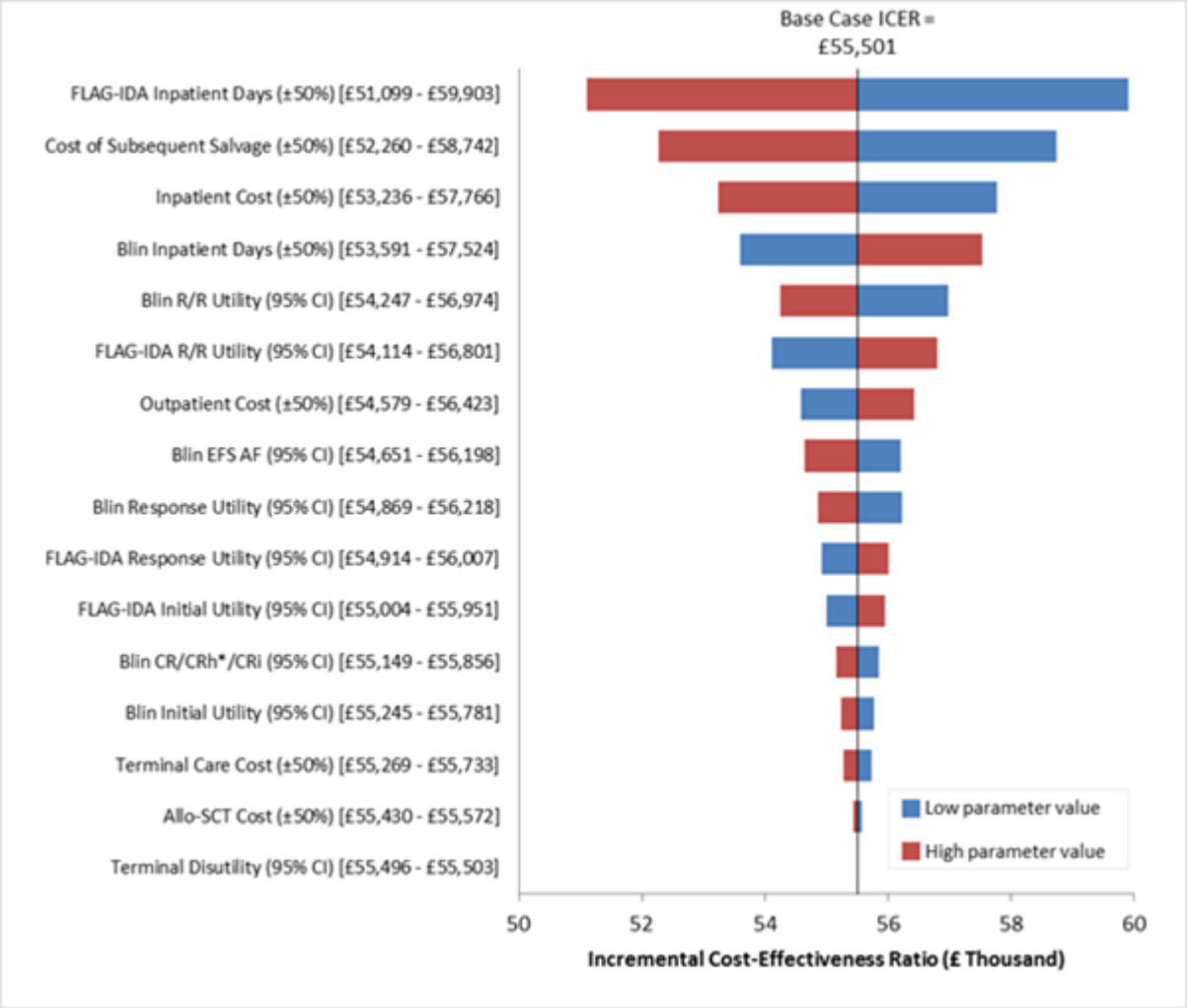
| Variable | Value | Measurement of uncertainty and distribution: 95% CI (distribution) |
|---|---|---|
| Utility Inputs | | |
| Blinatumomab | | |
| Initial | [redacted] | [redacted] (Lognormal (disutility)) |
| Response | [redacted] | [redacted] (Lognormal (disutility)) |
| Relapsed/refractory | [redacted] | [redacted] (Lognormal (disutility)) |
| FLAG-IDA | | |
| Initial | [redacted] | [redacted] (Lognormal (disutility)) |
| Response | [redacted] | [redacted] (Lognormal (disutility)) |
| Relapsed/refractory | [redacted] | [redacted] (Lognormal (disutility)) |
| Terminal decrement | [redacted] | [redacted] (Lognormal) |
| CI, confidence interval; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin | | |

This correction to the 95% CIs for the utility values has no material impact on the results of the probabilistic sensitivity analysis. At a willingness-to-pay threshold of £50,000 per QALY

gained, and with the blinatumomab simple PAS discount incorporated, the probability that blinatumomab is cost-effective in the overall TOWER trial population is estimated to be 33.4% with this correction implemented versus 35.2% as originally reported in the company submission.

An updated tornado plot for the deterministic sensitivity analyses using the corrected 95% CIs for the utility values is provided in Figure C-1 for the overall TOWER population with the blinatumomab simple PAS discount incorporated. Due to the modification to the range over which the utility values are evaluated, the model appears to be more sensitive to these parameters than originally reported in the company submission.

**Figure C-1 Deterministic sensitivity analyses tornado diagram on ICER for blinatumomab vs. FLAG-IDA with corrected 95% CIs for utility values used in the model (excluding OS treatment effect) (TOWER, FAS) – <u>with blinatumomab PAS</u>**




AF, accelerated failure; allo-SCT, allogenic stem cell transplant; Blin, blinatumomab; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ; PAS, patient access scheme; R/R, relapsed/refractory

**C3 (PRIORITY QUESTION): The company suggested that adverse events were not modelled explicitly as they would have been captured in the EORTC QLQ-C30, and costs for adverse events were assumed to be captured in inpatient and outpatient care. Please state the frequency of grade 3 or higher adverse events occurring in post-treatment follow-up.**

Data on post-treatment AEs in TOWER were collected during the 30-day post-treatment safety follow-up period only. Collecting data on AEs beyond this 30-day period would have been challenging and such data would be very difficult to interpret since many patients will have gone on to receive subsequent treatment off-study (including treatment with other anti-cancer therapies and allo-SCT). Given the short half-life of blinatumomab and its targeted mechanism of action, there is no reason to expect occurrence of AEs that are related to treatment after the 30-day safety follow-up period.

A summary of the incidence of ≥ Grade 3 AEs occurring during the 30-day post-treatment safety follow-up period is reported below in Table C-2. For brevity, only individual AEs occurring in ≥ 1% patients in the blinatumomab arm are reported. Given that the overall incidence of ≥ Grade 3 AEs in this post-treatment period was substantially higher in the SOC chemotherapy arm than in the blinatumomab arm ([redacted] % vs. [redacted] %), not explicitly modelling post-treatment AEs in the cost-effectiveness analysis is a potentially conservative approach.

**Table C-2 Summary of ≥ Grade 3 post-treatment adverse events among patients who ended treatment occurring in ≥ 1% patients in the blinatumomab arm (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = [redacted]) n (%) |
|---|---|---|
| Any ≥ Grade 3 AE occurring during the safety follow-up period | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Febrile neutropaenia | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Multi-organ failure | [redacted] | [redacted] |
| Bacterial sepsis | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |
| Abdominal pain | [redacted] | [redacted] |
| Bone pain | [redacted] | [redacted] |
| Bronchopulmonary aspergillosis | [redacted] | [redacted] |
| Gastrointestinal haemorrhage | [redacted] | [redacted] |
| Neutrophil count decreased | [redacted] | [redacted] |
| Seizure | [redacted] | [redacted] |
| Tumour lysis syndrome | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = [redacted]) n (%) |
|---|---|---|
| References: Amgen data on file, 2017[4]<br><br>Note: Adverse events occurred between the date treatment stopped until the end of the 30-day post-treatment safety follow-up period or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm<br><br>AE, adverse event; SAS, safety analysis set; SOC, standard of care. | | |

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# Appendix A – Additional subgroup analyses of TOWER safety data by intended SOC chemotherapy regimen at randomisation

**Table Appendix A-1 Summary of the most common treatment-emergent AEs (≥ 10% in either arm) in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Any treatment-emergent AE | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] |
| Neutropenia | [redacted] | [redacted] |
| Febrile neutropenia | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] |
| Cytokine release syndrome | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] |
| Cough | [redacted] | [redacted] |
| Oedema peripheral | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] |
| Pain in extremity | [redacted] | [redacted] |
| Device related infection | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| Hypomagnesaemia | [redacted] | [redacted] |
| Upper respiratory tract infection | [redacted] | [redacted] |
| Insomnia | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] |
| Constipation | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |
| Decreased appetite | [redacted] | [redacted] |
| Rash | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] |
| Epistaxis | [redacted] | [redacted] |
| Neutrophil count decreased | [redacted] | [redacted] |
| Platelet count decreased | [redacted] | [redacted] |
| Stomatitis | [redacted] | [redacted] |
| Dizziness | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Pneumonia | [redacted] | [redacted] |
| Chills | [redacted] | [redacted] |
| Hypertension | [redacted] | [redacted] |
| Abdominal pain | [redacted] | [redacted] |
| Blood bilirubin increased | [redacted] | [redacted] |
| Hypocalcaemia | [redacted] | [redacted] |
| Hypoalbuminaemia | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-2 Summary of the most common treatment-emergent AEs (≥ 10% in either arm) in the subgroup of patients intended to receive clofarabine or a clofarabine based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Any treatment-emergent AE | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] |
| Oedema peripheral | [redacted] | [redacted] |
| Constipation | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] |
| Hypotension | [redacted] | [redacted] |
| Alanine aminotransferase increased | [redacted] | [redacted] |
| Febrile neutropaenia | [redacted] | [redacted] |
| Hypomagnesaemia | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| Hyperglycaemia | [redacted] | [redacted] |
| Hypertension | [redacted] | [redacted] |
| Abdominal pain | [redacted] | [redacted] |
| Chills | [redacted] | [redacted] |
| Cough | [redacted] | [redacted] |
| Insomnia | [redacted] | [redacted] |
| Tremor | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] |
| Bone pain | [redacted] | [redacted] |
| Hypoalbuminaemia | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Aspartate aminotransferase increased | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] |
| Blood bilirubin increased | [redacted] | [redacted] |
| Pain in extremity | [redacted] | [redacted] |
| Platelet count decreased | [redacted] | [redacted] |
| Tachycardia | [redacted] | [redacted] |
| Anxiety | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Decreased appetite | [redacted] | [redacted] |
| Hypocalcaemia | [redacted] | [redacted] |
| Mucosal inflammation | [redacted] | [redacted] |
| Oral herpes | [redacted] | [redacted] |
| Pancytopenia | [redacted] | [redacted] |
| Rash | [redacted] | [redacted] |
| White blood cell count decreased | [redacted] | [redacted] |
| Arthralgia | [redacted] | [redacted] |
| Fluid retention | [redacted] | [redacted] |
| Stomatitis | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Chest pain | [redacted] | [redacted] |
| Dysphagia | [redacted] | [redacted] |
| Dyspnoea | [redacted] | [redacted] |
| Leukopenia | [redacted] | [redacted] |
| Mouth haemorrhage | [redacted] | [redacted] |
| Neutrophil count decreased | [redacted] | [redacted] |
| Abdominal distension | [redacted] | [redacted] |
| Confusional state | [redacted] | [redacted] |
| Dysuria | [redacted] | [redacted] |
| Petechiae | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Sinus tachycardia | [redacted] | [redacted] |
| Sinusitis | [redacted] | [redacted] |
| Ascites | [redacted] | [redacted] |
| Atelectasis | [redacted] | [redacted] |
| Erythema | [redacted] | [redacted] |
| Faecal incontinence | [redacted] | [redacted] |
| Hepatomegaly | [redacted] | [redacted] |
| Liver function test abnormal | [redacted] | [redacted] |
| Metabolic acidosis | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-3 Summary of the most common serious treatment-emergent AEs (≥ 2% in either arm) in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Any serious treatment-emergent AE | [redacted] | [redacted] |
| Febrile neutropaenia | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Overdose | [redacted] | [redacted] |
| Device related infection | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Cytokine release syndrome | [redacted] | [redacted] |
| Accidental overdose | [redacted] | [redacted] |
| Bacterial sepsis | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Neutropaenic sepsis | [redacted] | [redacted] |
| Staphylococcal infection | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Lactic acidosis | [redacted] | [redacted] |
| Lung infection | [redacted] | [redacted] |
| Multi-organ failure | [redacted] | [redacted] |
| Pneumonia fungal | [redacted] | [redacted] |
| Pseudomonas infection | [redacted] | [redacted] |
| Respiratory failure | [redacted] | [redacted] |
| Agranulocytosis | [redacted] | [redacted] |
| Bacteraemia | [redacted] | [redacted] |
| Brain abscess | [redacted] | [redacted] |
| Central nervous system abscess | [redacted] | [redacted] |
| Cholestasis | [redacted] | [redacted] |
| Citrobacter sepsis | [redacted] | [redacted] |
| Device related sepsis | [redacted] | [redacted] |
| Enterococcal bacteraemia | [redacted] | [redacted] |
| Enterococcal infection | [redacted] | [redacted] |
| Fungal infection | [redacted] | [redacted] |
| Gastrointestinal inflammation | [redacted] | [redacted] |
| Generalised tonic-clonic seizure | [redacted] | [redacted] |
| Hemiplegia | [redacted] | [redacted] |
| Hepatosplenic candidiasis | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Hyperkalaemia | [redacted] | [redacted] |
| Hypoglycaemia | [redacted] | [redacted] |
| Hypotension | [redacted] | [redacted] |
| Leukopenia | [redacted] | [redacted] |
| Lung infiltration | [redacted] | [redacted] |
| Metabolic acidosis | [redacted] | [redacted] |
| Pseudomonal sepsis | [redacted] | [redacted] |
| Rhinovirus infection | [redacted] | [redacted] |
| Seizure | [redacted] | [redacted] |
| Soft tissue infection | [redacted] | [redacted] |
| Streptococcal sepsis | [redacted] | [redacted] |
| Systemic candida | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-4 Summary of the most common serious treatment-emergent AEs (≥ 2% in either arm) in the subgroup of patients intended to receive clofarabine or a clofarabine based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Any serious treatment-emergent AE | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Bronchopulmonary aspergillosis | [redacted] | [redacted] |
| Febrile neutropenia | [redacted] | [redacted] |
| Pancytopenia | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Abscess fungal | [redacted] | [redacted] |
| Acute hepatic failure | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Haemorrhage intracranial | [redacted] | [redacted] |
| Mouth haemorrhage | [redacted] | [redacted] |
| Pancreatitis | [redacted] | [redacted] |
| Peripheral artery thrombosis | [redacted] | [redacted] |
| Pneumonia fungal | [redacted] | [redacted] |
| Shock | [redacted] | [redacted] |
| Supraventricular tachycardia | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-5 Summary of the most common treatment-emergent AEs related to IP (≥ 2% in either arm) in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Any treatment-emergent AE related to IP[a] | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Cytokine release syndrome | [redacted] | [redacted] |
| Neutropenia | [redacted] | [redacted] |
| Febrile neutropenia | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] |
| Alanine aminotransferase increased | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |
| Hepatic enzyme increased | [redacted] | [redacted] |
| Pain in extremity | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Aspartate aminotransferase increased | [redacted] | [redacted] |
| Gamma-glutamyltransferase increased | [redacted] | [redacted] |
| Tremor | [redacted] | [redacted] |
| Hypogammaglobulinaemia | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] |
| Neutrophil count decreased | [redacted] | [redacted] |
| Paraesthesia | [redacted] | [redacted] |
| Platelet count decreased | [redacted] | [redacted] |
| Tumour lysis syndrome | [redacted] | [redacted] |
| Blood bilirubin increased | [redacted] | [redacted] |
| Blood immunoglobulin G decreased | [redacted] | [redacted] |
| Dysarthria | [redacted] | [redacted] |
| Hypomagnesaemia | [redacted] | [redacted] |
| Hypophosphataemia | [redacted] | [redacted] |
| Myalgia | [redacted] | [redacted] |
| Neuropathy peripheral | [redacted] | [redacted] |
| Oedema peripheral | [redacted] | [redacted] |
| Rash | [redacted] | [redacted] |
| Somnolence | [redacted] | [redacted] |
| Tachycardia | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |
| Anxiety | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Arthralgia | [redacted] | [redacted] |
| C-reactive protein increased | [redacted] | [redacted] |
| Chills | [redacted] | [redacted] |
| Constipation | [redacted] | [redacted] |
| Decreased appetite | [redacted] | [redacted] |
| Hyperbilirubinaemia | [redacted] | [redacted] |
| Hyperkalaemia | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Urinary tract infection | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] |
| Atrial fibrillation | [redacted] | [redacted] |
| Cellulitis | [redacted] | [redacted] |
| Contusion | [redacted] | [redacted] |
| Cough | [redacted] | [redacted] |
| Dyspnoea | [redacted] | [redacted] |
| Hyperhidrosis | [redacted] | [redacted] |
| Leukopenia | [redacted] | [redacted] |
| Lymphocyte count decreased | [redacted] | [redacted] |
| Mucosal inflammation | [redacted] | [redacted] |
| Neutropenic sepsis | [redacted] | [redacted] |
| Pseudomonas infection | [redacted] | [redacted] |
| Staphylococcal infection | [redacted] | [redacted] |
| Stomatitis | [redacted] | [redacted] |
| Abdominal distension | [redacted] | [redacted] |
| Abdominal pain | [redacted] | [redacted] |
| Abdominal pain upper | [redacted] | [redacted] |
| Agranulocytosis | [redacted] | [redacted] |
| Altered state of consciousness | [redacted] | [redacted] |
| Anal fissure | [redacted] | [redacted] |
| Anal haemorrhage | [redacted] | [redacted] |
| Bacteraemia | [redacted] | [redacted] |
| Bacterial sepsis | [redacted] | [redacted] |
| Biliary sepsis | [redacted] | [redacted] |
| Blood alkaline phosphatase increased | [redacted] | [redacted] |
| Blood magnesium decreased | [redacted] | [redacted] |
| Blood urine present | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Bone pain | [redacted] | [redacted] |
| Candiduria | [redacted] | [redacted] |
| Cerebral haematoma | [redacted] | [redacted] |
| Cholecystitis | [redacted] | [redacted] |
| Citrobacter sepsis | [redacted] | [redacted] |
| Cystitis haemorrhagic | [redacted] | [redacted] |
| Dehydration | [redacted] | [redacted] |
| Depressed level of consciousness | [redacted] | [redacted] |
| Device occlusion | [redacted] | [redacted] |
| Device related infection | [redacted] | [redacted] |
| Device related sepsis | [redacted] | [redacted] |
| Diabetes mellitus | [redacted] | [redacted] |
| Dizziness | [redacted] | [redacted] |
| Dry mouth | [redacted] | [redacted] |
| Dysgeusia | [redacted] | [redacted] |
| Dyspepsia | [redacted] | [redacted] |
| Dysphagia | [redacted] | [redacted] |
| Enteritis | [redacted] | [redacted] |
| Enterococcal bacteraemia | [redacted] | [redacted] |
| Enterococcal infection | [redacted] | [redacted] |
| Enterocolitis | [redacted] | [redacted] |
| Epistaxis | [redacted] | [redacted] |
| Escherichia bacteraemia | [redacted] | [redacted] |
| Escherichia urinary tract infection | [redacted] | [redacted] |
| Eye pain | [redacted] | [redacted] |
| Fungal infection | [redacted] | [redacted] |
| Gastrointestinal inflammation | [redacted] | [redacted] |
| Gastrointestinal necrosis | [redacted] | [redacted] |
| Gastrooesophageal reflux disease | [redacted] | [redacted] |
| Haematemesis | [redacted] | [redacted] |
| Haemorrhage | [redacted] | [redacted] |
| Haemorrhoids | [redacted] | [redacted] |
| Hyperphosphataemia | [redacted] | [redacted] |
| Hypertension | [redacted] | [redacted] |
| Hypocalcaemia | [redacted] | [redacted] |
| Hypoglycaemia | [redacted] | [redacted] |
| Hypotension | [redacted] | [redacted] |
| Immunodeficiency common variable | [redacted] | [redacted] |
| Lactic acidosis | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Left ventricular dysfunction | [redacted] | [redacted] |
| Lethargy | [redacted] | [redacted] |
| Leukocytosis | [redacted] | [redacted] |
| Lip ulceration | [redacted] | [redacted] |
| Liver function test abnormal | [redacted] | [redacted] |
| Lung infiltration | [redacted] | [redacted] |
| Lymph node pain | [redacted] | [redacted] |
| Mouth ulceration | [redacted] | [redacted] |
| Multi-organ failure | [redacted] | [redacted] |
| Musculoskeletal pain | [redacted] | [redacted] |
| Neutropenic colitis | [redacted] | [redacted] |
| Ocular hyperaemia | [redacted] | [redacted] |
| Oedema | [redacted] | [redacted] |
| Oral candidiasis | [redacted] | [redacted] |
| Oropharyngeal pain | [redacted] | [redacted] |
| Pain | [redacted] | [redacted] |
| Paraesthesia oral | [redacted] | [redacted] |
| Periodontal disease | [redacted] | [redacted] |
| Petechiae | [redacted] | [redacted] |
| Pharyngeal erythema | [redacted] | [redacted] |
| Pneumatosis | [redacted] | [redacted] |
| Presyncope | [redacted] | [redacted] |
| Pseudomonal bacteraemia | [redacted] | [redacted] |
| Pseudomonal sepsis | [redacted] | [redacted] |
| Pulmonary mass | [redacted] | [redacted] |
| Rales | [redacted] | [redacted] |
| Rash erythematous | [redacted] | [redacted] |
| Rash generalised | [redacted] | [redacted] |
| Reticulocyte count decreased | [redacted] | [redacted] |
| Rhinorrhoea | [redacted] | [redacted] |
| Rhinovirus infection | [redacted] | [redacted] |
| Scleral disorder | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Sinusitis | [redacted] | [redacted] |
| Skin mass | [redacted] | [redacted] |
| Soft tissue infection | [redacted] | [redacted] |
| Splenomegaly | [redacted] | [redacted] |
| Staphylococcal bacteraemia | [redacted] | [redacted] |
| Staphylococcal sepsis | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Streptococcal sepsis | [redacted] | [redacted] |
| Subcutaneous abscess | [redacted] | [redacted] |
| Systemic candida | [redacted] | [redacted] |
| Type 2 diabetes mellitus | [redacted] | [redacted] |
| Urinary incontinence | [redacted] | [redacted] |
| Vision blurred | [redacted] | [redacted] |
| White blood cell count decreased | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

[a] As deemed by the study investigator

AE, adverse event; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; IP, investigational product; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-6 Summary of the most common treatment-emergent AEs related to IP (≥ 2% in either arm) in the subgroup of patients intended to receive clofarabine or a clofarabine based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Any treatment-emergent AE related to IP[a] | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Neutropaenia | [redacted] | [redacted] |
| Febrile neutropaenia | [redacted] | [redacted] |
| Thrombocytopaenia | [redacted] | [redacted] |
| Tremor | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Chills | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] |
| Alanine aminotransferase increased | [redacted] | [redacted] |
| Blood bilirubin increased | [redacted] | [redacted] |
| Hypogammaglobulinaemia | [redacted] | [redacted] |
| Aspartate aminotransferase increased | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] |
| Bone pain | [redacted] | [redacted] |
| Cytokine release syndrome | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] |
| Myalgia | [redacted] | [redacted] |
| Oedema peripheral | [redacted] | [redacted] |
| Platelet count decreased | [redacted] | [redacted] |
| Stomatitis | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] |
| White blood cell count decreased | [redacted] | [redacted] |
| Abdominal pain | [redacted] | [redacted] |
| Constipation | [redacted] | [redacted] |
| Cough | [redacted] | [redacted] |
| Hypoaesthesia | [redacted] | [redacted] |
| Hypocalcaemia | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] |
| Hyponatraemia | [redacted] | [redacted] |
| Hypotension | [redacted] | [redacted] |
| Leukopenia | [redacted] | [redacted] |
| Muscular weakness | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Neutrophil count decreased | [redacted] | [redacted] |
| Pancytopenia | [redacted] | [redacted] |
| Paraesthesia | [redacted] | [redacted] |
| Pruritus | [redacted] | [redacted] |
| Rash maculo-papular | [redacted] | [redacted] |
| Tachycardia | [redacted] | [redacted] |
| Confusional state | [redacted] | [redacted] |
| Decreased appetite | [redacted] | [redacted] |
| Dysarthria | [redacted] | [redacted] |
| Hypomagnesaemia | [redacted] | [redacted] |
| Immunoglobulins decreased | [redacted] | [redacted] |
| Lymphocyte count decreased | [redacted] | [redacted] |
| Mouth haemorrhage | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Abdominal discomfort | [redacted] | [redacted] |
| Abdominal distension | [redacted] | [redacted] |
| Abdominal pain upper | [redacted] | [redacted] |
| Abscess fungal | [redacted] | [redacted] |
| Acute hepatic failure | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Amylase increased | [redacted] | [redacted] |
| Anxiety | [redacted] | [redacted] |
| Ascites | [redacted] | [redacted] |
| Atelectasis | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] |
| Blood alkaline phosphatase increased | [redacted] | [redacted] |
| Catheter site infection | [redacted] | [redacted] |
| Chest pain | [redacted] | [redacted] |
| Cholecystitis | [redacted] | [redacted] |
| Clostridium difficile colitis | [redacted] | [redacted] |
| Coagulopathy | [redacted] | [redacted] |
| Cytomegalovirus infection | [redacted] | [redacted] |
| Device related infection | [redacted] | [redacted] |
| Diarrhoea infectious | [redacted] | [redacted] |
| Dysphagia | [redacted] | [redacted] |
| Dyspnoea | [redacted] | [redacted] |
| Ecchymosis | [redacted] | [redacted] |
| Epistaxis | [redacted] | [redacted] |
| Erythema | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Faecal incontinence | [redacted] | [redacted] |
| Fluid retention | [redacted] | [redacted] |
| Gamma-glutamyltransferase increased | [redacted] | [redacted] |
| Gastroenteritis | [redacted] | [redacted] |
| Gastrointestinal disorder | [redacted] | [redacted] |
| Gastrooesophageal reflux disease | [redacted] | [redacted] |
| Generalised oedema | [redacted] | [redacted] |
| Hepatomegaly | [redacted] | [redacted] |
| Human herpesvirus 6 infection | [redacted] | [redacted] |
| Hypercapnia | [redacted] | [redacted] |
| Hyperkalaemia | [redacted] | [redacted] |
| Hypoalbuminaemia | [redacted] | [redacted] |
| Hypophosphataemia | [redacted] | [redacted] |
| Lethargy | [redacted] | [redacted] |
| Lipase increased | [redacted] | [redacted] |
| Liver function test abnormal | [redacted] | [redacted] |
| Lung infiltration | [redacted] | [redacted] |
| Malaise | [redacted] | [redacted] |
| Metabolic acidosis | [redacted] | [redacted] |
| Mucosal inflammation | [redacted] | [redacted] |
| Multi-organ failure | [redacted] | [redacted] |
| Muscle twitching | [redacted] | [redacted] |
| Neutropaenic colitis | [redacted] | [redacted] |
| Oesophagitis | [redacted] | [redacted] |
| Oral candidiasis | [redacted] | [redacted] |
| Pain in extremity | [redacted] | [redacted] |
| Pain in jaw | [redacted] | [redacted] |
| Pancreatitis | [redacted] | [redacted] |
| Pericardial effusion | [redacted] | [redacted] |
| Petechiae | [redacted] | [redacted] |
| Pleural effusion | [redacted] | [redacted] |
| Pneumonia fungal | [redacted] | [redacted] |
| Rash macular | [redacted] | [redacted] |
| Rash pruritic | [redacted] | [redacted] |
| Salivary hypersecretion | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Shock | [redacted] | [redacted] |
| Sinus tachycardia | [redacted] | [redacted] |

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Sinusitis | [redacted] | [redacted] |
| Splenomegaly | [redacted] | [redacted] |
| Streptococcal bacteraemia | [redacted] | [redacted] |
| Subarachnoid haemorrhage | [redacted] | [redacted] |
| Supraventricular tachycardia | [redacted] | [redacted] |
| Tachypnoea | [redacted] | [redacted] |
| Toxic skin eruption | [redacted] | [redacted] |
| Urinary incontinence | [redacted] | [redacted] |
| Weight increased | [redacted] | [redacted] |
| White blood cell count | [redacted] | [redacted] |
| X-ray gastrointestinal tract abnormal | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

[a] As deemed by the study investigator

AE, adverse event; IP, investigational product; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-7 Summary of treatment-emergent AEs leading to treatment discontinuation in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Any treatment-emergent AE leading to treatment discontinuation | [redacted] | [redacted] |
| Acute myocardial infarction | [redacted] | [redacted] |
| Blood bilirubin increased | [redacted] | [redacted] |
| Bone pain | [redacted] | [redacted] |
| Cognitive disorder | [redacted] | [redacted] |
| Completed suicide | [redacted] | [redacted] |
| Fall | [redacted] | [redacted] |
| Fungal sepsis | [redacted] | [redacted] |
| Haematoma | [redacted] | [redacted] |
| Histiocytosis haematophagic | [redacted] | [redacted] |
| Leukoencephalopathy | [redacted] | [redacted] |
| Lung infection | [redacted] | [redacted] |
| Neutropaenic sepsis | [redacted] | [redacted] |
| Progressive multifocal leukoencephalopathy | [redacted] | [redacted] |
| Tumour lysis syndrome | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Agranulocytosis | [redacted] | [redacted] |
| Altered state of consciousness | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |
| Enterococcal bacteraemia | [redacted] | [redacted] |
| Enterococcal infection | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Systemic candida | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-8 Summary of treatment-emergent AEs leading to treatment discontinuation in the subgroup of patients intended to receive clofarabine or a clofarabine based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Any treatment-emergent AE leading to treatment discontinuation | [redacted] | [redacted] |
| Graft versus host disease in liver | [redacted] | [redacted] |
| Haemoptysis | [redacted] | [redacted] |
| Histiocytosis haematophagic | [redacted] | [redacted] |
| Lymphadenopathy | [redacted] | [redacted] |
| Mucormycosis | [redacted] | [redacted] |
| Pancytopaenia | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] |
| Respiratory failure | [redacted] | [redacted] |
| Status epilepticus | [redacted] | [redacted] |
| Stridor | [redacted] | [redacted] |
| Tremor | [redacted] | [redacted] |
| Febrile neutropaenia | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-9 Summary of fatal treatment-emergent AEs in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 49) n (%) |
|---|---|---|
| Any fatal treatment-emergent AE | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Fungal sepsis | [redacted] | [redacted] |
| Neutropenic sepsis | [redacted] | [redacted] |
| Cerebral haemorrhage | [redacted] | [redacted] |
| Completed suicide | [redacted] | [redacted] |
| Febrile bone marrow aplasia | [redacted] | [redacted] |
| Leukaemic infiltration extramedullary | [redacted] | [redacted] |
| Lung infection | [redacted] | [redacted] |
| Multi-organ failure | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Respiratory failure | [redacted] | [redacted] |
| Acute kidney injury | [redacted] | [redacted] |
| Bacteraemia | [redacted] | [redacted] |
| Brain abscess | [redacted] | [redacted] |
| Enterococcal infection | [redacted] | [redacted] |
| Metabolic acidosis | [redacted] | [redacted] |
| Pseudomonas infection | [redacted] | [redacted] |
| Systemic candida | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; FLAG, fludarabine, cytarabine, granulocyte colony stimulating factor; SAS, safety analysis set; SOC, standard of care.

**Table Appendix A-10 Summary of fatal treatment-emergent AEs in the subgroup of patients intended to receive clofarabine or a clofarabine based regimen at randomisation (TOWER, SAS)**

| | Blinatumomab (N = [redacted]) n (%) | SOC chemotherapy (N = 19) n (%) |
|---|---|---|
| Any fatal treatment-emergent AE | [redacted] | [redacted] |
| Acute respiratory failure | [redacted] | [redacted] |
| Bacterial sepsis | [redacted] | [redacted] |
| Bronchopulmonary aspergillosis | [redacted] | [redacted] |
| Leukocytosis | [redacted] | [redacted] |
| Mucormycosis | [redacted] | [redacted] |
| Pancytopenia | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Respiratory arrest | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] |
| Septic shock | [redacted] | [redacted] |
| Haemorrhage intracranial | [redacted] | [redacted] |
| Pneumonia fungal | [redacted] | [redacted] |

Reference: Amgen data on file, 2017[4]

Note: Treatment-emergent adverse events occurred between the date treatment started until the date treatment stopped plus 30 days or the data cut-off date, whichever came first. Adverse events were coded using MedDRA version 18.1. Preferred terms are presented in descending order of subject incidence in the blinatumomab arm.

AE, adverse event; SAS, safety analysis set; SOC, standard of care.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Patient/carer organisation submission (STA)

## Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

## *1. About you and your organisation*

**Your name:** [redacted]

**Name of your organisation:** Leukaemia CARE

**Your position in the organisation:** [redacted]

**Brief description of the organisation:**

Leukaemia CARE is a national blood cancer support charity – founded in 1967 and first registered with the Charity Commission in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. We support people affected by leukaemia, lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, myeloproliferative disorders and aplastic anaemia.

Our current membership database stands at approximately 18,500. This includes patients, carers, healthcare professionals etc.

Leukaemia CARE offers this care and support through our head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line
- Live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception over 25 years ago our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes

emotional effects of a blood cancer and help for those caring for a patient. Our focus is purely on information and support for everyone affected by a diagnosis of blood cancer. See http://www.leukaemiacare.org.uk

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a blood cancer to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia CARE receives funding from a wide range of pharmaceutical companies, but in total those funds do not exceed 15% of our total income. Any funds received from the pharmaceutical industry are received and dispersed in accordance with the ABPI Code of Practice and the Leukaemia CARE code of practice. Our Code of Practice is a commitment undertaken voluntarily by Leukaemia CARE to adhere to specific policies that regulate our involvement with the pharmaceutical industry.

A copy of our code of practice is available at:

- http://www.leukaemiacare.org.uk/resources/code-of-practice

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:** N/A

## *2. Living with the condition*

**What is it like to live with the condition or what do carers experience when caring for someone with the condition?**

Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. Like most blood cancers ALL is strongly correlated to age, although unusually the peak incidence is in children. There is a second peak incidence in patients over the age of 65. Five year survival outcomes vary greatly by age, from over 90% in the under 14s, 66% in those aged 15-24, less than 40% in those aged 25-64 and less than 15% in those aged 64 or

older. As such, the prognosis for adult patients with the condition is extremely poor.

The most common signs and symptoms are caused by the bone marrow being unable to produce enough normal blood cells. These include anaemia (due to lack of red blood cells), weakness, tiredness, shortness of breath, light-headedness, palpitations, frequent and persistent infections (due to lack of normal white blood cells), purpura (small bruises in skin), nosebleeds, bleeding gums, bleeding and bruising (due to lack of platelets), fever and sweating. Some patients may also have an enlarged liver, spleen or enlarged lymph nodes. Being diagnosed with ALL can also have a huge emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression.

Due to its relative rarity and non-specific symptoms, patients are usually diagnosed with ALL following the onset of symptoms, when it has often progressed significantly. NCIN conducted a report of patients 'Routes to Diagnosis' which showed that 64% of ALL patients are diagnosed following an emergency presentation (emergency GP referral or A&E). This figure was the highest of any cancer type in the report. Diagnosis at an advanced stage, along with a lack of effective treatment options, has a large impact on their prognosis.

As commented above, being diagnosed with ALL can also have a huge emotional impact, prompting both patients and their families to experience a range of complex thoughts and emotions, requiring emotional support. Many of these feelings can have a profound impact on both their physical and psychological wellbeing.

By the time patients reach this setting (relapsed or refractory) most will be extremely ill, having undergone (and not responded well to) highly toxic treatment. With patients facing such a poor prognosis, this does not affect a patient in isolation but instead creates a "ripple effect". This can place huge emotional strain on families and friends, many of whom may be affected by the diagnosis. 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.

## *3. Current practice in treating the condition*

**Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.**

Whilst survival is a key treatment outcome for patients, improved quality of life is also highly important. Any treatment that offers reduced side effects or positively impacts on patient experience, thus improving patients' quality of life, would be strongly welcomed.

**What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?**

Patients with ALL would often initially be treated with multi-agent chemotherapy or stem cell transplantation. A form of asparaginase (typical clinical practice would be the use of pegaspargase) would be part of the multi-agent chemotherapy regimen. As blinatumomab is indicated for adult patients with Philadelphia chromosome negative relapsed or refractory ALL, we have limited our response to this group of patients.

By the time they reach this setting most patients will be extremely ill, having undergone and not responded well to toxic chemotherapy treatment. Typically, the vast majority of patients (over 90%) will die from their disease within a short period of time, usually within a few months because there are such limited options for relapsed or refractory patients. For patients treated with chemotherapy at first relapse the median overall survival is around 5-9 months, for those who have failed multiple lines of therapy overall survival decreases to around 3-6 months. With the currently available options, the five-year overall survival rate for relapsed patients is less than 10%, which has been in part attributed to a lack of effective treatment agents. A small minority of patients may be eligible for stem cell transplant or clinical trials. Beyond this, for those who can tolerate it (given that the second peak incident rate is in patients over 65) second line options are likely to be limited to highly toxic salvage chemotherapy (including FLAG-Ida, Hyper-CVAD, high dose cytarabine or methotrexate with asparaginase). The majority of patients treated with chemotherapy would spend around half of their time in hospital, managing the complications of the disease, the toxicity of treatment and

potential comorbidities. In this setting, many patients (particularly older or less fit adults) would be unable to tolerate these aggressive options, so no further active therapeutic options would be available to them. As such, there is an urgent need for these patients in this setting to access further treatment options.

## *4. What do patients or carers consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

**Please list the benefits that patients or carers expect to gain from using the treatment being appraised.**

Blinatumomab is a novel therapeutic option that appears to offer durable responses in a heavily pre-treated population. If recommended, it would offer an additional option to patients, in an area where their options are extremely limited. A study of 609 adults after relapse of ALL (Fielding et al. Blood. 2006; 944-950) concluded “that most adults with recurring ALL, whatever their prior treatment, cannot be rescued using currently available therapies.” They recommended that “every eligible adult with recurring ALL be included in a prospective study involving novel therapeutic agents." These statements demonstrate the urgent need for patients to access any treatment that has the potential to improve their prognosis.

In clinical trials blinatumomab demonstrated potential to improve remission rates and survival in a difficult to treat patient population (compared to a historical analysis of patients treated with salvage chemotherapy). In addition to this, a key benefit of blinatumomab is its potential as a 'bridge to transplant' (enabling around 40% of responders to subsequently receive a stem cell transplant). As SCT remains the only potentially curative option for these patients, this is a key benefit which should not be overlooked.

In addition to this, blinatumomab offers a number of key quality of life benefits, improving patient experience and enabling them to live a more normal life. The administration schedule of blinatumomab (infusion over four weeks, followed by a two weeks off treatment before infusion begins again) offers patients the opportunity to benefit from a 'treatment-free' period. It also offers some patients the option to be treated in the outpatient setting, enabling them to spend time with their families and avoid spending significant periods of time in hospital.

**Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.**

Please see previous response.

**If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.**

N/A

## *5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?*

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

**Please list any concerns patients or carers have about current NHS treatments in England.**

As already indicated, treatment options for relapsed or refractory ALL patients are very limited and few patients would be fit enough to withstand a stem cell transplant. For those who are able to tolerate it, highly toxic salvage chemotherapy would be the next line of treatment. In this setting, however, many patients would be unable to tolerate these aggressive options, so no further active therapeutic options would be available to them.

**Please list any concerns patients or carers have about the treatment being appraised.**

Whilst blinatumomab is an innovative treatment, that has the potential to offer patients in the proposed setting significant benefits and improve outcome, it also has some disadvantages.

The requirement for blinatumomab to be given via continuous intravenous infusion (due to small molecular weight and rapid clearance from circulation) may be cumbersome for some patients, although this inconvenience must be balanced against the benefit offered by allowing some patients to be treated in an outpatient setting (proffering an improvement in quality of life).

Secondly, fatal adverse events (mostly infection related) occurred in 12% of patients. Other side effects included infusion-related reactions, pyrexia, cytokine release syndrome (CRS) and neurologic events. Whilst a risk of infection may occur, it is difficult to determine whether this is related to the effects of blinatumomab treatment or the underlying ALL. As comparative options for patients in this setting are either highly toxic or demonstrate limited results, the alternative treatment may be considered best supportive care. We would not consider this to be a viable option when directly compared to the potential benefits of blinatumomab.

Finally, despite promising results in this setting, there are a number of patients who do not respond to treatment with blinatumomab (or they experience relapse). However, for those who do respond to treatment significant benefits may be offered. Against a backdrop of extremely limited options blinatumomab represents a significant step forward (as the first single-agent immunotherapy to be approved for the treatment of patients with Philadelphia chromosome negative relapsed or refractory B-cell precursor ALL).

**If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.**

N/A

## *6. Patient population*

**Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.**

Blinatumomab may be of particular benefit for less fit or frailer patients who are unable to tolerate the more aggressive comparator treatment options.

**Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.**

N/A

## *7. Research evidence on patient or carer views of the treatment*

**Is your organisation familiar with the published research literature for the treatment?**

☑ Yes ☐ No

**If you answered 'no', please skip the rest of section 7 and move on to section 8.**

**Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.**

**Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?**

**If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?**

**Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?**

☐ Yes ☐ No

**If yes, please provide references to the relevant studies.**

## *8. Equality*

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

**Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.**

The Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) has recently appraised and approved

blinatumomab for ALL patients in this setting for patients in Scotland and Wales respectively. If blinatumomab were to receive a negative recommendation from NICE then this would create an inequitable situation in terms of access across the UK.

**Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.**

## *9. Other issues*

**Do you consider the treatment to be innovative?**

☑ Yes ☐ No

**If yes, please explain what makes it significantly different from other treatments for the condition.**

As suggested above, blinatumomab is a novel therapeutic option that offers a durable response in a disease area where there is an urgent need for access to new, effective follow up treatments. Existing follow up treatments are toxic and not always preferable for patients who are usually extremely ill by this stage and have already received similar toxic treatments (that did not work).

Blinatumomab has also proven to act as a bridge to stem cell transplant (considered the only “curative” treatment for ALL) which is a very welcome result in such a hard to treat disease area.

The administration of the treatment is done intravenously (via a pump) and includes treatment free intervals. This could lead to an improved quality of life for patients during their treatment that they would not experience if treated with the comparator options.

Overall, the introduction of blinatumomab would be considered an innovative treatment in this heavily pre-treated, difficult to treat patient population (with very limited existing available treatment options.)

**Are there any other issues that you would like the Appraisal Committee to consider?**

As indicated above, being diagnosed with ALL can have a huge emotional impact on the patient but emotional strain can also be placed on the patient’s family and friends. As such, improvements in a patients’ treatment and quality of life will also have a wider impact on the lives of those close to them.

## *10. Key messages*

**In no more than 5 bullet points, please summarise the key messages of your submission.**

- Acute lymphoblastic leukaemia (ALL) is a rare, rapidly progressing form of leukaemia.
- ALL has a significant symptom burden. Common symptoms include anaemia (due to lack of red blood cells), weakness, tiredness, shortness of breath, light-headedness, palpitations, frequent and persistent infections (due to lack of normal white blood cells), purpura (small bruises in skin), nosebleeds, bleeding gums, bleeding and bruising (due to lack of platelets), fever and sweating.
- Currently available treatment options for adult patients with relapsed or refractory ALL are limited to highly toxic salvage chemotherapy for most patients, resulting in an extremely poor prognosis (overall survival is around 5-9 months at first relapse, decreasing to 3-6 months for those who have failed multiple lines of therapy). For those that cannot tolerate such therapies, treatment is limited to best supportive care. As such, there is an urgent need for access to any therapies with the potential to offer an improvement in survival prospects.
- Blinatumomab offers a number of key benefits including improved remission rates and prolonged survival in a difficult to treat patient population. Other benefits include a 'treatment-free' period, possibility of treatment in an outpatient setting (spending time at home with families rather than in hospital) and as a potential 'bridge to transplant' (enabling around 40% of responders to subsequently receive a stem cell transplant – the only curative option for these patients).
- Overall, the introduction of blinatumomab would be considered an innovative treatment in this heavily pre-treated, difficult to treat patient population (with very limited existing available treatment options.)

**Submission by NHS England re the NICE appraisal of blinatumumab in the treatment of relapsed/refractory acute lymphoblastic leukaemia (ALL)**

1. The aim of salvage treatment for relapsed/refractory ALL is to either induce a durable complete remission or to maximise the rate of subsequent high-dose chemotherapy and stem cell transplantation (SCT) [and in this case an allogeneic SCT].

2. There are two new monoclonal antibodies that have recent phase 3 evidence as to their benefit in relapsed/refractory ALL: blinatumumab in this appraisal and inotuzumab ozogamicin which is due to be appraised in May 2017. The case mix of the patients entering the 2 trials is not the same as the patients in the blinatumumab trial were more heavily pre-treated. The drugs have different modes of action, different schedules of administration (inotuzumab is much easier to deliver) and different major toxicities (cytokine release syndrome, tumour lysis syndrome and neurotoxicity with blinatumumab and veno-occlusive disease with inotuzumab).

3. The blinatumumab TOWER trial used a comparator which was a choice of 4 main chemotherapy regimens, this partially reflecting the different treatments which patients had previously received and the fact that no one salvage treatment has been shown to be superior to another.

4. NHS England notes that the trial was balanced for baseline characteristics including prior allogeneic SCT (34-35% in both arms).

5. The overall survival data for the TOWER trial is immature as there are few patients at risk beyond 12-15 months after randomisation. The key issue is where the overall survival curves truly plateau at and whether there is a difference bewteen blinatumumab and standard chemotherapy.

6. The level of cross over from the chemotherapy arm to subsequent blinatumumab was low at 6% ie cross over is unlikely to have confounded the results.

7. There is no doubt that blinatumumab significantly increased the rate of complete remission within 12 weeks of starting treatment (34% vs 16%). Of note also is that the rate of subsequent allogeneic SCT was identical at 24% in both arms. Of the 24% who underwent SCT, an absolute 14% achieved remission in the blinatumumab arm without the need for further treatment, the figure being 9% for the chemotherapy arm. Of interest is that of those patients that achieved a complete remission/a complete remission with partial haematological recovery/complete remission with incomplete haematological recovery, the rate of previous allogeneic SCT was 32%

with blinatumumab vs 15% in the chemotherapy arm. Whether this finding is a chance occurrence or reflects some interaction between blinatumumab and previous allogeneic transplantation is unknown but it cannot be assumed that blinatumumab would otherwise result in a higher rate of allogeneic SCT than that observed in the TOWER trial.

8. NHS England notes the very different time to SCT in the two arms in the TOWER trial: 11.3 mo with blinatumumab vs 3.6 mo with chemotherapy. This could have several explanations which include the potential greater duration of treatment with the additional consolidation treatment of 3 cycles of blinatumumab and blinatumumab toxicity delaying the SCT.

9. NHS England notes the high level of dropouts in the trial that mainly occurred soon after randomisation (2% vs 19%) and thus the potential bias introduced into the trial as a consequence (whichever arm this bias could be seen to favour).

10. NHS England notes the differing toxicity of blinatumumab vs that of chemotherapy. It is confident that continued experience with the use of blinatumumab would minimise the risk of cytokine release/tumour lysis syndromes, at least in specialist centres.

11. NHS England regards with some concern the ERG's assumption that patients would remain as inpatients for all 4 weeks of each of the first 2 cycles of treatment. Whilst patients will be resident in hospital for a considerable proportion of the 1st cycle of blinatumumab, not all patients will be inpatients for the full 4 weeks. The second cycle of therapy is likely to have an increased component as an outpatient as patients and treating teams become accustomed to the drug and the continuous infusions. In addition, given that up to 4 day infusions are possible, it is unlikely that any outpatient treatment will just use 1 day infusion bags. Nevertheless, the infrastructure required to deliver blinatumumab is very significant, especially as any interruption to treatment necessitates a re-start at a lower dose as an inpatient and then increased doses given subsequently.

12. NHS England notes that 10% of patients had more than 5 cycles of treatment with blinatumumab. It is aware of the marketing authorisation and would enforce the commissioning of a maximum of 5 cycles in all, should blinatumumab be recommended by NICE.

13. NHS England notes that the probabilistic ICERs are significantly higher than the deterministic ones.

14. NHS England notes that a cost effective analysis was done for those patients in the TOWER trial in whom entry into the trial occurred at 1st relapse (the trial stratified for this criterion). This subgroup comprised just under half of the trial entry. The ICER for blinatumumab vs chemotherapy was significantly less than when done for the whole trial population. It is likely that the place of blinatumumab (or inotuzumab ozogamicin for that matter) will be at first relapse for most patients although there will be some patients that would receive blinatumumab at a later stage.

15. The management of patients with relapsed/refractory ALL is a specialist practice, the numbers of patients are small and the administration of bliniatumumab is intensive and thus requires significant infrastructure to deliver safely and as conveniently as possible for patients. NHS England would therefore wish blinatumumab to be used only in large centres which regularly assess and treat such relapsed patients.

16. NHS England notes that the license for blinatumumab restricts use to patients aged 18 and over. It is aware of published data in patients <18 years old in which a 39% complete remission rate was observed after treatment with 2 cycles of blinatumumab. If NICE recommends the use of blinatumumab within its marketing authorisation, the NHS England would potentially wish to commission its use in patients of less than 18 years in age, subject to NHS England ascertaining the impact of such a decision on currently running clinical trials.

Prof Peter Clark

Chair NHS England Chemotherapy Clinical Reference Group and National Clinical Lead for the Cancer Drugs Fund

3 March 2017

**Appendix G - professional organisation submission template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name:** [redacted]

**Name of your organisation: UCL/ UCLH**
**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? NO
- other? (please specify)
- Chair of the UK NCRI Adult ALL Group

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

*Currently treated by combination chemotherapy.*
*Outcome poor – low rate of competer remission, low 5 year OS and considerable toxicity/time spent in hospital*

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

*There are prognostic factors for outcome after relapse which have been identified by large studies of patient who relapsed after treatment on national studies - those poor risk factors are older age, shorter duration of first remission and inability to receive allogenenic hematopoietic stem cell transplant (alloHCT)*

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

*Secondary care in experienced centres as the drug needs to be given by 24 hours continuous IV infusion for 1 month. Patients do not need to be in patients for the duration but they require regular attendance for bag changes. If there are going to be adverse events, they usually occur soon after therapy has started. Centres should be experienced in knowing what to look for and how to treat them (CNS event, cytokine release – neither are common, but they do occur)*

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*There has been a compassionate use program in the UK*

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

*Nothing to add*

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

*The drug can potentially allow patients to receive therapy for relapsed ALL as outpatient as it is less toxic than standard of care – this could represent a considerable saving to the NHS and needs to be taken into account when comparing the cost of this agent with the drug costs of standard of care chemotherapy*
*The CR rate is higher and the OS is improved (recent phase 3 RCT)*

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

*Most patients respond within 1 cycle or not at all*

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

*The UK was a very active participant in the trials of this agent and was a large recruiting country. The trials were conducted in accordance with current UK practice*

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

*The drug is much preferable to patients than myelotoxic combination chemotherapy. Formal QofL studies are not yet published but are beginning to be submitted in abstract form.*

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

*Much of the evidence is by now published. The large phase 3 RCT was presented in the presidential symposium of the European Haematology Association and has been submitted for publication. I hope these data will be published by the time of NICE review but if they are not I recommend asking the company for a copy of any submitted manscripts*

**Implementation issues**

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

*Should all be possible within current NHS practice*

**Equality**
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

*Not aware of any issues*

**Appendix G - professional organisation submission template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name:** [redacted] **RCP** [redacted]

**Name of your organisation:**
**Are you (tick all that apply): NCRI-ACP-RCP**

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

***This condition relapsed ALL is currently treated either by combination chemotherapy OR by entering a clinical trial followed by allogeneic stem cell transplant wherever possible***

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

***All adult patients with relapsed ALL have an appalling prognosis. With conventional chemotherapy alone, there would be expected to be zero long term OS. With allogeneic bone marrow transplant as consolidation for salvage chemotherapy, the anticipated survival would be about 25% at 5 years, so despite the poor prognosis overall, there is a possibility to be cured (long term DFS/OS) - a very different situation from, for example, relapsed epithelial malignancies. Younger persons and those with the longer duration of first remissions have the best prognosis. This summary of the outcome of relapsed ALL is supported by a lot of published data from large international studies of patients who relapse after front-line therapy as well as a large metaanalysis of several thousand patients.***

***With novel immunotherapies such as the technology blinatumomab, the question of whether there is long term benefit to the technology as it stands (ie without the need for allogeneic stem cell transplant in all patients) remains open, but there is no doubt that the technology can potentially benefit all patients with relapsed ALL (regardless, for example, of genetic subtype or age) but with a bias towards better outcome if the agent is used earlier in salvage. In the recent analysis of the phase 3 trial, those patients with second or subsequent salvage were a subgroup least likely to derive survival benefit. However, the phase 2 study in Lancet Oncology did not show a CR difference within salvage subgroups.***

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

***Any centre with British Committtee on Standards in Haematology level 4 facilties which is 'allowed' to treat acute leukaemias and carry out stem cell transplants. The drug is given by 24 hour infusion, so a competent day unit or***

***ambulatory care facility which can deal with the twice weekly bag changes is necessary.***
***It is noteworthy that this drug can be given as an outpatient in many cases (not the case at all with the salvage chemotherapy approaches typically used) which can have many benefits for patients and the NHS***

***Please note the original trials required the patients to remain in hospital for 9 days at the beginning of the cycle; this was a trial-related safety measure and was subsequently made optional - the mandatory duration of hospitalisation was 48 hours. In clinical practice, this could also be 'ambulatory care' as long as the patient has a person to remain with them***

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

***Available recently in Wales and Scotland. Too early to be sure of indications. Has been available on compassionate program in England.***

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

***No NICE guidelines in ALL. EMSO Guidelines recently published: before blin was licensed***

***Ann Oncol. 2016 Apr 7. pii: mdw025 Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.***
***Hoelzer D[1], Bassan R[2], Dombret H[3], Fielding A[4], Ribera JM[5], Buske C[6]; ESMO Guidelines Committee.***

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

***The technology potentially represents a HUGE advance for patients both in terms of potential outcomes but in term of patient experience. The adverse effects specifically due to the drug are vastly different in clinical practice from those seen with chemotherapy. The published trial data don't reflect that very well because of the system of reporting of AE and SAE but in practice it is***

***vastly easier to deliver than combination chemotherapy and could save patients weeks of in patient stay.***

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

***If patients do not respond (complete remission) to 2 courses, there is no point to continue. Most patients respond within 1 course.***

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

***Our experts are very familiar with the evidence base as they were employed at a centre who took part in 4 clinical trials with this agent. The studies were conducted in highly relevant settings. In the phase 3 RCT, the standard of care agents were at investigators discretion so what was chosen was an honest reflection of standard practice. It should be noted that there is NOT any agreed national or international standard of care in this setting and several different regimens are used both in UK and internationally. The phase 3 RCT reflects this accurately.***

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

***The side effects profile is favourable compared with standard of care chemotherapy - the drug is not a cytotoxic so patients who are no cytopaenic do not necessarily become so. Hair does not fall out. There are no gastrointestinal toxicities or mucostitis.***
***There is 'cytokine release syndrome' reported in patients with large disease burdens. This is typically controllable and manageable with corticosteroids. It is advisable for patients to be observed closely for the first 48 hours of treatment as the side effects most typically occur straight away (or otherwise, not at all). Side effects can be controlled also by stopping the infusion.***

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

***As far as I am aware all relevant data on which decision can be made have been published in the academic literature or are submitted pending publication.***

**Implementation issues**

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

***The NHS units which would deliver this drug would be able to manage as currently established***

**Equality**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**
**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

***Nothing to add***

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Prof Adele K. Fielding**

**Name of your organisation**

**UCL**
**University College London Hospital**

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:**

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no national guidelines for the therapy of relapsed ALL. This is, at least in part because we have hitherto have had to rely (in *BCR-ABL1*/Philadelphia chromosome negative ALL) upon relatively ineffective and highly toxic regimens of combination chemotherapy composed largely of agents used during the initial therapy of ALL. For patients with *BCR-ABL1*/Philadelphia chromosome positive ALL, targeted oral agents - tyrosine kinase inhibitors - can be successfully employed to obtain remissions at relapse; however agents such as dasatinib are not reimbursed in the NHS and ponatinib is only reimbursed in very specific and relatively rare circumstances.

The overall goal of treatment of relapsed ALL in adults is long term disease-free survival equating to 'cure'. This is not common, but remains formally possible.
The steps to this taken by most centres, based on the published literature, as opposed to specific guidance, are

**1. To achieve complete remission (CR).** It is worth noting that the definition of CR is strict – fewer than 5% leukaemic blasts in the bone marrow accompanied by adequate peripheral blood counts with neutrophils and

platelets being the critical cells. There are other definitions of response such as CRi (CR with incomplete haematopoetic recovery) the predictive meaning of which is not clear; they may relate simply to the protocol-related timing of the assesement or they may relate to toxicity of the agent on the bone marrow, or impending relapse. Increasingly, publications in relapsed ALL refer to the quantification of minimal residual disease which is a measure of 'deep' response and is a predictive biomarker for outcome in de novo ALL. It should be noted that the predictive value of MRD in relapse OR after using non-chemo agents is NOT YET ESTABLISHED.

2. **To achieve an allogeneic bone marrow transplant wherever possible.** It is a pre-requisite in most countries for CR to be obtained prior to allograft. Many countries do allow/fund second allograft, but this is rare in the UK. Allograft is currently thought to be the only curative option.

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Inotuzumab ozogamicin (IO) is a new agent in the therapy of ALL. To understand the potential value of a novel agent such as inotuzumab, it is necessary to look at the known prognostic subgroups of patients who can benefit as well as the benefit to the group as a whole.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

There are numerous papers which clearly summarise the poor outcome of ALL after relapse and detail the major prognostic factors for survival in this situation. Listed below are the main prognostic factors for outcome after relapse.

- Early relapse (within 1 -2 years of diagnosis)
- Relapse after allograft
- Older patients in relapse
- Second or subsequent relapse

The drug IO seems to show **benefit in remission rate and in survival; importantly, the benefit applies even in some of the worst prognostic groups**.

**Ease of delivery** – the drug IO is easily delivered, by weekly injection, including the possibility to treat on an out-patient basis, whereas the combination chemotherapy drugs used often necessitate inpatient stays lasting several weeks

**Relative lack of side effects compared to combination chemotherapy** – the agent is well tolerated. The SAE and AE profile as reported in formal trials can be hard to interpret as patients often already have deranged bone marrow function due to the underlying disease; infections and so on are common place.

A **particular adverse effect of potential concern is veno-occlusive disease of the liver** (VOD). VOD is a rare event seen almost exclusively after bone marrow allograft. There was a higher than expected rate of this rare event in some patients who subsequently received allograft. These patients had been pre-treated (conditioned) with a combination of alkylating agents “dual alkylator conditioning” not typically used in the UK. Outside of these circumstances – which can be readily avoided – VOD does not seem to be much of an issue.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**Equality and Diversity**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

**None known**

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**None known**

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

**The agent is easy to administer requiring less time and skill to prescribe, administer and monitor than complex standard of care regimens**
**Patients can receive the agent as out patients if they have no other reason for inpatient hospitalisation**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Prof Adele K. Fielding**

**Name of your organisation**

**UCL**
**University College London Hospital**

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no national guidelines for the therapy of relapsed ALL. This is, at least in part because we have hitherto have had to rely (in *BCR-ABL1*/Philadelphia chromosome negative ALL) upon relatively ineffective and highly toxic regimens of combination chemotherapy composed largely of agents used during the initial therapy of ALL. For patients with *BCR-ABL1*/Philadelphia chromosome positive ALL, targeted oral agents - tyrosine kinase inhibitors - can be successfully employed to obtain remissions at relapse; however agents such as dasatinib are not reimbursed in the NHS and ponatinib is only reimbursed in very specific and relatively rare circumstances.

The overall goal of treatment of relapsed ALL in adults is long term disease-free survival equating to 'cure'. This is not common, but remains formally possible.
The steps to this taken by most centres, based on the published literature, as opposed to specific guidance, are

**1. To achieve complete remission (CR).** It is worth noting that the definition of CR is strict – fewer than 5% leukaemic blasts in the bone marrow accompanied by adequate peripheral blood counts with neutrophils and

platelets being the critical cells. There are other definitions of response such as CRi (CR with incomplete haematopoetic recovery) the predictive meaning of which is not clear; they may relate simply to the protocol-related timing of the assesement or they may relate to toxicity of the agent on the bone marrow, or impending relapse. Increasingly, publications in relapsed ALL refer to the quantification of minimal residual disease which is a measure of 'deep' response and is a predictive biomarker for outcome in de novo ALL. It should be noted that the predictive value of MRD in relapse OR after using non-chemo agents is NOT YET ESTABLISHED.

2. **To achieve an allogeneic bone marrow transplant wherever possible.** It is a pre-requisite in most countries for CR to be obtained prior to allograft. Many countries do allow/fund second allograft, but this is rare in the UK. Allograft is currently thought to be the only curative option.

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Inotuzumab ozogamicin (IO) is a new agent in the therapy of ALL. To understand the potential value of a novel agent such as inotuzumab, it is necessary to look at the known prognostic subgroups of patients who can benefit as well as the benefit to the group as a whole.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

There are numerous papers which clearly summarise the poor outcome of ALL after relapse and detail the major prognostic factors for survival in this situation. Listed below are the main prognostic factors for outcome after relapse.

- Early relapse (within 1 -2 years of diagnosis)
- Relapse after allograft
- Older patients in relapse
- Second or subsequent relapse

The drug IO seems to show **benefit in remission rate and in survival; importantly, the benefit applies even in some of the worst prognostic groups**.

**Ease of delivery** – the drug IO is easily delivered, by weekly injection, including the possibility to treat on an out-patient basis, whereas the combination chemotherapy drugs used often necessitate inpatient stays lasting several weeks

**Relative lack of side effects compared to combination chemotherapy** – the agent is well tolerated. The SAE and AE profile as reported in formal trials can be hard to interpret as patients often already have deranged bone marrow function due to the underlying disease; infections and so on are common place.

A **particular adverse effect of potential concern is veno-occlusive disease of the liver** (VOD). VOD is a rare event seen almost exclusively after bone marrow allograft. There was a higher than expected rate of this rare event in some patients who subsequently received allograft. These patients had been pre-treated (conditioned) with a combination of alkylating agents “dual alkylator conditioning” not typically used in the UK. Outside of these circumstances – which can be readily avoided – VOD does not seem to be much of an issue.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**Equality and Diversity**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

**None known**

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**None known**

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

**The agent is easy to administer requiring less time and skill to prescribe, administer and monitor than complex standard of care regimens**
**Patients can receive the agent as out patients if they have no other reason for inpatient hospitalisation**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

## Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Dr.N.J.Morley**

**Name of your organisation: Sheffield Teaching Hospitals NHS Foundation Trust**

**Are you (tick all that apply):**

✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?

✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

✓ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:**

**None.**

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

*Adults with relapsed Philadelphia chromosome negative Acute Lymphoblastic Leukaemia are a difficult to treat group who generally have a poor outcome. However there are some long term survivors who are cured and return to 'tax paying status'. Those who are fit enough for second line treatment would usually receive an intensive multi-agent chemotherapy regimen given as an inpatient and requiring 4 to 6 weeks stay in hospital to recover from this. The most commonly used regimen in this situation is known as FLAG (+/-Ida) which has a high treatment related morbidity and mortality and a disappointing response rate. Other treatments used include Clofarabine based chemotherapy (often for younger patients) and repeating the initial chemotherapy treatment (known as Phase I Induction chemotherapy) for later relapses. The aim of second line treatment is to induce remission as a bridge to an allogeneic stem cell transplant. This is a potentially curative option.*
*Due to lack of good evidence there is some variation in clinical practise where the regimen used depends on personal preference or experience.*
*There are two new agents that have both been the subject of Phase 3 clinical trials in this situation and both show improved response rates and reduced toxicity. Neither are currently routinely funded by the NHS but increasing numbers of centres have been accessing them through compassionate use schemes.*
*The main advantages of Blinatumomab in the treatment of Adults with relapsed Philadelphia chromosome negative Acute Lymphoblastic Leukaemia are,*
*1. A statistically significant and clinically meaningful increase in response rates.*
*2. Reduced toxicity for the patient.*
*3. Treatment can be given via an ambulatory care programme rather than solely as an inpatient reducing the burden on inpatient beds.*

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

*Patients' fitness is a limiting factor in deciding who is suitable for second line treatment. If Blinatumomab were available potentially more patients would be suitable for second line treatment both as a potentially curative option as a bridge to transplant and also as a palliative life prolonging treatment. i.e. it could especially benefit older and frailer patients.*

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

*The technology is not straight forward to administer and requires the use of special pumps especially if it is to be given in an ambulatory care setting. In order for such pumps to acquired, staff trained and to retain daily working familiarity with the equipment I strongly believe that this technology should only be used by Teaching Hospitals and those with JACIE accredited allogeneic stem cell transplant facilities.*

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*It has been available through a company compassionate use scheme but I am not completely aware of the uptake of this.*
*It is also in use for other indications within the context of clinical trials.*

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

*There are currently no relevant national clinical guidelines covering this situation.*
*The American National Comprehensive Cancer Network (NCCN) has clinical guidelines for ALL which make a number of recommendations but Blinatumomab is stated as the preferred treatment for relapsed ALL. These guidelines are comprehensive, well referenced and internationally respected.*

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

*To use this technology there is a requirement for specific pumps, which if not already in use at a centre would have implications for procurement, training, maintenance and maintaining staff competencies. Those centres that already have an ambulatory care facility may well already have these pumps in routine use. Despite the technical difficulties in getting set up the treatment is easy to administer and in comparison with the alternative treatments is much better tolerated by patients. The need for supportive care treatments e.g. blood transfusions, antibiotics etc is much reduced in practise.*

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

*In the setting of Adults with relapsed Philadelphia chromosome negative Acute Lymphoblastic Leukaemia patients would have a reassessment bone marrow test following one course of second line treatment and this should be done both with current practise and Blinatumomab. If treatment is not working then it should be discontinued. A strict definition of response should be avoided due to technical aspects in the timing of reassessment.*

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

*In my opinion the evidence base for Blinatumomab does reflect current UK practise. The primary evidence is from the TOWER study (NCT02013167). The primary endpoint was Overall Survival which is the most appropriate endpoint.*

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

*In my opinion the rates of reported side effects in this study does not demonstrate how well tolerated Blinatumomab is in practise when compared for example to FLAG chemotherapy.*

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

*There has been a concern about neurologic toxicity but I would be reassuring about this in clinical practise for a number of reasons. If patient selection is appropriate (i.e. no central nervous system involvement), if appropriate pre-medication is given then this is less of an issue. Also it is considered fully reversible.*

**Equality and Diversity**

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

**In my opinion there are no specific equality and diversity concerns identified.**

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal (STA)

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None.

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

*If use of this technology is restricted to limited centres as above then the impact of this would be reduced.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Patient/carer expert statement (STA)

### Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

the experience of having the condition or caring for someone with the condition

the experience of receiving NHS care for the condition

the experience of having specific treatments for the condition

the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)

preferences for different treatments and how they are given

expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

a patient

a carer (who may be voicing views for a patient who is unable to) or

somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

## *About you*

**Your name:** Chloe Pinder
**Name of your nominating organisation:** Leukemia Foundation
**Do you know if your nominating organisation has submitted a statement?**

☐ Yes ☒ No

**Do you wish to agree with your nominating organisation's statement?**

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

**Are you:**

a patient with the condition?

☒ Yes ☐ No

a carer of a patient with the condition?

☐ Yes ☒ No

a patient organisation employee or volunteer?

☐ Yes ☒ No

**Do you have experience of the treatment being appraised?**

☒ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

**Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:**

## *Living with the condition*

**What is your experience of living with the condition as a patient or carer?**

Being a patient, living with my condition has been difficult. I would not even call it living, everything you do is because you have to, not because you want to.

## *Current practice in treating the condition*

**Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.**

The most important outcome of teatment to me would be to not feel so tired, not to loose your hair is a big one aswell because that changed my identity and made me loose all confidence. But the biggest outcome is for it to 100% cure the condition.

**What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?**

I have had very positive NHS treatment and care. All the consultants, nurses are very understanding and caring. There has been times when you are waiting around a lot at hospitals for check ups etc but this is due to them being so busy. Specific treatments that i have had include Chemotherpay and Blinotumomab. I prefered the Blinotumomab 100% as there was a lot less side effects.

## *What do you consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

the course and/or outcome of the condition

physical symptoms

pain

level of disability

mental health

quality of life (such as lifestyle and work)

other people (for example, family, friends and employers)

ease of use (for example, tablets rather than injection)

where the treatment has to be used (for example, at home rather than in hospital)

any other issues not listed above

**Please list the benefits that you expect to gain from using the treatment being appraised.**

Having already been on this treatment, the effects that it had physically were little. I still felt very well and healthy in both mind and body. The only downfall was being attached to this treatment constantly for 28 days however it would fit in a back pack and was easy to hide, also in comparison to being able to live out the rest of my life, 28 days is nothing.

I experienced no pain whilst on this treatment, I also had no side effects (except a high temperature within the first 24hours of infusion). This meant that the effects that it had on my family and friends was very little as I did not need to depend on them, compared to how much I depended on them whilst on Chemotherapy treatment.

My quality of life was also good, I managed to have a social life, catch up with friends and family. Rather than having to stay in hospital.

**Please explain any advantages that you think this treatment has over other NHS treatments in England.**

The side effects was a big advantage. I experienced hardly any. I also didnt loose my hair, whereas when i was on Chemotherapy teatment I lost all of it within weeks. You are actually able to maintain a lifestyle for yourself, not having to stay over in hospital. I wish I could of had the Blinotumomab straight away instead of going through chemotherapy first as this would of saved a lot of pain, upset and time for me and my family.

**If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.**

## *What do you consider to be the disadvantages of the treatment being appraised?*

Disadvantages of a treatment might include:

aspects of the condition that the treatment cannot help with or might make worse

difficulties in taking or using the treatment (for example, injection rather than tablets)

side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

where the treatment has to be used (for example, in hospital rather than at home)

impact on others (for example, family, friends and employers)

financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)

any other issues not listed above

**Please list any concerns you have about current NHS treatments in England.**

A dis-advantage of this treatment is that you are constantly attached. I was attached to this treatment for 28days and had to travel to Sheffield from Grimsby to have the bag changed every 4 days. This was quite time consuming but only because i live so far away.

Also the fact that you are attached to something for so long is quite strange, however once I got my head around it, I would hide the treatment in my bag and could carry on a normal everyday life.

**Please list any concerns you have about the treatment being appraised.**

Because it is so new, any long term side effects.

**If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.**

## *Patient population*

**Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.**

I think people would benefit hugely from this treatment rather than other treatments because there is no pain, no side effects and you are able to carry on with your life.

**Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.**

Everyone is different and for some people this treatment might not work, just like chemotherapy did not work to cure me of my Leukemia. However, like any treatment... It depends on the person.

## *Research evidence on patient or carer views of the treatment*

**Are you familiar with the published research literature for the treatment?**

☐ Yes ☒ No

**If you answered 'no', please skip the rest of section 7 and move on to section 8.**

**Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.**

**Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?**

**If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?**

**Are you aware of any relevant research on patient or carer views of the condition or existing treatments?**

☐ Yes ☐ No

**If yes, please provide references to the relevant studies.**

## *Equality*

**NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.**

## *Other issues*

**Do you consider the treatment to be innovative?**

X Yes ☐ No

**If yes, please explain what makes it significantly different from other treatments for the condition.**

The fact that it is constant. When having chemotherapy, it takes hours but never more than 24 hours. This is 28 days. You can also be at home with this treatment, whereas on other treatments they require you to stay in hospital.

**Is there anything else that you would like the Appraisal Committee to consider?**

## *Key messages*

**In no more than 5 bullet points, please summarise the key messages of your submission.**

Positive feedback of the treatment

People would go through a lot less upset, pain and trauma than other treatments

Few side effects to this treatment

Able to carry on with every day life whilst on the treatment.

**Title: Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia**

**Produced by:** Warwick Evidence

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**Date completed:** 9 February 2016

**Source of funding**: This report was commissioned by the NIHR HTA Programme as project number ID804.

**Declared competing interests of the authors:** None.

**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows:** Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia. A single technology appraisal. Warwick Evidence, February 2017.

**Contributions of authors:** G.J. Melendez-Torres (Assistant Professor) co-ordinated the project, led the review of clinical effectiveness and contributed to the drafting of the report. Peter Auguste (Research Fellow) led the review of cost effectiveness and contributed to the drafting of the report. Jacoby Patterson and Christine Clar (Independent research consultants) contributed to the review of clinical effectiveness and to the drafting of the report. Rachel Court (Information Specialist) contributed to the reviews of clinical and cost effectiveness and contributed to the drafting of the report. Jason Madan (Associate Professor) contributed to the review of cost effectiveness. Prem Mahendra (Consultant Haemato-Oncologist) contributed clinical input. Aileen Clarke (Professor of Public Health Research) supervised the project.

**Please note that:** Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AC | Appraisal Committee |
| AE | Adverse Event |
| AIC | Akaike information criterion |
| ALL | Acute Lymphoblastic Leukaemia |
| allo | Allogeneic |
| ALLSS | Acute Lymphoblastic Leukaemia Symptom Scale |
| α | The shape parameter for a Gompertz distribution |
| ANC | Absolute Neutrophil Count |
| BIC | Bayesian Information Criterion |
| blin or blina | Blinatumomab |
| BNF | British National Formulary |
| CAR | Chimeric Antigen Receptors |
| CBA | Cost-Benefit Analysis |
| CD | Cluster of Differentiation (cell surface markers) |
| CEA | Cost-Effectiveness Analysis |
| CEAC | Cost-Effectiveness Acceptability Curve |
| chemo | Chemotherapy |
| CI | Confidence Interval |
| CIC | Commercial in confidence |
| CMA | Cost-Minimisation Analysis |
| CNS | Central Nervous System |
| CR | Complete Remission |
| CRD | Centre for Reviews and Dissemination |
| CRh* | Complete Remission with partial haematological recovery |
| CRi | Complete Remission with incomplete haematological recovery |
| CRsg | Complete Remission as defined by different study groups in historical comparator study |
| CS | Company submission |
| CSR | Clinical Study Report |
| CUA | Cost Utility Analysis |
| ECOG | Eastern Cooperative Oncology Group |
| EED | Economic Evaluation Database |
| EFS | Event-Free Survival |
| EMA | European Medicines Agency |
| eMit | electronic Market information tool |
| EMTREE | Embase thesaurus |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EQ-5D | Euro-Qol five dimensions |
| ERG | Evidence Review Group |
| EWALL | European Working group for adult ALL |
| exp | explode search terms to retrieve citations that carry the specified MeSH heading (or subheading) and also retrieve citations that carry any of the |

| Abbreviation | Definition |
|---|---|
| | more specific MeSH headings (or subheadings) indented beneath it in the Tree structure. |
| FAS | Full Analysis Set |
| FLAG | Fludarabine, cytarabine and GCSF based combination chemotherapy |
| FLAG-IDA | FLAG with or without idarubicin |
| GCSF | Granulocyte Colony Stimulating Factor |
| GHS | Global Health Status |
| h | Hours |
| HCHS | Hospital and Community Health Service |
| HiDAC | High-Dose Cytarabine |
| HR | Hazard Ratio |
| HRQoL | Health Related Quality of Life |
| HSCT | Haematopoietic Stem Cell Transplantation |
| HTA | Health Technology Assessment |
| Hyper-CVAD | Hyperfractionated Cyclophosphamide, Vincristine, Adriamycin (=doxorubicin) and Dexamethasone |
| ICER | Incremental Cost-Effectiveness Ratio |
| ITT | Intention-To-Treat |
| IPTW | Inverse Probability Of Treatment Weighting |
| IQR | Inter-Quartile Range |
| IVRS | Interactive Voice-Response System |
| λ | The scale parameter for a Gompertz distribution |
| LYG | Life Years Gained |
| MeSH | Medical Subject Headings |
| MRC | Medical Research Council |
| MRC UKALLXII/ECOG 2993 | Short title of study: Stem Cell Transplantation Compared With Standard Chemotherapy in Treating Patients With Acute Lymphoblastic Leukemia in First Remission, an international ALL trial involving a collaboration between the Medical Research Council (UKALL XII) in the UK and the Eastern Cooperative Oncology Group (ECOG E2993) in the USA |
| MRD | Minimal Residual Disease |
| MS | Manufacturer's Submission |
| MT103 | Former name for blinatumomab |
| MT103-211 | Short title of study: Clinical Study With Blinatumomab in Patients With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) |
| N or n | Number |
| NA | Not Applicable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIH | National Institutes of Health |
| NIHR | National Institute for Health Research |
| NMA | Network Meta-Analysis |
| OR | Odds Ratio |

| Abbreviation | Definition |
|---|---|
| OS | Overall Survival |
| PAS | Patient Access Scheme |
| PD | Pharmacodynamics |
| PFS | Progression-Free Survival |
| Ph- | Philadelphia-chromosome-negative |
| PICO | Population, Intervention, Comparator, Outcome |
| PK | Pharmacokinetics |
| PR | Partial Response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PRO | Patient Reported Outcome |
| PSA | Probabilistic Sensitivity Analysis |
| PSS | Personal Social Services |
| Pts | Patients |
| QALY | Quality Adjusted Life Years |
| QLQ-C30 | Quality of Life Questionnaire-Core 30 |
| QoL | Quality of Life |
| RCT | Randomised Controlled Trial |
| RFS | Relapse-Free Survival |
| R/R | Relapsed or Refractory |
| SAE | Serious Adverse Event |
| SAS | Safety Analysis Set |
| $S_A[t]$ | Adjusted Kaplan-Meier survival distribution for matched historical comparator |
| SCT | Stem Cell Transplant |
| SD | Standard Deviation |
| SE | Standard Error |
| SmPC | Summary of Product Characteristics |
| SOC | Standard Of Care |
| S [t] | Unadjusted Kaplan-Meier survival distribution for matched historical comparator |
| STA | Single Technology Assessment |
| STROBE | STrengthening the Reporting of OBservational studies in Epidemiology |
| TA | Technology Assessment |
| tab | Tablet |
| TEAE | Treatment-Emergent Adverse Event |
| TOWER | Short title of study: Ph 3 Trial of Blinatumomab vs Investigator's Choice of Chemotherapy in Patients With Relapsed or Refractory ALL |
| TTO | Time Trade-Off |
| UK | United Kingdom |
| US or USA | United States of America |
| WTP | Willingness-To-Pay |

# 1 SUMMARY

## 1.1 Critique of the decision problem in the company's submission

The CS decision problem as stated matches the intervention and population described in the final NICE scope; that is, blinatumomab for people with relapsed or refractory Philadelphia-chromosome-negative B-precursor acute lymphoblastic leukaemia (ALL). Comparators in the scope were FLAG with or without idarubicin (FLAG-IDA), clofarabine-based regimens, and best supportive care. Evidence presented by the company related principally to FLAG-IDA, as the company suggested that clofarabine-based regimens and best supportive care were not relevant comparators in this instance. While the ERG clinical advisor agreed that best supportive care was not a useful comparator in practice, the advisor did note that clofarabine is sometimes used for treatment of ALL.

The CS decision problem as stated matched the outcomes included in the final NICE scope. However, relapse-free survival was not specifically defined in the randomised evidence submitted, though the company suggested that duration of haematological response was an equivalent measure.

The intervention, blinatumomab, is administered intravenously in 4 week cycles (starting dose 9 μg/day during the first week, thereafter 28 μg/day), followed by a 2-week treatment-free interval. Patients may receive two cycles of treatment. If complete remission is achieved after two cycles, patients may receive up to three additional cycles of blinatumomab based on an individual benefits-risks assessment. Blinatumomab has a marketing authorisation in the UK for 'adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)'.

## 1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included a systematic review to search for evidence to meet the decision problem. While the ERG considered the systematic review to be of reasonable quality, the chance of systematic error in the review was uncertain, principally owing to changes in inclusion and exclusion criteria and possible errors in the search. However, upon considering responses to clarification and after

additional work undertaken by the ERG, the ERG regarded that all relevant evidence had been included.

The CS systematic review yielded one randomised trial, TOWER, and one single-arm trial, Study MT103-211, which was then compared to a historical cohort. The ERG did not regard the single-arm trial per se as relevant and thus focused on the comparison between the single-arm trial and the historical cohort.

TOWER randomised patients to either blinatumomab or a standard of care chemotherapy arm, in which patients could receive one of four protocols: FLAG with or without anthracyclines (which would include FLAG-IDA), clofarabine-based regimens, the HiDAC protocol, or a high-dose methotrexate-based regimen. Throughout the submission, the company used the pooled standard of care chemotherapy arm as a proxy for FLAG-IDA on the basis of expert opinion that there would be no expected difference between regimens. Because investigator choice of standard of care chemotherapy was recorded prior to randomisation, patients receiving blinatumomab who were 'FLAG-eligible' could be compared against patients in the standard of care arm who received FLAG with or without anthracyclines, and similarly for clofarabine. The non-randomised evidence compared blinatumomab against a similar set of standard of care chemotherapy treatments from a historical cohort.

Most of the outcomes in the NICE scope are reflected in the clinical evidence. In TOWER, blinatumomab appeared to have several statistically significant effects on key outcomes.

- **Overall survival.** Compared to the pooled standard of care chemotherapy arm, blinatumomab prolonged survival (HR 0.71, 95% CI [0.55, 0.93]).

- **Event-free survival.** Patients receiving blinatumomab delayed death or, for those who achieved remission in the first 12 weeks of treatment, relapse as compared to patients receiving standard of care chemotherapy (HR 0.55, 95% CI [0.43, 0.71]).

- **Haematologic response.** More patients in the blinatumomab arm achieved complete remission within 12 weeks of treatment initiation than patients in the blinatumomab arm (33.6% vs. 15.7%; $p < 0.001$). Similarly, the proportion of patients who achieved a complete remission, including with incomplete or partial haematological recovery, within 12 weeks of treatment initiation was statistically significantly higher in the blinatumomab

arm compared with the SOC chemotherapy arm (43.9% vs. 24.6%, p < 0.001). Findings for the difference between arms were similar for minimal residual disease.

- **Duration of response.** Patients receiving blinatumomab and who achieved complete remission did not have a significantly longer response than patients in the standard of care chemotherapy arm who achieved complete remission ([redacted] months vs [redacted] months, [redacted]). This did not change when complete remission with incomplete or partial haematological recovery was used as the marker for response (7.3 months vs 4.6 months, [redacted]).

- **Allogeneic stem cell transplant outcomes.** The rate of allogeneic stem cell transplant was similar in the blinatumomab arm as in the standard of care chemotherapy arm (24.0% vs 23.9%, descriptive p = [redacted]).

- **Adverse events.** The exposure-adjusted incidence rates for all treatment-emergent AEs, serious AEs, and AEs of interest were substantially lower in the blinatumomab arm than in the standard of care chemotherapy arm. However, a higher proportion of patients in the blinatumomab arm experienced some types of treatment-emergent AE than in the standard of care chemotherapy arm, including serious AEs and AEs leading to interruption and discontinuation of treatment.

- **Health-related quality of life.** Patients in the blinatumomab arm had a significantly longer time to clinically meaningful decrease in health-related quality of life (measured by the EORTC QLQ-C30 GHS questionnaire) as compared to patients in the standard of care chemotherapy arm ([redacted], *p*=[redacted]).

Outcomes presented from the non-randomised evidence for overall survival and complete remission, including with partial haematological recovery, matched in magnitude and significance findings from TOWER. Relapse-free survival was not defined as an outcome in TOWER, and findings from the non-randomised evidence on relapse-free survival were not presented due to data quality.

## 1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG appraisal of TOWER substantially agreed with the company's appraisal of TOWER, except the ERG further noted that the analysis set used for health-related quality of life were only undertaken on those who had a non-missing baseline and at least one post-baseline assessment, and no strategy was used to account for missing data. The ERG did not regard that the approach used by the company to appraise the non-randomised evidence was appropriate, and thus it undertook its own appraisal.

The ERG generally agreed with the approach to outcome selection and the trial statistics in both TOWER and the non-randomised comparison.

The ERG noted the following issues with the clinical evidence submitted:

- In TOWER, the use of the standard of care chemotherapy arm as a proxy for the scoped comparator of FLAG-IDA relied solely on expert opinion. Moreover, while the company did provide upon clarification requests subgroup analyses for all 'FLAG-eligible' and 'clofarabine-eligible' patients on scoped outcomes, these analyses rely on small numbers and TOWER was not powered to undertake these subgroup analyses.

- In TOWER, dropout was imbalanced between arms (and was higher in the standard of care chemotherapy arm, 18.7% vs 1.5%), though this did not affect balance on known demographic characteristics.

- Data presented for TOWER drew from interim analyses, and thus the study data presented are not at full maturity.

- In TOWER, a notable percentage of patients ([redacted]) in the blinatumomab arm received more than the five cycles of blinatumomab described in the marketing authorisation, and [redacted] of patients in the standard of care chemotherapy arm received blinatumomab subsequently.

- In the non-randomised comparison provided, the definition of complete remission was inconsistent between the blinatumomab arm and the standard of care chemotherapy natural history comparator, and was heterogeneous within the standard of care arm.

### 1.3.1 Strengths

This CS had several strengths.

- In the main, quality of the systematic review was adequate, and assessment of the randomised evidence was appropriate.
- The trial as a whole was large and generally of good quality.
- Approach to outcome selection and trial statistics was clear and appropriate.
- Patients in the included trials were considered to be generalizable to those in England by the ERG clinical advisor.

### 1.3.2 Weaknesses

However, this CS had several weaknesses as well:

- Though this may have been unavoidable, TOWER was an open-label trial. Furthermore, the consolidation criteria used in TOWER to determine if further treatment after two cycles is appropriate does not match precisely the consolidation criteria in the marketing authorisation.
- The data from TOWER had not reached full maturity at the time of reporting.
- It is empirically unclear the degree to which the standard of care chemotherapy arm in TOWER is an appropriate substitute for FLAG-IDA, the scoped comparator; furthermore, clofarabine-based regimens were not discussed though clofarabine was a scoped comparator.

## 1.4 Summary of cost effectiveness evidence submitted by the company

The submission received by the ERG included an economic model with relapsed or refractory Philadelphia-chromosome-negative B-precursor ALL, along with supporting systematic reviews of a) economic evaluations and b) patient-reported outcome measures and health-related quality of life.

### 1.4.1 Economic model

The company used a partitioned survival Markov model to show the experience of a cohort of people with refractory or relapsed Philadelphia chromosome–negative acute lymphoblastic leukaemia who may undergo treatment with blinatumomab and standard care chemotherapy over a 50-year time horizon. The model defined health states of initial (pre-response), refractory/relapsed, response to treatment and death. The model started from a cohort of people, all of whom began in the initial health state. People remained in this health state for 12 weeks, unless they died. After 12 weeks, people could move to the refractory/relapsed health state or the response health state. The model cycles weekly to show the movement of people through the model. In each cycle, people incurred costs and benefits (QALYs) depending on the health state occupied.

Clinical effectiveness inputs to the model relied solely on the TOWER trial. As in the earlier aspects of this submission, the clinical effectiveness of FLAG-IDA was represented by the effectiveness of the pooled SOC chemotherapy arm. Hence, the company did not undertake any formal evidence synthesis through network meta-analysis. Clinical parameters related to overall survival and event free survival for blinatumomab were derived from parametric survival curves fitted to Kaplan-Meier plots of the data from the TOWER study. For the comparator arm, inputs related to OS and EFS were based on fitting survival curves to a Kaplan-Meier plot of a retrospective natural history cohort, which was used to test the plausibility of the survival data generated by the SOC chemotherapy arm in TOWER.

Health-related quality of life values depended on each health state and treatment. Utility values were based on information collected on the EORTC QLQ-C30 and mapped onto the EQ-5D. The EORTC QLQ C-30 was administered at baseline and again periodically throughout the five treatment cycles. The company suggested that quality of life losses associated with treatment related adverse events would have been captured by EORTC QLQ-C30 collected in the trial, no additional disutilities for treatment related adverse events were included in the base case.

Key costs in the model included the cost of blinatumomab and of FLAG-IDA, the scoped comparator, both of which were based on the NHS list prices. Inpatient hospitalisation, costs of allogeneic stem cell transplant, costs of subsequent therapy and costs of terminal care were included as well.

### 1.4.2 Base case results

The company base case results indicate that blinatumomab will provide an additional [redacted] QALYs as compared to FLAG-IDA, and will cost an additional [redacted], with an ICER of [redacted] per QALY. Using the company's PAS for the cost of blinatumomab ([redacted]), the ICER was estimated at £55,501 per QALY gained. As suggested by one-way sensitivity analyses in which parameters were varied by 50%, the analysis was most sensitive to differences between drugs in overall survival; other parameters had little impact on the ICER, though the number of inpatient days assumed for the comparator, FLAG-IDA, was the next most influential factor. Probabilistic sensitivity analysis demonstrated greater uncertainty around incremental QALYs than incremental costs. At a willingness-to-pay threshold of £50,000 per QALY, there is a [redacted] probability of blinatumomab being cost-effective as compared to FLAG-IDA.

## 1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

### 1.5.1 Strengths of the cost-effectiveness evidence

The company's submitted model had several strengths:

- The quality of the company's submitted systematic reviews was reasonable.
- The model appears to capture the key features of ALL, and the population used was sufficiently similar to the UK population.
- The model specifications (perspective, time horizon and discount rates) are in line with NICE recommendations.
- Face validity checks on the model at various time points for probability of survival suggest satisfactory agreement with results from the TOWER trial.

### 1.5.2 Weaknesses of the cost-effectiveness evidence

The company's submitted economic evidence also had several weaknesses:

- The scenario analysis model that included a 'cured' health state was not viewed by the ERG to be a clinically reasonable model.

- A notable number of patients in the blinatumomab arm received more than the five cycles specified in the marketing authorisation.

- The plausibility of findings depends on whether FLAG-IDA could be viewed as commensurate to the SOC chemotherapy arm in TOWER, an assumption that appears to rely on expert opinion.

- The ERG was concerned that the company's use of parametric curves with the observed data from TOWER represented a set of strong assumptions, given that visual inspection of Kaplan-Meier plots relating to overall survival and event-free survival from TOWER suggests that hazards are not proportional.

- Analysis of utility values did not account for baseline differences between arms.

- Costs were derived from studies implemented in different contexts, and some costs were converted using non-standard indices.

## 1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG explored a variety of scenarios, including limiting the model time horizon to two years (the length of time in the trial overall survival curves) and varying the resource use. In the ERG's preferred base case, patients were hospitalised for the full four weeks of active treatment in the first two cycles and then had daily bag changes in the subsequent three treatment cycles. This yielded a base case ICER of approximately [redacted] per QALY.

The ERG noted several sources of uncertainty remaining in the economic model: generalisability of the scoped comparator, FLAG-IDA, to the clinical effectiveness of the SOC chemotherapy arm from TOWER; analysis of pump costs under the assumption that pumps could not be reused between patients; and extrapolation of treatment effects. In respect of the last point, the ERG explored a variety of approaches to better and more accurately extrapolate treatment benefits, but it was unable to apply these approaches to the economic model. The ERG believed it likely that a revision of the optimistic extrapolation methods used in the company submission would cause an increase in the ICER, but noted this would be uncertain given data availability.

# 2 BACKGROUND

## 2.1 Critique of company's description of underlying health problem

The company describes acute lymphoblastic leukemia (ALL) on CS pp. 38-39 and the ERG clinical advisor agrees that this is an appropriate summary of the condition. The CS describes ALL as a type of acute leukaemia affecting immature lymphocytes (lymphoblasts) that are derived from B- or T-lymphocyte stem cells. Proliferating lymphoblasts crowd out and supress the production of normal blood cells in the bone marrow, causing haematological deficiencies, including anaemia, immune system impairment, and platelet count deficiency. The leukaemic lymphoblasts express the same antigens as normally developing B- and T-cells. ALL can be classified into three sub-groups based on immunophenotyping: B-precursor ALL, mature B-cell ALL and T-cell ALL. Precursor B-cells typically express CD10, CD19, and CD34 cell surface markers. [1, 2]

The CS states that patients experience severe symptoms that cause them to seek urgent medical attention. Symtoms include overwhelming fatigue, intolerance to physical exercise, bruising, bleeding, enlarged lymph nodes, fever with infections, headache, vomiting, and lethargy.[3, 4]

The condition of interest here is previously treated Philadelphia-chromosome-negative (Ph-) B-precursor acute lymphoblastic leukaemia in adults. The CS states that based on epidemiological data from the UK, 42% of ALL patients are adults. In 82% of these, B-cells are affected, and in 87% of the B-cell cases, the malignancy occurs in precursor B-cells. Of the adult patients with precursor-B-cell ALL, 78% are Philadelphia-chromosome-negative and of those, 49% have relapsed/refractory disease.[3, 5] Data were derived from a UK cytogenetic population-based study of 349 patients aged >15 years with ALL diagnosed between 1983 and 2001[5] and from an analysis of cytogenetic data of 1522 aged 15 to 65 years with ALL enrolled in the MRC UKALLXII/ECOG 2993 study.[3]

The CS states that the annual number of incident adult relapsed/refractory Ph- B-precursor ALL patients (i.e., the number of patients who would become eligible for treatment with blinatumomab per its marketing authorisation) was estimated to be 86 in 2015 (data based on incidence data from 2013 from Cancer Research UK).[6] The prognosis for adult patients with relapsed/refractory Ph B precursor ALL is extremely poor, with a life expectancy of around 3 to 6 months.[7]

## 2.2 Critique of company's overview of current service provision

The company reviews current service provision for adult patients with relapsed/refractory Ph- B-precursor ALL on CS pp. 43-50. The company argues that there has been a lack of progress in the treatment of patients with the disease, and there are no targeted treatments specifically licensed for the management of adult relapsed/refractory Ph- B-precursor ALL in the UK. They also point out that active treatment options are limited to a range of poorly effective and highly toxic salvage chemotherapy regimens, with or without allogeneic stem cell transplant (allo-SCT) which is currently the only potentially curative treatment.[8, 9] They state that the primary treatment goal is to achieve and maintain haematological remission, typically defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full haematological recovery (absolute neutrophil count > 1,000/μL and platelet count > 100,000/μL). The company states that there are no relevant published NICE clinical guidelines or technology appraisal guidance and that other available European guidelines and regional NHS protocols.[10-12] provide limited specific recommendations around the management of adult patients with relapsed/refractory Ph- B-precursor ALL, listing options for salvage chemotherapy regimens and recommending entering a clinical trial; the guideline of the US National Comprehensive Cancer Network[13] recommends blinatumomab as a preferred option. The company further states that UK treatment patterns data and feedback from UK clinical experts suggest that FLAG-IDA is the most commonly used regimen for the treatment of adult patients with relapsed/refractory Ph- B-precursor ALL in England and Wales.[14] Other treatments used include hyper-CVAD-based regimens, high-dose cytarabine (HiDAC)-based regimens, methotrexate with L-asparaginase-based regimens, clofarabine-based regimens, and vincristine sulfate liposome-based regimens.[8, 11, 14-16] They add that UK treatment patterns data show that there is substantial heterogeneity around the approach to allo-SCT in clinical practice.[14] The company points out that haematological remission rates with existing salvage chemotherapy regimens are poor (around 20 to 30%)[16-18] and that toxicities are significant.[14, 19, 20] They state that blinatumomab is proposed for use in England and Wales in accordance with its full marketing authorisation i.e. for use in all adult patients with relapsed/refractory Ph- B-precursor ALL.

The company states that blinatumomab requires the assistance of a healthcare professional to handle and prepare the medicinal product and that the infusion bag must be changed at least every 96 hours by a professional.[21] The company also argues that no additional diagnostic tests or National Health Service (NHS) infrastructure is expected to be needed to incorporate

blinatumomab into the clinical pathway of care. Hospitalisation is recommended during the first 9 to 14 days of the first cycle and supervision by a healthcare professional of hospitalisation at the beginning of subsequent cycles. The company states that this does not present any additional burden to healthcare providers as hospitalisation during treatment is standard practice with current treatment options. However, the ERG clinical advisor suggested that in practice, day unit facilities may not be set up to cater for patients coming in to have infusion bags changed and that patients may be hospitalised for the whole of each treatment cycle. Day units catering for these patients would theoretically be possible, but would only be possible at larger specalialised centres which would have greater experience in treating these patients; the ERG clinical advisor further noted that any centre would treat between 5 and 8 patients a year with this condition.

In response to the clinical clarification question A2 (p. 12-13 of responses and Table A-3 of responses), the company responded that according to the summary of product characteristics, renal and liver function are monitored within 48 hours of initiation of treatment. Further monitoring of renal function, parameters related to neutropaenia and febrile neutropaenia, and parameters related to liver function is anticipated to occur twice weekly at bag changes (compared to between daily and three times per week for standard of care [SOC] chemotherapy). Signs and symptoms of pancreatitis (serum amylase and serum lipase) are conducted according to summary of product characteristics, but this is not anticipated to be conducted routinely in clinical practice (compared to no assessment with SOC chemotherapy). Additional assessments include measurement of bone marrow blasts at the ends of each of the first and second cycle of treatment (compared to no assessment with SOC chemotherapy). Patients receiving SOC would also have a bone marrow examination after cycle 1 and cycle 2 of chemotherapy). Overall, the company argues that laboratory testing is anticipated to occur less frequently with blinatumomab than with SOC chemotherapy in clinical practice. The ERG clinical advisor did not find exception with these statements.

# 3 Critique of company's definition of decision problem

The decision problem from the final NICE scope is summarised in Table 1 below.

**Table 1 Decision problem from the final NICE scope**

| | |
|---|---|
| **Population** | People with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia |
| **Intervention** | Blinatumomab |
| **Comparators** | • Fludarabine, cytarabine and granulocyte colonystimulating factor (GCSF) based combination chemotherapy, with or without idarubicin (FLAG-IDA)<br>• Clofarabine based combination chemotherapy<br>• Best supportive care (including palliative care) |
| **Outcomes** | • Overall survival<br>• Event-free survival<br>• Relapse-free survival<br>• Treatment response rates (including minimal residual disease and haematology responses and complete remission)<br>• Time to and duration of response<br>• Rate of stem-cell transplant<br>• Adverse effects of treatment<br>• Health-related quality of life |
| **Subgroups** | If the evidence allows the following subgroup will be considered: people for whom allogeneic stem cell transplantation is considered an appropriate treatment option |

## 3.1 Population

The patient population in the decision problem matches the population described in the final scope. The company defines the included population as "Adults (aged ≥15 years) with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia" while the final scope states "people with…", but as blinatumomab is authorised in the UK for use in adults only, these statements are judged to be equivalent. The included trials examined patients aged ≥18 years with relapsed/repractory Ph-, B-precursor ALL, therefore they covered the population specified in the decision problem and the final scope.

## 3.2 Intervention

The intervention in both the company's decision problem and in the final scope is blinatumomab. The company describes the technology on pp. 31-32 of the submission. Blinatumomab is a T-cell engager antibody targeting CD19 expressed on the surface of B-cells and CD3 expressed on the surface of T-cells. Blinatumomab mediates the formation of a cytolytic immunological synapse

between the T-cell and the malignant B-cell, triggering release of proteolytic enzymes to kill target cells. Blinatumomab is administered intravenously in 4 week cycles (starting dose 9 μg/day during the first week, thereafter 28 μg/day), followed by a 2-week treatment-free interval. Patients may receive two cycles of treatment. If complete remission is achieved after two cycles, patients may receive up to three additional cycles of blinatumomab based on an individual benefits-risks assessment.

Blinatumomab has a marketing authorisation in the European Union for 'adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)'. The marketing authorisation was approved on 23 November 2015 following a positive opinion in September 2015 from the Committee for Medicinal Products for Human Use.

## 3.3 Comparators

The final scope specified FLAG (fludarabine, cytarabine and GCSF based combination chemotherapy) with or without idarubicin, clofarabine-based chemotherapy and best supportive care as comparators. The company only included FLAG with idarubacin (FLAG-IDA) as a comparator. They argue that FLAG-IDA is the most commonly used salvage chemotherapy regimen in the UK and that clofarabine is licenced as monotherapy for paediatric use and funding and availability for the adult population remain unclear since the expiration of the previous Cancer Drug Fund. The also argue that best supportive care is generally reserved for patients who do not respond to salvage chemotherapy, have reached end-of-life, and have experienced substantial toxicity with salvage chemotherapy and that blinatumomab would therefore generally be used before best supportive care in the clinical pathway. Subgroup analyses by intended SOC chemotherapy in the company submission include subgroups of FLAG with or without anthracycline and clofarabine-based therapies. Additional data for these groups were provided in the responses to the clinical queries. The ERG clinical advisor agrees that best supportive care is not an appropriate comparator and that in clinical practice in the UK, FLAG-based regimens are used in the vast majority of cases as SOC chemotherapy and that clofarabine, while a treatment option, is used infrequently.

## 3.4 Outcomes

The outcomes in the final scope mostly match those in the decision problem. Relapse-free survival was not specifically defined as an endpoint in the main randomised trial examined, but

the company argues that the secondary endpoints of duration of complete remission (CR) or duration of complete remission, including with partial (CRh*) or incomplete (CRi) haematological recovery (together described as CR/CRh*/CRi), can be seen as broadly equivalent to relapse-free survival.

## 3.5 Other relevant factors

The NICE scope included a subgroup of patients for whom allo-SCT is a treatment option. The company did not address this subgroup in their submission, citing the heterogeneity in criteria across clinicians for proceeding to allo-SCT. The ERG clinical advisor noted that while certain haematological markers are needed to proceed to allo-SCT, the decision to proceed relies substantially on clinical judgment.

The company submission states that there are no equity / equality issues relating to the use of blinatumomab for the treatment of adult relapsed/refractory Ph- B-precursor ALL. The company has propsed a simple Patient Access Scheme which has been approved by the UK Department of Health. The company states that treatment with blinatumomab meets the NICE end-of-life criteria: it is indicated for patients with a short life expectancy (normally less than 24 months) and there is sufficient evidence to indicate that the treatment offers an extension to life (normally of at least an additional 3 months) compared with current NHS treatment. This is discussed further in Section 6. The company further makes a case for innovation, which is discussed in Section 7.

# 4 CLINICAL EFFECTIVENESS

## 4.1 Critique of the company's approach to systematic review

The CS conducted a systematic review for evidence of clinical effectiveness, and the ERG's quality assessment of this is summarised in Table 2 below. While the overall quality of the company's systematic review was reasonable, the ERG had concerns regarding the inclusion of some scoped outcomes, but not others, in the inclusion and exclusion criteria, and the application of a subsequent set of inclusion and exclusion criteria (sample size >50 patients; inclusion of blinatumomab in trials). These concerns are discussed below.

The process for study selection was adequate (two independent reviewers), but the processes for data extraction and quality assessment were not described in the CS.

The submitted evidence generally reflects the decision problem, although it should be noted that subgroup analyses against specific scoped comparators were not available for the non-randomised study. Appraisal and discussion of the single-arm phase 2 trial (Study MT103-211) is presented below primarily as context for the comparison with a historical cohort.

The ERG identified several issues with the conduct and reporting of the systematic review for evidence of clinical effectiveness and thus there is an uncertain chance of systematic error, however we believe that all relevant available randomised evidence has been located.

**Table 2 Quality assessment of the CS systematic review of clinical effectiveness**

| CRD Quality Item | ERG Response |
|---|---|
| 1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question? | Yes—however, an additional set of criteria were applied at the final stage. Following clarifications, the ERG was satisfied that the criteria were appropriate. |
| 2. Is there evidence of a substantial effort to search for all relevant research? | Yes—search was thorough and included relevant databases. |
| 3. Is the validity of included studies adequately assessed? | Uncertain—while the ERG generally agreed with the company's assessment of TOWER, the CS appraisal of the non-randomised evidence was inappropriate. |
| 4. Is sufficient detail of the individual studies presented? | Yes – details of methods, statistical analysis and results were available in the CS, though additional results for subgroups including scoped comparators required a clarification. |
| 5. Are the primary studies summarised appropriately? | Yes – data were narratively synthesised with effect estimates and 95% CI. |

### 4.1.1 Description of company's search strategy

The company reports one set of broad searches for published RCTs and observational studies (see CS section 4.1.2). These searches were undertaken in October 2015 and updated in November 2016 in a wide range of sources. These searches aimed to retrieve literature for the clinical effectiveness of current treatments in adult patients with R/R Ph- B-precursor ALL.

Search terms for interventions and date limits were not included and most search terms and lines were combined appropriately. Furthermore, hand searching of reference lists of identified reviews, checking relevant organisations and websites, conference proceedings, HTAs and systematic reviews is also reported. There are some issues in the medical bibliographic database searches that may have resulted in some records being missed, but the use of other search terms and searching in other sources mean that overall the clinical effectiveness searches appear to be comprehensive and should have retrieved all studies that met the inclusion criteria. Our targeted independent searches identified no additional relevant studies.

### 4.1.2 Statement of the inclusion / exclusion criteria used in the study selection

The inclusion criteria for the systematic review were in the main clearly stated (see CS Table 4-3 p 53), though a secondary set of inclusion and exclusion criteria were applied not included in this table. Inclusion criteria for the population matched the decision problem, focusing on adult patients with relapsing/refractory Philadelphia-chromosome-negative B-precursor ALL. Appropriately, paediatric, non-relapsing/refractory, non-B-precursor populations were excluded, as were studies not conducted in human subjects.

Inclusion criteria for the intervention specified that studies were to test blinatumomab or any other available pharmacological interventions for relapsing/refractory ALL, and inclusion criteria for comparators specified inclusion of placebo, best supportive care or any active interventions. This was appropriate given the inclusion of several scoped comparators (FLAG with or without idarubicin, or clofarabine-based regimens, or best supportive care). The appropriately broad set of comparators could hypothetically have permitted network meta-analysis of interventions.

Inclusion criteria for outcomes included some, but not all, scoped outcomes. Outcomes relating to efficacy included overall survival (OS), progression-free survival (PFS), clinically-relevant PFS, rates and duration of response, disease-free survival and time-to-treatment failures. Of concern is that the CS did not distinguish between PFS and 'clinically-relevant' PFS. Moreover, scoped outcomes not included related to health-related quality of life (HRQoL) and allogeneic stem cell transplant (allo-SCT), both of which are of importance in decision-making. Upon request for clarification by the ERG, the company specified in clarification response A5 that reviewers did not exclude studies solely on outcomes in the inclusion/exclusion criteria.

Inclusion criteria for trial design specified RCTs, including crossover studies, and non-randomised clinical trials, observational studies, case-control studies, and single-arm studies. Excluded study designs stated in the criteria were case reports, guidelines, letters, editorials, pharmacokinetic studies or narrative reviews. These criteria appeared appropriate, though the company subsequently excluded two small single-arm studies under a subsequent set of exclusion criteria.

At the final stage, the company applied additional exclusion. It excluded studies with sample size of less than 50 patients or that did not include blinatumomab within trial. The exclusion criterion relating to sample size was especially concerning given the relative rarity of the disease. The ERG was initially concerned that application of these secondary inclusion and exclusion criteria could possibly result in the exclusion of trials that could inform a network meta-analysis. However, in response to clarification question A5, the company noted that any RCTs excluded under these secondary criteria would have included irrelevant comparators and would not have informed an NMA. Furthermore, excluded non-randomised studies would not have included helpful comparisons between blinatumomab and scoped comparators. On balance, the ERG agrees that excluding these studies was reasonable and would not have provided additional information relevant to the decision problem.

The company did not discuss review-level biases. Though the ERG believes that key sources of bias at the review level, such as non-retrieval of articles and publication bias, were unlikely to have affected this review (particularly in light of the company's response in clarification question A5), it is unable to say with certainty that there is little systematic error in this review.

### 4.1.3 Identified Studies

#### 4.1.3.1 Randomised evidence: TOWER trial

The included RCT was summarised in CS Table 4-4, p 56. This RCT was TOWER. As discussed above, the ERG was satisfied upon response to clarification questions that excluded RCTs would not have contributed to analysis. The ERG was provided with the CSR of the interim analysis of TOWER electronically. This trial was sponsored and funded by Amgen.

Information on TOWER is summarised in CS Tables 4-5 (location, design and eligibility criteria, CS p 57), 4-6 (study drugs and concomitant medications, CS p 59), 4-7 (study endpoints and pre-specific subgroups, CS p 61), 4-8 (statistical analyses, CS p 64) and 4-9 (patient characteristics, CS p 68). Patient disposition is summarised in CS Figure 4-3 (p 67). All key details of study samples, analysis, groups, patient disposition and related information are presented, with the exception of specific outcome data that were requested in clarification and information on the significance of differences between groups, also requested in clarification.

TOWER was designed as a two-armed, open-label trial to compare blinatumomab against standard of care (SOC) chemotherapy. Dosing of blinatumomab was as in the marketing authorisation. SOC chemotherapy consisted of one of four regimens: FLAG with or without anthracycline, clofarabine-based regimen, high-dose cytarabine arabinoside (also known as HiDAC) with or without anthracycline, or high-dose methotrexate-based regimen. The company observes on CS p 16 (as well as pp 44 and 60) that FLAG with or without anthracycline is similar to the scoped comparator, FLAG with or without idarubicin, as idarubicin is an anthracycline-type drug. The ERG clinical advisor agreed that this was reasonable. The company argued on CS p 25 that the whole SOC chemotherapy arm could be used to stand for FLAG with or without anthracycline in analyses based on the views of clinical experts consulted by the company. The ERG clinical advisor did agree that it would be reasonable not to expect a large difference between SOC treatment options. However, the treating investigator's decision as to which SOC chemotherapy arm to be used was recorded before randomisation, allowing for meaningful subgroups comparisons between, e.g., 'clofarabine-eligible' patients who received blinatumomab and patients in the SOC chemotherapy arm who received clofarabine. While noting that subgroup analyses were underpowered and included small sample sizes, the ERG noted that clofarabine appeared to be numerically superior to blinatumomab, though not significantly so, in analyses for

OS and EFS; this was not the case for comparisons between blinatumomab and FLAG-based regimens (see sections 4.2.1 and 4.2.2).

Patient disposition is summarised in a flowchart (Figure 4-3, CS p 67). The ERG summarises patient disposition for TOWER in Table 3. Arms were imbalanced in terms of number not receiving the allocation treatment; as noted on CS p 66 18.7% of patients in the SOC chemotherapy arm did not receive the intended treatment as opposed to 1.5% in the blinatumomab arm. Reasons for this were provided in the flowchart and are documented in Table 4. Moreover, the ERG noted on CS pp. 108-109 that [redacted] of those enrolled in the blinatumomab arm started six or more cycles of the study drug. This was not explained in the CS and the ERG clinical advisor was not able to suggest a plausible reason for this. Additionally, [redacted] of patients in the SOC chemotherapy arm received blinatumomab subsequently (see CS p 111, Table 4-32), which suggests an issue of drop-in. More patients in the SOC arm also received innovative therapies than in the blinatumomab arm ([redacted], CS p 110). The ERG reconstructed patient disposition for 'FLAG-eligible' and 'clofarabine-eligible' subgroups based on CS Table 4-9 (p 68) and clarification tables A-13, A-18 and A-20.

The ERG notes two additional considerations for trial validity. First, patients with relapse after greater than 12 months in remission were excluded from this trial. The company notes on CS p 123 that these patients enjoy better prognosis, and the ERG clinical advisor agreed with this assertion. Second, consolidation criteria for blinatumomab (i.e. the point at which the decision is made to continue after two cycles of treatment) varied in TOWER from the marketing authorisation. As noted on CS p 124, the marketing authorisation for blinatumomab notes that patients should reach CR or CRh* to continue; whereas in TOWER, patients needed to reach CR, CRh* or CRi, or have ≤5% bone marrow blasts. However, the company notes that of patients achieveing CR, CRh* or CRi, 93.4% of them were included in the CR or CRh* categories. The company did not provide in the CS evidence of how many patients would have been included on the basis of ≤5% bone marrow blasts, though the ERG clinical advisor suggested that this was, in practice, not a major issue to trial validity.

Key patient characteristics from the full analysis set are reproduced in Table 5 below, and are presented in Table 4-9 (CS p 68) as well as clarification Tables A-18 and A-19. The company did not present significance tests for differences between arms, nor did the company provide in the CS evidence of balance between arms on time from initial diagnosis to randomisation or on time

from last relapse to randomisation, but these were supplied in response to clarification question A8. The arms were not significantly different on any of these characteristics. The ERG further requested, tests for difference between arms in the safety analysis set and received these in response to clarification question A10. No significant or noticeable differences were found. Demographic characteristics for patients within comparator subgroups (e.g. 'FLAG-eligible' blinatumomab patients vs. FLAG patients in SOC chemotherapy) were not provided.

**Table 3 Participant disposition in TOWER (from CS Table 4-9, CS Appendix III, clarification Table A-13)**

| | All patients | | 'FLAG-eligible' patients | | 'Clofarabine-eligible' patients | |
|---|---|---|---|---|---|---|
| | **Blinatumomab** | **SOC chemotherapy** | **Blinatumomab** | **FLAG with or without anthracycline** | **Blinatumomab** | **Clofarabine-based regimens** |
| [redacted] | | | | | | |

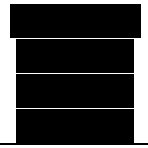
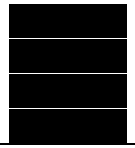
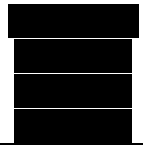
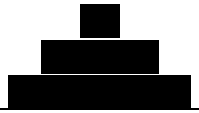
**Table 4 Reasons for discontinuation of treatment in TOWER (from CS Figure 4-3)**

| | |
|---|---|
| [redacted] | |

**Table 5 Characteristics between arms in TOWER FAS (from clarification Tables A-18 and A-19)**

| **Baseline characteristic** | **Blinatumomab (N = 271)** | **SOC chemotherapy (N = 134)** | **Total (N = 405)** | **p-value between arms** |
|---|---|---|---|---|
| Sex, n (%) | | | | [redacted] |
| Men | 162 (59.8) | 77 (57.5) | 239 (59.0) | |
| Women | 109 (40.2) | 57 (42.5) | 166 (41.0) | |
| Age | | | | [redacted] |
| Median (IQR), years | 37.0 (25.0, 54.0) | 37.0 (26.0, 58.0) | 37.0 (26.0, 56.0) | |
| Mean (IQR), years | [redacted] | [redacted] | [redacted] | |
| < 35 years, n (%) | [redacted] | [redacted] | [redacted] | |
| 35 to 54 years, n (%) | [redacted] | [redacted] | [redacted] | |
| 55 to 64 years, n (%) | [redacted] | [redacted] | [redacted] | |

| Baseline characteristic | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | Total (N = 405) | p-value between arms |
|---|---|---|---|---|
| ≥ 65 years, n (%) | [redacted] | [redacted] | [redacted] | |
| Maximum of central/local bone marrow blasts, n (%) | | | | [redacted] |
| < 50% | 69 (25.4) | 30 (22.4) | 99 (24.5) | |
| ≥ 50% | 201 (74.2) | 104 (77.6) | 305 (75.3) | |
| Unknown | 1 (0.4) | 0 (0) | 1 (0.2) | |
| Key ALL entry criterion, n (%) | | | | [redacted] |
| Refractory to primary or salvage therapy | 115 (42.4) | 54 (40.3) | 169 (41.7) | |
| In 1st relapse with 1st remission < 12 months | 76 (28.0) | 37 (27.6) | 113 (27.9) | |
| In untreated 2nd or greater relapse | 32 (11.8) | 16 (11.9) | 48 (11.9) | |
| Relapse after allo-SCT | 46 (17.0) | 27 (20.1) | 73 (18.0) | |
| No criteria met | 2 (0.7) | 0 (0) | 2 (0.5) | |
| Prior salvage therapy (per randomised strata), n (%) | | | | [redacted] |
| Yes | [redacted] | [redacted] | [redacted] | |
| No[a] | [redacted] | [redacted] | [redacted] | |
| Number of prior salvage regimens, n (%) | | | | [redacted] |
| 0[a] | 114 (42.1) | 65 (48.5) | 179 (44.2) | |
| 1 | 91 (33.6) | 43 (32.1) | 134 (33.1) | |
| 2 | 45 (16.6) | 16 (11.9) | 61 (15.1) | |
| 3 | 14 (5.2) | 5 (3.7) | 19 (4.7) | |
| > 3 | 7 (2.6) | 5 (3.7) | 12 (3.0) | |
| Prior allo-SCT, n (%) | 94 (34.7) | 46 (34.3) | 140 (34.6) | [redacted] |

| Baseline characteristic | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | Total (N = 405) | p-value between arms |
|---|---|---|---|---|
| Intended SOC chemotherapy regimen at randomisation<br>FLAG ± anthracycline based regimen<br>High-dose methotrexate based regimen<br>Clofarabine or clofarabine based regimen<br>HiDAC based regimen |  |  |  |  |
| Time from initial diagnosis to randomisation, months<br>Mean (SD)<br>Median (IQR) |  |  | |  |
| Time from last relapse to randomisation, months<br>N<br>Mean (SD)<br>Median (IQR) |  |  | |  |

#### 4.1.3.2 Non-randomised evidence: comparison of Study MT103-211 against a historical comparator

The company presented a single-arm, phase 2 trial, Study MT103-211, and a comparison of data from this trial against a historical cohort. In the presence of comparative evidence, the ERG did not regard the single-arm trial *per se* as relevant and thus the remainder of this critique is focused on the comparison between Study MT103-211 and a historical cohort. The ERG was provided with the publication arising from this comparison.[22] The study was funded and sponsored by Amgen.

Information on the single-arm trial of blinatumomab is summarised in CS Table 4-22 (demographic characteristics, CS p 96), and in CS section 4.11.2 onwards. Information on the design of the historical comparator study is summarised in CS Table 4-26 (CS p 102). Patient disposition for the single-arm, phase 2 trial was summarised in CS Figure 4-13 (p 95). Demographic characteristics for the historical comparator were presented in CS Appendix V. Key details of study samples, analysis, groups, patient disposition and related information are presented either in the CS or in the relevant publication.

According to CS Figure 4-13, Study MT103-211 enrolled 189 patients to receive blinatumomab with dosing according to its marketing authorisation. All 189 patients received treatment. Two patients terminated the study prematurely for reasons other than death (one due to withdrawal of consent and one due to loss to follow-up). All 189 patients were retained for statistical analyses. The historical comparator, which was based on a sample of 1139 patients drawn from long-term follow-up of first-line trials, included 694 patients with data on CR and 1112 patients with OS data.[7] Patients enrolled in the historical comparator received one of four SOC chemotherapy regimens similar to regimens prescribed in the SOC chemotherapy arm in TOWER. Subgroup analyses by type of SOC chemotherapy were not presented.

Because populations in Study MT103-211 and the historical comparator are non-equivalent, the company presented in Appendix V of the CS results from matching the two arms using a weighting methodology. These findings are reproduced below in Table 6. The arms were not significantly different once matched except for on region. Of note is that the company did not provide evidence of covariate balance using the remission analyses.

**Table 6 Descriptors and covariate balance between Study MT103-211 and historical comparator in OS analysis (from CS Appendix V)**

| Factor | Before adjustments | | | | After adjustments | | | |
|---|---|---|---|---|---|---|---|---|
| | **Blinatumomab Trial (Study MT103-211) (N=189)** | **Historical Dataset (Study 20120310) (N=1131)** | **Standardized Difference** | **p-value** | **Blinatumomab Trial (Study MT103-211) (N=189)** | **Historical Dataset (Study 20120310) (N=1131)** | **Standardised Difference** | **p-value[a]** |
| Age<br>Mean (SD) | 41.1 (17.3) | 37.4 (14.2) | 0.233 | 0.0014 | 36.9 (15.7) | 38.1 (14.5) | -0.078 | 0.4694 |
| Female<br>n (%) | 70 (37) | 477 (42) | -0.105 | 0.1850 | 68 (36) | 475 (42) | -0.122 | 0.2913 |
| Duration since initial diagnosis in months<br>Mean (SD) | 28.1 (36.5) | 12.2 (12.3) | 0.585 | <0.0001 | 15.6 (18.0) | 13.8 (15.1) | 0.106 | 0.1740 |
| Region-- Europe<br>n (%) | 95 (50) | 822 (73) | -0.473 | <0.0001 | 89 (47) | 780 (69) | -0.452 | 0.0001 |
| Prior allo-SCT<br>n (%) | 64 (34) | 209 (18) | 0.355 | <0.0001 | 38 (20) | 238 (21) | -0.019 | 0.8475 |
| Number of prior salvage therapies[b]<br>Mean (SD) | 2.36 (0.99) | 1.52 (0.82) | 0.924 | <0.0001 | 1.69 (0.87) | 1.64 (0.89) | 0.061 | 0.5334 |
| Primary refractory and in first salvage<br>n (%) | 4 (2) | 62 (5) | -0.177 | 0.0587 | 19 (10) | 57 (5) | 0.194 | 0.1882 |
| Refractory to preceding salvage<br>n (%) | 98 (52) | 259 (23) | 0.627 | <0.0001 | 51 (27) | 305 (27) | -0.002 | 0.9833 |

[a] p-value is from a logistic regression model for the binary variables and a linear regression for the continuous variables
[b] Includes the last line of treatment, which is blinatumomab for blinatumomab patients
Note: based on survival data analysis set

### 4.1.4 Relevant studies not included in the submission

All relevant completed RCTs were identified by the CS.

The ERG identified several ongoing studies. See section 4.4.

### 4.1.5 Description and critique of the approach to validity assessment

The CS included a quality assessment for TOWER using criteria recommended by NICE. The quality assessment was presented in tabular format in CS Table 4-10 (p 70) and is reproduced below in Table 7. The ERG substantially agrees with the company assessment of study quality, except for the characterisation of all analyses being undertaken as ITT. Analyses of HRQoL used a smaller complete-case analysis set. The ERG further noted several additional issues with trial quality. According to the TOWER CSR (p 248), 11.1% of patients in the blinatumomab arm and 11.9% of patients in the SOC chemotherapy arm were incorrectly stratified. However, analyses for complete remission (CR) within 12 weeks of treatment initiation or complete remission including with partial of incomplete haematological recovery (CR/CRh*/CRi) within 12 weeks of treatment initiation were unchanged (CS Appendix III, Table 3) and analyses for event-free survival matched closely (alternative stratification values: HR=0.50, 95% CI [0.39, 0.65], from Table 4, Appendix III of CS; cf. HR=0.55 in main analyses). Furthermore, twice as many patients in the blinatumomab arm as in the SOC chemotherapy arm had an 'important protocol deviation' (18.5% vs. 9.0%, CSR p 59). The ERG is unable to assess the impact of this difference on trial validity.

Another issue with respect to trial quality and, specifically, quality of subgroup analyses is that TOWER was not powered to detect subgroup differences. This is especially relevant when interpreting the focused subgroup analyses relating to the scoped comparators of FLAG and clofarabine.

**Table 7 Assessment of TOWER trial quality (from CS Table 4-10)**

| CRD question | CS response | ERG response |
|---|---|---|
| Was randomisation carried out appropriately? | Yes, after eligibility into the study was confirmed, patients were randomised in a 2:1 ratio to receive blinatumomab or SOC chemotherapy using an IVRS. | Agreed |
| **Was the concealment of treatment allocation adequate?** | Yes, allocation was concealed by using an IVRS. | Agreed |
| **Were the groups similar at the outset of the study in terms of prognostic factors?** | Yes, baseline characteristics were well balanced between treatment groups. | Agreed |
| **Were the care providers, participants and outcome assessors blind to treatment allocation?** | • No, the study was open label so care providers, participants, and investigators were not blinded to treatment.<br>• The complexity of combination SOC chemotherapy regimens means that it would have been extremely difficult and unethical to conduct a double-blind study of a single-agent intervention in this disease area. | Agreed |
| **Were there any unexpected imbalances in drop-outs between groups?** | • Yes, following randomisation there was a greater number of dropouts in the SOC chemotherapy arm (18.7%) than in the blinatumomab arm (1.5%). The most common reason for drop-out in patients who did not receive their allocated intervention in the SOC chemotherapy arm was patient choice, which is | Agreed |

| | | |
|---|---|---|
| | unsurprising given the extremely poor prognosis and substantial morbidity associated with SOC chemotherapy.<br>• However, no overall imbalance in drop outs was reported in patients who received at least one dose of study drug. | |
| **Is there any evidence to suggest that the authors measured more outcomes than they reported?** | • Yes, data on the secondary endpoint of time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event and exploratory endpoint of changes in ALLSS scores over time were not included in the expedited primary analysis CSR – PRO outcomes will be reported at a later date in a separate report.<br>• However, data on the secondary endpoint of time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event have been included in this dossier as data were available for analysis at the time of submission. | Agreed |
| **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?** | Yes, an ITT analysis was reported for all efficacy outcomes. | Analyses for HRQoL presented in CS section 4.7.7 (p 81) and Appendix III were only undertaken on those who had a non-missing baseline and at least one post-baseline assessment. |
| ALLSS, acute lymphoblastic leukaemia symptom scale; CSR, clinical study report; EFS, event-free survival; EORTC QLQ-C30 GHS/QoL, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Global Health Status/Quality of Life; ITT, intention-to-treat; IVRS, interactive voice-response system; PRO, patient reported outcome; SOC, standard of care. | | |

In CS Appendix V, the company presents appraisal of both the single-arm Study MT103-211 and the comparison with a historical cohort using STROBE. The ERG regards that this is inappropriate given that STROBE is a reporting guideline, not a tool for critical appraisal. The ERG reappraised the quality of both the single-arm study and its comparison against a historical cohort using NIH guidelines for appraisal of observational studies.[23]. The ERG reappraisal is presented in Table 8 below. Several quality issues in the comparative analysis are worth noting, particularly with respect to the comparative analysis, and the examination of CR within this analysis. Aside from the challenges to generalizability and similarity that accrue from comparing a contemporaneous study with a historical cohort, the population in the historical cohort for which CR data were available was considerably smaller than available patients in the larger cohort. Moreover, CR was defined differently by the study groups contributing data to the historical cohort, and these definitions were not always commensurate with the definition in the blinatumomab arm. The ERG is unable to assess the impact of these quality issues on study findings.

**Table 8 ERG reappraisal of Study MT103-211 and comparison with historical cohort**

| Criteria | MT103-211 (Topp 2015)[17] | Comparative study (Gokbuget 2016)[22] |
|---|---|---|
| 1. Was the research question or objective in this paper clearly stated? | Yes—'We aimed to confirm the activity and safety profile of blinatumomab for acute lymphoblastic leukaemia'. | Yes—'To provide context for the clinical trial, we conducted a 'historical comparator' study to evaluate CR and OS with standard of care salvage chemotherapy in adults with Ph-negative, B-precursor R/R ALL'. |
| 2. Was the study population clearly specified and defined? | Yes—relevant patient population to decision problem | Yes—relevant patient population to decision problem |
| 3. Was the participation rate of eligible persons at least 50%? | Yes—189 of 267 patients screened | Yes—flow from historical database to patients in analysis documented[7] |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes—protocol changes do not appear to relate to recruitment or changes in criteria | No—populations were not recruited contemporaneously, and minor differences in key inclusion/exclusion criteria (i.e. extramedullary relapse) though patients in historical comparator were further selected |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | Yes—description of multi-stage sample size estimation | No—for comparison between historical cohort and treatment cohort |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | Yes—blinatumomab administration prior to outcomes | Yes—chemotherapy before outcomes |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes—given median survival is measured in months | Yes |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | NA—chemotherapy administered per protocol | NA |

| | | |
|---|---|---|
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes—exposure to blinatumomab | No—treatment intensity not available for most patients (see Gokbuget 2016 on international reference analysis) |
| 10. Was the exposure(s) assessed more than once over time? | NA | NA |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes—measures in CSR match measures in published report and CS | No—differences in definition of CR between intervention and control; and within control group |
| 12. Were the outcome assessors blinded to the exposure status of participants? | No—open label trial | No |
| 13. Was loss to follow-up after baseline 20% or less? | Yes—9 discontinued before first response assessment, 1 lost to follow-up and 1 withdrew consent | No—high levels of missingness in CR data for historical comparator (e.g. for CR—694/1139, 61% used in stratum analysis) |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | Yes—stratification of results by prespecified patient subgroups | Yes—use of IPTW and weighted analysis to compare on outcomes |

### 4.1.6 Description and critique of company's outcome selection

The NICE scoped outcomes were OS, event-free survival (EFS), relapse-free survival, treatment response rates (including minimal residual disease [MRD], haematological responses and complete remission [CR]), time to and duration of response, rate of stem cell transplant, adverse effects of treatment and HRQoL. The CS reports in the decision problem (CS p. 20) that effectiveness of blinatumomab in relation to all of these outcomes is discussed. On clarification, the ERG received a table of outcomes reported in the CS against scoped outcomes (clarification A1). Table 9 below is based on the company's response. While the ERG agreed that outcomes as presented generally met scoped outcomes, data for relapse-free survival were not in fact presented in the comparison between Study MT103-211 and the historical comparator, and definition of CR is opaque and difficult to interpret in this non-randomised comparison.

**Table 9 Outcomes in relevant included studies as compared to scoped outcomes (from clarification A1)**

| NICE scope outcome | TOWER data presented in the company submission | Comparison between Study MT103-211 and historical cohort |
|---|---|---|
| Overall survival | Yes | Yes |
| Event-free survival | Yes | No--results not presented in comparison |
| Relapse-free survival | Partial--company states that duration of CR and of CR/CRh*/CRi are similar to relapse-free survival | No--analyses planned, but results not presented |
| Treatment response rates (including MRD) | Yes--MRD, CR and CR/CRh*/CRi within 12 weeks of treatment initiation | Yes--rate of CR and remission-related outcomes |
| Time to and duration of response | Time to response: no<br>Duration of response: yes (duration of CR, and of CR/CRh*/CRi) | No--results not presented in comparison |
| Rates of stem cell transplant | Yes--incidence of post-baseline allo-SCT | Yes--proportion of patients receiving allo-SCT |
| AEs of treatment | Yes | No |
| HRQoL | Yes--time to 10-point decrease in quality of life questionnaire or EFS event; time to 10-point decrease in quality of life questionnaire; change from baseline on quality of life scales | No |

#### 4.1.6.1 TOWER

Outcomes in TOWER were defined in Table 4-7 (CS p 61). The ERG regarded that outcome definitions were reasonable and appropriate. Overall survival was defined as time from randomisation to death. Event-free survival (EFS) was defined on CS p 61 as time to relapse after achieving CR/CRh*/CRi or death, with patients who did not recover being assigned a duration of 1 day.

Outcomes relating to treatment response rates were defined in several different ways: minimal residual disease (MRD), complete remission (CR) and either CR, CR with partial haematological recovery (CRh*) or CR with incomplete haematological recovery (CRi). The ERG clinical advisor noted that each definition related to a progressively lesser definition of treatment response, but that there was no major difference between CRh* and CRi. MRD was defined as 'MRD level below $10^{-4}$ by quantitative PCR or flow cytometry' (CS p 61); that is, a level of leukaemia cells in the bone marrow below 1 in 10000 bone marrow cells. CR was defined on CS p 61 as '≤5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/μL, and ANC > 1,000/μL)'; that is, the immature blood cells that cause ALL are under control, the patient is not experiencing signs or symptoms of the disease, and levels of platelets and neutrophils are above a stated threshold. CRh* was defined as '≤ 5% blasts in the bone marrow, but with partial recovery of peripheral blood counts (platelets > 50,000/μL and ANC > 500/μL)' and CRi was defined as '≤ 5% blasts in the bone marrow, but with incomplete recovery of peripheral blood counts (platelets > 100,000/μL **or** ANC > 1000/μL)'. Outcomes presented included rates of MRD, CR and CR/CRh*/CRi within 12 weeks of treatment initiation, as 12 weeks is the duration of the two induction cycles of treatment. The company also presented proportion of those achieving CR/CRh*/CRi who went on to attain MRD within 12 weeks of treatment initiation.

The company stated that duration of CR, and duration of CR/CRh*/CRi, could be considered similar to RFS, and measured duration of response. The ERG agreed that this was a reasonable equivalence.

Incidence of allo-SCT was measured using the proportion of patients receiving allo-SCT after randomisation. The company also presented 100-day mortality following allo-SCT.

HRQoL was measured using the EORTC QLQ-C30 and ALLSS (ALL Symptom Scale) but only data from the EORTC QLQ-C30 were presented in the CS. The questionnaire includes a general quality of life subscale and several subscales: five functional scales, three symptom scales and six additional single items. Data on HRQoL were collected at the start of each cycle, and then at the end of two and four weeks in each cycle. In the first two cycles, HRQoL data were also collected at the start of the second week of each cycle. The CS did not present specific information to support the validity or reliability of the EORTC QLQ-C30, though the ERG notes that it appears to be a widely used tool. The CS stated on p 81 that a change in scale score of between 5 and 10 points is clinically meaningful, but it was not clear how the cited evidence supported this assertion. HRQoL was presented in several forms: time to either a decrease in the quality of life subscale of the EORTC QLQ-C30 of 10 points, death or relapse (CS p 81); time to a decrease in the quality of life subscale of the EORTC QLQ-C30 of 10 points (response to clarification A17); and change from baseline at each measurement point in the first five cycles of treatment (Appendix III). The company further presented change from baseline for each subscale and single item in an attached file. The ERG noted that while the approach to analysis of HRQoL was reasonable, interpretation of the analysis of time to HRQoL decline or relapse or death is not intuitive.

#### 4.1.6.2 Comparison of Study MT103-211 against a historical comparator

Three outcomes were presented as part of the comparison of MT103-211 against a historical comparator: OS, complete remission and rate of allo-SCT. OS and rate of allo-SCT were defined in this comparison as in TOWER. However, the complete remission outcome, which is described in the CS as 'complete remission by study groups', or CRsg, is more challenging to interpret. According to the main study publication from this comparison, CRsg refers to the presence of either CR or CRh*, using similar definitions to those used in TOWER, within 12 weeks of treatment initiation in the blinatumomab arm (i.e. data collected in Study MT103-211) and of one of several definitions of CR in the historical comparator, at times including recovery of peripheral counts and at times relying on proportion of bone marrow blasts alone. Thus, patients in the historical comparator were required, depending on study group, to meet one of several definitions of CR. This suggests that definitions of CR are incommensurate between arms, and thus analyses of this outcome are difficult to interpret.

Though this analysis set out to compare RFS between arms, findings were not presented for this result.

### 4.1.7 Description and critique of the company's approach to trial statistics

#### 4.1.7.1 TOWER

**Key analyses.** Data from TOWER are interim data with a cutoff date of 4 January 2016. Data are currently unpublished, and thus presented as AIC. Data were supplied to the ERG in the CS as well as in a CSR. The company notes that data for CR, as well as for CR/CRh*/CRi, are complete, whereas other analyses will be updated. In the main, the ERG believed that the company's approach to trial statistics was reasonable, though it notes that interpretation of EFS is complicated by the analysis strategy chosen and analyses on HRQoL used a smaller analysis set than the FAS. The trial was closed early for efficacy because effectiveness on the primary outcome, OS, was significantly different at a p-value lower than the interim stopping boundary. The ERG believed this decision was adequately justified.

The CS reports data from TOWER for a full analysis set, which includes all randomised participants in each arm. The CS also includes data for a safety analysis set, which includes all participants in each arm who received at least one dose of blinatumomab or SOC chemotherapy as appropriate. Analyses in TOWER on the full analysis set were in the main ITT, but for the analyses of HRQoL which were performed on only those with non-missing baseline data and at least one non-missing post-baseline observation (CS p 81).

Details of analysis methods used in TOWER were presented in CS table 4-8 (p 64). The ERG regarded that methods used for analyses were reasonable, though it notes the use of special methods for the analysis of EFS. OS was analysed using a log rank test stratified by the age group, prior salvage therapy and prior allo-SCT, as these were the factors used in randomisation stratification. The CS also included a hazard ratio estimated using a stratified Cox regression model. Though this is a standard analysis method, the ERG could not find evidence of testing of the proportional hazards assumption. EFS was analysed using similar methods; however, the CS notes in a footnote to table 4-8 (p 65) that relapse times were analysed discretely to account for differing cycle lengths between the blinatumomab and SOC chemotherapy arms, and within the SOC chemotherapy arm. Thus, even though blinatumomab cycles are six weeks (four weeks on treatment, two weeks off) in duration, patients who relapsed in the second cycle of treatment were assigned an EFS duration of 8 weeks, 1 day, and patients who relapsed in the third cycle of treatment were assigned an EFS duration of 12 weeks, 1 day. Patients who never achieved

CR/CRh*/CRi were analysed as if their EFS duration was 1 day. While this is appears to be a reasonable approach, the ERG notes that it complicates interpretation of the summary hazard ratio generated from this analysis.

CR within 12 weeks of treatment initiation, CR/CRh*/CRi within 12 weeks of treatment initiation, MRD remission within 12 weeks of treatment initiation, MRD remission within 12 weeks of treatment initiation amongst those who achieved CR/CRh*/CRi, and incidence of post-baseline allo-SCT were analysed using a two-sided Cochran-Mantel-Haenszel test adjusted for the same stratification factors as noted above. The ERG regarded that this was a reasonable method.

Duration of haematological response (either of CR, or of CR/CRh*/CRi) was analysed using Kaplan-Meier plots, but without a significance test, and thus presented descriptively in the CS. An unstratified (i.e., not accounting for randomisation factors) log-rank test was presented by the company in clarification response A16.

Time to allo-SCT, and 100-day mortality following allo-SCT, were similarly analysed using Kaplan-Meier plots. Though mortality following allo-SCT was presented in the CS, Kaplan-Meier plots with unstratified log-rank tests were presented in response to clarification question A15.

HRQoL was analysed in a variety of ways. Time to EFS or a clinically meaningful decrease in HRQoL, defined as a 10-point decrease in the quality of life scale in the EORTC QLQ-C30, or relapse or death was analysed using similar methods to EFS. The ERG also sought analyses for time to clinically meaningful decrease in HRQoL alone and these were provided using Kaplan-Meier plots with a stratified log-rank test in response to clarification question A16. Individual scales and single items in the EORTC QLQ-C30 were also examined for change and summarised using a repeated-measures mixed-effects model. The ERG regarded that these methods were reasonable, though it noted that a smaller analysis population with non-missing baseline assessments and at least one post-baseline assessment was used, with no methods described to account for missing data.

**Sensitivity analyses.** Sensitivity analyses were presented in Appendix III for OS, EFS, CR within 12 weeks of treatment initiation, CR/CRh*/CRi within 12 weeks of treatment initiation, MRD remission within 12 weeks of treatment initiation, duration of CR and duration of CR/CRh*/CRi,

Sensitivity analyses generally restricted the sample to the safety analysis set, accounted for errors in stratification, censored (where appropriate) analyses at time of allo-SCT, and examined patients with evaluable post-baseline assessments. The ERG believed these subgroup analyses to be reasonable. Of note is that the sensitivity analyses of OS included an analysis accounting for 'drop-in' of patients in the SOC chemotherapy arm to blinatumomab; this affected [redacted] of the patients in the SOC chemotherapy arm.

**Subgroup analyses.** Subgroup analyses were reported in the CS. The only subgroup presented in the NICE scope was 'people for whom allogeneic stem cell transplantation is considered an appropriate treatment option', though this was not directly addressed in the scope. As mentioned by the ERG clinical advisor, the decision to undertake allo-SCT requires significant clinical judgment; thus, the ERG believes the company's decision to not present subgroup analyses for the scoped subgroup to be reasonable.

Subgroup analyses reported in the CS are discussed below. A 'global' p-value to test for heterogeneity in subgroup effects was presented for each model, though it is not clear how this global p-value was derived for models with more than two subgroups.

#### 4.1.7.2 Study MT103-211

Discussion of trial statistics focuses on the comparative analysis as the ERG believed this comparison to be probative, rather than the single-arm trial. Data from this comparison are now published in a separate paper[22] and findings from this paper are reproduced in the CS. The ERG believed that the approach to trial statistics in this comparison was reasonable.

Two strategies were used to compare blinatumomab against SOC chemotherapy (CS p 102-103). First, patients in both groups were stratified by age (<35 or ≥35) and whether patients had history of allo-SCT, or were otherwise in first salvage or in second or later salvage without allo-SCT. Comparisons were then undertaken between blinatumomab patients and historical comparator patients within strata, and then findings were reweighted across strata by the proportions in each strata in the blinatumomab arm. Second, patient characteristics were used to derive numerical weights to balance characteristics between arms. These weights, derived using inverse probability of treatment weighting (IPTW), were estimated using age, sex, region, duration between initial diagnosis and salvage therapy, and characteristics of disease and treatment history (number of salvage therapies, refractory status, allo-SCT). Diagnostic statistics for the weights presented in

Appendix V suggested that groups were appropriately balanced between arms, though some imbalance on region remained. On the whole, the ERG regarded that this analysis was appropriate.

Reweighted analyses were presented for proportion achieving CR or CRh* in the blinatumomab arm as compared to a remission-related outcome in the SOC chemotherapy arm, and for proportion receiving allo-SCT after salvage therapy. A weighted analysis was also presented for OS in terms of median survival and survival and 6 and 12 months using Kaplan-Meier methods.

IPTW analyses were undertaken for proportions achieving CR/CRh* or a remission-related outcome. Findings from this analyses were summarised in a logistic regression. Similar analyses were undertaken for OS, summarised using Cox proportional hazards regression. The ERG regards these methods as appropriate, but notes no explanation was provided for the absence of an allo-SCT analysis. As the company noted in response to clarification A19, the success of IPTW in approximating a randomised comparison relies on adjusting for all relevant covariates. While the source publication noted that the analysis included 'nearly all known important prognostic factors'[22] it is impossible to assert that there is no residual confounding in the analysis.

RFS was to be analysed but the company noted that the rate of missingness was too high to permit analysis. The ERG believed this decision to be reasonable at face.

No subgroup analyses were presented (beyond estimates used in the reweighting analyses for CR/CRh* and for OS) and no sensitivity analyses were presented.

### 4.1.8 Description and critique of the company's approach to the evidence synthesis

A narrative review of the evidence from TOWER and Study MT103-211 is presented in the CS. Where possible the ERG has checked key data presented in the CS against those in the publications and CSRs provided by the company. Data presented in the CS match the relevant CSRs and study publications. However, HRQoL data were not available in the CSR for TOWER, so the ERG were unable to verify these data specifically.

Because only one RCT and one non-randomised study (including comparison against a historical cohort) were submitted, meta-analysis was not undertaken. The ERG regards that this was

reasonable and appropriate. The ERG was further satisfied that any additional RCTs related to treatments for ALL would not have permitted a network meta-analysis.

The company provided comparisons from TOWER between blinatumomab and SOC chemotherapy, defined as an investigator choice of one of four protocol-specified treatment regimens: FLAG with or without anthracycline, clofarabine-based regimen, high-dose cytarabine arabinoside, or high-dose methotrexate-based regimen. Because investigator choice of SOC chemotherapy was recorded before randomisation, the company presented subgroup analyses between patients in the SOC arm who received FLAG +/- anthracycline and 'FLAG-eligible' patients who received blinatumomab, as well as between patients in the SOC arm who received a clofarabine-based regimen and 'clofarabine-eligible' patients who received blinatumomab. These subgroup results were initially presented in CS Appendix IV for outcomes OS, EFS, CR within 12 weeks of treatment initiation and CR/CRh*/CRi within 12 weeks of treatment initiation. Because of the importance of these subgroup analyses in understanding effectiveness of blinatumomab against each comparator, the ERG requested subgroup analyses for 'clofarabine-eligible' and 'FLAG-eligible' patients across all scoped outcomes. These were provided as part of clarification response A6.

The company also presented pre-specified subgroup analyses from TOWER on OS, EFS, CR within 12 weeks of treatment initiation and CR/CRh*/CRi within 12 weeks of treatment initiation. The subgroups related to age (<35 years or ≥35 years), prior salvage therapy, and prior allo-SCT, each of which was a randomisation stratification factor. Additional variables used to create subgroups were sex; race; an alternate age grouping (<35, 35-54, 55-64, or ≥65 years); number of prior salvage therapies (none, 1 or ≥2), including in a restricted sample of patients without prior allo-SCT; and relapse/refractory status (primary refractory, 1 prior relapse, ≥2 relapses, or unknown), including in a restricted sample of patients without prior allo-SCT; baseline laboratory values for bone marrow blasts and for platelet count; and region of the world.

## 4.2 Summary of submitted evidence

### 4.2.1 Overall survival

Overall survival (OS) was the primary efficacy endpoint in the TOWER study (see Table 10). Of the 405 randomized subjects, 251 deaths from any cause were reported: [redacted] in the SOC chemotherapy arm and [redacted] in the blinatumomab arm (CS Table 4-12, p74). The median

follow-up time was similar, 11.8 months in the SOC chemotherapy arm vs 11.7 months in the blinatumomab arm (CS Table 4-12, p74). The median OS (95% CI) was 4.0 months (2.9, 5.3) in the SOC chemotherapy arm compared with 7.7 months (5.6, 9.6) in the blinatumomab arm with a p-value = 0.012 (stratified log-rank test) (CS Table 4-12 p 74). The hazard ratio (95% CI) was 0.71 (0.55, 0.93) between treatment arms indicating a 29% reduction in hazard rate (improved survival) in the blinatumomab arm (CS Table 4-12 p 74).

Subgroup analyses were performed to explore the consistency of OS by the intended SOC chemotherapy regimen (determined prior to randomisation to blinatumomab or SOC chemotherapy) (Appendix IV, Table 1, p8). Results for patients receiving a FLAG-based or clofarabine-based SOC regimen (and the corresponding groups randomised to blinatumomab) are also shown in the Table below (Appendix IV, Table 1, p8). A hazard ratio less than 1 favours blinatumomab treatment. The hazard ratio favoured blinatumomab over FLAG-based SOC chemotherapy but was not significant compared with clofarabine-based chemotherapy; however, the ERG notes that only [redacted] people were randomised to clofarabine-based chemotherapy) (Appendix IV, Table 1, p8).

**Table 10 Overall survival, TOWER**

| | **Final analysis set** | | **FLAG-eligible patients** | | **Clofarabine-eligible patients** | |
|---|---|---|---|---|---|---|
| | **Blina**<br>**N = 271** * | **Total SOC chemo**<br>**N = 134** * | **Blina** [redacted] | **FLAG** [redacted] | **Blina** [redacted] | **Clofarabine** [redacted] |
| Overall survival | | | | | | |
| Died n (%)<br>Censored n (%)<br>Median follow up for OS (IQR) | [redacted]<br><br>11.7 [redacted] | [redacted]<br><br>11.8 [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS duration, median months (95% CI) | 7.7 (5.6, 9.6) †† | 4.0 (2.9, 5.3) †† | | | | |
| Hazard ratio blinatumomab:SOC (95% CI)<br>p value | 0.71 (0.55, 0.93) ††<br>p=0.012 | | [redacted] | | [redacted] | |

* = CS Figure 4-3, p 68
** = Clarification document Table A-11, p 28
*** = Clarification document Table A-14, p 32
**** = CS Table 4-12, p74
† = Appendix IV, Table 1, p8
†† = CS Table 4-12 p 74

The single-arm design of MT103-211 precludes direct comparison with comparator treatment regimens for R/R Ph- B-precursor ALL, so an observational historical comparator study (Study 20120310) was conducted to assess outcomes with SOC salvage chemotherapy regimens in a comparable patient population to MT103-211 (CS, p 101). Estimation of OS was a key secondary objective (CS, p 101). In order to address these differences in patient characteristics and allow a meaningful comparison of outcomes across studies, two approaches were taken: a reweighted analysis and an IPTW analysis (CS, p 102).

In the reweighted analysis (see Table 11), a weighted average of study outcomes from the historical cohort was derived based on the frequency distribution of known prognostic factors for R/R ALL in Study MT103-211 (CS, p 102–103). Six strata were defined by a combination of age (< 35 or ≥ 35 years) and prior lines of treatment (allo-SCT, in first salvage, in second or greater salvage) (CS, p 102–103). For OS, the Kaplan–Meier median and Kaplan–Meier proportions at 6 and 12 months were estimated within each stratum of the historical cohort, together with 95% CIs (CS, p 102–103). The proportions across strata were then pooled into a combined estimate with each stratum weighted to the percentage of patients observed in that stratum from Study MT103-211 (CS, p 102–103). The weighted median OS in the historical cohort was 3.3 months (95% CI 2.8, 3.6) compared with 6.1 months (4.2, 7.5) in Study MT103-211 (CS, p 103). The weighted 6- and 12-month survival percentages were 30% and 15% in the historical cohort compared with 50% and 28% in Study MT103-211 (CS, p 103).

**Table 11 Overall survival, reweighting analysis, comparison of MT103-211 with historical cohort**

| Stratum | | Historical cohort | | | | | Blinatumomab (Study MT103-211)** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age, years** | **Prior lines of treat-ment** | **N** | **Stratum %** | **Median OS, months (95% CI)** | **6 month survival, % (95% CI)** | **12 month survival, % (95% CI)** | **N** | **Stratum %** | **Median OS, months (95% CI)** | **6 month survival, % (95% CI)** | **12 month survival, % (95% CI)** |
| < 35 | allo-SCT*** | 108 | 9.7 | 3.8 (2.9, 4.5) | 35 (26, 44) | 14 (8,21) | 40 | 21.2 | 7.6 (3.5, 9.4) | 59 (41, 73) | 28 (11, 47) |
| < 35 | In 1st salvage **** | 258 | 23.2 | 5.7 (4.9, 6.3) | 46 (40, 52) | 25 (20, 30) | 10 | 5.3 | NE (4.1, NE) | 80 (41, 95) | 53 (17, 80) |
| < 35 | In 2nd+ salvage **** | 161 | 14.5 | 2.9 (2.3,4.0) | 28 (21, 35) | 16 (11, 22) | 40 | 21.2 | 6.3 (3.7, 12.6) | 53 (36, 68) | 38 (22, 550 |
| ≥ 35 | allo-SCT*** | 79 | 7.1 | 4.0 (2.8, 4.7) | 33 (23, 44) | 20 (12, 29) | 24 | 12.7 | 9.3 (3.3, NE) | 62 (40, 78) | 28 (6, 57) |
| ≥ 35 | In 1st salvage **** | 341 | 30.7 | 3.7 (3.2, 4.4) | 34 (29, 39) | 15 (11, 19) | 19 | 10.1 | 5.1 (2.8, 7.0) | 30 (11, 53) | 0.0 (NE, NE) |
| ≥ 35 | In 2nd+ salvage **** | 165 | 14.8 | 2.2 (1.7, 2.9) | 24 (17,30) | 13 (8, 19) | 56 | 29.6 | 3.7 (1.9, 6.5) | 39 (26, 51) | 19 (8, 32) |
| **Combined weighted estimate** | | **1112** | **-** | **3.3 (2.8, 3.6)** | **30 (27, 34)** | **15 (8,19)** | **189** | **-** | **6.1 (4.2, 7.5)** | **50 (43, 57)** | **28 (20, 36)** |

Data from CS, Table 4-28, p 106
** = Primary analysis data cut-off date (10 Oct 2013)
*** = all patients with a history of allo-SCT (could be in 1st, 2nd or greater salvage)
**** = all patients without a history of allo-SCT

A propensity score analysis was performed to balance measured patient characteristics in the historical cohort and Study MT103-211 (CS, p 103). The 6-month and 12-month OS rates were higher in blinatumomab patients (see Table 12), and the OS HR (blinatumomab vs. historical control) was 0.54 (CS, p 107).

**Table 12 Overall survival, IPTW analysis, comparison of MT103-211 and historical cohort**

| | **Historical cohort** | **Blinatumomab (Study MT103-211)** |
|---|---|---|
| OS, 6-month survival rate (95% CI) | 33% (31, 36) | 58% (55, 60) |
| OS, 12-month survival rate (95% CI) | 17% (15, 19) | 39% (36, 42) |
| OS, HR (95% CI) | 0.54 (0.40, 0.73) | |
| CS Table 4-29, p 107 | | |

### 4.2.2 Event-free survival

In the TOWER study, a total of [redacted] patients ([redacted]) in the blinatumomab arm and [redacted] patients ([redacted]) in the SOC chemotherapy arm had an EFS event (CS Table 4-16 p 78) (see Table 13). Blinatumomab improved EFS compared with the SOC chemotherapy with a HR of 0.55 (descriptive $p < 0.001$) (CS Table 4-16 p 78).

In the subgroup analysis, the hazard ratio also favoured blinatumomab over FLAG-based SOC chemotherapy, but was not significant compared with clofarabine-based chemotherapy.

### 4.2.3 Relapse-free survival

RFS was not explicitly defined as a TOWER endpoint, but the secondary endpoints of duration of CR and CR/CRh*/CRi have been considered (by the manufacturers) broadly synonymous with RFS (Clarification document p 10). These findings are presented below in discussion of duration of response. Analyses comparing Study MT103-211 to a historical cohort were intended to include RFS but these analyses were not presented due to high levels of missing data.

**Table 13 Event-free survival, TOWER**

| | Final analysis set | | FLAG-eligible patients | | Clofarabine-eligible patients | |
|---|---|---|---|---|---|---|
| | **Blina**<br><br>**N = 271*** | **Total SOC chemo; N = 134*** | **Blina** | **FLAG** | **Blina** | **Clofarabine** |
| Event-free survival | | | | | | |
| Events<br><br>Censored | [redacted]**** | [redacted]**** | [redacted]† | [redacted]† | [redacted]† | [redacted]† |
| EFS duration, median months (95% CI) | 0.0 [redacted]**** | 0.0 [redacted]**** | | | | |
| Hazard ratio blinatumomab: SOC (95% CI), p value | 0.55 (0.43, 0.71), p< 0.001**** | | [redacted]† | | [redacted]† | |

* = CS Figure 4-3, p 68
** = Clarification document Table A-11, p 28
*** = Clarification document Table A-14, p 32
**** = CS Table 4-16 p 78
† = Appendix IV, Table 2, p13

### 4.2.4 Haematologic response

#### 4.2.4.1 Complete remission-related outcomes

In the TOWER study, the proportion of patients achieving a CR within 12 weeks of treatment initiation was statistically significantly higher in the blinatumomab arm compared with the SOC chemotherapy arm (33.6% vs. 15.7%; $p < 0.001$) (see Table 14). Similarly, the proportion of patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation was statistically significantly higher in the blinatumomab arm compared with the SOC chemotherapy arm (43.9% vs. 24.6%, $p < 0.001$).

The odds ratios were not significant in the FLAG or clofarabine subgroups.

**Table 14 Complete remission-related outcomes, TOWER**

| | **Final analysis set** | | **FLAG-eligible patients** | | **Clofarabine-eligible patients** | |
|---|---|---|---|---|---|---|
| | **Blina N = 271*** | **Total SOC chemo N = 134 *** | **Blina** [redacted] | **FLAG** [redacted] | **Blina** [redacted] | **Clofarabine** [redacted] |
| Treatment response rates (haematologic responses): Rates of CR and CR/CRh*/CRi within 12 weeks of treatment initiation | | | | | | |
| CR, n (%)<br>95% CI [for % value] | 91 (33.6)****<br>(28.0, 39.5) | 21 (15.7) ****<br>(10.0, 23.0) | [redacted]† | [redacted]† | [redacted]†<br>† | [redacted]† |
| Odds ratio<br>p-value | [redacted]< 0.001 **** | | [redacted]† | | [redacted]† | |
| CR/CRh*/CRi, n (%)<br>95% CI [for % value] | 119 (43.9) ****<br>(37.9, 50.0) | 33 (24.6) ****<br>(17.6, 32.8) | [redacted]†† | [redacted]†† | [redacted]†† | [redacted]†† |
| Odds ratio<br>p-value | < 0.001**** | | [redacted]†† | | [redacted]†† | |

* = CS Figure 4-3, p 68
** = Clarification document Table A-11, p 28
*** = Clarification document Table A-14, p 32
**** = CS Table 4-14 p 76
† = Appendix IV, Table 3, p18
†† = Appendix IV, Table 4, p23

The predicted CR/CRh* rate in Study MT103-211 was higher than the CRsg rate in the historical cohort (49% vs. 26%) with the odds of achieving haematological remission significantly higher with blinatumomab (CS p 107) (see Table 15).

**Table 15 Complete remission, IPTW analysis, comparison of Study MT103-211 with historical cohort**

| | **Historical cohort** | **Blinatumomab (Study MT103-211)** |
|---|---|---|
| CRsg (historical cohort) and CR/CRh* (MT103-211) predicted rate (95% CI) | 26% (23, 30) | 49% (33, 65) |
| CR/CRh* vs. CRsg, OR (95% CI)*** | 2.68 (1.67, 4.31) | |
| CS Table 4-29, p 107 | | |

#### 4.2.4.2 Minimal residual disease

In the TOWER study, in the blinatumomab arm, 76.3% of CR/CRh*/CRi responders in the blinatumomab arm with at least one post-baseline MRD disease assessment had an MRD remission compared with 48.5% of responses in the SOC chemotherapy arm (descriptive [redacted]) (CS, p 79) (see Table 16). MRD remission rates also favoured blinatumomab when all randomised patients (i.e., the FAS) was used as the denominator rather than patients who achieved a CR/CRh*/CRi and had at least one post-baseline MRD assessment ([redacted]%) (CS, p 79).

In the subgroup analysis, MRD rate was higher (odds ratio >1) with blinatumomab than FLAG-based chemotherapy, but was not significantly different between blinatumomab and clofarabine (Clarification document, p 28).

**Table 16 Minimal residual disease rates, TOWER**

| | Final analysis set | | FLAG-eligible patients | | Clofarabine-eligible patients | |
|---|---|---|---|---|---|---|
| | **Blina** **N = 271*** | **Total SOC chemo** **N = 134 *** | **Blina** [redacted] | **FLAG** [redacted] | **Blina** [redacted] | **Clofarabine** [redacted] |
| Treatment response rates (Minimal residual disease remission [MRD]) | | | | | | |
| Patients with post-baseline assessment | [redacted]**** | [redacted]**** | | | | |
| Patients with CR/CRh*/CRi | 97 | 33 | | | | |
| MRD remission, n (% [of n with CR/CRh*/CRi]) | 74 (76.3) | 16 (48.5) | | | | [redacted] |
| 95 % CI (of % value) | [redacted] | [redacted] | | | | |
| p value | [redacted]**** | | | | | |
| MRD remission within 12 weeks of treatment initiation n/N (all patients) (%) | [redacted]† | [redacted]† | [redacted]** | [redacted]* * | [redacted]** | [redacted]** |
| p value | [redacted]† | | | | | |
| Odds ratio blinatumomab: SOC chemo (95% CI) | | | [redacted]** | | [redacted]** | |

* = CS Figure 4-3, p 68
** = Clarification document Table A-11, p 28
*** = Clarification document Table A-14, p 32
**** = CS Table 4-17 p 79
† = CS Appendix III, Table 6, p 15

### 4.2.5 Duration of response

In the TOWER study, of the patients who achieved best response of CR, median durations of response were longer in the blinatumomab arm: [redacted] months in the blinatumomab arm and [redacted] months in the SOC chemotherapy arm (CS, p 77), but this difference was not significant (Clarification document, p 59) (see Table 17).

**Table 17 Duration of response after CR, TOWER**

| | Final analysis set | | FLAG-eligible patients | | Clofarabine-eligible patients | |
|---|---|---|---|---|---|---|
| | **Blina N = 271*** | **Total SOC chemo N = 134 *** | **Blina** [redacted] | **FLAG** [redacted] | **Blina** [redacted] | **Clofarabine** [redacted] |
| Duration of response: Duration of haematological response (after CR) | | | | | | |
| Median time to event, months (95% CI)<br><br>Median follow-up time, months | [redacted]**** | [redacted]**** | | | | |
| p value | [redacted]† | | | | | |
| Events (death or relapse) in patients who achieved a CR within 12 weeks of treatment initiation n/N (pts achieving CR within 12 weeks) | | | [redacted]†† | [redacted]†† | [redacted]†† | [redacted]†† |
| Duration of CR in pts who achieved a CR within 12 weeks: HR (95% CI) | | | [redacted]†† | | [redacted]†† | |

* = CS Figure 4-3, p 68
** = Clarification document Table A-11, p 28
*** = Clarification document Table A-14, p 32
**** = CS Table 4-15 p 77
† = Clarification Table A-26, p59
†† = Clarification document Table A-8, p 25

In the TOWER study, for patients who achieved CR/CRh*/CRi, the median duration of response was 7.3 months in the blinatumomab arm and 4.6 months in the SOC chemotherapy arm (CS, p 77), but this was also not significantly different (Clarification document, p 59) (see Table 18).

**Table 18 Duration of response after CR/CRh*/CRi, TOWER**

| | Final analysis set | | FLAG-eligible patients | | Clofarabine-eligible patients | |
|---|---|---|---|---|---|---|
| | Blina N = 271* | Total SOC chemo N = 134 * | Blina [redacted] | FLAG [redacted] | Blina [redacted] | Clofarabine [redacted] |
| Duration of response: Duration of haematological response (after CR/CRh*/CRi) | | | | | | |
| Median time to event, months (95% CI)<br><br><br><br>Median follow-up time, months | 7.3<br>[redacted]****<br><br>[redacted] | 4.6<br>[redacted]<br>****<br>[redacted] | | | | |
| p value | [redacted]† | | | | | |
| Events (death or relapse) in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation n/N (pts achieving CR/CRh*/CRi) | | | [redacted]†† | [redacted]†† | [redacted]†† | [redacted]†† |
| Duration of CR/CRh*/CRi in pts who achieved a CR/CRh*/CRi within 12 weeks: HR (95% CI) | | | [redacted]†† | | [redacted]†† | |

* = CS Figure 4-3, p 68
** = Clarification document Table A-11, p 28
*** = Clarification document Table A-14, p 32
**** = CS Table 4-15 p 77
† = Clarification Table A-26, p59
†† = Clarification document Table A-9, p 26

### 4.2.6 Allogeneic stem cell transplant outcomes

Overall, the incidence of allo-SCT was similar across treatment arms (CS, p 80). In the blinatumomab arm, 65 patients (24.0%) underwent allo-SCT compared with 32 (23.9%) patients in the SOC chemotherapy arm (descriptive p = [redacted]) (CS, p 79) (see Table 19).

**Table 19 Incidence of allo-SCT, TOWER**

| | Final analysis set | | FLAG-eligible patients | | Clofarabine-eligible patients | |
|---|---|---|---|---|---|---|
| | Blina N = 271* | Total SOC chemo N = 134 * | Blina [redacted] | FLAG [redacted] | Blina [redacted] | Clofarabine [redacted] |
| Rates of stem cell transplant | | | | | | |
| Patients receiving post-baseline allo-SCT, n (%) | 65 (24.0)**** | 32 (23.9) **** | [redacted]† | [redacted]† | [redacted]† | [redacted]† |
| 95% CI (for % value) | [redacted] | [redacted] | | | | |
| Odds ratio (95% CI) | [redacted]**** | | [redacted]† | | [redacted]† | |
| p value | | | | | | |

* = CS Figure 4-3, p 68
** = Clarification document Table A-11, p 28
*** = Clarification document Table A-14, p 32
**** = CS Table 4-18, p 80
† = Clarification document Table A-12, p 29

In the TOWER study, 100-day mortality following post-baseline allo-SCT was assessed only in patients who achieved a CR/CRh*/CRi within 12 weeks of treatment initiation and did not receive additional anticancer therapy prior to allo-SCT (CS, p 80). Of these patients, 38 patients in the blinatumomab arm and 12 patients in the SOC chemotherapy arm had a post-baseline allo-SCT (CS, p 80–81) (see Table 20). The Kaplan–Meier estimate of 100-day mortality rate following post-baseline allo-SCT in these patients was [redacted] in the blinatumomab arm and [redacted] in the SOC chemotherapy arm (CS, p 81).

**Table 20 100-day mortality after allo-SCT in patients with CR/CRh*/CRi within 12 weeks of treatment initiation and no other anticancer therapies, TOWER**

| | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) |
|---|---|---|
| Number of patients with allo-SCT, n who achieved CR/CRh*/CRi within 12 weeks of treatment initiation and did not receive other anticancer therapies before allo-SCT | 38 | 12 |
| Died, n (%) | 10 (26.3) | 3 (25.0) |
| Censored, n (%) | [redacted] | [redacted] |
| 100-day mortality (Kaplan–Meier estimate), % (95% CI) | [redacted] | [redacted] |
| Data from CS Table 4-19, p 81 | | |

A reweighted analysis of incidence of allo-SCT after salvage therapy was presented for the comparison of Study MT103-211 against the historical cohort. More patients who received blinatumomab went on to receive allo-SCT as compared to patients in the historical cohort (25% vs 18%), but a significance test was not presented for this comparison.

### 4.2.7 Adverse events

In the TOWER study, 99.1% patients in the SOC chemotherapy arm and 98.5% of patients in the blinatumomab treatment arm had experienced at least one TEAE (CS, p 112). The total exposure in patients treated with SOC chemotherapy was lower than for patients treated with blinatumomab ([redacted] subject years vs. [redacted] subject years; CS, p 112) (see Table 21). The exposure-adjusted incidence rates for all TEAEs, serious AEs, and AEs of interest were substantially lower in the blinatumomab arm than in the SOC chemotherapy arm (CS, p 112). Results were not available for FLAG or clofarabine subgroups.

More patients in the blinatumomab arm experienced some types of TEAE than in the SOC chemotherapy arm, including serious AEs, and AEs leading to interruption and discontinuation of treatment (CS, p 112) (see Table 22). Rates of ≥ Grade 3 TEAEs and treatment-related AEs were lower in the blinatumomab arm than in the SOC chemotherapy arm. Rates of AEs of interest, life-threatening AEs, and fatal AEs were similar across study arms (CS, p 112).

**Table 21 Exposure-adjusted rates of AEs, TOWER**

| | **Blina N = 267** | **Total SOC chemo N = 109** |
|---|---|---|
| AEs of treatment: AEs that occurred after the first dose of study drug and up to 30 days after the last dose of study drug (i.e., treatment-emergent AEs [TEAEs]) are presented.** | | |
| **Exposure-adjusted rates of TEAEs:**<br>Exposure, subject years<br>**TEAEs**<br>Pts:<br>Events:<br>Exposure-adjusted event rate per 100 subject years:<br>**Serious events**<br>Pts:<br>Events:<br>Rate/100 p-yr<br>**AEs of interest**<br>Pts:<br>Events:<br>Rate/100 p-yr | [redacted]<br><br>[redacted]<br><br>[redacted]<br><br>349.4<br><br>[redacted] | [redacted]<br><br>[redacted]<br><br>641.9<br><br>[redacted] |
| CS Table 4-35, p 113 | | |

**Table 22 Treatment emergent adverse events, TOWER**

| | Safety analysis set* | | FLAG-eligible patients | | Clofarabine-eligible patients | |
|---|---|---|---|---|---|---|
| | **Blina** | **Total SOC chemo** | **Blina** | **FLAG** | **Blina** | **Clofarabine** |
| | **N = 267** | **N = 109** | [redacted] | [redacted] | [redacted] | [redacted] |
| AEs of treatment: AEs that occurred after the first dose of study drug and up to 30 days after the last dose of study drug (i.e., treatment-emergent AEs [TEAEs]) are presented.**** | | | | | | |
| TEAEs n (%) | 263 (98.5) | 108 (99.1) | [redacted]*** | [redacted]*** | [redacted]*** | [redacted]*** |
| Grade ≥ 3 | 231 (86.5) | 100 (91.7) | [redacted] | [redacted] | [redacted] | [redacted] |
| Serious AE | 165 (61.8) | 49 (45.0) | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment-related | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Led to interruption of investigational product | 86 (32.2) | 6 (5.5) | [redacted] | [redacted] | [redacted] | [redacted] |
| Led to discontinuation of product | 33 (12.4) | 9 (8.3) | [redacted] | [redacted] | [redacted] | [redacted] |
| AE of interest | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Life-threatening | [redacted] | [redacted] | | | | |
| Fatal | 51 (19.1) | 19 (17.4) | [redacted] | [redacted] | [redacted] | [redacted] |

* = CS Table 4-34, p112, referenced to TOWER primary analysis CSR (Tables 12-4 and 12-11)
** = Clarification document Table A-11, p 28, referenced to Amgen data on file, 2017
*** = Clarification document Table A-14, p 32, referenced to Amgen data on file, 2017.
**** = CS Section 4.12, p108

### 4.2.8 Health-related quality of life

In the TOWER study, blinatumomab delayed the time to clinically meaningful 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event (CS, p 81) (see Table 23). The HR for the blinatumomab versus the SOC chemotherapy arm was 0.67 (descriptive p = 0.0051) (CS, p 81). Blinatumomab also delayed the time to clinically meaningful decrease alone, irrespective of EFS event (*p*=[redacted]). Subgroup analyses were not presented for FLAG or clofarabine

Additional cycle-by-cycle HRQoL data were presented in CS Appendix III. The CS states on p 83 that the test for treatment effect in differences on HRQoL from a mixed effects model accounting for changes in HRQoL over time suggests a significant improvement in trend from blinatumomab (p=[redacted]).

**Table 23 Time to clinically meaningful HRQoL decrease or EFS event, TOWER**

| | **Full analysis set** | |
|---|---|---|
| | **Blina N = 240*** | **Total SOC chemo N = 95*** |
| HRQoL: Summary of EORTC QLQ-C30 GHS/QoL score and change from baseline at each scheduled assessment over time | | |
| Time to 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event | HR 0.67 (descriptive p = 0.0051).** | |
| Time to 10-point decrease in EORTC QLQ-C30 GHS/QoL, months, n/N Median (95% CI) IQR | [redacted]*** 8.1 (2.8, NE) [redacted] | [redacted]*** 1.0 (0.5, 1.8) [redacted] |
| p-value | [redacted]*** | |

* = CS Figure 4-3, p 68
**CS Section 4.7.7.1, p 81
***Clarification response A17

### 4.2.9 Subgroup analyses

In Appendix IV of the CS, the company provided subgroup analyses for the outcomes of OS, EFS, CR within 12 weeks of treatment initiation, and CR/CRh*/CRi within 12 weeks of treatment initiation. Subgroups tested related to age (<35 years or ≥35 years), prior salvage therapy, and prior allo-SCT, each of which was a randomisation stratification factor. Additional variables used to create subgroups were sex; race; an alternate age grouping (<35, 35-54, 55-64, or ≥65 years); number of prior salvage therapies (none, 1 or ≥2), including in a restricted sample of patients without prior allo-SCT; and relapse/refractory status (primary refractory, 1 prior relapse, ≥2

relapses, or unknown), including in a restricted sample of patients without prior allo-SCT; baseline laboratory values for bone marrow blasts and for platelet count; and region of the world.

Interaction findings in OS were not statistically significant for any subgroup analyses, nor were they significant for any subgroup analyses in CR within 12 weeks of treatment initiation or CR/CRh*/CRi within 12 weeks of treatment initiation. In EFS, there was evidence significant difference in effect depending on prior allo-SCT: HR [redacted] with prior allo-SCT and HR [redacted] without prior allo-SCT. There was also a significant difference in effect depending on number of prior relapses: HR [redacted] for those whose ALL was primary refractory, HR [redacted] for those with prior relapse, and HR [redacted] for those with ≥2 prior relapse; however, a large number of participants ([redacted] in the blinatumomab arm and [redacted] in the SOC chemotherapy arm) had an unknown relapse/refractory status.

## 4.3 Critique of the indirect comparison and/or multiple treatment comparison

There was no multiple treatment comparison undertaken in this analysis; thus, none was appraised.

## 4.4 Additional work on clinical effectiveness undertaken by the ERG

To address potential errors in the CS search, the ERG validated the the CS search using a combination of subject heading terms. Specifically, the main thesaurus headings for ALL (MeSH (exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/) and EMTREE (acute lymphoblastic leukemia/)) were not included in the CS search strategy. The ERG ran a test search in Ovid Medline and Ovid Embase for records with either of these terms and retrieved approx. 69,000 indicating that automatic mapping from the MeSH entry term used in line 1 of the company search (exp leukemia, lymphoblastic, acute/), which had retrieved 27,551, to both these terms had not occurred. However, further testing by the ERG indicates that the inclusion in the company searches of free-text terms for ALL in title and abstract appear to largely mitigate this problem.

The ERG also sought out ongoing studies on clinicaltrials.gov. Six studies were listed as 'ongoing', assessing blinatumomab among adults with Philadelphia negative relapse/refractory

ALL. Of these, two have already been linked in the clinicaltrials.gov website to published papers (Topp 2015 and Topp 2014, respectively), and a third is the TOWER study. Of the other three, one is an open-label study to evaluate the efficacy, safety, PK, PD and tolerability of blinatumomab in adult and paediatric Japanese patients, which will provide information on the dose limiting toxicities, steady state concentrations and clearance of blinatumomab. The second is a phase III randomised study in young people (aged 1-30 years) with a first relapse of childhood B-Lymphoblastic Leukaemia, which will contribute understanding of effectiveness in that population group. The third is a retrospective observational chart review study of Philadelphia chromosome-negative R/R ALL patients in the US. This is likely to provide evidence on the prognosis of patients initiating treatment for Philadelphia chromosome-negative R/R ALL between June 2014 and December 2016 at participating clinical sites in the US.

## 4.5 Conclusions of the clinical effectiveness section

The CS included a systematic review that was of reasonable quality, though the ERG noted that the chance of systematic error in the review was uncertain. This was principally owing to changes in inclusion and exclusion criteria and possible errors in the search. Upon considering responses to clarification and after additional work undertaken by the ERG, the ERG regarded that all relevant evidence had been included.

Three studies were submitted—an RCT, TOWER, which compared blinatumomab to SOC chemotherapy, a single-arm Phase 2 trial, and a comparison between the single-arm trial and historical cohort data receiving SOC chemotherapy. The ERG regarded that the single-arm trial *per se* was not relevant and thus focused on it in relation to the non-randomised comparison. The quality of both TOWER and the non-randomised comparison was generally good, and the ERG believed that the trials generally met the decision problem. However, the ERG noted several potential issues with trial validity in TOWER, including differential dropout between arms, the use of interim data in analysis, 'drop-in' to blinatumomab and use of innovative anticancer therapies. Moreover, the company suggested that the SOC chemotherapy arm as a whole was a proxy for FLAG-IDA, which was a scoped comparator, though this assertion relied on expert opinion alone. The non-randomised evidence corroborated TOWER, though the ERG found the analysis of remission-related outcomes (CR/CRh*) unreliable due to heterogeneity in outcome definitions between arms.

Findings from TOWER suggested that compared to SOC chemotherapy, blinatumomab prolongs OS and EFS, and results in higher numbers of patients achieving CR, CR/CRh*/CRi, or MRD within 12 weeks of treatment initiation. Blinatumomab also appears to delay time to clinically meaningful decrease in HRQoL. There does not appear to be a difference between arms in rate of allo-SCT or in duration of treatment response.

# 5 COST EFFECTIVENESS

This chapter focuses on the economic analysis submitted by Amgen, and additional information received in response to the ERG's clarification questions. We critically appraised the evidence used in the analysis and examined the company's electronic model.

The chapter starts with a summary of the company's systematic reviews and methods and their results (base-case, sensitivity analyses and proposed patient access scheme) as reported in the submission. We then provide a critique, using frameworks on best practices for reporting economic evaluation and economic modelling,[24, 25] to assess the overall quality and validity of these analyses (see Appendix 1 for checklists). In the subsequent chapter, where possible, we have addressed our concerns in the form of additional analyses undertaken by the ERG.

The submission received by the ERG included:

- A systematic review of the economic evidence for the management of people with relapsed/refractory B-precursor acute lymphoblastic leukaemia,
- Methods used to undertake the economic analysis, and the company's base-case and sensitivity analysis results, and
- Electronic version of the *de novo* survival Markov model built in Microsoft Excel.

## 5.1 Overview of the submitted cost effectiveness evidence

The company has undertaken a systematic review of the cost-effectiveness literature to identify studies reporting the results of economic analyses for people who received therapy for the management of relapsed/refractory B-precursor acute lymphoblastic leukaemia. This search was also used to identify resource use information and studies reporting health-related quality of life (HRQoL) for people with relapsed/refractory B-precursor acute lymphoblastic leukaemia. In brief, the company searched MEDLINE, EMBASE, the Cochrane library, EconLit and the NHS Economic Evaluation Database for potentially relevant studies and selected studies based on a pre-defined inclusion/exclusion. Additional searches of conference proceedings and grey literature were undertaken to identify potentially relevant studies. The systematic review identified three studies[26-28] that assessed the cost-effectiveness of blinatumomab versus standard of care chemotherapy. The company suggested that these economic analyses were based on non-randomised clinical evidence and were thus not relevant to the current submission.

The company used a de novo partitioned survival Markov model to show the experience of a cohort of people with refractory or relapsed Philadelphia-chromosome–negative B-precursor acute lymphoblastic leukaemia who may undergo treatment with blinatumomab or with FLAG-IDA (using SOC chemotherapy as a proxy) over a 50-year time horizon. The model defined health states of initial (pre-response), refractory/relapsed, response and dead. The model starts from a hypothetical cohort of people, all of whom began in the initial health state. People remained in this health state for 12 weeks (unless they had died), after which they can move to the refractory/relapsed health state or the response health state. Response was defined as people who obtained complete remission, complete remission with partial haematological recovery or complete remission with incomplete haematological recovery. Weekly cycles were used to show the movement of people through the model. In each cycle, people incurred costs and benefits [quality adjusted life-years (QALYs)] depending on the health state occupied.

Information relating to OS and EFS among responders for blinatumomab was derived from parametric survival curves fitted to Kaplan-Meier plots of the observed data from the TOWER study. Evidence for the clinical effectiveness of blinatumomab in this model relied solely on the TOWER trial; hence, the company did not undertake any formal evidence synthesis through network meta-analysis.

Health-related quality of life values depended on each health state and treatment. Utility values were based on information collected with the EORTC QLQ-C30 and mapped onto the EQ-5D. The company suggested that quality of life losses associated with treatment-related adverse events would have been captured by EORTC QLQ-C30 collected in the trial, and thus no additional disutilities for treatment related adverse events were included in the base case.

Costs of treatment with blinatumomab were based on the dose regimen used in the TOWER trial, using the list price to the National Health Service (NHS) (£2017 per vial). Costs of treatment with FLAG-IDA were based on the dosage and treatment duration, as per protocol from the Royal Surrey NHS Foundation Trust, and unit costs were obtained from the British National Formulary. (BNF)[29] The analysis was undertaken from the NHS and PSS perspective, and the outcomes are reported in terms of life years gained (LYG) and QALYs, and results are reported in terms of an ICER, expressed as cost per QALY gained. Both costs and benefits are discounted at 3.5% per annum. A number of scenario analyses and deterministic one-way sensitivity analyses were undertaken, as well as probabilistic sensitivity analysis (PSA) based on the outcome cost per

QALY. The company has provided results using a proposed patient access scheme (PAS) of [redacted] for cost per vial of blinatumomab.

The company's base case results showed that the ICER for the strategy blinatumomab compared to FLAG-IDA was estimated at [redacted] per LYG, and [redacted] per QALY gained. Sensitivity analysis results showed that the hazard rate for OS in blinatumomab had the greatest impact on the ICER, which ranged from [redacted] to [redacted] per QALY gained. The majority of the other input parameters were robust to changes. Results for the PSA showed that at a willingness-to-pay threshold of £50,000 per QALY gained, blinatumomab had a [redacted] probability of being cost-effective. Using the company's proposed PAS for the cost of blinatumomab ([redacted]), the ICER was estimated at £55,501 per QALY gained. Probabilistic results using the proposed PAS suggested that the probability of blinatumomab being cost-effective was 0.352 at a willingness-to-pay threshold of £50,000 per QALY gained.

## 5.2 ERG comment on company's review of cost-effectiveness evidence

The company has provided an appropriate description of the cost-effectiveness systematic review, which includes the search strategy, the inclusion/exclusion criteria, and a description of included and excluded studies. A summary of the eligibility criteria are given in Table 24.

**Table 24 Eligibility criteria for cost-effectiveness searches**

| Category | Definition |
|---|---|
| **Patient population** | Adults with Philadelphia chromosome-negative relapsed/refractory B-precursor acute lymphoblastic leukaemia |
| **Interventions** | Blinatumomab |
| **Comparator** | Any therapy used to manage relapsed/refractory B-precursor acute lymphoblastic leukaemia |
| **Indication** | Relapsed / refractory B-precursor acute lymphoblastic leukaemia |
| **Study type** | Full economic evaluations: cost utility analyses (CUAs), cost-effectiveness analyses (CEAs), cost-benefit analyses (CBAs), cost-minimisation analyses (CMAs) and cost-consequence studies. Also studies reporting resource use and treatment costs for the management of acute lymphoblastic leukaemia |
| **Limitations** | English language studies pertaining to humans |

### 5.2.1 Systematic review for economic evaluations (CS 5.1 and Appendix VII)

The company reports one search that aimed to retrieve cost-effectiveness evaluations and literature reporting resource use and treatment costs in adult R/R Ph- B-precursor ALL. These searches were undertaken in July 2015 and updated on 16 November 2016 in an appropriate range of databases and other sources. The database searches included terms for the population appropriate to the inclusion criteria. Searches of other sources, such as checking relevant organisations and websites, conference proceedings, HTAs and systematic reviews, are also reported. It is unclear if these additional sources were searched for blinatumomab only. There are some issues in the bibliographic database searches that may have resulted in some records being missed.

The main thesaurus headings for ALL (MeSH (exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/) and EMTREE (acute lymphoblastic leukemia/)) were not included. The ERG ran a test search in Ovid Medline and Ovid Embase for records with either of these terms and retrieved approximately 69,000 hits. This indicated that automatic mapping from the MeSH entry term used in line 1 of the company search (exp leukemia, lymphoblastic, acute/), which had retrieved 27,551 hits, to both the thesaurus terms had not occurred. However, further testing by the ERG indicated that the inclusion in the company searches of free-text terms for ALL in title and abstract appeared to largely mitigate this problem. The ERG noted several additional issues with the search strategy as presented:

- The cost-effectiveness search filter is not comprehensive, missing some common terms (e.g. 'resource use', 'resource utilisation', 'economic evaluation', 'health economics')
- Cost-effectiveness search terms should not have been used in health economic databases (e.g. NHS EED)
- The use of age limits. Any results not yet indexed, not indexed by age or indexed incorrectly would be left
- The placement of brackets at the end of line 11 is not appropriate '…) and Benefits) or Benefits) and Costs)'
- The simultaneous searching of databases

The systematic review located three potentially relevant studies,{#107;#13;#108} presented in the form of HTA summary reports, which compared blinatumomab against SOC chemotherapy. Due

to the limitations of the clinical information included in the reports, these studies were not considered to be relevant to the current submission. The ERG also undertook highly targeted searches of CEA registry, titles in Medline and Embase, other fields in Medline and Embase with a limit to UK terms, NHSEED and the HTA database for relevant studies.

### 5.2.2 Systematic review for HRQoL studies (CS 5.1 and Appendix VI)

The company reports a separate search that aimed to retrieve patient reported outcome studies in adult R/R Ph- B-precursor ALL. These searches were undertaken in July 2015 and updated on 16 November 2016 in an appropriate range of databases and other sources. The database searches included terms for the population appropriate to the inclusion criteria. Searches of other sources, such as checking relevant organisations and websites, conference proceedings, HTAs and systematic reviews, were also reported. It is unclear, however, if these additional sources were searched for blinatumomab only. There are some issues in the bibliographic database searches that may have resulted in some records being missed. The ERG noted similar issues as in the searches for economic evaluations:

- The main thesaurus headings for ALL (MeSH (exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/) and EMTREE (acute lymphoblastic leukemia/)) were not included. The ERG ran a test search in Ovid Medline and Ovid Embase for records with either of these terms and retrieved approximately 69,000 indicating that automatic mapping from the MeSH entry term used in line 1 of the company search (exp leukemia, lymphoblastic, acute/), which had retrieved 27,551 hits, to both these terms had not occurred. However, further testing by the ERG indicates that the inclusion in the company searches of free-text terms for ALL in title and abstract appear to largely mitigate this problem
- The HRQoL search filter is not comprehensive, missing some common terms (e.g. specific generic measures and methods, such as ‘EQ-5D’ and ‘time trade off’, ‘utilities’, ‘health status’, ‘health state’)
- The use of age limits. Any results not yet indexed, not indexed by age or indexed incorrectly would be missed
- The simultaneous searching of databases prevents an understanding of the relative contribution of different databases to the final number of hits

### 5.2.3 ERG summary

In both reviews, the search strategy appeared to have some minor issues. However, targeted searches undertaken by the ERG were unable to identify any relevant studies that might have been missed by the company. The three potentially relevant studies located by the company systematic review were not considered to be relevant to the current submission.

## 5.3 Summary and critique of company's submitted economic evaluation by the ERG

In this section, we provide details of the illustrative model structure, as well as the evidence on clinical (e.g. survival analysis and HRQoL) and economic (e.g. cost of blinatumomab, FLAG-IDA and terminal illness) inputs, which were used to inform the cost-effectiveness of blinatumomab as compared to FLAG-IDA for the treatment of people with R/R Ph- B-precursor ALL. We present in Table 25 the ERG's assessment of the company's economic analysis against the NICE reference case for technology assessment[29], then we present a narrative of our critical assessment.

**Table 25 NICE reference case checklist**

| Attribute | Reference case and TA Methods guidance | Does the *de novo* economic evaluation match the reference case |
|---|---|---|
| **Defining the decision problem** | The scope developed by NICE | Yes |
| **Comparator(s)** | Therapies routinely used in the NHS, including technologies regarded as current best practice for this population | Blinatumomab is being compared with FLAG-IDA, which is assumed to have the same outcomes as people receiving standard of care chemotherapy (including four strategies, one of which is FLAG ± anthracyclines)<br><br>The economic analysis does not consider comparisons with clofarabine or best supportive care (including palliative care), both of which are scoped comparators |
| **Patient group** | As per NICE final scope, the population refers to:<br>Adults with R/R Ph- B-precursor ALL | Population from the TOWER trial, which is argued to be representative of the UK treatment population |
| **Perspective costs** | NHS & Personal Social Services | Yes |
| **Perspective benefits** | All health effects on individuals | Yes |
| **Form of economic evaluation** | Cost-effectiveness analysis | Cost-effectiveness analysis |

| | | |
|---|---|---|
| **Time horizon** | Sufficient to capture differences in costs and outcomes between the technologies being compared | Lifetime horizon (50 years) |
| **Synthesis of evidence on outcomes** | Systematic review | As the sole source of data on blinatumomab, OS, EFS, response rates, adverse effects of treatment, and HRQoL are drawn from TOWER |
| **Outcome measure** | Quality adjusted life years | Yes |
| **Health states for QALY** | Described using a standardised and validated instrument | Yes<br>Utility values are dependent on the health state and treatment. Health states are evaluated using information collected from the EORTC QLQ-C30 in the TOWER trial and mapped onto EQ-5D data |
| **Benefit valuation** | Time-trade off or standard gamble | The standard UK EQ-5D tariff is used, which is based upon time-trade off |
| **Source of preference data for valuation of changes in HRQoL** | Representative sample of the public | Yes |
| **Discount rate** | An annual rate of 3.5% on both costs and health effects | Yes |
| **Equity** | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| **Probabilistic modelling** | Probabilistic modelling | Yes |
| **Sensitivity analysis** | | A range of sensitivity and scenario analyses are presented |
| EQ-5D, Euro-Qol five dimensions; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire, FLAG-IDA, fludarabine, cytarabine, granulocyte stimulating factor, idarubicin; HRQoL, health related quality of life; NHS, National Health Service; NICE, National institute for health and care excellence; QALY, quality-adjusted life year; TA, technology assessment | | |

### 5.3.1 Model structure

The company constructed a *de novo* partitioned survival model to show the experience of a cohort of people with R/R Ph- B-precursor ALL who may undergo treatment with either blinatumomab or FLAG-IDA (using the SOC chemotherapy arm from TOWER as a proxy). Partitioned survival considers the progression-free survival curve and the overall survival curve directly, with the time in progression calculated using the difference in area between the two curves. Markov decision analytical modelling studies considers progression-free, progression and death and the relevant health states between them.[30] The company's model is characterised by four health states, which are based on the disease progression: initial (pre-response), response, refractory/relapsed and dead. Figure 1 shows the illustrative model structure.

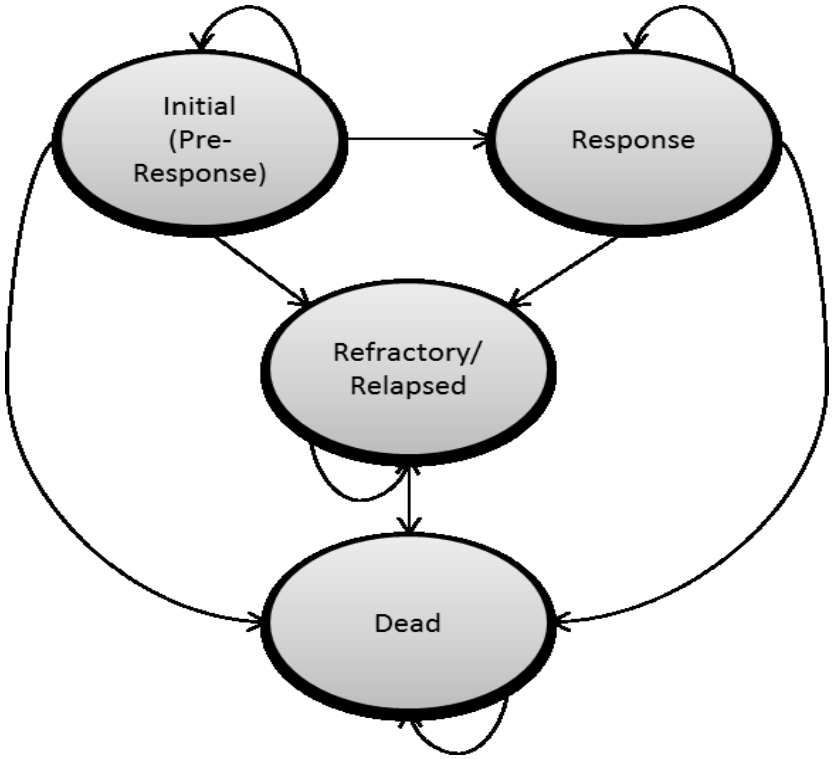



**Figure 1 Illustrative de novo model structure**

The model starts from a hypothetical cohort of people, all of whom began in the initial (pre-response) health state. People remained in this health state for 12 weeks (unless they died), after which they could move to the refractory/relapsed health state or the response health state. The model cycles weekly to show the movement of people through the model. Each cycle, people incurred costs and benefits (QALYs) depending on the health state they occupy.

As described in Section 5.3.5, the proportions of people who progressed to the response and refractory/relapse health states after 12 weeks in the initial (pre-response) health state are based on the information from the blinatumomab and from the SOC chemotherapy arms in the phase III TOWER trial. The company suggested that the analysis is not based on a Markov cohort structure; it is based on a partitioned survival model, which meant that the time in progression was calculated using the difference in area between the OS and the EFS survival curves among responders. Transition probabilities after the initial health state for the blinatumomab arm were derived based on parametric extrapolations of the Kaplan-Meier plots of observed data from TOWER. Transition probabilities for the SOC chemotherapy arm were derived based on the assumption of proportional hazards.

#### 5.3.1.1 ERG summary

The de novo model developed appears to capture the key important features (overall survival and event-free survival) of acute lymphoblastic leukaemia. The cycle length of one week is adequate to capture the changes of the disease over short periods of time, and the time horizon is long enough to capture the costs and benefits of the intervention.

### 5.3.2 Population

The population considered in the model is that from TOWER, which according to the ERG clinical advisor is generalizable to the UK treatment population. The population consists of adults with R/R Ph- B-precursor ALL. The model assumed that people began in the initial (pre-response) health state, and unless they died, would remain there for 12 weeks.

#### 5.3.2.1 ERG summary

The ERG considers the treatment population to be sufficiently similar to the UK population. Results are based on using the overall survival and event-free survival for people who responded to treatment in the TOWER trial.

### 5.3.3 Interventions and comparators

The base-case analysis evaluates the cost-effectiveness of blinatumomab compared to FLAG-IDA. In TOWER, blinatumomab was administered by continuous intravenous infusions over four weeks by receiving 9µg/day during week one of cycle one, then 28µg/day for the remainder of the cycle and subsequent cycles; followed by a treatment free period of two weeks. This was in keeping with its marketing authorisation. It should be noted that a proportion of people ([redacted]) who had ≤5% bone marrow blasts/complete remission (CR)/complete remission with partial haematological recovery (CRh*)/complete remission with incomplete haematological recovery (CRi), received up to 12 additional months of blinatumomab treatment after the three consolidation cycles. These additional cycles are not included in the marketing authorisation for blinatumomab.

The comparator arm of TOWER included people who received standard of care chemotherapy (one of four treatment protocols: FLAG with or without anthracyclines, clofarabine-based regimens, HiDAC, or high-dose methotrexate-based regimens.). However, in the economic analysis the comparator was FLAG-IDA, whereby the company assumed that outcomes were generalizable to people who received FLAG-IDA treatment. Hence, life-years and thus quality

adjusted life-years gained from treatment with one of the four treatment strategies in the SOC chemotherapy arm are assumed to be the same as people who received treatment with FLAG-IDA. This assumption is based entirely on expert opinion. It should be noted that this assumption, assumes that any utility value associated with the pooled SOC chemotherapy arm is the same as FLAG-IDA, and that adverse events are the same.

The model allows for discontinuation of treatment. People in the blinatumomab arm could discontinue treatment within and between cycles, and people in the FLAG-IDA arm could discontinue treatment between cycles. However, it is not clear if an assumption was made that people received no further treatment or if they received palliative care. The ERG clinical advisor suggested that people who discontinue treatment are likely to begin an end-of-life care pathway.

The NICE scope includes clofarabine as a comparator, which is licensed for the treatment of people with ALL, and is currently used in practice as a possible alternative, though the ERG clinical advisor noted that it is not frequently used for adult ALL. Though not included in the base-case analysis, the company has undertaken a scenario analysis which included the cost of clofarabine as part of standard of care chemotherapy. In this analysis, the company assumes that 17.4% of people in the standard of care chemotherapy arm received clofarabine in cycle 1, as seen in the TOWER trial. This approach assumes that the clinical outcomes associated with clofarabine are similar to those of FLAG-IDA; an assumption which was not made in the clinical effectiveness aspects of the submission. No evidence has been provided to support the clinical equivalence of clofarabine and FLAG-IDA.

#### 5.3.3.1 ERG summary

The company's approach to estimating the economic impact of blinatumomab compared to FLAG-IDA depends on the assumption of equal treatment efficacy of FLAG-IDA and the pooled SOC chemotherapy arm, which included four different treatment regimens. Therefore, the plausibility of these findings depend entirely on whether the outcomes (overall survival and event-free survival) for FLAG-IDA are generalizable to SOC chemotherapy as defined in TOWER. Our clinical advisor has suggested that this may be a plausible assumption.

A proportion of people being treated with blinatumomab received up to 12 months maintenance therapy, which is not consistent with the marketing authorisation.

### 5.3.4 Perspective, time horizon and discounting

The perspective/viewpoint of the analysis is that of the NHS and personal social services (PSS) perspective, which is in line with the NICE 2013 Guide to the Methods of Technology Appraisal.[31] The model assumes a lifetime horizon of 50 years, which is long enough to capture the long-term costs and benefits of treatment. In the base-case, costs and benefits are discounted at a rate of 3.5% per annum. A number of sensitivity and scenario analyses were undertaken by the company. The company presented sensitivity results based on a 10-year, 20-year and a 60-year time horizon. Additionally, in a scenario analysis the company discounted costs and benefits at a rate of 1.5% per annum.

Due to the uncertainty in the long-term benefit of treatment with blinatumomab, the ERG recommended undertaking a within-trial analysis. In response to the ERG's clarifications, the company has undertaken this analysis, which is based on the trial time horizon of two years. The rationale for a within-trial analysis is discussed below in Section 5.4.1, which is also where results for the corresponding ERG scenario analysis are presented.

#### 5.3.4.1 ERG summary

The perspective, time horizon and discount rates chosen by the company are in line with the NICE recommendations,[31] and are appropriate to the decision problem. For reasons, which are discussed under the sub-heading 'treatment effectiveness and extrapolation', the ERG proposed to the company to undertake a within-trial analysis.

### 5.3.5 Treatment effectiveness and extrapolation

Seven clinical outcomes from TOWER were used to inform the transitions between health states in the model:

- Overall survival
- Event-free survival
- Treatment response rates
- Time to and duration of response
- Rate of stem cell transplant

- Adverse events of treatment
- Health-related quality of life

Overall survival and event-free survival are discussed in depth here. Adverse events and health-related quality of life are discussed in subsequent sections.

#### 5.3.5.1 Overall survival

Estimation of long-term overall survival comprised two phases. In the first phase, survival was estimated based on fitting parametric curves to the observed Kaplan-Meier survival data in TOWER. In the second phase, it was assumed that people who survived more than four years were cured, and their survival was estimated by applying age- and sex-matched UK general population mortality rates. Figure 2 shows the Kaplan-Meier plots for overall survival for the blinatumomab, standard of care chemotherapy arm, and a natural history cohort. In the trial, up to three months post-randomisation, the Kaplan-Meier plots appear to overlap, then diverge until month 15 before overlapping again. The Kaplan-Meier plot for the overall survival in the historical cohort was based on matched patients from Study 20120310 to patients who received standard of care chemotherapy in the TOWER trial. The Kaplan-Meier plots for the natural history cohort and standard of care appear to have overlapped up to three months, and then show that OS is lower in the natural history cohort.

Parametric models were fitted to the Kaplan-Meier plots for overall survival for blinatumomab arm of TOWER. Various parametric model fits were tested (e.g. exponential, Gompertz, log-logistic, log-normal and Weibull) using restricted and unrestricted models. The preferred parametric fit was chosen by a combination of visual inspection of goodness-of-fit, long-term plausibility informed by historical data and expert opinion, and using the Bayesian Information Criterion (BIC). Based on the BIC, the lognormal restricted model had the best fit to the overall survival for the blinatumomab arm. However, the Gompertz model, which was the 8$^{th}$ best fitting model was used in the base-case analysis. Figure 3 shows the chosen fitted overall survival curves among the responders, together with the Kaplan-Meier plots from TOWER. Cox proportional hazards were assessed and used to show the treatment effect.

**Figure 2 Kaplan-Meier plots for overall survival for blinatumomab, SOC chemotherapy and matched historical cohort**

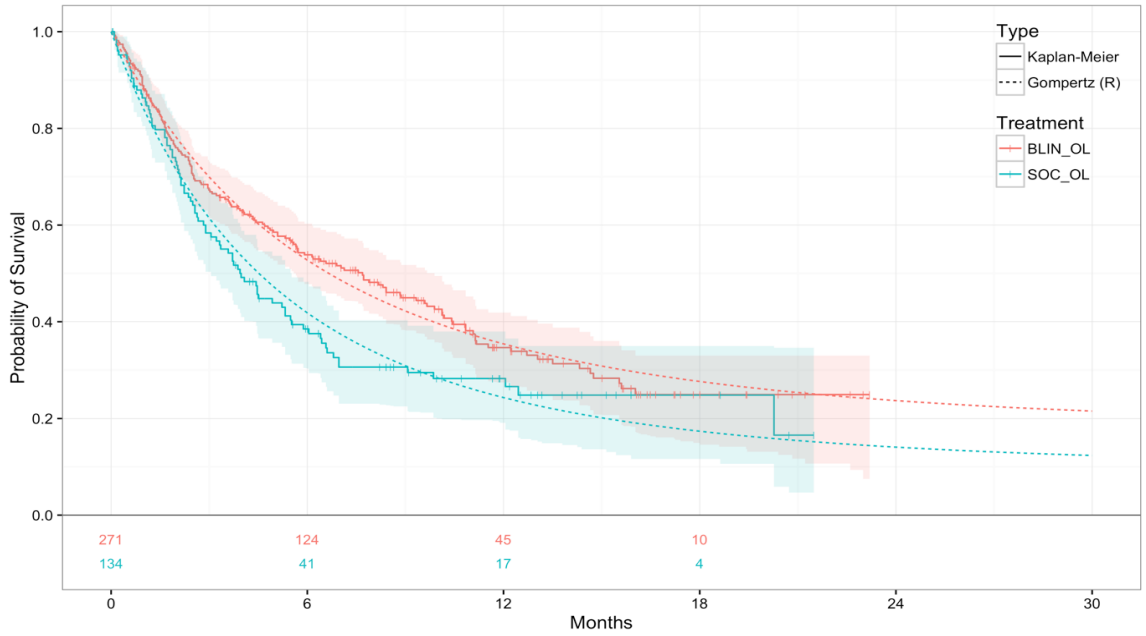



**Figure 3 Kaplan-Meier plots with the restricted Gompertz model for overall survival among responders**

Figure 4 shows the projected overall survival curves in the TOWER trial, together with the Kaplan-Meier plot based on observed data from Study 20120310. On clarification, the company suggested that the Kaplan-Meier plot based on the natural history data was used to assess the plausibility of long-term projections of the overall survival of people in the standard care arm. Briefly, the natural history cohort consists of people from Europe or the US who were diagnosed with refractory/relapsed Philadelphia chromosome–negative acute lymphoblastic leukaemia from year 2000 onwards, and had been treated with chemotherapy. People were eligible if they were ≥18 years at relapse, relapsed within 12 months from initial diagnosis, or a) relapsed after allogenic stem cell transplantation (allo-SCT) b) were refractory to initial or subsequent treatments, or c) were in second or later relapse.[32] In the submission, people from the historical cohort were matched to people in Study MT103-211, in order to have a comparable cohort of patients. As seen in Figure 4, the Kaplan-Meier plot for the natural history cohort is somewhat lower than the fitted survival curve to the standard of care arm in the TOWER trial. The company suggested that the differences in overall survival between these two groups (historical cohort and standard of care in TOWER) may be a result of [redacted] of people in the standard of care eventually receiving anticancer therapies [blinatumomab, inotumomab, or chimeric antigen receptors (CAR T cells)]. The company has applied an arbitrary hazard ratio of 0.85 to the survival distribution for the matched historical cohort to show the similarity or goodness of fit of the Gompertz curve against the observed data.

**Figure 4 Gompertz model fit to overall survival projections from TOWER and Kaplan-Meier plot for Study 20120310**

The ERG noted several concerns regarding the overall survival analysis undertaken. These include:

- Treatment switching in the standard of care chemotherapy arm
- Natural history cohort
- Assessment of effectiveness using parametric models

**Treatment switching in the standard of care arm.** It should be noted that [redacted] of people randomised to the standard of care chemotherapy arm received treatment with blinatumomab, inotuzumab, or chimeric antigen receptors (CAR T cells) during the course of the trial. The company has undertaken sensitivity analysis by controlling for treatment switching to estimate overall survival for those people who were randomised to the standard of care arm, and suggested that the hazard ratios were equivalent. The hazard ratios based on the full analysis set, and adjusting for 'drop-in' to blinatumomab, are presented in Table 26.

**Table 26 Cox proportional hazards analysis of overall survival**

| **Analysis** | Hazard ratio (95% CI) | Log-rank p-value |
|---|---|---|
| Full analysis set | 0.71 (0.55, 0.93) | 0.012 |
| Adjusting for drop-in | [redacted] | [redacted] |
| CI, confidence interval | | |

**Natural history cohort.** The ERG was unclear about how the company used information from the matched natural history cohort, and how the arbitrary adjusted hazard ratio of 0.85 was applied to the overall survival as shown in Figure 4. On clarification, the company outlined that '*the adjusted OS curve for the matched historical comparator was not used explicitly in the model. Rather, it was used to assess the plausibility of the model projections based on the Gompertz distribution and general population mortality.*' Additionally, the company stated that '*the adjusted OS curve for the matched historical comparator was calculated using the formula below:*

$S_A[t] = S[t]^{HR}$

where

$S_A[t]$ = Adjusted Kaplan-Meier survival distribution for matched historical comparator

$S[t]$ = Unadjusted Kaplan-Meier survival distribution for matched historical comparator

HR = Hazard ratio for adjusted vs. unadjusted Kaplan-Meier survival distribution for the matched historical comparator

The HR for the adjusted versus unadjusted Kaplan-Meier survival distribution (0.85) was obtained using trial and error and visual inspection.'

With this in mind, the ERG considers this method for adjusting the Kaplan-Meier curve to be inaccurate for two reasons. First, the survival function for a Gompertz distribution is given as

$S[t] = \exp\{ [(\lambda 1 / \alpha] * (1 - \exp(\alpha * t)) \}$

where $\lambda$ is the scale parameter, and $\alpha$ is the shape parameter.

Second, the survival function for a Gompertz distribution cannot simply multiplied be by a hazard ratio to derive an adjusted survival distribution. The ERG's approach to adjusting the Kaplan-Meier curve for the historical cohort is:

$$S[t] = \exp\{ [(\lambda 1 * HR / \alpha] * (1 - \exp(\alpha * t)) \}$$

where HR is the hazard ratio. This equation assumes that the shape parameter, α, is kept constant in both models.

**Assessment of effectiveness using parametric models.** The main source of treatment efficacy on overall survival is based on the TOWER trial. As noted above, the treatment effect is based on fitting a restricted Gompertz parametric model to the blinatumomab arm of the trial, and then assuming proportional hazards for the standard of care arm. The ERG is concerned that the proportional hazards assumption is invalid, given that the Kaplan-Meier plots (Figure 2) appear to cross from month 15 through the remainder of the trial time horizon. The proportionality assumption leads to overestimating the treatment benefit of blinatumomab.

#### 5.3.5.2 Event-free survival among responders

Like OS, EFS was estimated by fitting parametric survival curves to the Kaplan-Meier data for responders in the TOWER trial. Responders were considered to be people who achieved complete remission, complete remission with partial haematological recovery or complete remission with incomplete haematological (CR/CRh*/CRi) recovery within 12 weeks of initiation of treatment. Estimation of long-term EFS comprised two phases. In the first phase, survival was estimated based on the observed Kaplan-Meier survival data for responders in TOWER. In the second phase, EFS was extrapolated beyond trial time horizon. Figure 5 shows the Kaplan-Meier plots for EFS among people who achieved (CR/CRh*/CRi) within 12 weeks after treatment in the blinatumomab and in the SOC chemotherapy arms. In the trial, 43.6% (n=119) and 24.6% (n=33) achieved response in the blinatumomab and standard of care arm, respectively. It can be seen from Figure 5 that EFS among responders was higher in the blinatumomab arm during the first 11 months after which observed data from the SOC chemotherapy arm crossed the blinatumomab arm. The company has suggested that this is likely to be a result of the small number of people in the SOC chemotherapy arm at risk of relapsing.

**Figure 5 Kaplan-Meier plots for event-free survival among responders**

In the first phase, the restricted generalised gamma model was fitted to data from the blinatumomab arm. Model selection was made based on the BIC, visual fit to the data, and clinical plausibility. The fitted parametric curves to the Kaplan-Meier data for responders are shown in Figure 6. It should be noted that unlike the restricted Gompertz model, which assumed proportionality of hazards in the overall survival, the restricted generalised gamma model used an accelerated failure time model. Here, treatment is assumed to have a proportional effect on failure times as opposed to hazards. Also, it should be noted that counterfactual plots for EFS were not presented, unlike the analyses of OS. Other assumptions included:

- Decreasing hazard for relapse over time
- Hazards for blinatumomab not greater than those for SOC chemotherapy during the model time horizon

From Figure 6, it can be seen that the fitted curve overestimates EFS in blinatumomab and underestimates EFS in SOC chemotherapy.

**Figure 6 Kaplan-Meier plots for event-free survival for responders with restricted generalised gamma parametric model fit**

In the second phase, as with OS, the company assumed that people who survived more than four years were cured, and their survival was estimated by applying age- and sex-matched UK general population mortality rates additively to event-free survival. Extrapolations for EFS beyond the trial time horizon are shown in Figure 7. It can be seen from Figure 7 that the proportion of people in the SOC chemotherapy arm is lower than those in the blinatumomab arm.

**Figure 7 Kaplan-Meier plots for event-free survival for responders with restricted generalised gamma parametric model fit for model time horizon**

#### 5.3.5.3 ERG summary

OS and EFS have been estimated based on fitting parametric curves to the Kaplan-Meier plots of the observed data in the blinatumomab arm, and assuming proportional hazards to determine the treatment effect. The ERG considers this to be a strong assumption given that the Kaplan-Meier plots do not appear to be proportional.

### 5.3.6 Health related quality of life

Utility values used in the model were assumed to be health state and treatment related. Utility values were derived based on information collected on the EORTC QLQ-C30 in the TOWER trial. Estimated mean EQ-5D values were mapped from the EORTC QLQ-C30, using the mapping algorithm developed by Longworth and colleagues.[33] The company stated that the quality of life assessments were made during the 12 weeks prior to categorising people as responding or relapsing. A generalised estimating equation-based regression, which accounts for autocorrelations caused by repeated measurements from the same participants, was then fitted to

these data to estimate health state utilities for each health state for both the intervention and the comparator arms. Table 27 shows the utility values derived by the company.

**Table 27 Estimated mean EQ-5D utility values for people with ALL**

| Health state | Estimate | Standard Error |
|---|---|---|
| **Blinatumomab** | | |
| Initial (pre-response) | [redacted] | [redacted] |
| Response | [redacted] | [redacted] |
| Relapsed/refractory | [redacted] | [redacted] |
| **Standard of care chemotherapy** | | |
| Initial (pre-response) | [redacted] | [redacted] |
| Response | [redacted] | [redacted] |
| Relapsed/refractory | [redacted] | [redacted] |

Due to the uncertainty in the duration of the utility values by treatment derived from the TOWER trial, general population health state values were used for people surviving more than four years. Age- and sex-matched UK general population values are given in Table 28.

**Table 28 Health state utility values for a UK general population**

| Age (years) | EQ-5D utility values | |
|---|---|---|
| | Male | Female |
| <25 | 0.94 | 0.94 |
| 25-34 | 0.93 | 0.93 |
| 35-44 | 0.91 | 0.91 |
| 45-54 | 0.84 | 0.85 |
| 55-64 | 0.78 | 0.81 |
| 65-74 | 0.78 | 0.78 |
| 75+ | 0.75 | 0.71 |

In the base case, the company acknowledged that they had not adjusted for differences in baseline utility values (i.e. mean baseline utility values were greater for people receiving standard of care chemotherapy), and they had not included baseline utility values in the overall analysis.

The company suggested that no additional utility decrements associated with adverse events were included in the economic analyses. All observed adverse events were assumed to occur while people are on treatment and receiving inpatient/outpatient care, and would have been captured by the EORTC QLQ-C30.

The ERG notes several concerns with the utility values used in the analyses. First, the company acknowledged that they had not included baseline values in their analyses. Ideally, to determine the impact of treatment on the outcome of quality of life, the assessment should be based on information collected at baseline and one or more time point.[34] Second, the ERG considers the company's statement that improvements in utility values seen in the blinatumomab arm and the decline seen in the SOC chemotherapy arm reflect actual treatment effects to be strong, as there are no statistical analyses provided to justify this statement, and given that the company did not adjust for baseline differences. Failure to adjust for these imbalances in utility values could result in misleading cost-effectiveness results.[34] Third, the company used utility values from the general population for people surviving more than four years. However, it was unclear to the ERG if any uncertainty was placed around these estimates in order to inform the probabilistic sensitivity analyses.

Given the ERG concerns with the analytic methods used to determine the impact of treatment on quality of life, the preferred approach by the ERG would be to include and control for these baseline differences, then map these values from the EORTC QLQ-C30 to the EQ-5D to be used in the economic analysis. However, the ERG does not have access to these patient-level data, hence this scenario analysis was not undertaken.

#### 5.3.6.1 ERG summary

In the base case, utility values were based on mapped EQ-5D utility values derived from the EORTC QLQ-C30 assessment tool, which was administered at baseline and during the treatment period. The company stated that there were differences in baseline utility values between the two treatment arms. In the base case, the company had not adjusted for baseline differences and the values were excluded from the analysis. The ERG would prefer an analysis whereby the adjusted baseline utility values are included.

### 5.3.7 Resources and costs

Costs considered in the economic analyses included drug acquisition and administration costs for blinatumomab and FLAG-IDA, cost of allogeneic stem cell transplantation, cost of subsequent therapy and terminal care costs. Costs associated with adverse events were assumed to be captured in inpatient and outpatient care for administration of blinatumomab and FLAG-IDA.

#### 5.3.7.1 Blinatumomab costs

The drug regimen for blinatumomab used in the model was based on the dosing schedule as per protocol in TOWER. In the intervention arm, 9µg per day of blinatumomab was administered intravenously during week 1 of cycle 1, then 28µg per day for the remainder of the cycle. As per the blinatumomab Summary of product Characteristics (SmPC), hospitalisation was required for the initiation of therapy: a minimum of nine days in cycle 1 and two days in cycle 2. Additionally in cycle 1, it was assumed that people with a history of central nervous system involvement required 14 days hospitalisation. In the model, it was assumed that on average people who received blinatumomab treatment required 10 days inpatient stay. This is based on an assumption that 91% of people in the UK would not have a history of central nervous system involvement and 9% would have a history. Based on correspondence with the ERG's clinical expert, people receiving blinatumomab treatment are likely to spend eight weeks in care for cycles 1 and 2, which is considerably higher than what the company suggested. The ERG has explored this in a scenario analysis. Additionally, our clinical advisor did note that there is a lack of infrastructure at hospitals to support outpatient care, and as a result these patients are frequently hospitalised for the entirety of the treatment cycle. Therefore, the ERG has also undertaken scenario analyses whereby people received all treatment in inpatient care, that is, assuming that people spent 28 days in hospital for each of the five cycles.

Drug acquisition costs were based on the list price to the NHS (£2017 per 38.5µg vial, of which 28µg was useable) and inpatient cost for administration (£682.36), which was obtained from the 2014/15 NHS reference costs.[35] Drug costs for cycle 1 were based on the assumption that the contents of a single vial can be used over multiple days, hence requiring six vials. The underlying assumption is that there is no drug wastage.

Cycles 3-10 were assumed to be administered on an outpatient basis. The administration cost per visit was estimated at £204, and this was based on a visit to an outpatient infusion centre. It was assumed that home infusion pumps were required for outpatient administration of blinatumomab, which was estimated at £107.59 per 28 days of use.

In the model, the proportion of people who discontinued blinatumomab treatment reflected the percentages who discontinued in the trial (Table 29). It can be seen that people could discontinue within cycles and between cycles. It was unclear to the ERG if these people commenced end-of-

life therapy. Our clinical advisor suggested that people who discontinued treatment normally start end-of-life care.

**Table 29 Proportion of people starting and completing each cycle of blinatumomab therapy (from the company submission)**

| Cycle number | People starting cycle (%) | People completing cycle (%) |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] |
| 7 | [redacted] | [redacted] |
| 8 | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] |
| 10 | [redacted] | [redacted] |

#### 5.3.7.2 FLAG-IDA costs

The drug acquisition costs are based on FLAG-IDA. Costs for FLAG-IDA were estimated based on the dosage and treatment duration, as per protocol from the Royal Surrey NHS Foundation Trust, and unit costs were obtained from the British National Formulary (BNF) (BNF, 2016) and NHS Generic Pharmaceuticals eMit (2015).[36] It was assumed that in each cycle, drug administration required 16.8 days in an inpatient setting, which was based on a *'retrospective chart review study'* undertaken in France.[37] Table 30 shows the unit costs for each component of FLAG-IDA per day, and the total drug acquisition cost, which was estimated to be £1,974.34 per day. These costs appear to be correctly estimated.

**Table 30 Unit costs for FLAG-IDA**

| FLAG-IDA drug component | Dose per day of treatment | Basis of dosing | Days treatment per cycle | Cost per item (£) | Mg per item | Daily dose (mg) | Items per day | Cost per day (£) | Cost per cycle (£) |
|---|---|---|---|---|---|---|---|---|---|
| Filgrastim | 0.005 | mg/kg | 9 | 79.90 | 0.48 | 0.368 | 1 | 79.90 | 719.10 |
| Fludarabine | 30 | mg/m$^2$ | 5 | 35.64 | 50 | 55.271 | 2 | 71.28 | 356.40 |
| Cytarabine | 2000 | mg/m$^2$ | 5 | 5.63 | 1000 | 3,684.745 | 4 | 22.52 | 112.60 |
| Idarubicin | 8 | mg/m$^2$ | 3 | 87.36 | 5 | 14.739 | 3 | 262.08 | 786.24 |
| **Estimated total costs** | | | | | | | | | **£1,974.34** |
| FLAG-IDA, fludarabine, cytaribine, granulocyte colony stimulating factor, idarubicin | | | | | | | | | |

The estimated costs for treatment with FLAG-IDA is based on the proportion of people who started and completed treatment in the SOC chemotherapy arm of TOWER (Table 31). In the model, people in this arm received four cycles of treatment, and it can be seen that people who started FLAG-IDA treatment in that cycle, adhered to treatment.

**Table 31 Proportion of people starting and completing each cycle of SOC chemotherapy (from the company submission)**

| Cycle number | People starting cycle (%) | People completing cycle (%) |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] |

#### 5.3.7.3 Cost of allogeneic stem-cell transplantation

Cost of allogeneic stem-cell transplantation (allo-SCT) was estimated at £104,000 per patient. Costs were estimated based on a study undertaken by the NHS Blood and Transplant Service,[38] which obtained resource use information from a Dutch cost study.[39] Resource use was combined with UK specific costs, which were obtained from the PSSRU. In the absence of UK costs, costs where obtained from the Dutch costing study and converted using the Health and Social Care Pay and Price index. Of note, obtaining resource use from the Dutch study assumes that treatment pathways are the same as in the UK. Additionally, the ERG are not aware of using the Health and Social Care Pay and Price index to convert from one currency to another; using the purchasing power parity would have been more appropriate.[40]

**Table 32 Unit cost of allogeneic stem cell transplantation (from company submission)**

| | Value |
|---|---|
| Initial treatment cost (£) | 60,092.84 |
| Follow-up treatment, percent of patients receiving (%) | |
| 1-6 months | 90 |
| 7-12 months | 48 |
| 13-24 months | 31 |
| >24 months, cyclosporin | 20 |
| Cost | |
| 1-6 months cost (£) | 28,963 |
| 7-12 months (£) | 19,896 |
| 13-24 months (£) | 14,357 |
| >24 months, cyclosporin | |
| Mg per day | 100 |

| | Value |
|---|---|
| Cost per tab (£) | 0.85 |
| Mg per tab | 50.00 |
| Allo-SCT, allogenic stem-cell transplant | |

#### 5.3.7.4 Costs of subsequent salvage therapy

Costs of subsequent salvage therapy were included in the model and were estimated at £128,785 and £14,240 per course per patient receiving blinatumomab and FLAG-IDA, respectively. These costs were estimated based on the proportion of people in the TOWER trial who subsequently received salvage therapy, and assuming costs are the same as the initial salvage treatment. As regards innovative anticancer therapies, [redacted] and [redacted] of people received blinatumomab, inotuzumab and CAR T cells in the blinatumomab and SOC chemotherapy arm, respectively (see Table 33). Moreover, [redacted] and [redacted] of people received other systemic anticancer therapies in the blinatumomab and SOC chemotherapy arm, respectively. It should be noted that these proportions are based on TOWER safety analysis set (SAS) as opposed to the FAS, which is used throughout the submission. The company has suggested that subsequent salvage therapy was not routinely captured for people in the FAS who did not receive study drug. Additionally, only the proportion of people undergoing subsequent salvage therapy during the trial were included in the model. Hence, from two years onwards, it was assumed that people would not undergo subsequent salvage therapy.

**Table 33 Proportion of people receiving subsequent treatment (from company submission)**

| Initial salvage treatment | Subsequent salvage therapy | |
|---|---|---|
| | Innovative anticancer therapies (%) | Systemic anticancer therapies (%) |
| **Blinatumomab** | [redacted] | [redacted] |
| **Standard of care chemotherapy** | [redacted] | [redacted] |

#### 5.3.7.5 Costs of terminal care

Cost of terminal care was estimated at £8,602 per patient. This cost was calculated based on the average length of time of eight weeks that people spent in a hospital receiving end-of-life care.[41] Unit cost was calculated as £145 per day, using estimates from Marie Curie and inflated using the hospital and community health service (HCHS) price and pay index.[42] In the model, terminal care cost was applied as a one-off cost to those people who had not survive more than 48 months. The nature of the treatment people received following discontinuation of chemotherapy was unclear to

the ERG. Our clinical expert suggested that people who discontinued treatment normally commence and end-of-life care pathway.

#### 5.3.7.6 Adverse events

Costs associated with the treatment of adverse events (AEs) were not explicitly modelled, but were assumed to be captured in the costs for inpatient and outpatient care. This assumes that people are not at risk of developing an adverse event while not on treatment.

#### 5.3.7.7 ERG summary

Resource use information on allo-SCT was obtained from a Dutch study, under the assumption that the treatment pathway is the same as in the UK. Additionally, it is unclear to the ERG which costs (or component) were obtained from this study in order to estimate the cost per patient receiving allogenic stem-cell transplantation. Hence, the ERG was unable to use the purchasing power parity to convert costs obtained from one setting to UK. The proportions of people receiving subsequent salvage therapy are based on the TOWER safety analysis set as opposed to the full analysis set.

### 5.3.8 Overview of model assumptions and overview of ERG critiques

Key assumptions were made in order to ensure a workable model. These assumptions are presented in Table 34, along with the company's justification and the ERG's comments.

**Table 34 Key modelling assumptions with ERG comments**

| Assumption | Justification | ERG comments |
|---|---|---|
| The whole SOC chemotherapy arm from TOWER is used to model costs and outcomes for FLAG-IDA | Available clinical guidelines, including the EWALL guidelines, suggest that there is no clearly superior salvage chemotherapy regimen in R/R Ph- B-precursor ALL. UK clinical experts consulted by Amgen considered the outcomes in the SOC chemotherapy arm in TOWER to be broadly generalisable to the relevant comparator for this appraisal, FLAG-IDA.<br><br>A scenario analysis has been conducted on the pre-specified subgroup of patients intended to receive a FLAG ± anthracycline based regimen at randomisation. As the OS HR for blinatumomab versus SOC chemotherapy was more favourable in the subgroup of patients intended to receive a FLAG ± anthracycline based regimen, this suggest the base-case approach (i.e., using the whole SOC chemotherapy arm) is potentially conservative. | The ERG consulted with our clinical advisor, and this assumption was considered plausible. |
| After 4 years, the hazard rates for OS are the same for blinatumomab and SOC chemotherapy | Based on UK clinical expert opinion, patients remaining alive after 4 years are likely to be cured. If patients are cured, then there should be no difference in mortality by treatment group. | The ERG clinical advisor suggested that people who survive 5 years or more are likely to have been cured |
| Mortality after 4 years is equal to sum of that based on parametric distributions fit to trial data and UK general population mortality rates | Mortality rates will decline initially as patients who are not cured die, and then are expected to increase over time due to increasing non–disease-related mortality in cured patients. | Given the advice received from our clinical advisor on people being cured after 5 years, we assumed UK general population mortality rates from this time point onwards |
| Utility values after 4 years are the same for blinatumomab and FLAG-IDA and assumed to be equal to UK general population norms for EQ-5D | Patients surviving for 4 years are likely to be cured and to no longer suffer from disease-related decrements in HRQoL. As a consequence, utility values will be the same for patients receiving blinatumomab and FLAG-IDA. Over time, utility | As above, people surviving 5 years or more are assumed to have been cured. Hence, utility values for people surviving 5 years or more are the same in both arms, and assumed to be equal to UK sex- and age- |

| Assumption | Justification | ERG comments |
|---|---|---|
| | values will decrease due to age-related reductions in HRQoL. | specific utility values for the general population |
| Patients without history of CNS involvement receiving blinatumomab will be hospitalised for the first 9 days of Cycle 1. Those with active CNS pathology or history of CNS involvement will be hospitalised for 14 days of the Cycle 1. All patients will be hospitalised for the first 2 days of Cycle 2. | Consistent with the minimum hospitalisation requirements described in the blinatumomab SmPC | The ERG clinical advisor suggested that 14 days is the minimum days that people are hospitalised whilst receiving treatment. It was further suggested that people are generally hospitalised for four weeks in both cycles 1 and 2 and consolidation cycles. |
| Costs of AEs are captured in costs of inpatient and outpatient administration of medications | Since blinatumomab is administered initially in hospital, the treatment of AEs is likely to be provided during the hospital stay and therefore included in the hospitalisation cost. As patients are assumed to visit outpatient infusion centres every 4 days when receiving the drug out of hospital, it is likely AEs could be managed during these scheduled visits. For FLAG-IDA, patients are assumed to be hospitalised for 16.8 days each cycle. As with blinatumomab, the treatment of AEs is likely to be provided during the hospital stay. | The ERG considers this assumption to be feasible. |
| Only the costs of subsequent salvage observed during the TOWER trial were included in the model | Given the relatively small proportion of patients receiving subsequent salvage during the TOWER trial, projections of utilisation beyond the end of the trial would be associated with substantial uncertainty. Since utilisation of innovative therapies such as blinatumomab, inotuzomab, and CAR T-cells was greater in the SOC chemotherapy arm than the blinatumomab arm, the use of trial results only may be conservative. | The ERG considers this assumption to be plausible. However, it should be noted that [redacted] of people in the blinatumomab arm of the TOWER trial received six or more cycles |

AE, adverse event; ALL, acute lymphoblastic leukaemia; CNS, central nervous system; EWALL, European Working Group for adult ALL; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; HRQoL, health-related quality of life; Ph-, Philadelphia chromosome negative, R/R, relapsed or refractory; SmPC, summary of product characteristics; SOC, standard of care.

### 5.3.9 Cost effectiveness results: base case

The company reports deterministic base-case and sensitivity analysis results, as well as probabilistic results for the comparison between blinatumomab with FLAG-IDA (using SOC chemotherapy as a proxy). In a confidential appendix, results are also presented for a proposed discount of [redacted] on blinatumomab under a patient access scheme (PAS) approved by the Department of Health. Outcomes are reported in terms of life-years gained and quality adjusted life years and the results are reported in the form of an incremental cost-effectiveness ratios expressed as a cost per LYG and cost per QALY.

Table 35 and Table 36 show the base-case results for blinatumomab as compared to FLAG-IDA (modelled using SOC chemotherapy) based on the outcomes LYG and QALY. Results show that blinatumomab is approximately [redacted] than FLAG-IDA and more effective with 1.78 and 1.45 more LYG and QALYs, respectively and, these equate to an ICER of approximately [redacted] per LYG and [redacted] per QALY gained, respectively.

**Table 35 Deterministic results based on life years gained (discounted)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean LYG | Incremental LYG | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental life years gained; LYG, life years gained | | | | | |

**Table 36 Deterministic results based on quality-adjusted life years gained (discounted)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

### 5.3.10 Sensitivity analyses

#### 5.3.10.1 Probabilistic sensitivity analyses

The company has undertaken probabilistic sensitivity analysis (PSA) to determine the impact of joint parameter uncertainty in key model input parameters. PSA was undertaken for both costs per life years gained and cost per quality-adjusted life years gained. In PSA, each parameter is assigned a distribution which reflects the pattern of its variation and the ICER results are calculated based on randomly selecting, variables from each distribution. It should be noted that probability distributions were applied to the majority of model input parameters; however, they were not applied to:

- Duration of benefit with blinatumomab treatment
- Days per bag change
- Inpatient days per cycle received for the blinatumomab arm

Table 37 and Table 38 show the PSA results for the cost per LYG and cost per QALY, respectively. Based on the outcome cost per LYG, PSA results were generally similar to those presented in the base-case. Similarly, based on the cost per QALY, PSA results were generally in line with the deterministic base-case results.

**Table 37 PSA results based on life years gained (undiscounted)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean LYG | Incremental LYG | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental life years gained; LYG, life years gained | | | | | |

**Table 38 PSA results based on quality-adjusted life years (discounted)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

For the outcome cost per QALY, each simulation for the incremental costs and incremental QALYs for blinatumomab as compared to FLAG-IDA was plotted on a cost-effectiveness plane (see Figure 8), along with the respective cost-effectiveness acceptability curve (see Figure 9).

**Figure 8 Scatterplot using distributions around model input parameters**

For the 1000 runs of the Monte Carlo simulation, the scatterplot shows considerable uncertainty about the incremental QALYs, and less so for the incremental costs. This may be a result of the company assuming some costs, or resource use estimates to derive costs, to be constant/fixed.

**Figure 9 Cost-effectiveness acceptability curve for blinatumomab and FLAG-IDA**

Figure 9 shows the results of the PSA presented in the form of cost-effectiveness acceptability curve (CEAC) for the comparison between blinatumomab and FLAG-IDA. The curve shows the proportion of simulations in which blinatumomab is cost-effective at different willingness-to-pay (WTP) thresholds for a QALY. At a WTP threshold of £50,000 per QALY, [redacted] of the simulations were below and up to this threshold. It should also be noted that proportion ([redacted]) of simulations are in the north-west quadrant, which signifies that standard of care chemotherapy dominated treatment with blinatumomab.

In general the ERG considers the distributions used around key model input parameters to be appropriate. However, the ERG noted that the 95% confidence intervals around the utility inputs were in reverse order and their standard errors provided in Table 5-7 of the submission did not match. On clarification, the company has provided the utility values with their respective 95% confidence intervals (Table 39). The confidence intervals appear to be in line with the ERGs estimates, which are based on the standard errors provided.

**Table 39 Utility values used in the model with their standard errors and 95% confidence intervals**

| Health state | Value | Standard errors | 95% confidence interval |
|---|---|---|---|
| **Blinatumomab** | | | |
| **Initial** | [redacted] | [redacted] | [redacted] |
| **Response** | [redacted] | [redacted] | [redacted] |
| **Relapsed/refractory** | [redacted] | [redacted] | [redacted] |
| **FLAG-IDA** | | | |
| **Initial** | [redacted] | [redacted] | [redacted] |
| **Response** | [redacted] | [redacted] | [redacted] |
| **Relapsed/refractory** | [redacted] | [redacted] | [redacted] |
| **Terminal decrement** | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin | | | |

#### 5.3.10.2 One-way sensitivity analyses

A number of one-way sensitivity analyses were undertaken to explore the impact on the ICER to making changes to key model input parameters. Parameters were varied according to the lower and upper bound of their respective 95% confidence interval (CI) or by assuming uncertainty of ±50% of the point estimate. The results of varying each parameter at a time are shown in Figure 10 and Figure 11.

It can be seen in Figure 10 that the treatment effect for overall survival has the largest impact on the ICER. Using the lower and upper 95% CI, the results showed that the ICER ranges from approximately [redacted] to [redacted] per QALY, respectively. Varying other parameters had little impact on the ICER.

**Figure 10 Tornado diagram for blinatumomab vs FLAG-IDA**

In Figure 11, the company has excluded the overall survival treatment effect. Varying the inpatient stay by ±50% had the largest impact on the ICER.

**Figure 11 Tornado diagram for blinatumomab vs FLAG-IDA excluding overall survival treatment effect**

It should be noted that these analyses consider varying each parameter separately, and are therefore less informative in capturing the overall uncertainty in the model than the results of a full probabilistic sensitivity analysis.

Additionally, as mentioned in Section 4.2.8, the ERG noticed that there was an error in the 95% CIs for the utility values. The company has corrected these, and provided the results in the form of a tornado diagram for blinatumomab versus FLAG-IDA (excluding overall survival treatment effect), but based on the patient access scheme (PAS) (see Figure 12).

**Figure 12 Tornado diagram for blinatumomab vs FLAG-IDA excludiong overall survival treatment effect, including PAS for blinatumomab**

#### 5.3.10.3 Scenario analyses

A number of scenario analyses were undertaken:

- Overall survival based on the restricted cubic spline log-logistic model fit
- Event-free survival among responders based on the lognormal model fit
- 10-year model timeframe
- 1.5% discount rate on costs and effects
- 10 inpatient days for blinatumomab administration for all cycles
- Clofarabine costs included in standard of care chemotherapy
- Time trade-off (TTO) utilities from Aristides et al. (2015)[43] vignettes study

**Table 40 Results for overall survival based on the restricted cubic spline log-logistic model fit**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Using the log-logistic parametric model, (noted in Table 5-3 of the CS as the second-best fitting distribution), to model the overall survival showed an increase in the ICER from approximately [redacted] per QALY to approximately [redacted] per QALY. These results (Table 40) suggest and reiterate that the model is sensitive to the assumptions made on the curve fit used to model overall survival.

**Table 41 Results based on event-free survival among responders based on the lognormal model fit**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Results (Table 41) showed that by using the lognormal parametric model fitted to the EFS amongst responders had little impact on the ICER. The lognormal parametric model was noted in CS Table 5-4 as the best fitting distribution for EFS.

**Table 42 Results based on a 10-year model time horizon**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Table 42 presents the results from an analysis of assuming a 10-year model time horizon. These results showed that mean expected costs remained constant, and mean QALYs decreased, which equated to an ICER of approximately £166,400 per QALY. These results suggest that the model is sensitive to the time horizon.

**Table 43 Results based on a 1.5% discount rate on costs and effects**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Table 43 includes results from an analysis assuming a 1.5% discount rate on costs and effects, as compared to the standard 3.5% discount rate. The ICER for costs per QALYs gained in this analysis was lower than in the base case, at [redacted].

**Table 44 Results based on 10 inpatient days for blinatumomab administration for all cycles**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

In Table 44, an analysis including a full 10 days of hospitalisation for all cycles shows an ICER for costs per QALYs gained of [redacted].

**Table 45 Results based on clofarabine costs included instead of FLAG-IDA costs**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

In Table 45, an analysis using costs for clofarabine instead of for FLAG-IDA showed an ICER for cost per QALYs gained of [redacted], lower than in the base case.

**Table 46 Results based on TTO utilities from Aristides et al 2015 vignettes study**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

An analysis using alternative utility values, presented in Table 46, yielded an ICER for costs per QALYs gained of [redacted], higher than in the base case.

An additional scenario analysis was undertaken that assumed people alive after four years would be 'cured'. For this analysis, an additional health state is included in the illustrative diagram, as shown in

Figure 13. People in the 'cured' health state are assumed to be not at risk of relapsing or disease-specific mortality. People are assumed to have the same utility as the general population and are only at risk of all-cause mortality. All-cause mortality rates were based on UK general population mortality rates.

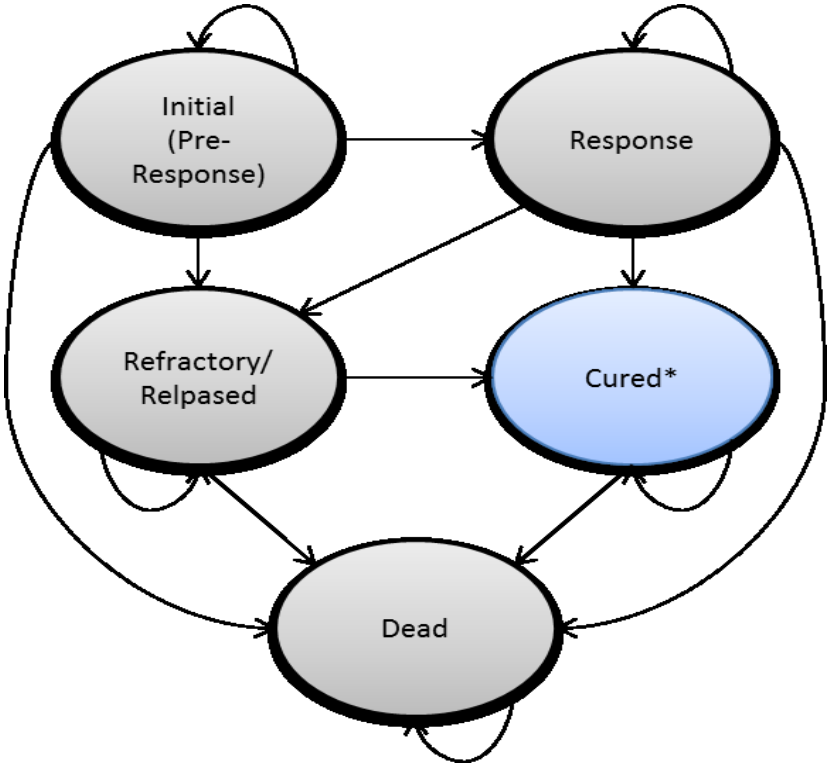



**Figure 13 Illustrative model structure used in the scenario analysis**

Using the assumption that people who are alive at 48 months are cured, the results in Table 47 showed that blinatumomab compared to FLAG-IDA had an ICER of [redacted] per QALY. It should be noted here that this analysis is based on the assumption that people who are in the refractory/relapse health state can be 'cured'. The ERG clinical advisor noted that a transition from refractory/relapse health state to a cure health state would be unrealistic.

**Table 47 Results based on survivors cured at 48 months**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

#### 5.3.10.4 Additional comparators

Base-case analyses compared blinatumomab versus FLAG-IDA, using SOC chemotherapy treatment effects from TOWER as a proxy; hence assuming that outcomes (overall and event-free survival) from these two treatment options to be generalizable. The ERG considers that a more robust estimate on cost-effectiveness would have been to use data from a study that used FLAG-IDA, rather than assuming equal efficacy to the SOC chemotherapy arm from TOWER.

The ERG has attempted to include clofarabine as a comparator in the economic analysis, but due to the paucity of evidence on the use of clofarabine in people with acute lymphoblastic leukaemia alone (studies included people with acute myeloid leukaemia), we were unable to obtain information on overall survival and progression-free survival from these studies. Hence, we were unable to undertake this analysis. Additionally, our clinical advisor suggested that clofarabine is an appropriate comparator but it is not routinely used.

#### 5.3.10.5 Subgroup analysis

The company has provided a subgroup analysis based on people who had not received prior salvage therapy. Clinical results showed that people in this subgroup had more favorable outcomes compared to people who received prior salvage therapy. The overall treatment effect for blinatumomab as compared to SOC chemotherapy for those without prior salvage therapy was HR [redacted], and for those with prior salvage therapy, HR [redacted]. Figure 14 and Figure 15 show the Kaplan-Meier data along with their respective parametric model fits for the overall survival and event-free curves, respectively. As in the base-case analysis, the restricted Gompertz and the generalized gamma parametric curves were fitted to the overall survival and the event-free Kaplan-Meier observed data.

**Figure 14 Kaplan-Meier plots for overall survival with restricted Gompertz parametric model fit (people without prior salvage therapy)**

**Figure 15 Kaplan-Meier plots for event-free survival for responders with restricted generalised gamma parametric model fit (people without prior salvage therapy)**

Estimation of the cost-effectiveness in this subgroup involved calculating OS, EFS among responders, response rates, proportion of people initiating and completing treatment in each cycle, probabilities of all-SCT, utilisation of subsequent salvage therapy and utility values, all specific to this subgroup. All other model input parameters remained unchanged.

**Table 48 Subgroup analysis based on people who had not received prior salvage therapy**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | | [redacted] | - | - |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Results for the subgroup analysis (see Table 48) showed that over the 50-year time horizon of the model, blinatumomab was approximately [redacted] more costly than FLAG-IDA and expected to yield 1.98 more QALYs, which equates to an ICER of approximately [redacted] per QALY. Compared to the base-case results, these incremental costs are greater but in this subgroup blinatumomab produces more incremental QALYs, and thus a reduced ICER. However, while it appears at first glance that these results are more favourable in this subgroup, it should be noted that there is still considerable uncertainty in terms of the treatment efficacy, as the TOWER trial was not powered to detect these differences, and clinical results for the difference between subgroups did not reach statistical significance.

#### 5.3.10.6 ERG summary

The electronic model supplied by the company matches that described in the company's report, and the results derived from the economic analyses accurately reflect those results reported in the report. Scenario analyses results based on the 'cured model' were not presented in the report

### 5.3.11 Model validation and face validity check

The company has undertaken an internal model validation check by entering the model inputs into a partitioned survival model, which had previously been used in economic analyses of oncology therapies. However, the company has not provided any references or examples for this statement. The company has suggested that the results from this validity check (not presented by the company) were not different to those used in the current submission; any minor differences could be explained by the model calculations.

In terms of external validity, the ERG agrees with the company that it is difficult to assess longer-term projections of survival. Nonetheless, the company has suggested that model projections for overall survival for FLAG-IDA were similar to the overall survival for the matched historical cohort. However, it should be noted that the Kaplan-Meier plot used in this submission, which is based on the observed data from natural history cohort, is unpublished. Additionally, the company has applied an arbitrary hazard ratio of 0.85 to the survival function for the historical cohort.

Face validity checks, though not presented in the Validation section of the submission, were obtained from other sections and the electronic models. The ERG has presented face validity checks for the company's model, comprising comparisons of the model predicted overall survival, event-free survival with data on the same from TOWER.

**Table 49 Comparison of probabilities of survival in the model and in TOWER at selected landmarks (from company submission)**

| Month | Blinatumomab | | SOC chemotherapy[a] | |
|---|---|---|---|---|
| | TOWER | Model | TOWER | Model |
| 6 | 53.9% | 52.3% | 38.5% | 41.3% |
| 12 | 34.7% | 35.2% | 28.3% | 24.1% |
| 21.5[b] | 24.9% | 25.0% | 16.6% | 15.1% |

[a] Used as a proxy for FLAG-IDA
[b] Maximum failure or censor time for the SOC chemotherapy arm in TOWER
FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SOC, standard of care

The ERG notices some slight differences in the overall survival seen in the trial and that projected from the model (see Table 49). Noticeably, at the month 12 and 21.5, the model slightly underestimated the overall survival in the standard of care chemotherapy arm.

**Table 50 Comparison of probabilities of event-free survival from TOWER and the model at selected landmarks (from company submission)**

| Month | Blinatumomab | | SOC chemotherapy[a] | |
|---|---|---|---|---|
| | TOWER | Model | TOWER | Model |
| 6 | 29.7% | 32.7% | 11.4% | 14.3% |
| 12 | 12.4% | 17.6% | 8.2% | 6.8% |
| 20.3[b] | 9.1% | 10.5% | 0.0% | 3.9% |

[a] Used as a proxy for FLAG-IDA
[b] Maximum failure or censor time for the SOC chemotherapy arm in TOWER
FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; SOC, standard of care

Results from the model and trial are more pronounced for event-free survival (Table 50). The model appears to overestimate the event-free survival for the blinatumomab arm at all time-points. Similar results can be seen for the standard of care arm except at month 12, where the model underestimated event-free survival.

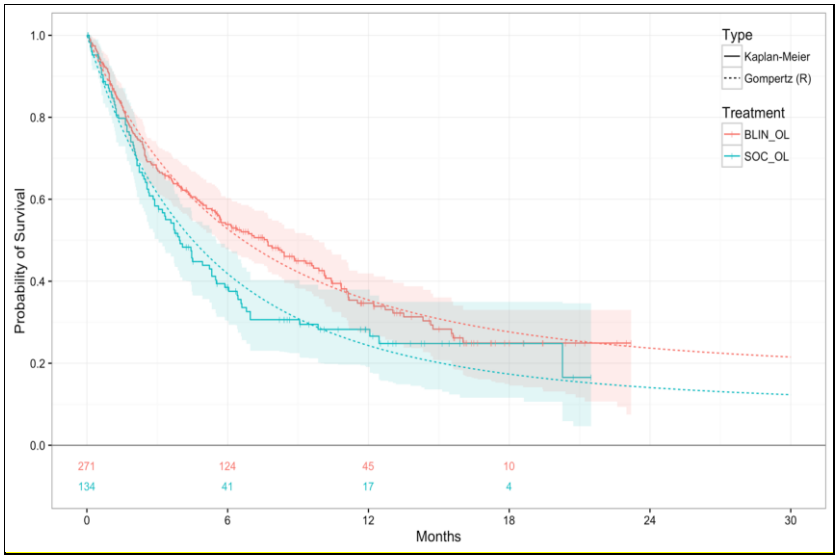
Though these discrepancies may be considered minor, overall survival and event-free survival are key components in a partition survival model. Any differences could have an impact on the treatment effect, and could be transferred to the cost-effectiveness analysis. Additionally, it would have assisted the ERG's appraisal for the company to have provided validity checks, including comparisons of model predicted treatment effects.

Also reported are comparisons between Kaplan-Meier plots and parametric model fits with extrapolation (zFigure 16 and

Figure 17), as well as survival model traces (Figure 18), which show the proportions of people in each state of the model over time. The results in the traces are consistent with the parametric survival model fits to the trial data. However, they are not consistent to the Kaplan-Meier plots of the observed data from the TOWER trial.

#### 5.3.11.1 ERG summary

The company has undertaken validity checks by assessing the model's internal, face and external validity. At the 6, 12 and 21.5 month time-points, the model results obtained for overall survival are satisfactory given the expected clinical progression of the disease, and have fair agreement with comparable results taken directly from the TOWER trial, though comparisons to Kaplan-Meier plots do not suggest good agreement. Agreement is less satisfactory for event-free survival, where the model overestimates survival at start and end of the trial data.



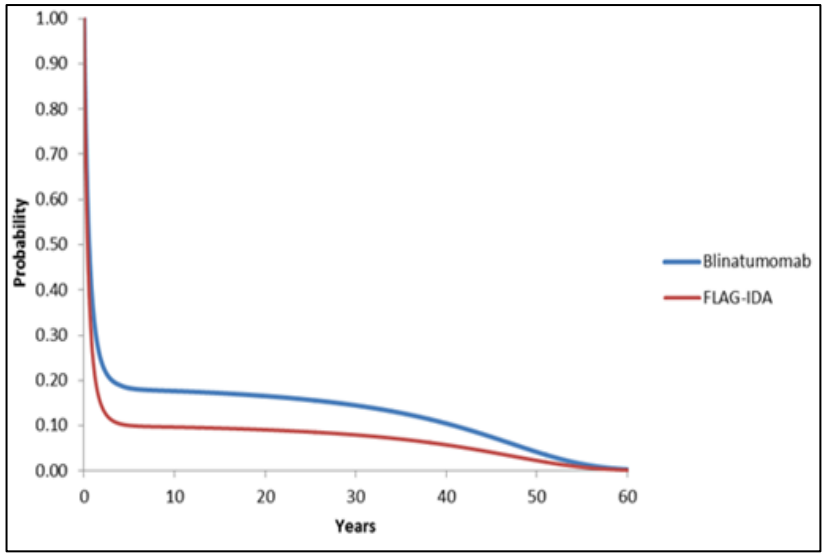




**Figure 16 Overall survival from TOWER compared to projected overall survival from the Markov model**

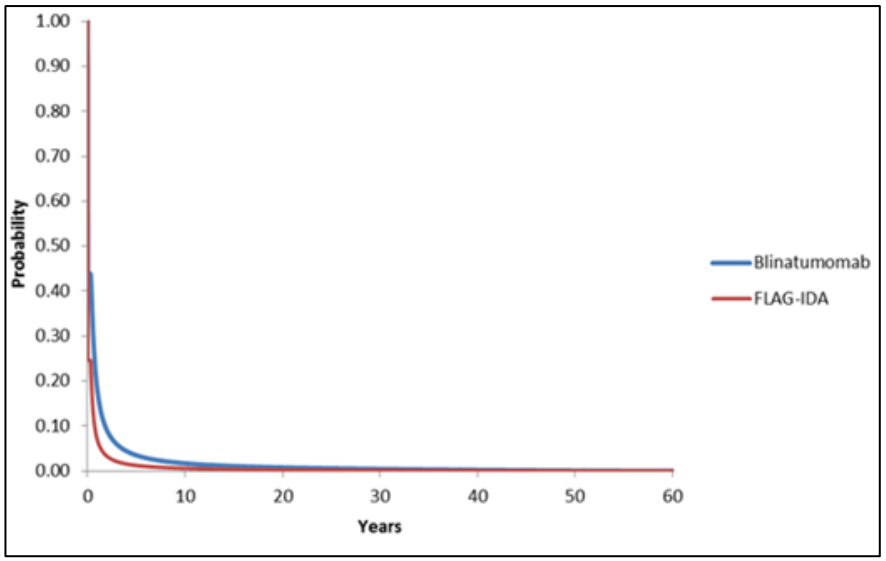



**Figure 17 Event-free survival from TOWER compared to projected event-free survival from the Markov model**

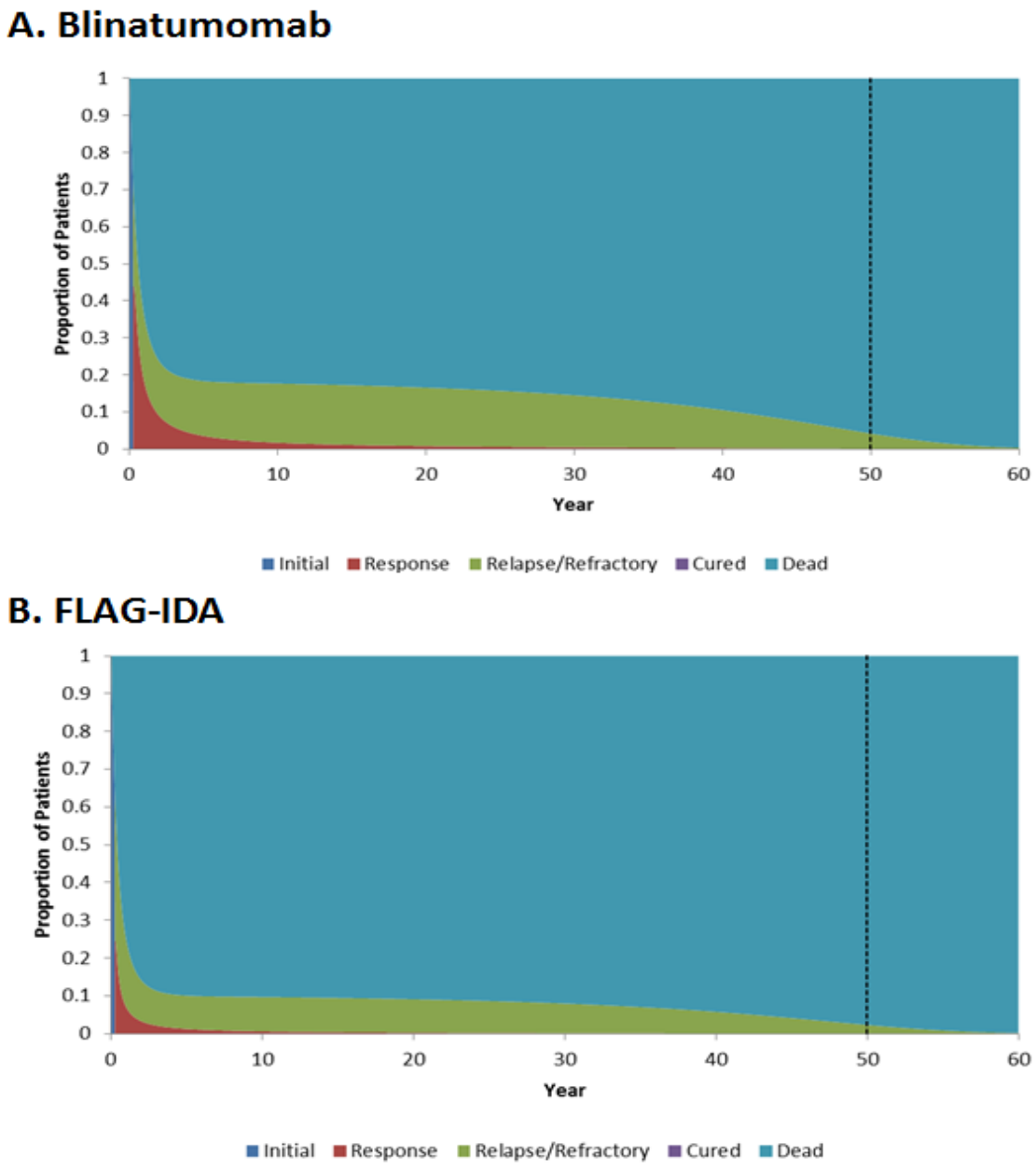



**Figure 18 Survival trace with the proportion of people in each health state, by treatment**

## 5.4 Exploratory and sensitivity analyses undertaken by the ERG

Based on the ERG's concerns noted above, we have used a modified version of the company's base case model to undertake scenario analyses, by incorporating the following changes/assumptions:

- Two-year time horizon
- Additional inpatient treatment
    - Inpatient stay for cycles one and two
    - Assuming blinatumomab is administered in an inpatient setting (five cycles with inpatient stays)
- Intravenous bag changes daily, as opposed to every four days
- **ERG preferred base case, including probabilistic sensitivity analysis:** Inpatient stay for cycles one and two and for subsequent cycles people would receive intravenous bag changes every day, as opposed to every four days
- Correction to the 95% CI to the utility values and its impact on the probabilistic sensitivity analysis

### 5.4.1 Two-year time horizon

This analysis is based on a two-year time horizon; that is, it could be considered as the within-trial analysis. The ERG considers that the trial time horizon and follow-up are not sufficiently long enough to allow for 60-year extrapolations. Projections based on these immature data increase the clinical and modelling uncertainty. Therefore using shorter time horizons may reduce uncertainty, and allows greater confidence in clinical and cost-effectiveness results.[44]

Results are presented in Table 51. As the majority of the costs are incurred in the first year, the expected mean costs for the blinatumomab arm and the FLAG-IDA arm are very similar to the base-case results ([redacted] and [redacted]). However, there has been a reduction in the QALYs accrued over time, with blinatumomab expecting to yield 0.19 more QALYs than FLAG-IDA, with an ICER of approximately [redacted].

**Table 51 Results based on assuming a two-year time horizon of the model**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | | [redacted] | | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

### 5.4.2 Inpatient stay

The ERG clinical advisor noted that the minimum hospitalisation periods in the marketing authorisation, and thus as used in the company's model, were unlikely to be realistic given the demands of treatment and the infrastructure required to support outpatient treatment, with hospitalisation during the entirety of active treatment in each of the five cycles being possible, if not likely. The ERG tested two alternative scenarios in response to this concern: first, an analysis in which patients are hospitalised for the entirety of the active treatment periods in the first two cycles, and second, an analysis in which patients are hospitalised for the entirety of the active treatment periods in the five maximum cycles.

### 5.4.3 Hospitalisation in active treatment periods for the first two cycles

This analysis assumes that people receiving blinatumomab treatment accrue 56 days of hospitalisation during cycles 1 and 2; that is, that patients are hospitalised for the two four-week active treatment periods in the first two cycles.

**Table 52 Results based on the assumption that patients are hospitalised for active treatment periods in the first two cycles**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Increasing the duration of time spent in inpatient care for cycles one and two resulted in an ICER of approximately [redacted] per QALY gained (see Table 52).

### 5.4.4 Hospitalisation in active treatment periods in the five maximum cycles

The ERG has undertaken a scenario analysis that assumes that people would receive five cycles of blinatumomab treatment in a hospital inpatient setting, thus spending 28 days in care for each cycle. All other model inputs and assumptions are kept constant. As expected, these results showed an increase in the mean costs in the blinatumomab arm, and a slight increase in the FLAG-IDA arm. This increase in the comparator arm, may reflect that some people in the TOWER trial subsequently receive blinatumomab. Results in terms of LYG and QALYs were approximately [redacted] and [redacted], respectively (see Table 53 and Table 54).

**Table 53 Results based on the assumption that patients are hospitalised for active treatment periods in five cycles (undiscounted lfe years gained)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean LYG | Incremental LYG | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental life years gained; LYG, life years gained | | | | | |

**Table 54 Results based on the assumption that patients are hospitalised for active treatment periods in five cycles (discounted QALYs)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental life years gained; LYG, life years gained | | | | | |

### 5.4.5 Intravenous bag changes daily

The ERG undertook a scenario analysis assuming daily bag changes for intravenous chemotherapy, instead of every four days as in the base case. We expect that this may represent a more realistic estimate of everyday practice.

The results of this analysis (see Table 55) led to an increase in the ICER, driven by an increase in costs for both treatment strategies. The ICER was approximately [redacted] per QALY gained.

**Table 55 Results based on daily intravenous bag changes**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental life years gained; LYG, life years gained | | | | | |

### 5.4.6 ERG preferred base case: inpatient treatment in cycles one and two, daily bag changes in subsequent cycles

The ERG preferred base case includes inpatient treatment in cycles one and two as well as daily bag changes in the subsequent three cycles permitted by the marketing authorisation. For the reasons presented above, the ERG believes that this presents a more realistic estimate of the resource-intensive aspects of treatment with blinatumomab.

The deterministic analysis, presented in Table 56 below, shows an increase in QALYs of [redacted] against an increase in costs of [redacted]. This results in an ICER of approximately [redacted] per QALY gained.

**Table 56 Results based on the ERG preferred base case (inpatient treatment in cycles one and two, daily bag changes in subsequent cycles)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

The ERG then undertook a probabilistic sensitivity analysis for the ERG preferred base case. These results, presented below in Table 57, result in an ICER of approximately [redacted] per QALY gained.

**Table 57 Probabilistic sensitivity analysis results based on the ERG preferred base case (inpatient treatment in cycles one and two, daily bag changes in subsequent cycles)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Blinatumomab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Results for 1000 runs of the Monte Carlo simulation (see Figure 19) show considerable uncertainty about the incremental QALYs, and less so for the incremental costs.

Figure 20 shows the results of the probabilistic sensitivity analysis presented in the form of cost-effectiveness acceptability curve for the comparison between blinatumomab and FLAG-IDA. At a WTP threshold of £50,000 per QALY, [redacted] of the simulations were below and up to this

threshold. It should also be noted that proportion ([redacted]) of simulations are in the north-west quadrant, which signifies that standard of care chemotherapy dominated treatment with blinatumomab.

**Figure 19 Scatterplot, ERG preferred base case probabilistic sensitvity analysis**

**Figure 20 Cost-effectiveness acceptability curve, ERG preferred base case probabilistic sensitivity analysis**

### 5.4.7 Correction to the 95% CI to the utility values and its impact on the probabilistic sensitivity analysis

At the clarification stage, the company has provided the correct 95% CI around the utility values used in the model, and reported probabilistic sensitivity analysis results based on the PAS. The ERG has therefore explored the impact this change has made on the base case analysis, by using beta distributions as opposed to the lognormal distributions.

PSA results showed that at a willingness-to-pay threshold of £50,000 per QALY gained, the probability of blinatumomab being cost-effective when compared to FLAG-IDA is [redacted] (see Figure 21 and Figure 22). However, it should be noted that these PSA results do not incorporate a full complement of uncertainty around all key parameters.

**Figure 21 Scatterplot using distributions around input parameters, ERG corrected PSA from company submission**

**Figure 22 Cost-effectiveness acceptability curve for blinatumomab and FLAG-IDA, ERG corrected PSA from company submission**

## 5.5 Conclusions of the cost effectiveness section

Cost-effectiveness evidence included in the CS was based on two systematic reviews of reasonable quality. The company used a partitioned survival Markov model to show the experience of a cohort of people with refractory or relapsed Philadelphia chromosome–negative acute lymphoblastic leukaemia who may undergo treatment with blinatumomab and standard care chemotherapy over a 50-year time horizon. The model defined health states of initial (pre-response), refractory/relapsed, response to treatment and death. Clinical effectiveness inputs to the model relied solely on the TOWER trial. As in the earlier aspects of this submission, the clinical effectiveness of FLAG-IDA was represented by the effectiveness of the pooled SOC chemotherapy arm. Key costs in the model included the cost of blinatumomab and of FLAG-IDA, the scoped comparator, both of which were based on the NHS list prices. Inpatient hospitalisation, costs of allogeneic stem cell transplant, costs of subsequent therapy and costs of terminal care were included as well. While the model appeared to capture the key features of ALL and used a sufficiently similar population, the scenario analysis, which included a 'cured' health state, was not viewed by the ERG to be a clinically reasonable model. Among other concerns noted by the ERG, the company's use of parametric curves with the observed data from TOWER represented a set of strong assumptions, given that visual inspection of Kaplan-Meier plots relating to overall survival and event-free survival from TOWER suggests that hazards are not proportional.

The company's base case analyses yielded an ICER of [redacted] per QALY. In one-way sensitivity analyses, the model was most sensitive to changes in overall survival, though the number of inpatient days assumed for the comparator was the next most influential factor. At a willingness-to-pay threshold of £50,000 per QALY, the company's probabilistic sensitivity analysis yielded a [redacted] probability of blinatumomab being cost-effective as compared to FLAG-IDA.

## 5.6 Impact on the ICER of additional analyses undertaken by the ERG

### 5.6.1 Summary of ERG scenario analyses

Across ERG scenario analyses, the effect of changes to parameters—was to raise the ICER (see Table 58). In the ERG preferred base case, which incorporated changes to resource use that the ERG believed more accurately reflected clinical management of relapsed/refractory ALL in the

UK context, adjusting inpatient days and increasing the frequency of bag changes had a notable effect on the ICER.

**Table 58 Summary of ERG deterministic scenario analyses, cost per QALY**

| ERG scenario | ICER (£) |
|---|---|
| Two-year time horizon | [redacted] |
| Inpatient stay for cycles one and two | [redacted] |
| Inpatient stay for five cycles | [redacted] |
| Intravenous bag changes daily | [redacted] |
| ERG preferred base case: inpatient stay for cycles one and two, bag changes daily | [redacted] |

### 5.6.2 Additional areas of uncertainty

The ERG note that several areas of uncertainty remain in the economic model. These are discussed below alongside likely direction of travel for the ICER.

#### 5.6.2.1 Generalisability of SOC chemotherapy arm to FLAG-IDA and clofarabine

As the ERG noted throughout the report, the clinical effectiveness evidence, and thus the economic model, rely on the assumption that the pooled SOC chemotherapy arm is an appropriate proxy for FLAG-IDA. The company supported this assertion via expert opinion alone. While the company's subgroup analyses in TOWER would suggest similarity of effectiveness in comparisons of overall survival and event-free survival between FLAG regimens and the pooled SOC chemotherapy arm, this comparison is hampered by relatively small numbers in the subgroups. The plausibility of this comparison is even less clear for the difference between clofarabine and the pooled SOC chemotherapy arm, though the ERG was unable to locate a suitable source of data to conduct exploratory analyses addressing clofarabine more specifically.

The expected direction of travel of the ICER as a result of these changes is unclear, especially given the limitations of the evidence base presented in the company submission.

#### 5.6.2.2 Pump costs

As part of clarifications, the ERG requested a scenario analysis in which pumps were assumed to not be reusable; that is, an analysis that, unlike the company's base case, does not assume transferability of pumps and, thus, pro-rated costs for duration of treatment. The company's response, provided in clarification Table B-3, included an analysis assuming that pumps were not

reusable, but this analysis was only presented with PAS pricing. In its attempts to replicate this analysis without PAS pricing, the ERG was unable to ascertain exactly how pump costs were assigned under this scenario. While the company observes that this is unlikely to materially affect the ICER, it is the ERG's view that including pumps as non-reusable may be a more accurate reflection of actual resource use. Under this scenario, the ICER would be likely to increase.

#### 5.6.2.3 Extrapolation of treatment effectiveness

As the ERG noted throughout the cost effectiveness section, we have concerns about whether the long-term effectiveness assumed in the submitted cost-effectiveness model is the most appropriate interpretation of the information available on this parameter from the trial.

Though model face validity checks supported generally good agreement for OS (but not EFS) on survival at different time points, visual inspection of the Kaplan-Meier plots for these outcomes reveals [redacted]. Thus, a conservative interpretation of these plots is that additional costs and benefits are unlikely to accrue past the trial time horizon, and extrapolation of effectiveness beyond the trial time horizon is thus unnecessary. As noted in Section 5.4.1, the ERG's scenario analysis of a two-year time horizon corresponds to this within-trial analysis. However, while the ERG believed the company submission extrapolation was optimistic, limiting the time horizon to two years may underestimate costs and benefits, given that some in the SOC arm went on to receive blinatumomab or other therapies that are not routinely used in practice.

The ERG explored a variety of approaches to resolve the question of extrapolation and of violation of proportional hazards in OS and EFS, but was unable to apply these approaches to the economic model. The ERG has outlined their concerns with the assumption of proportional hazards, which was used to derive the treatment effectiveness for overall survival. The ERG has not formally tested this assumption but have reconstructed the individual patient level data to derive the Kaplan-Meier plots, and fitted (and extrapolated) parametric models to these reconstructed data. Fitting individual parametric models to each K-M plot relaxes the assumption of proportional hazards, and it may provide a superior fit. Based on information criteria, the Gompertz and lognormal models were the best fit to the Kaplan-Meier plot for the blinatumomab and standard of care, respectively. Though the Gompertz was the best fitting model, it predicted that 20% of people would be immortal apart from additional age-related mortality hazards; this appears to be because it underestimates hazard for death at times beyond 12 months. In this case,

parametric model fitting, and thus extrapolations, are heavily influenced by the flat tails seen in the Kaplan-Meier plots of the observed data (especially for the blinatumomab arm).

In order to reduce the uncertainty in OS, and were data to be available, it would be useful to consider other methods such as using survival data from the Kaplan-Meier plot directly in the model, and modelling survival in the blinatumomab arm using the clearly linear trend in cumulative hazard seen for times between 9 and 18 months. This linear trend indicates that hazard is constant during this time and that extrapolation of an exponential fit from approximately 9 months to 18 months will more faithfully reflect the observed data.

It is likely that a revision of the optimistic extrapolation methods used in the company submission would cause an increase in the ICER, but it would be difficult to assert this with certainty given that the ERG was limited by data availability in exploring the feasibility of alternative survival curves in the economic model.

# 6 END OF LIFE

The company argues that treatment with blinatumomab meets the NICE end-of-life criteria: it is indicated for patients with a short life expectancy (normally less than 24 months) and there is sufficient evidence to indicate that the treatment offers an extension to life (normally of at least an additional 3 months) compared with current NHS treatment.

In section 3.2.2 of the company submission, the company quotes a large, international, retrospective study of 1706 adult patients with relapsed/refractory Ph- B-precursor ALL diagnosed between 1990 and 2013 in Europe and the USA (including 427 patients from the UK) which showed that overall median survival was 5.8 months, 3.9 months, and 2.9 months from the start of first, second, and third or later salvage, respectively.[7] Of the patients in first salvage, 49% were alive after 6 months, 26% were alive after 1 year, and just 11% were alive after 3 years. Median overall survival from the start of first salvage remained low at 6.5 months in the most recent cohort of patients (2005-2013). In a retrospective analysis from the UK of outcomes in 609 adult newly diagnosed ALL patients enrolled in the MRC UKALL12/ECOG 2993 study, median survival after relapse was 24 weeks (5.5 months, data from 2003 to 2005).[4]

In the clinical evidence presented in the company submission (clinical study report sections 4.7.2 and 4.11.6.2), median overall survival was increased by 3.7 months in the TOWER RCT with blinatumomab compared to SOC chemotherapy.[45] In the non-randomised evidence quoted, weighted median overall survival was 3.3 months in the historical cohort and 6.1 months in the blinatumomab group (2.8 months more) [22].

Based on the rationale submitted by the company, the ERG agrees that a case exists to support the company's statement that treatment with blinatumomab fulfils NICE end-of-life criteria.

# 7 INNOVATION

The company submission discusses the issue of innovation in section 2.4, p. 37. The company argues that meaningful progress in the treatment of adult relapsed/refractory Ph- B-precursor ALL has been lacking for decades and that, with the exception of blinatumomab, there are no targeted treatments licensed specifically for this disease.

The company describes the novel mechanism of action of blinatumomab, a T-cell engaging immunotherapy harnessing the body's own immune system to recognise and eliminate malignant cells. They report that based on promising results from non-randomised evidence and provision of data from the TOWER trial, blinatumomab was approved on an accelerated assessment pathway by EMA, reflecting a substantial unmet need. In the TOWER trial [45], the treatment nearly doubled the median overall survival time from 4.0 months with SOC chemotherapy to 7.7 months with blinatumomab. The company suggests that with a young patient population (median age at diagnosis 34 to 39 years) this may present a benefit to wider society if the treatments contribute to more young people achieving long term remission and survival.

The company submission also states that in the TOWER trial, incidence of important adverse events commonly associated with cytotoxic SOC chemotherapies were lower in the blinatumomab arm than SOC chemotherapy arm: these include adverse events such as neutropaenia (17.6% with blinatumomab versus 26.6% with SOC chemotherapy), febrile neutropaenia (21.3% with blinatumomab versus 34.9% with SOC chemotherapy), anaemia ([redacted] with blinatumomab versus [redacted] with SOC chemotherapy), thrombocytopaenia ([redacted] with blinatumomab versus [redacted] with SOC chemotherapy), and infections (e.g., pneumonia, 4.1% with blinatumomab versus 11.9% with SOC chemotherapy). However, treatment-related AEs leading to interruption of treatment occurred more frequently in the blinatumomab arm ([redacted] versus [redacted]). Also, serious neurologic adverse events of interest occurred in [redacted] of the blinatumomab arm and [redacted] of the SOC chemotherapy arm. Cytokine release syndrome occurred in [redacted] of patients in the blinatumomab arm, 4.9% of this was Grade 3 or more and in [redacted] this led to treatment discontinuation. No such events were seen in patients on SOC chemotherapy. Some other adverse events were also more common with blinatumomab, this included infusion reactions [redacted] vs [redacted] ≥ Grade 3: 3.4% vs 0.9%), decreased immunoglobulins ([redacted] ≥ Grade 3: 2.6% vs 0.0%) and tumour lysis syndrome ([redacted] vs [redacted] ≥ Grade 3: 3.0% vs 0.9%).

The company submission also stresses that blinatumomab provides the option of an effective therapy that can be administered in the outpatient setting and therefore has the potential to reduce duration of hospitalisation compared with current salvage chemotherapy regimens. However, the ERG clinical advisor pointed out that outpatient treatment with blinatumomab requires an appropriate infrastructure and specialised centres where more than a few patients are treated per week and that in practice, while outpatient treatment would in theory be possible, patients are currently still hospitalised for the duration of the treatment.

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# 9 APPENDIX 1: APPRAISAL OF THE COST EFFECTIVENESS SUBMISSION

**Quality assessment against the CHEERS checklist**

| Assessment | Submission | Comments |
|---|---|---|
| Title | Y | |
| Abstract | Y | |
| **Introduction** | | |
| Background and objectives | Y | |
| **Methods** | | |
| Target population and subgroups | Y | |
| Setting and location | Y | |
| Study perspective | Y | |
| Comparators | Y | |
| Time horizon | Y | |
| Discount rate | Y | |
| Choice of health outcomes | Y | |
| Measurement of effectiveness | Y | |
| Measurement and valuation of preference-based outcomes | Y | |
| Estimating resources and costs | Y | |
| Currency, price date, and conversion | Y | |
| Choice of model | Y | |
| Assumptions | Y | |
| Analytical methods Results | Y | |
| Study parameters | Y | |
| Incremental costs and outcomes | Y | |
| Characterising uncertainty | Y | |
| **Discussion** | | |
| Study findings | Y | |
| Limitations | Y | |
| Generalizability | Y | |
| **Other** | | |
| Source of funding | NA | |
| Conflicts of interest | NA | |
| N, no; NA, not applicable; UNC, unclear; Y, yes | | |

**Quality appraisal using the Philips criteria**

| Philips' criteria | | Submission | Comments |
|---|---|---|---|
| **Structure** | | | |
| 1. | Is there a clear statement of the decision problem? | Y | |
| 2. | Is the objective of the model specified and consistent with the stated decision problem? | Y | |
| 3. | Is the primary decision maker specified? | Y | |
| 4. | Is the perspective of the model stated clearly? | Y | |
| 5. | Are the model inputs consistent with the stated perspective? | Y | |
| 6. | Has the scope of the model been stated and justified? | Y | |
| 7. | Are the outcomes of the model consistent with the perspective, scope and overall objective of the model? | Y | No formal comparison with clofarabine |
| 8. | Is the structure of the model consistent with a coherent theory of the health condition under evaluation? | Y | The model in scenario analysis includes a transition that may not be clinically feasible |
| 9. | Are the sources of the data used to develop the structure of the model specified? | Y | |
| 10. | Are the causal relationships described by the model structure justified appropriately? | Y | |
| 11. | Are the structural assumptions transparent and justified? | Y | |
| 12. | Are the structural assumptions reasonable given the overall objective, perspective and scope of the model? | Y | |
| 13. | Is there a clear definition of the options under evaluation? | Y | |
| 14. | Have all feasible and practical options been evaluated? | N | Clofarabine and best supportive care have been excluded |
| 15. | Is there justification for the exclusion of feasible options? | N | Not justified given that these comparators were included in the scope. |
| 16. | Is the chosen model type appropriate given the decision problem and specified casual relationships within the model? | Y | |
| 17. | Is the time horizon of the model sufficient to reflect all important differences between the options? | Y | However, extrapolations appeared to be optimistic |

| Philips' criteria | | Submission | Comments |
|---|---|---|---|
| 18. | Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified? | Y | Time horizon appears to be sufficient but with lots of uncertainty |
| 19. | Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions? | Y | The model in scenario analysis includes a transition (refractory/relapse)that may not be clinically feasible |
| 20. | Is the cycle length defined and justified in terms of the natural history of disease? | Y | |
| **Data** | | | |
| 21. | Are the data identification methods transparent and appropriate given the objectives of the model? | Y | Sources appear to be transparent |
| 22. | Where choices have been made between data sources are these justified appropriately? | UNC | |
| 23. | Has particular attention been paid to identifying data for the important parameters of the model? | Y | |
| 24. | Has the quality of the data been assessed appropriately? | UNC | |
| 25. | Where expert opinion has been used are the methods described and justified? | UNC | Expert opinion has be sought, but the company has not elaborated on these methods |
| 26. | Is the data modelling methodology based on justifiable statistical and epidemiological techniques? | Y | |
| 27. | Is the choice of baseline data described and justified? | Y | |
| 28. | Are transition probabilities calculated appropriately? | | |
| 29. | Has a half-cycle correction been applied to both costs and outcomes? | NA | |
| 30. | If not, has the omission been justified? | NA | |
| 31. | If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques? | NA | Treatment effects were obtained from one trial |
| 32. | Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified? | Y | Methods used have been discussed |
| 33. | Have alternative extrapolation assumptions been explored through sensitivity analysis? | Y | |

| Philips' criteria | | Submission | Comments |
|---|---|---|---|
| 34. | Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? | Y | |
| 35. | Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis | Y | |
| 36. | Are the costs incorporated into the model justified? | Y | |
| 37. | Has the source for all costs been described? | Y | |
| 38. | Have discount rates been described and justified given the target decision maker? | Y | |
| 39. | Are the utilities incorporated into the model appropriate? | Y | |
| 40. | Is the source of utility weights referenced? | Y | |
| 41. | Are the methods of derivation for the utility weights justified? | Y | |
| 42. | Have all data incorporated into the model been described and referenced in sufficient detail? | Y | |
| 43. | Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?) | Y | |
| 44. | Is the process of data incorporation transparent? | Y | |
| 45. | If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified? | Y | Choice of distributions have been stated |
| 46. | If data have been incorporated as distributions, is it clear that second order uncertainty is reflected? | Y | |
| 47. | Have the four principal types of uncertainty been addressed? | N | |
| 48. | If not, has the omission of particular forms of uncertainty been justified? | N | |
| 49. | Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions? | Y | |
| 50. | Is there evidence that structural uncertainties have been addressed via sensitivity analysis? | N | |
| 51. | Has heterogeneity been dealt with by running the model separately for different sub-groups? | Y | |
| 52. | Are the methods of assessment of parameter uncertainty appropriate? | Y | In general, however, not all parameters were varied |

| Philips' criteria | | Submission | Comments |
|---|---|---|---|
| 53. | If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified? | Y | |
| 54. | Is there evidence that the mathematical logic of the model has been tested thoroughly before use? | UNC | |
| 55. | Are any counterintuitive results from the model explained and justified? | NA | |
| 56. | If the model has been calibrated against independent data, have any differences been explained and justified? | NA | |
| 57. | Have the results been compared with those of previous models and any differences in results explained? | N | Other assessments were considered not to be relevant |

**Erratum for**

**Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia**

**Produced by:** Warwick Evidence

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**Date completed:** 23 February 2016

**Source of funding**: This report was commissioned by the NIHR HTA Programme as project number ID804.

**Declared competing interests of the authors:** None.

**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows:** Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia. A single technology appraisal. Warwick Evidence, February 2017.

**Contributions of authors:** G.J. Melendez-Torres (Assistant Professor) co-ordinated the project, led the review of clinical effectiveness and contributed to the drafting of the report. Peter Auguste (Research Fellow) led the review of cost effectiveness and contributed to the drafting of the report. Jacoby Patterson and Christine Clar (Independent research consultants) contributed to the review of clinical effectiveness and to the drafting of the report. Rachel Court (Information Specialist) contributed to the reviews of clinical and cost effectiveness and contributed to the drafting of the report. Jason Madan (Associate Professor) contributed to the review of cost effectiveness. Prem Mahendra (Consultant Haemato-Oncologist) contributed clinical input. Aileen Clarke (Professor of Public Health Research) supervised the project.

**Please note that:** Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are [redacted] Figures that are CIC have been bordered with blue.

**Factual Accuracy Check**

| Issue | ERG response | Page number |
|---|---|---|
| 1-5 | No change necessary | |
| 6 | Amended | 26 |
| 7-8 | No change necessary | |
| 9 | Amended | 33 |
| 10 | No change necessary | |
| 11 | Amended | 35 |
| 12-15 | No change necessary | |
| 16 | Amended | 67 |
| 17-21 | No change necessary | |
| 22 | Amended | 87-88 |
| 23-25 | No change necessary | |
| 26-27 | Amended | 95 |
| 28-30 | No change necessary | |
| 31 | Amended | 117 |
| 32 -36 | No change necessary | |

# 3 Critique of company's definition of decision problem

The decision problem from the final NICE scope is summarised in Table 1 below.

**Table 1 Decision problem from the final NICE scope**

| | |
|---|---|
| **Population** | People with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia |
| **Intervention** | Blinatumomab |
| **Comparators** | • Fludarabine, cytarabine and granulocyte colonystimulating factor (GCSF) based combination chemotherapy, with or without idarubicin (FLAG-IDA)<br>• Clofarabine based combination chemotherapy<br>• Best supportive care (including palliative care) |
| **Outcomes** | • Overall survival<br>• Event-free survival<br>• Relapse-free survival<br>• Treatment response rates (including minimal residual disease and haematology responses and complete remission)<br>• Time to and duration of response<br>• Rate of stem-cell transplant<br>• Adverse effects of treatment<br>• Health-related quality of life |
| **Subgroups** | If the evidence allows the following subgroup will be considered: people for whom allogeneic stem cell transplantation is considered an appropriate treatment option |

## 3.1 Population

The patient population in the decision problem matches the population described in the final scope. The company defines the included population as "Adults with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia" while the final scope states "people with…", but as blinatumomab is authorised in the UK for use in adults only, these statements are judged to be equivalent. The included trials examined patients aged ≥18 years with relapsed/repractory Ph-, B-precursor ALL, therefore they covered the population specified in the decision problem and the final scope.

## 3.2 Intervention

The intervention in both the company's decision problem and in the final scope is blinatumomab. The company describes the technology on pp. 31-32 of the submission. Blinatumomab is a T-cell engager antibody targeting CD19 expressed on the surface of B-cells and CD3 expressed on the surface of T-cells. Blinatumomab mediates the formation of a cytolytic immunological synapse

OS and EFS; this was not the case for comparisons between blinatumomab and FLAG-based regimens (see sections **Error! Reference source not found.** and **Error! Reference source not found.**).

Patient disposition is summarised in a flowchart (Figure 4-3, CS p 67). The ERG summarises patient disposition for TOWER in Table 2. Arms were imbalanced in terms of number not receiving the allocation treatment; as noted on CS p 66 [redacted] of patients in the SOC chemotherapy arm did not receive the intended treatment as opposed to [redacted] in the blinatumomab arm. Reasons for this were provided in the flowchart and are documented in Table 3. Moreover, the ERG noted on CS pp. 108-109 that [redacted] of those enrolled in the blinatumomab arm started six or more cycles of the study drug. This was not explained in the CS and the ERG clinical advisor was not able to suggest a plausible reason for this. Additionally, [redacted] of patients in the SOC chemotherapy arm received blinatumomab subsequently (see CS p 111, Table 4-32), which suggests an issue of drop-in. More patients in the SOC arm also received other systemic anticancer therapies in general than in the blinatumomab arm ([redacted], CS p 110). The ERG reconstructed patient disposition for 'FLAG-eligible' and 'clofarabine-eligible' subgroups based on CS Table 4-9 (p 68) and clarification tables A-13, A-18 and A-20.

The ERG notes two additional considerations for trial validity. First, patients with relapse after greater than 12 months in remission were excluded from this trial. The company notes on CS p 123 that these patients enjoy better prognosis, and the ERG clinical advisor agreed with this assertion. Second, consolidation criteria for blinatumomab (i.e. the point at which the decision is made to continue after two cycles of treatment) varied in TOWER from the marketing authorisation. As noted on CS p 124, the marketing authorisation for blinatumomab notes that patients should reach CR or CRh* to continue; whereas in TOWER, patients needed to reach CR, CRh* or CRi, or have ≤5% bone marrow blasts. However, the company notes that of patients achieveing CR, CRh* or CRi, [redacted] of them were included in the CR or CRh* categories. The company did not provide in the CS evidence of how many patients would have been included on the basis of ≤5% bone marrow blasts, though the ERG clinical advisor suggested that this was, in practice, not a major issue to trial validity.

Key patient characteristics from the full analysis set are reproduced in Table 4 below, and are presented in Table 4-9 (CS p 68) as well as clarification Tables A-18 and A-19. The company did not present significance tests for differences between arms, nor did the company provide in the CS evidence of balance between arms on time from initial diagnosis to randomisation or on time

**Table 2 Participant disposition in TOWER (from CS Table 4-9, CS Appendix III, clarification Table A-13)**

| | All patients | | 'FLAG-eligible' patients | | 'Clofarabine-eligible' patients | |
|---|---|---|---|---|---|---|
| | Blinatumomab | SOC chemotherapy | Blinatumomab | FLAG with or without anthracycline | Blinatumomab | Clofarabine-based regimens |
| [redacted] | | | | | | |

**Table 3 Reasons for not receiving allocated treatment in TOWER (from CS Figure 4-3)**

| | |
|---|---|
| [redacted] | |

**Table 4 Characteristics between arms in TOWER FAS (from clarification Tables A-18 and A-19)**

| Baseline characteristic | Blinatumomab (N = 271) | SOC chemotherapy (N = 134) | Total (N = 405) | p-value between arms |
|---|---|---|---|---|
| Sex, n (%) | | | | [redacted] |
| Men | [redacted] | [redacted] | [redacted] | |
| Women | [redacted] | [redacted] | [redacted] | |
| Age | | | | [redacted] |
| Median (IQR), years | [redacted] | [redacted] | [redacted] | |

**Table 5 Treatment emergent adverse events, TOWER**

| | Safety analysis set* | | FLAG-eligible patients | | Clofarabine-eligible patients | |
|---|---|---|---|---|---|---|
| | **Blina** | **Total SOC chemo** | **Blina** | **FLAG** | **Blina** | **Clofarabine** |
| | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| AEs of treatment: AEs that occurred after the first dose of study drug and up to 30 days after the last dose of study drug (i.e., treatment-emergent AEs [TEAEs]) are presented.**** | | | | | | |
| TEAEs n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade ≥ 3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Serious AE | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Treatment-related | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Led to interruption of investigational product | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Led to discontinuation of product | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| AE of interest | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Life-threatening | [redacted] | [redacted] | | | | |
| Fatal | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

* = CS Table 4-34, p112, referenced to TOWER primary analysis CSR (Tables 12-4 and 12-11)
** = Clarification document Table A-11, p 28, referenced to Amgen data on file, 2017
*** = Clarification document Table A-14, p 32, referenced to Amgen data on file, 2017.
**** = CS Section 4.12, p108

**Table 6 Cox proportional hazards analysis of overall survival**

| **Analysis** | Hazard ratio (95% CI) | Log-rank p-value |
|---|---|---|
| Full analysis set | [redacted] | [redacted] |
| Adjusting for drop-in | [redacted] | [redacted] |
| CI, confidence interval | | |

**Natural history cohort.** The ERG was unclear about how the company used information from the matched natural history cohort, and how the arbitrary adjusted hazard ratio of 0.85 was applied to the overall survival as shown in **Error! Reference source not found.**. On clarification, the company outlined that '*the adjusted OS curve for the matched historical comparator was not used explicitly in the model. Rather, it was used to assess the plausibility of the model projections based on the Gompertz distribution and general population mortality.*' Additionally, the company stated that '*the adjusted OS curve for the matched historical comparator was calculated using the formula below:*

$S_A[t] = S[t]^{HR}$

*where*

$S_A[t]$ *= Adjusted Kaplan-Meier survival distribution for matched historical comparator*

$S[t]$ *= Unadjusted Kaplan-Meier survival distribution for matched historical comparator*

*HR = Hazard ratio for adjusted vs. unadjusted Kaplan-Meier survival distribution for the matched historical comparator*

*The HR for the adjusted versus unadjusted Kaplan-Meier survival distribution (0.85) was obtained using trial and error and visual inspection.*'

**Assessment of effectiveness using parametric models.** The main source of treatment efficacy on overall survival is based on the TOWER trial. As noted above, the treatment effect is based on fitting a restricted Gompertz parametric model to the blinatumomab arm of the trial, and then assuming proportional hazards for the standard of care arm. The ERG is concerned that the proportional hazards assumption is invalid, given that the Kaplan-Meier plots (**Error! Reference source not found.**) appear to cross from month 15 through the remainder of the trial time horizon. The proportionality assumption leads to overestimating the treatment benefit of blinatumomab.

#### 5.3.5.2 Event-free survival among responders

Like OS, EFS was estimated by fitting parametric survival curves to the Kaplan-Meier data for responders in the TOWER trial. Responders were considered to be people who achieved complete remission, complete remission with partial haematological recovery or complete remission with incomplete haematological (CR/CRh*/CRi) recovery within 12 weeks of initiation of treatment. Estimation of long-term EFS comprised two phases. In the first phase, survival was estimated based on the observed Kaplan-Meier survival data for responders in TOWER. In the second phase, EFS was extrapolated beyond trial time horizon. **Error! Reference source not found.** shows the Kaplan-Meier plots for EFS among people who achieved (CR/CRh*/CRi) within 12 weeks after treatment in the blinatumomab and in the SOC chemotherapy arms. In the trial, [redacted] and [redacted] achieved response in the blinatumomab and standard of care arm, respectively. It can be seen from **Error! Reference source not found.** that EFS among responders was higher in the blinatumomab arm during the first 11 months after which observed data from the SOC chemotherapy arm crossed the blinatumomab arm. The company has suggested that this is likely to be a result of the small number of people in the SOC chemotherapy arm at risk of relapsing.

life therapy. Our clinical advisor suggested that people who discontinued treatment normally start end-of-life care.

**Table 7 Proportion of people starting and completing each cycle of blinatumomab therapy (from the company submission)**

| Cycle number | People starting cycle (%) | People completing cycle (%) |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] |
| 7 | [redacted] | [redacted] |
| 8 | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] |
| 10 | [redacted] | [redacted] |

#### 5.3.7.2 FLAG-IDA costs

The drug acquisition costs are based on FLAG-IDA. Costs for FLAG-IDA were estimated based on the dosage and treatment duration, as per protocol from the Royal Surrey NHS Foundation Trust, and unit costs were obtained from the British National Formulary (BNF) (BNF, 2016) and NHS Generic Pharmaceuticals eMit (2015).[36] It was assumed that in each cycle, drug administration required 16.8 days in an inpatient setting, which was based on a *'retrospective chart review study'* undertaken in France.[37] Table 8 shows the unit costs for each component of FLAG-IDA per day, and the total drug acquisition cost, which was estimated to be £1,974.34 per cycle. These costs appear to be correctly estimated.

**Table 8 Unit costs for FLAG-IDA**

| FLAG-IDA drug component | Dose per day of treatment | Basis of dosing | Days treatment per cycle | Cost per item (£) | Mg per item | Daily dose (mg) | Items per day | Cost per day (£) | Cost per cycle (£) |
|---|---|---|---|---|---|---|---|---|---|
| Filgrastim | 0.005 | mg/kg | 9 | 79.90 | 0.48 | 0.368 | 1 | 79.90 | 719.10 |
| Fludarabine | 30 | $mg/m^2$ | 5 | 35.64 | 50 | 55.271 | 2 | 71.28 | 356.40 |
| Cytarabine | 2000 | $mg/m^2$ | 5 | 5.63 | 1000 | 3,684.745 | 4 | 22.52 | 112.60 |
| Idarubicin | 8 | $mg/m^2$ | 3 | 87.36 | 5 | 14.739 | 3 | 262.08 | 786.24 |
| **Estimated total costs** | | | | | | | | | **£1,974.34** |
| FLAG-IDA, fludarabine, cytaribine, granulocyte colony stimulating factor, idarubicin | | | | | | | | | |

**Figure 1 Event-free survival from TOWER amongst responders compared to projected event-free survival from the Markov model for all patients**

**Cost-effectiveness results, using the [redacted] PAS: confidential appendix**

The company reports deterministic base-case and sensitivity analysis results, as well as probabilistic sensitivity analysis (PSA) results, for the comparison between blinatumomab and FLAG-IDA using the discount of [redacted] on the cost of blinatumomab under a patient access scheme (PAS) approved by the Department of Health. Including this discount reduces the cost per vial of blinatumomab from £2017 to [redacted]. Outcomes are reported in terms of life-years gained and quality adjusted life years and the results are reported in the form of an incremental cost-effectiveness ratios expressed as a cost per LYG and cost per QALY. As in the non-PAS analyses, comparisons between blinatumomab and FLAG-IDA rely on evidence from TOWER, in which the SOC chemotherapy arm is considered generalisable to FLAG-IDA.

**Base-case results including the PAS for blinatumomab**

Table 1 and Table 2 show the base-case results for blinatumomab compared to FLAG-IDA based on the outcomes LYG and QALY. Results show that blinatumomab is approximately £80,446 more costly than FLAG-IDA and more effective with 1.78 and 1.45 more LYG and QALYs, respectively; these equate to an ICER of approximately £45,194 per LYG and £55,501 per QALY gained, respectively.

**Table 1 Deterministic results based on life years gained (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean LYG | Incremental LYG | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,165 | - | 2.61 | - | - |
| **Blinatumomab** | 144,611 | 80,446 | 4.38 | 1.78 | 45,194 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental life years gained; LYG, life years gained | | | | | |

**Table 2 Deterministic results based on quality adjusted life years gained (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,165 | - | 1.90 | - | - |
| **Blinatumomab** | 169,648 | 80,446 | 3.35 | 1.45 | 55,501 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

**Sensitivity analysis results including the PAS for blinatumomab**

*Probabilistic sensitivity analysis*

The company has undertaken a PSA to determine the impact of joint parameter uncertainty in key model input parameters. Table 3 shows the PSA results for cost per QALY. PSA results generally matched results from the deterministic analysis.

**Table 3 PSA results based on quality adjusted life years gained (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,327 | | 1.91 | - | - |
| **Blinatumomab** | 144,692 | 80,365 | 3.30 | 1.40 | 57,602 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Each simulation including the incremental costs and incremental QALYs for blinatumomab as compared to FLAG-IDA was plotted on a cost-effectiveness plane (see Figure 1), along with the respective cost-effectiveness acceptability curve (see Figure 2).

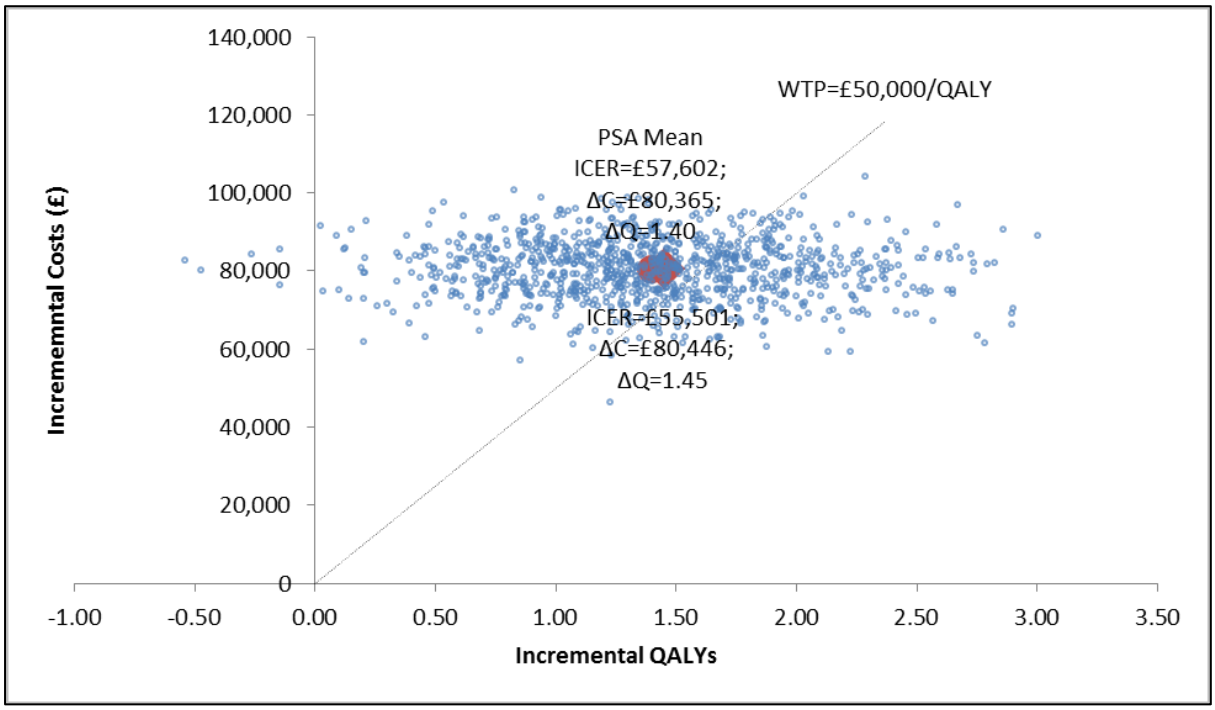


**Figure 1: Scatterplot using distributions around model input parameters**

For the 1000 runs of the Monte Carlo simulation, the scatterplot shows considerable uncertainty about the incremental QALYs, and less so for the incremental costs.

Figure 2 shows the results of the PSA presented in the form of a cost-effectiveness acceptability curve for the comparison between blinatumomab and FLAG-IDA. The curve shows the proportion of simulations in which blinatumomab is cost-effective at different willingness-to-pay (WTP) thresholds for a QALY. At a WTP threshold of £50,000 per QALY, 35.2% of the simulations were below and up to this threshold.

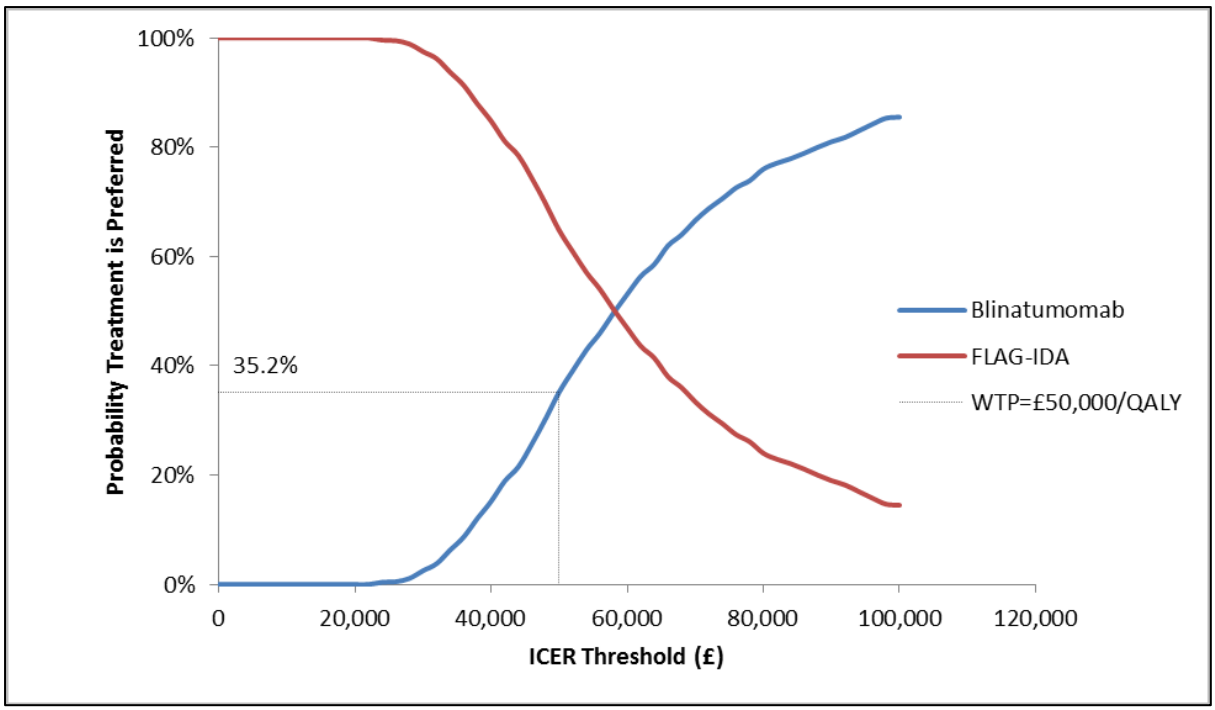


**Figure 2: Cost-effectiveness acceptability curve for blinatumomab and FLAG-IDA**

*Deterministic sensitivity analyses*

A number of one-way sensitivity analyses were undertaken to explore the impact on the ICER to making changes to key model input parameters. Parameters were varied according to the lower and upper bound of their respective 95% confidence interval (CI) or by assuming uncertainty of ±50% of the point estimate. The results of varying each parameter one at a time are shown in Figures 3 and 4. As can be seen in Figure 3 the treatment effect for overall survival (OS) continues to have the largest impact on the ICER. Using the lower and upper 95% CI, the results showed that the ICER ranges from approximately £28,300 to £288,600 per QALY, respectively. Varying other parameters had little impact on the ICER.

In Figure 4, the company has excluded the overall survival treatment effect. Varying the inpatient stay by ±50% continued to have the second-largest impact (after overall survival) on the ICER, ranging from approximately £51,100 to £59,900 per QALY gained.

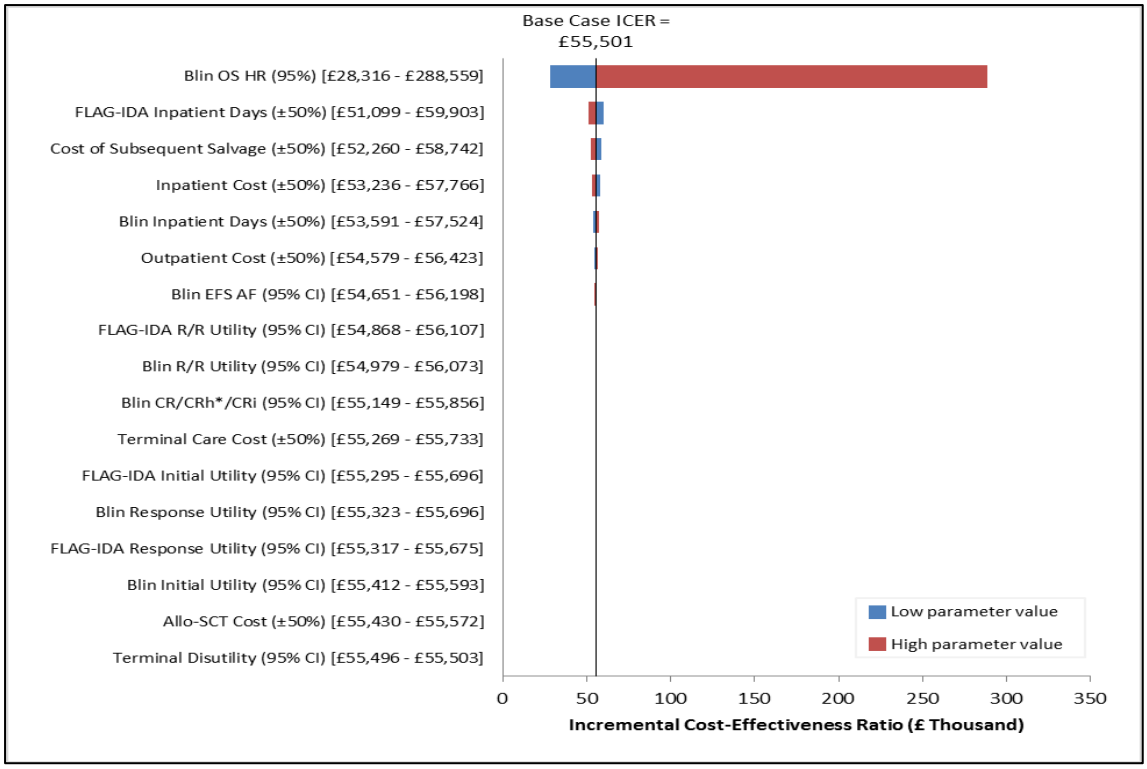


**Figure 3: Tornado diagram for blinatumomab versus FLAG-IDA (with PAS for blinatumomab)**

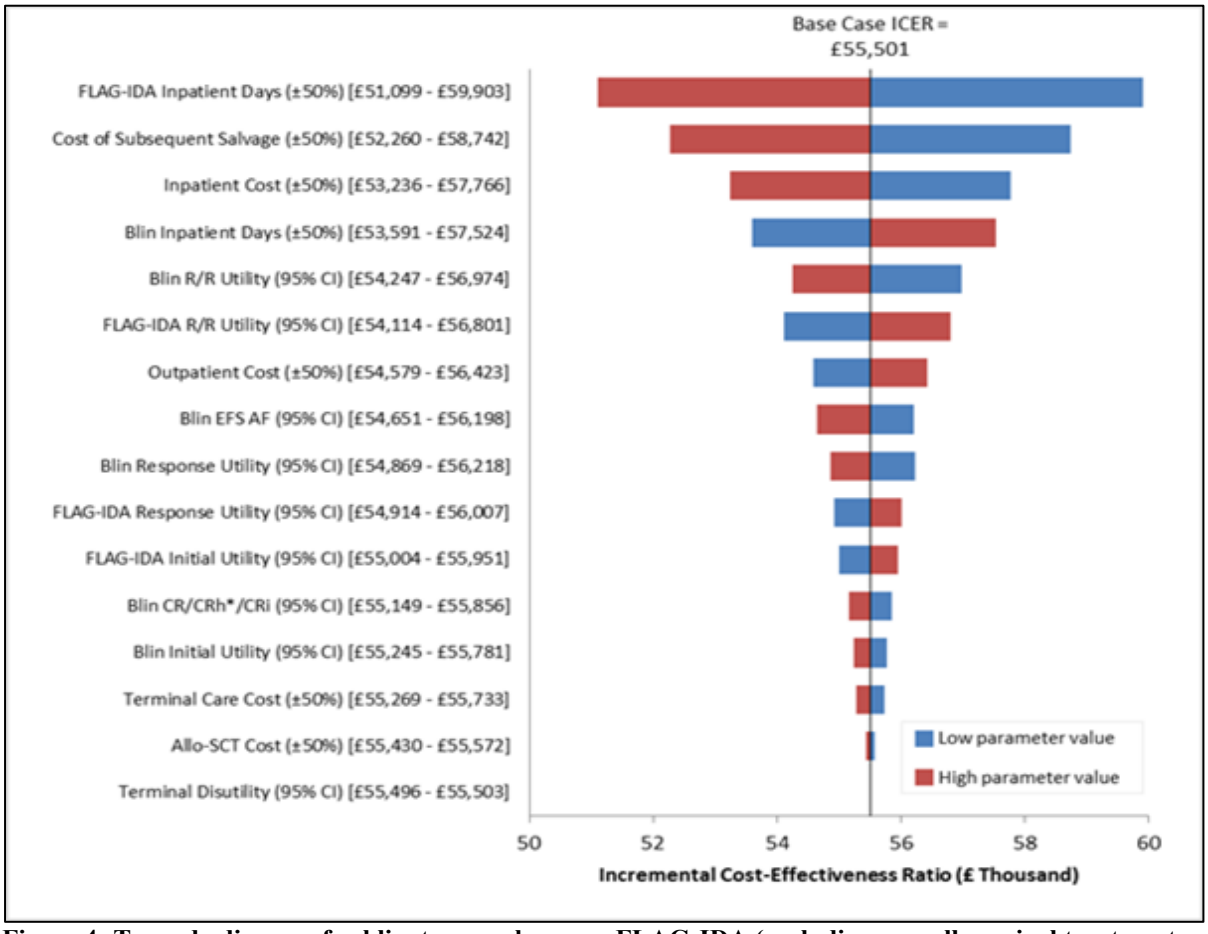


**Figure 4: Tornado diagram for blinatumomab versus FLAG-IDA (excluding overall survival treatment effect) (with PAS for blinatumomab)**

**Scenario analyses including the PAS for blinatumomab**

A number of scenario analyses were undertaken:

- OS based on the restricted cubic spline log-logistic model fit
- Event-free survival (EFS) among responders based on the lognormal model fit
- 10-year model timeframe
- 1.5% discount rate on costs and effects
- 10 inpatient days for blinatumomab administration for all cycles
- Clofarabine costs included in standard of care chemotherapy
- Time trade-off (TTO) utilities from Aristides et al. (2015) vignettes study

**Table 4 Results for overall survival based on the restricted cubic spline log-logistic model fit (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,298 | - | 0.95 | - | - |
| **Blinatumomab** | 145,123 | 80,824 | 1.42 | 0.47 | 171,487 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Using the log-logistic parametric model, noted in Table 5-3 of the CS as the second-best fitting distribution, to model the overall survival showed that there was an increase in the ICER from approximately £55,500 per QALY to approximately £171,500 per QALY. These results (Table 4) suggest and reiterate that the model is sensitive to the assumptions made on the curve fit used to model overall survival.

**Table 5 Results based on event-free survival among responders based on the lognormal model fit (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,165 | - | 1.89 | - | - |
| **Blinatumomab** | 144,611 | 80,446 | 3.34 | 1.45 | 55,659 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Results (Table 5) showed that using the lognormal parametric model fitted to the EFS amongst responders had little impact on the ICER. The lognormal parametric model was noted in CS Table 5-4 as the best fitting distribution for EFS amongst responders.

**Table 6 Results based a 10-year model time horizon (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,244 | - | 0.91 | - | - |
| **Blinatumomab** | 144,710 | 80,466 | 1.54 | 0.63 | 126,896 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Table 6 presents the results from an analysis of assuming a 10-year model time horizon. These results showed that mean expected costs remained constant, and mean QALYs decreased, which equated to an ICER of approximately £126,900 per QALY. These results suggest that the model is also sensitive to the time horizon.

**Table 7 Results based on a 1.5% discount rate on costs and effects (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,594 | - | 2.53 | - | - |
| **Blinatumomab** | 145,446 | 80,852 | 4.50 | 1.97 | 41,081 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Table 7 includes results from an analysis assuming a 1.5% discount rate on costs and effects. Results showed that the ICER for costs per QALYs gained was lower than in the base-case, at £41,081.

**Table 8 Results based on 10 inpatient days for blinatumomab administration for all cycles (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 65,046 | - | 1.90 | - | - |
| **Blinatumomab** | 153,115 | 88,069 | 3.35 | 1.45 | 60,760 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

In Table 8, an analysis including a full 10 days of hospitalisation for all cycles shows an ICER for costs per QALYs gained of approximately £60,800.

**Table 9 Results based on Clofarabine costs included in standard of care chemotherapy (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 69,372 | - | 1.90 | - | - |
| **Blinatumomab** | 145,578 | 76,206 | 3.35 | 1.45 | 52,576 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

In Table 9, an analysis using costs for clofarabine instead of for FLAG-IDA showed an ICER for cost per QALYs gained of approximately £52,600.

**Table 10 Results based on Time trade-off (TTO) utilities from Aristides et al. (2015)(Aristides et al., 2015) vignettes study**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 64,165 | - | 1.78 | - | - |
| **Blinatumomab** | 144,611 | 80,446 | 3.18 | 1.40 | 57,438 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

An analysis using alternative utility values, presented in Table 10, yielded an ICER for costs per QALYs gained of approximately £57,400.

### ERG summary

The ERG considers these scenario analyses and results to be appropriate to show the impact of making changes to key model input parameters.

**ERG scenario analyses including the PAS for blinatumomab**

In these analyses, we have used a modified version of the company's base case model, but including the company's PAS:

- Two-year time horizon
- Additional inpatient treatment
    - Inpatient stay for cycles one and two
    - Assuming blinatumomab is administered in an inpatient setting (five cycles with inpatient stays)
- Intravenous bag changes daily, as opposed to every four days
- **ERG preferred base case, including probabilistic sensitivity analysis:** Inpatient stay for cycles one and two and for subsequent cycles people would receive intravenous bag changes every day, as opposed to every four days
- Correction to the 95% CI to the utility values and its impact on the probabilistic sensitivity analysis

*Two-year time horizon*

In an analysis using a two-year time horizon (i.e. a within-trial analysis), the ICER for blinatumomab as compared to FLAG-IDA increased over the base case to approximately £432,500 (see Table 11).

**Table 11 Results based on assuming a two-year time horizon of the model**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 63,678 | - | 0.38 | - | - |
| **Blinatumomab** | 144,120 | 80,442 | 0.57 | 0.19 | 432,478 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

*Inpatient stay for cycles one and two*

In the company's base-case analysis, it was assumed that people required 10 inpatient days and two inpatient days in the first and second treatment cycles of blinatumomab administration. In this analysis, we assumed that the first two cycles are administered on an inpatient basis, hence patients are required to spend 28 days in hospital for each cycle. Results (Table 12) from this analysis showed the ICER increased to approximately £67,400 per QALY gained.

**Table 12 Results based on assuming inpatient stay for cycles one and two**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 66,156 | - | 1.90 | - | - |
| **Blinatumomab** | 163,842 | 97,686 | 3.35 | 1.45 | 67,395 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

*Assuming blinatumomab is administered in an inpatient setting*

In this analysis, which has been informed by our clinical advisor, people would receive blinatumomab treatment in an inpatient setting. That is, spending 28 days in inpatient care for each of the five cycles. This analysis is of importance because some hospitals do not have the infrastructure for treatment in an outpatient setting. These results show that the ICER increases to approximately £74,900 per QALY gained (see Table 13).

**Table 13 Results based on assuming inpatient care for administration of blinatumomab**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 67,409 | - | 1.90 | - | - |
| **Blinatumomab** | 175,941 | 108,532 | 3.35 | 1.45 | 74,878 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

*Assuming daily intravenous bag changes*

In this analysis, bag changes for blinatumomab are undertaken every day instead of every four days, as in the model. This results in an increase in the ICER to approximately £60,700 per QALY gained (see Table 14).

**Table 14 Results based on daily intravenous bag changes**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean LYG | Incremental LYG | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 65,030 | - | 1.90 | - | - |
| **Blinatumomab** | 152,960 | 87,931 | 3.35 | 1.78 | 60,665 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental life years gained; LYG, life years gained | | | | | |

*ERG preferred analysis*

Table 15 presents deterministic results for the ERG's preferred analysis including the PAS. The preferred analysis includes inpatient administration of blinatumomab for cycles one and two alongside daily bag changes. The deterministic ICER increases to £69,700 per QALY gained.

**Table 15 Deterministic results based on assuming full inpatient care for cycles one and two, and IV bag changes every day**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 66,550 | - | 1.90 | - | - |
| **Blinatumomab** | 167,644 | 101,094 | 3.35 | 1.78 | 69,746 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Table 16 presents PSA results for the ERG's preferred analysis including the PAS. The ICER generated from the PSA differ when compared to our deterministic results. However, it should be noted that incremental results for costs are in good agreement, but slightly lower for incremental QALYs in the PSA. This difference in incremental QALYs results in an increase in the PSA ICER, which is approximately £73,400 per QALY gained.

**Table 16 PSA results based on ERG's preferred analysis (with PAS)**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 66,543 | | 1.85 | - | |
| **Blinatumomab** | 167,590 | 101,047 | 3.22 | 1.38 | 73,383 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

Results for the 1000 runs of the Monte Carlo simulation, the scatterplot (Figure 5) show considerable uncertainty about the incremental QALYs, and less so for the incremental costs. Figure 6 shows the results of the PSA presented in the form of cost-effectiveness acceptability curve for the comparison between blinatumomab and FLAG-IDA. At a WTP threshold of £50,000 per QALY, 14.7% of the simulations were below and up to this threshold. It should also be noted that proportion (1.1%) of simulations are in the north-west quadrant, which signifies that standard of care chemotherapy dominated treatment with blinatumomab.

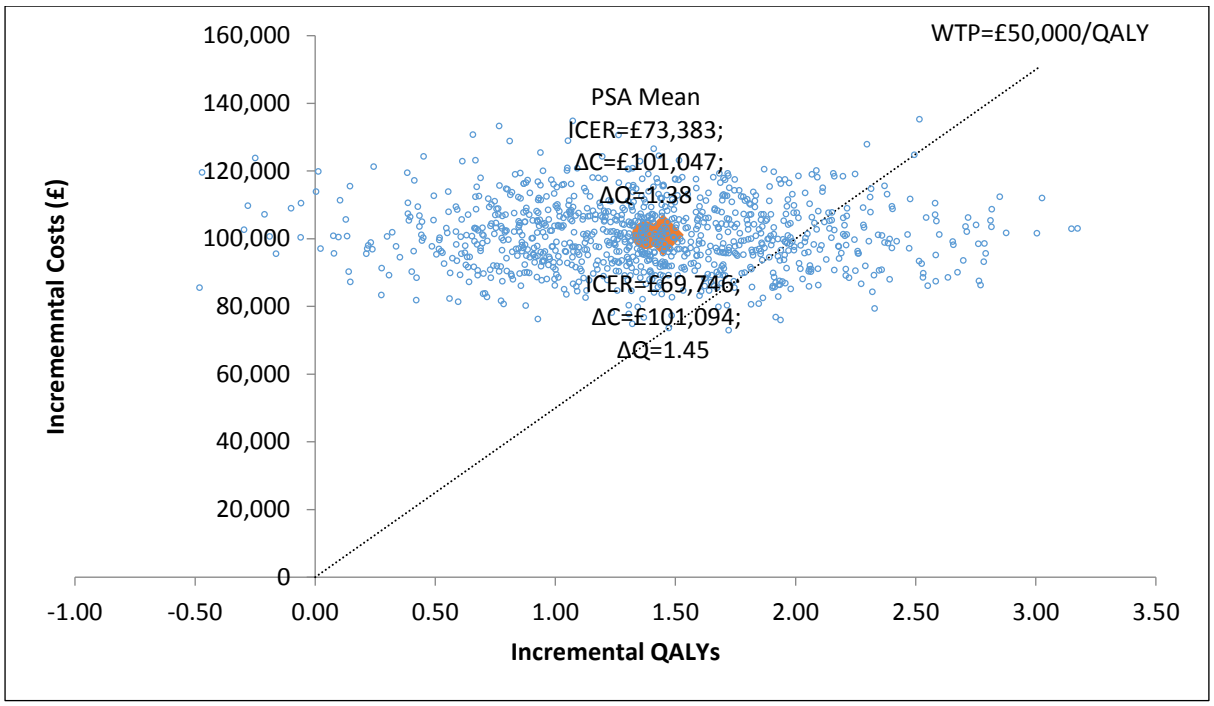


**Figure 5 Scatterplot using distributions around model input parameters**

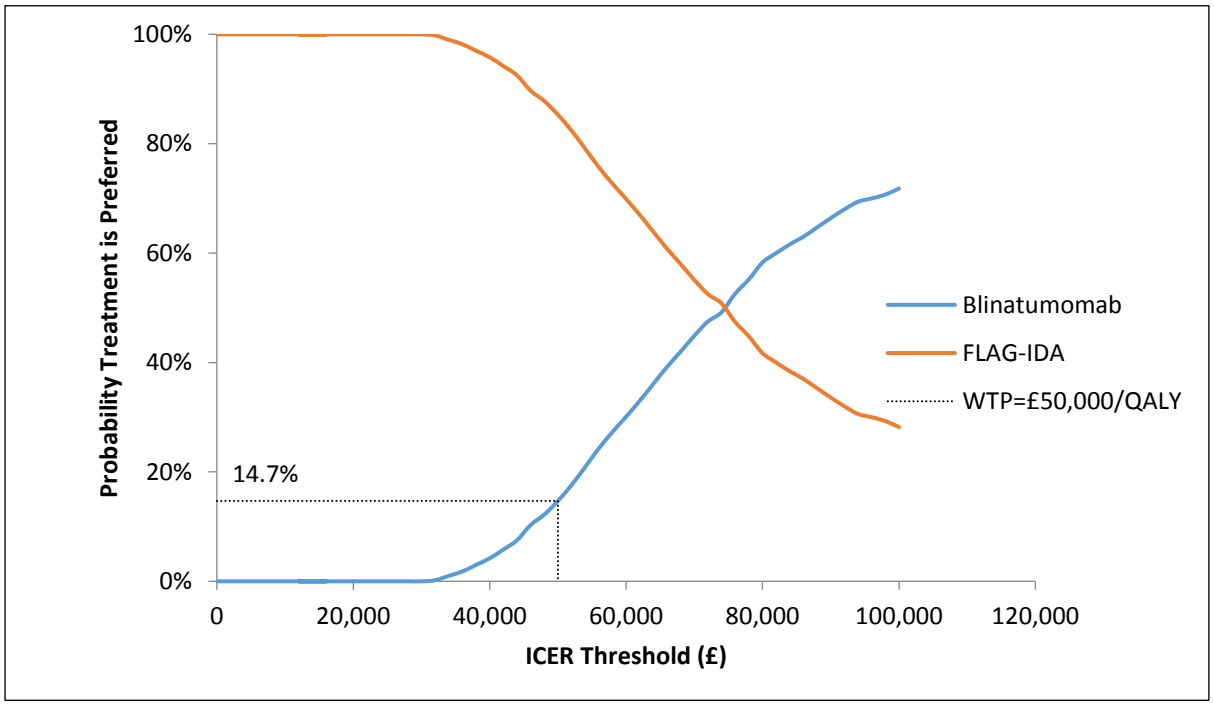


**Figure 6 Cost-effectiveness acceptability curve for blinatumomab and FLAG-IDA**

*Correction to the 95% CI to the utility values and its impact on the probabilistic sensitivity analysis*

At clarification, the company acknowledged that an error had been made with the 95% CIs around the utility values, which have now been corrected. The ERG has rerun the PSA by using the beta distributions around the confidence intervals. Results from the PSA (see Table 17) showed the ICER to be approximately £60,000 per QALY.

**Table 17 Results based on assuming a correction to the 95% CI around the utility values**

| Strategy | Expected mean costs (£) | Incremental costs (£) | Expected mean QALY | Incremental QALY | ICER (£) |
|---|---|---|---|---|---|
| **FLAG-IDA** | 63,528 | - | 1.90 | - | - |
| **Blinatumomab** | 144,565 | 81,036 | 3.25 | 1.35 | 60,028 |
| FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor; ICER, incremental life years gained; QALY, quality adjusted life years gained | | | | | |

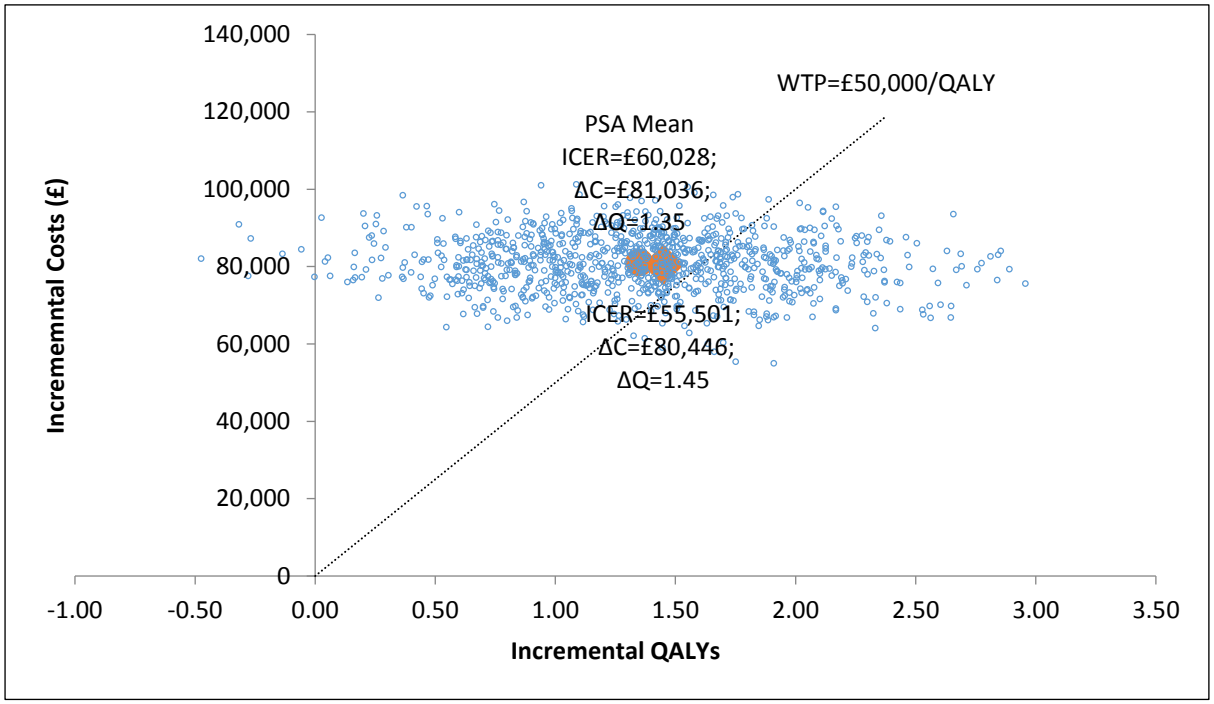


**Figure 7 Scatterplot using distributions around model input parameters**

Results for the 1000 runs of the Monte Carlo simulation, the scatterplot (Figure 7) shows considerable uncertainty about the incremental QALYs, and less so for the incremental costs. The majority of the simulations are in the north-east quadrant, which suggests that blinatumomab is expected to yield more QALYs at higher costs. It should also be noted that a proportion (0.7%) of simulations are in the north-west quadrant, which signifies that standard of care chemotherapy dominated treatment with blinatumomab.

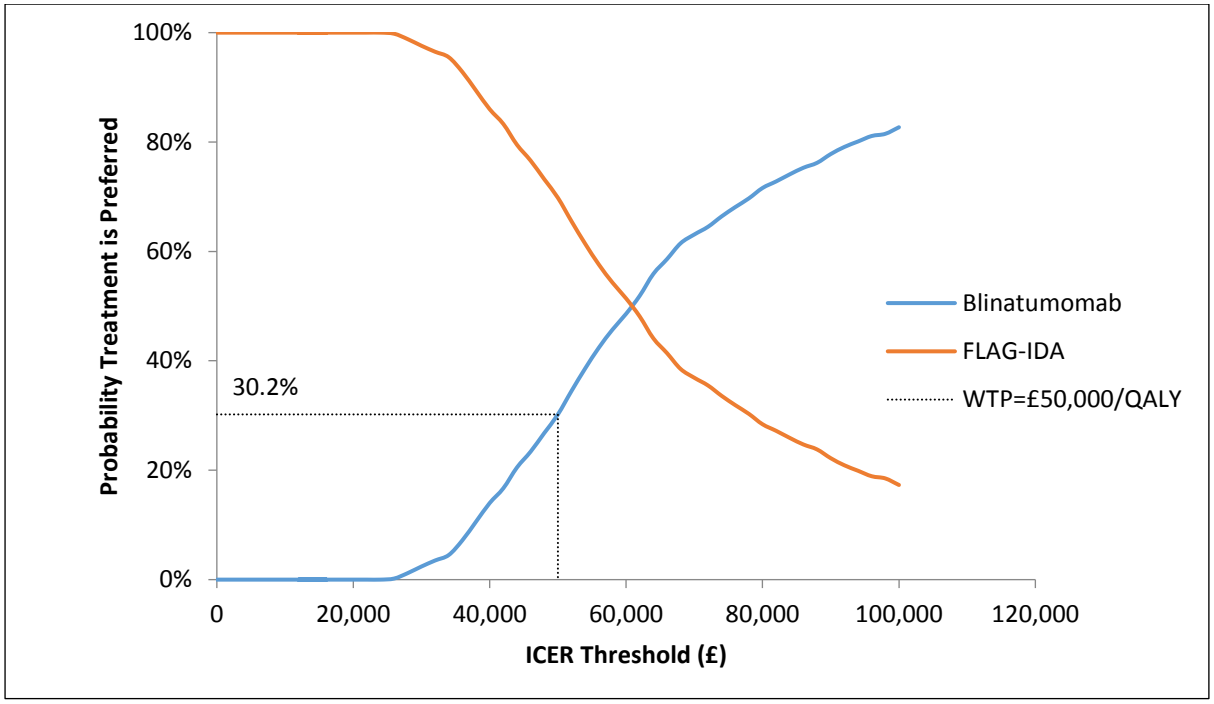


**Figure 8 Cost-effectiveness acceptability curve for blinatumomab and FLAG-IDA**

Figure 8 shows the results of the PSA presented in the form of a cost-effectiveness acceptability curve for the comparison between blinatumomab and FLAG-IDA. The curve shows the proportion of simulations in which blinatumomab is cost-effective at different willingness-to-pay (WTP) thresholds for a QALY. At a WTP threshold of £50,000 per QALY, 30.2% of the simulations were below and up to this threshold.

# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## Pro-forma Amgen Response - ERG report
## Blinatumomab for previously treated B-precursor acute lymphoblastic leukaemia [ID804]

We welcome the opportunity to review and comment on the very thorough Evidence Review Group (ERG) report. We have listed below the few factual inaccuracies we found (Issues 1 to 33) with most of them being minor typographical or reporting mistakes. In addition, we have listed a series of issues (Issues 34 to 36) we have around the ERG's interpretation and reporting of our evidence submission that may lead to misleading and potentially factually inaccurate conclusions. These principally relate to:

1. **The ERG's assessment and revised base case assumptions on hospitalisation requirements and frequency of intravenous infusion bag changes for administration of blinatumomab**
   The ERG suggests in the report that the feedback from its clinical advisor was that only larger specialised centres would potentially have day unit facilities to cater for patients coming in to have intravenous (IV) infusion bags changed and that patients may be hospitalised for the entire duration of each treatment cycle. Our understanding based on feedback from UK haemato-oncology nurses is that treatment with blinatumomab is likely to be given in the outpatient setting (either hospital or home visits) after at least the minimum period of hospitalisation recommended by the blinatumomab summary of product characteristics (SmPC). We acknowledge that this is likely to be specifically at larger specialised centres where appropriate facilities and specialised staff are available as highlighted by the ERG's clinical advisor, but anticipate that a substantial proportion of patients would be treated in such a setting given the rarity and severity of the disease. The ERG's revised base case assumption that all patients will be hospitalised for the entire duration of Cycle 1 and Cycle 2 with blinatumomab is therefore highly implausible. Furthermore, no explanation or rationale is provided for the ERG's assertion that daily bag changes better reflect clinical practice and revised base case assumption, in contrast to the availability of additional 48-hour, 72-hour, and 96-hour bag change options as per the blinatumomab SmPC. If the ERG's revised assumption of daily bag changes is a consequence of the revised assumption around hospitalisation duration (daily bag changes may be standard practice in the hospital setting), this assumption is similarly implausible.

2. **The ERG's assessment around validity of the proportional hazards assumption and approach to survival modelling**
   The ERG suggests in the report that the proportional hazards (PH) assumption was not adequately explored and making this assumption is inappropriate based on visual inspection of Kaplan–Meier (KM) plots (the only evidence cited by the ERG as the basis for their position) from the TOWER randomised controlled trial (RCT) used to model survival. As described in the company submission, we comprehensively evaluated the PH assumption using counterfactual diagnostic plots, plots of the hazards over time, and examination of Schoenfeld residuals. None of these approaches provided strong evidence to suggest the PH assumption was invalid. Although the KM

plots cited by the ERG converge and overlap after approximately 15 months, there are very few patients (8% of the ITT population) at risk after this time point, and rejecting the PH assumption based on these plots alone is inappropriate.

3. **The ERG's assessment of the impact of not adjusting for baseline utility values in the model**
   The ERG suggests in the report that not adjusting for the (small) imbalances in baseline utility values could result in misleading cost-effectiveness results. However, the ERG does not acknowledge anywhere that, as outlined in the company submission, baseline utilities were slightly higher in the TOWER standard of care (SOC) chemotherapy arm than in the blinatumomab arm, and our approach is therefore likely to be a conservative one (i.e. biased in favour of SOC chemotherapy).

**The ERG presents its responses to these comments below. In sum, the ERG's response to these points reflect the ERG's interpretation of the evidence presented, reasonable and appropriate model assumptions, and best analytic practice in cost effectiveness modelling.**

# Issues relating to factual accuracies

## Issue 1 Pages 17+

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report inconsistently applies the 'descriptive' prefix to define p-values when describing results for outcome measures in which formal inferential testing was not carried out in the interim analysis reported in the company submission, and inaccurately and inconsistently refers to the significance of results. For example, the ERG report states:<br><br>*'Haematologic response. More patients in the blinatumomab arm achieved complete remission within 12 weeks of treatment initiation than patients in the blinatumomab arm (33.6% vs. 15.7%; p < 0.001). Similarly, the proportion of patients who achieved a complete remission, including with incomplete or partial haematological recovery, within 12 weeks of treatment initiation was statistically significantly higher in the blinatumomab arm compared with the SOC chemotherapy arm (43.9% vs. 24.6%, p < 0.001).' (ERG report, pages 16 and 17)*<br><br>*'Duration of response. Patients receiving blinatumomab and who achieved complete remission did not have a significantly longer response than patients in the standard of care chemotherapy arm who achieved complete remission (8.3 months vs 7.8 months, p=0.59).' (ERG report, page 17)*<br><br>*'Allogeneic stem cell transplant outcomes. The rate of allogeneic stem cell transplant was similar in the blinatumomab arm as in the standard of care chemotherapy* | Removal of 'significant' in the text to describe results for outcomes where formal inferential testing was not conducted, and addition of 'significant' in the text to describe for all results where formal inferential testing was conducted and a significant benefit for blinatumomab was observed.<br><br>Either removal of the 'descriptive' prefix throughout the report or consistent use across all appropriate outcome results throughout the report. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

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| *arm (24.0% vs 23.9%, descriptive p = 0.95).' (ERG report, page 17)*<br><br>*'Patients in the blinatumomab arm had a significantly longer time to clinically meaningful decrease in health-related quality of life (measured by the EORTC QLQ-C30 GHS questionnaire) as compared to patients in the standard of care chemotherapy arm (8.1 months vs 1.0 months, p=0.003).(ERG report, page 17)*<br><br>*'Blinatumomab also delayed the time to clinically meaningful decrease alone, irrespective of EFS event (p=0.003). Subgroup analyses were not presented for FLAG or clofarabine.' (ERG report, page 68)*<br><br>*'The CS states on p 83 that the test for treatment effect in differences on HRQoL from a mixed effects model accounting for changes in HRQoL over time suggests a significant improvement in trend from blinatumomab (p=0.0004).' (ERG report, page 68)*<br><br>Given that 'descriptive' is sometimes used to define the p-value for outcomes where no formal inferential testing was carried out, omission of this definition in other instances of outcome reporting is inaccurate.<br><br>Furthermore, describing results as 'significant' when no formal inferential testing has been carried out is inappropriate. The ERG inaccurately references the company submission by suggesting that it stated that a test for health-related quality of life (HRQoL) treatment effect 'suggests a significant improvement', when a claim of significance was not made.<br><br>As outlined in the company submission, the only TOWER outcomes for which formal inferential testing was conducted and for which results should be described as 'significant' are overall survival (OS) and rates of complete remission (CR) | | | |

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| and complete remission/complete remission with partial haematological recovery/complete remission with incomplete haematological recovery (CR/CRh*/CRi) within 12 weeks of treatment initiation. | | | |

**Issue 2 Page 17**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states:<br>*'Relapse-free survival was not defined as an outcome in TOWER, and findings from the non-randomised evidence on relapse-free survival were not presented due to data quality.' (ERG report, page 17)*<br>Relapse-free survival (RFS) data were presented for the non-randomised MT103-211 study alone in Section 4.11.6.1 of the company submission, though a comparison with the historical cohort was not conducted due to the high amount of missing data. The blanket statement that non-randomised evidence on RFS was not presented is therefore inaccurate. | 'Relapse-free survival was not defined as an outcome in TOWER, and findings from the non-randomised evidence on relapse-free survival **(specifically, the comparison with the historical control cohort)** were not presented due to data quality.' | Factual inaccuracy. | No comment required. No change necessary. As the ERG stated in the report it regarded the comparison with the historical cohort as the only probative aspect of the non-randomised evidence. |

**Issue 3 Pages 18, 29, and 43**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states:<br>*'The ERG did not regard that the approach used by the company to appraise the non-randomised evidence was appropriate, and thus it undertook its own appraisal.' (ERG report, page 18)*<br>*'Is the validity of included studies adequately assessed? Uncertain—while the ERG generally agreed with the company's assessment of TOWER, the CS appraisal of the non-randomised evidence was inappropriate.' (ERG report, page 29)*<br>*'In CS Appendix V, the company presents appraisal of both the single-arm Study MT103-211 and the comparison with a historical cohort using STROBE. The ERG regards that this is inappropriate given that STROBE is a reporting guideline, not a tool for critical appraisal' (ERG report, page 43)*<br>Reference to STROBE as 'a reporting guideline, not a tool for critical appraisal' and its use in the company submission as 'inappropriate' is not factually accurate. While we acknowledge the purpose of the checklist is to ensure clear presentation of what was planned, done, and found in observational studies, STROBE is specifically discussed within Section 4.2 ('How to evaluate the quality of an analysis on treatment effect using non-randomised data') of NICE DSU TSD 17 which states that checklists such as STROBE 'can be a useful tool for critical appraisal.' This was highlighted as the key reference point for guidance on non-randomised evidence by the ERG in the scoping meeting. | The ERG's description of STROBE and blanket statements that it is 'inappropriate' for assessing quality of non-randomised evidence should be amended. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 4 Page 20**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states:<br>*'Clinical parameters related to overall survival and event free survival for blinatumomab were derived from parametric survival curves fitted to Kaplan-Meier plots of the data from the TOWER study. For the comparator arm, inputs related to OS and EFS were based on fitting survival curves to a Kaplan-Meier plot of a retrospective natural history cohort, which was used to test the plausibility of the survival data generated by the SOC chemotherapy arm in TOWER.' (ERG report, page 20)*<br>Inputs related to OS and event-free survival (EFS) were based parametric survival curves fitted to TOWER for both the blinatumomab and SOC chemotherapy arms. Stating that inputs related to OS and EFS for the comparator arm were based on the historical comparator cohort is factually inaccurate, as this was only used to assess clinical plausibility of the long-term survival projections for the SOC chemotherapy arm and the historical control data were not used directly in the model. | 'Clinical parameters related to overall survival and event free survival for blinatumomab **and SOC chemotherapy** were derived from parametric survival curves fitted to Kaplan-Meier plots of the data from the TOWER study. ~~For the comparator arm, inputs related to OS and EFS were based on fitting survival curves to~~ A Kaplan-Meier plot of **long-term OS from** a retrospective natural history cohort~~, which~~ was used to test the plausibility **of the shape** of the survival **curve** generated ~~by~~ **for** the SOC chemotherapy arm in TOWER.' | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 5 Pages 20, 23, 72, 73, 77, and 85**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states:<br>*The company used a partitioned survival Markov model to show the experience of a cohort of people with refractory or relapsed Philadelphia chromosome–negative acute lymphoblastic leukaemia who may undergo treatment with blinatumomab and standard care chemotherapy over a 50-year time horizon.' (ERG report, page 20)*<br>*'The prognosis for adult patients with relapsed/refractory Ph B precursor ALL is extremely poor, with a life expectancy of around 3 to 6 months.' (ERG report, page 23)*<br>*'A systematic review of the economic evidence for the management of people with relapsed/refractory B-precursor acute lymphoblastic leukaemia' (ERG report, page 72)*<br>*'The company has undertaken a systematic review of the cost-effectiveness literature to identify studies reporting the results of economic analyses for people who received therapy for the management of relapsed/refractory B-precursor acute lymphoblastic leukaemia. This search was also used to identify resource use information and studies reporting health-related quality of life (HRQoL) for people with relapsed/refractory B-precursor acute lymphoblastic leukaemia.' (ERG report, page 72)*<br>*'The company used a de novo partitioned survival Markov model to show the experience of a cohort of people with refractory or relapsed Philadelphia-chromosome–negative B-precursor acute lymphoblastic leukaemia who may undergo* | Accurate description of the population under consideration in the decision problem and addressed in the clinical- and cost-effectiveness analyses.<br>For consistency, the ERG may wish to use the 'adult R/R Ph- B-precursor ALL' acronym used in the company submission throughout the report. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

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| *treatment with blinatumomab or with FLAG-IDA (using SOC chemotherapy as a proxy) over a 50-year time horizon.' (ERG report, page 73)*<br><br>*'…which were used to inform the cost-effectiveness of blinatumomab as compared to FLAG-IDA for the treatment of people with R/R Ph- B-precursor ALL.' (ERG report, page 77)*<br><br>*'Briefly, the natural history cohort consists of people from Europe or the US who were diagnosed with refractory/relapsed Philadelphia chromosome–negative acute lymphoblastic leukaemia from year 2000 onwards, and had been treated with chemotherapy.' (ERG report, page 85)*<br><br>*'The company used a partitioned survival Markov model to show the experience of a cohort of people with refractory or relapsed Philadelphia chromosome–negative acute lymphoblastic leukaemia who may undergo treatment with blinatumomab and standard care chemotherapy over a 50-year time horizon.' (ERG report, page 126)*<br><br>The population under consideration in the decision problem and addressed in the clinical- and cost-effectiveness analyses (as per the marketing authorisation for blinatumomab) is inaccurately defined, with details of patient age (i.e. adult), cell lineage, and Philadelphia chromosome status not consistently provided. | | | |

**Issue 6 Page 26**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'The company defines the included population as "Adults (aged ≥15 years) with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia" while the final scope states "people with…", but as blinatumomab is authorised in the UK for use in adults only, these statements are judged to be equivalent.' (ERG report, page 26)*<br>This is a misquote of the wording in the company submission as no year cut-off was specified for 'adults' in the description of the population under consideration in the decision problem. | 'The company defines the included population as "Adults ~~**(≥15 years)**~~ with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia" while the final scope states "people with…" but as blinatumomab is authorised in the UK for use in adults only, these statements are judged to be equivalent.' | Factual inaccuracy. | We have amended the text as requested. |

**Issue 7 Pages 27 and 81**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'They argue that FLAG-IDA is the most commonly used salvage chemotherapy regimen in the UK and that clofarabine is licenced as monotherapy for paediatric use and funding and availability for the adult population remain unclear since the expiration of the previous Cancer Drug Fund.' (ERG report, page 27)*<br>*'The NICE scope includes clofarabine as a comparator, which is licensed for the treatment of people with ALL, and is currently used in practice as a possible alternative, though the ERG clinical advisor noted that it is not frequently used for adult ALL.' (ERG report, page 81)*<br>The descriptions of the licensed indication for clofarabine are factually inaccurate, as it is licensed specifically for the treatment of paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response, as highlighted in both the company submission and our response to clarification questions. | 'They argue that FLAG-IDA is the most commonly used salvage chemotherapy regimen in the UK and that clofarabine is licenced as monotherapy for paediatric use **(in patients who have received at least two prior regimens and where there is no other treatment option anticipated to result in a durable response),** and funding and availability for the adult population remain unclear since the expiration of the previous Cancer Drug Fund.'<br>'The NICE scope includes clofarabine as a comparator, which is licensed for the treatment of ~~people~~ **paediatric patients** with ALL **who have received at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.** ~~and~~ **Clofarabine** is currently used in practice as a possible alternative in **adult patients,** though the ERG clinical advisor noted that it is not frequently used for adult ALL.' | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 8 Page 27**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'Blinatumomab is administered intravenously in 4 week cycles (starting dose 9 µg/day during the first week, thereafter 28 µg/day), followed by a 2-week treatment-free interval. Patients may receive two cycles of treatment. If complete remission is achieved after two cycles, patients may receive up to three additional cycles of blinatumomab based on an individual benefits-risks assessment.' (ERG report, page 27)*<br>The wording describing the criterion for receiving up to three additional consolidation cycles of blinatumomab is not aligned with the blinatumomab SmPC or company submission. Specifically, 'complete remission' is not appropriately defined as CR/CRh* and could therefore be interpreted as CR only. | 'Blinatumomab is administered intravenously in 4 week cycles (starting dose 9 µg/day during the first week, thereafter 28 µg/day), followed by a 2-week treatment-free interval. Patients may receive two cycles of treatment. If complete remission **(CR/CRh*)** is achieved after two cycles, patients may receive up to three additional cycles of blinatumomab based on an individual benefits-risks assessment.' | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 9 Page 33**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'More patients in the SOC arm also received innovative therapies than in the blinatumomab arm ([redacted]% vs [redacted]%, CS p 110).' (ERG report, page 33)*<br>The ERG report has qualified the statement with numbers for the proportion of patients receiving subsequent treatment with 'other systemic anticancer therapies' in general, not just those considered to be innovative per the ERG report text. | Amend the numbers or text as appropriate depending on the intention:<br>'More patients in the SOC arm also received innovative therapies than in the blinatumomab arm ([redacted]**% vs [redacted]%**, CS p 110).'<br>OR<br>'More patients in the SOC arm also received ~~innovative~~ **other systemic anticancer therapies in general** than in the blinatumomab arm ([redacted]% vs [redacted]%, CS p 110).' | Factual inaccuracy. | We have amended the text as requested to reflect a reference to other systemic anticancer therapies in general. |

**Issue 10 Page 33**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states:<br>*'Moreover, the ERG noted on CS pp. 108-109 that 10.1% (n=27) of those enrolled in the blinatumomab arm started six or more cycles of the study drug. This was not explained in the CS and the ERG clinical advisor was not able to suggest a plausible reason for this.' (ERG report, page 33'*<br>A description of the TOWER protocol-specified criteria for maintenance treatment with blinatumomab was provided in the company submission (Section 4.3.2), and the implications of this with respect to external validity of TOWER are discussed later in the company submission (Section 4.13.3). The blanket statement that maintenance treatment with blinatumomab in TOWER was not explained in the company submission is therefore factually inaccurate. It is unclear whether the ERG's statement refers to explanation of maintenance treatment in TOWER in general, or explanation of the rationale for its inclusion in the TOWER protocol. | Removal of sentence stating that no explanation was provided, or clarification of what is being referred to by the ERG. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 11 Page 35**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report caption for Table 4 states:<br>*'Table 4 Reasons for discontinuation of treatment in TOWER (from CS Figure 4-3).' (ERG report, page 35)*<br>The numbers included in the table pertain to reasons for not receiving allocated study drug, not reasons for discontinuation of study drug. Given the accompanying ERG report text that cross-references this table, we assume the caption text rather than the numbers are an error. | 'Table 4 Reasons for ~~discontinuation of~~ **not receiving allocated** treatment in TOWER (from CS Figure 4-3).' | Factual inaccuracy. | We have amended the text as requested. |

**Issue 12 Page 51**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br><br>*'Furthermore, twice as many patients in the blinatumomab arm as in the SOC chemotherapy arm had an 'important protocol deviation' (18.5% vs. 9.0%, CSR p 59). The ERG is unable to assess the impact of this difference on trial validity.' (ERG report, page 51)*<br><br>The TOWER clinical study report (CSR) provided to the ERG describes that an initially planned sensitivity analysis on the per-protocol analysis set (i.e. patients with no protocol deviations) were removed from the statistical analysis plan and not done 'because few subjects had important protocol deviations that affected the efficacy evaluation' (CSR page 53). The ERG's blanket statement that it was unable to assess the impact of protocol deviations on trial validity is therefore factually inaccurate as it could have referenced this, with the caveat that it was unable to validate this statement given the absence of specific data in the CSR if considered necessary. | Removal of the sentence stating that the ERG is unable to assess the impact of protocol violations on trial validity, or amendment to e.g.:<br><br>'Furthermore, twice as many patients in the blinatumomab arm as in the SOC chemotherapy arm had an 'important protocol deviation' (18.5% vs. 9.0%, CSR p 59). ~~The ERG is unable to assess the impact of this difference on trial validity.~~ **The TOWER CSR states that an initially planned sensitivity analysis of the per-protocol analysis set was removed from the statistical analysis plan and not done because few subjects had important protocol violations that would have affected the efficacy evaluation.'** | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 13 Page 51**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'Sensitivity analyses generally restricted the sample to the safety analysis set, accounted for errors in stratification, censored (where appropriate) analyses at time of allo-SCT, and examined patients with evaluable post-baseline assessments. The ERG believed these subgroup analyses to be reasonable.' (ERG report, page 51)*<br>Reference to 'subgroup analyses' appears to be in error given the context of this paragraph. | 'Sensitivity analyses generally restricted the sample to the safety analysis set, accounted for errors in stratification, censored (where appropriate) analyses at time of allo-SCT, and examined patients with evaluable post-baseline assessments. The ERG believed these ~~subgroup~~ **sensitivity** analyses to be reasonable.' | Typographical error | No comment required. |

### Issue 14 Pages 55, 59, 60, 62, 63, 64, and 65

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report refers to 'final analysis set' in column headings for Table 10, Table 13, Table 14, Table 16, Table 17, Table 18, and Table 19<br>'Full analysis set' is used to describe this analysis set (i.e. the TOWER intention-to-treat [ITT] population) elsewhere in the ERG report and in the company submission and TOWER CSR. | Use of '**full** analysis set' throughout to describe analyses of the TOWER ITT population. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

### Issue 15 Pages 55, 59, 60, 62, 63, 64, 65, 66, 67, and 68

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Tables of results from TOWER (Tables 10, 13, 14, 16, 17, 18 19, 21, 22 and 23) appear to contain missing or incorrect footnotes. For example:<br>• Table 10 includes a footnote labelled '***' but this is not included within the table.<br>• Table 22 (treatment-emergent adverse events) contains a footnote labelled '**' that references to Table A-11 in our response to clarification questions (subgroup analyses of post-baseline allo-SCT) | Validation and correction of table footnotes and included cross-references to source materials. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 16 Page 67**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The overall patient numbers in ERG report Table 22 for the subgroups of patients intended to receive a FLAG ± anthracycline based regimen and clorarabine or clofarabine based regimen at randomisation are incorrect. These appear to have been taken from a table in our response to clarification questions reporting efficacy outcomes for these subgroups (based on the TOWER FAS), but should have been taken from the tables reporting safety outcomes for these subgroups (based on the TOWER safety analysis set [SAS]) e.g. Table A-14. | Amendment of subgroup patient numbers based on the TOWER SAS:<br>• Subgroup intended to receive a FLAG ± anthracycline based regimen at randomisation: blinatumomab N = [redacted]; SOC chemotherapy N = [redacted]<br>• Subgroup intended to receive a clofarabine or clofarabine based regimen at randomisation: blinatumomab N = [redacted]; SOC chemotherapy N = [redacted]<br>Update of footnote cross reference to Table A14 in the response to clarification questions. | Factual inaccuracy. | We have amended the text as requested. |

**Issue 17 Page 68**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The heading for Table 23 in the ERG report states:<br>*'Time to clinically meaningful HRQoL decrease or EFS event, TOWER.'*<br>However, the table presents results for both time to clinically-meaningful HRQoL decrease or EFS event and time to clinically-meaningful HRQoL decrease alone.<br>In addition, Table 23 includes a subheading row for 'HRQoL: Summary of EORTC QLQ-C30 GHS/QoL score and change from baseline at each scheduled assessment over time'.<br>This appears to have been included in error as the table presents time-to-event analyses only. | Amendment of table heading to:<br>'Time to clinically meaningful HRQoL decrease or EFS event, **and clinically meaningful HRQoL decrease alone,** TOWER.'<br>Removal of subheading row. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 18 Page 68**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'In the TOWER study, blinatumomab delayed the time to clinically meaningful 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event (CS, p 81) (see Table 23). The HR for the blinatumomab versus the SOC chemotherapy arm was 0.67 (descriptive p = 0.0051) (CS, p 81). Blinatumomab also delayed the time to clinically meaningful decrease alone, irrespective of EFS event (p=0.003). Subgroup analyses were not presented for FLAG or clofarabine.' (ERG report, page 68)*<br>In this paragraph summarising HRQoL data, the ERG states that subgroup analyses were not presented for the subgroups of patients intended to receive a FLAG ± anthracycline based regimen and clofarabine or clofarabine based regimen at randomisation. This blanket statement is not factually accurate as the ERG requested HRQoL data for these subgroups at the clarification questions stage; this request did not specify time-to-event HRQoL data, and so we provided a summary of EORTC QLQ-C30 GHS/QoL scores and change from baseline at different scheduled visits for these subgroups. | Removal of the sentence stating that subgroup analyses were not presented or amendment to e.g.:<br>'In the TOWER study, blinatumomab delayed the time to clinically meaningful 10-point decrease in EORTC QLQ-C30 GHS/QoL or EFS event (CS, p 81) (see Table 23). The HR for the blinatumomab versus the SOC chemotherapy arm was 0.67 (descriptive p = 0.0051) (CS, p 81). Blinatumomab also delayed the time to clinically meaningful decrease alone, irrespective of EFS event (p=0.003). Subgroup analyses ~~were not presented for FLAG or clofarabine~~ **relating to EORTC QLQ-C30 GHS/QoL scores and change from baseline at different scheduled visits for the FLAG and clofarabine subgroups were provided in response to clarification questions; the ERG did not specifically request time-to-event HRQoL analyses for these subgroups.'** | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

### Issue 19 Page 83

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'Cox proportional hazards were assessed and used to show the treatment effect.' (ERG report, page 82)*<br>This statement is factually inaccurate as Cox PH analyses were run not 'to show the treatment effect', but to evaluate the validity of the PH assumption. | 'Cox proportional hazards analyses were ~~assessed and used to show the treatment effect~~ **run to derive Schoenfeld residuals to assess the validity of the proportional hazards assumption'** | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

### Issue 20 Page 84

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The heading for Figure 3 in the ERG report states:<br>*'Figure 3 Kaplan-Meier plots with the restricted Gompertz model for overall survival among responders.' (ERG report, page 84)*<br>This title appears to be an error as the presented KM plots are for all patients, not just 'among responders' | 'Figure 3 Kaplan-Meier plots with the restricted Gompertz model for overall survival ~~among responders~~' | Factual inaccuracy. | This is not an inaccuracy on the part of the ERG. Figure 5-4 on p 139 of the CS specifies that the relevant curves are among responders only. |

## Issue 21 Pages 85, 87, and 114

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*The company has applied an arbitrary hazard ratio of 0.85 to the survival distribution for the matched historical cohort to show the similarity or goodness of fit of the Gompertz curve against the observed data.' (ERG report, page 85)*<br><br>*'The ERG was unclear about how the company used information from the matched natural history cohort, and how the arbitrary adjusted hazard ratio of 0.85 was applied to the overall survival as shown in Figure 4.' (ERG report, page 87)*<br><br>*'Additionally, the company has applied an arbitrary hazard ratio of 0.85 to the survival function for the historical cohort.' (ERG report, page 114)*<br><br>Reference to the HR as 'arbitrary' is inaccurate as it was obtained by solving the equation for the value such that the OS distribution for the historical cohort visually matched that for the SOC arm in TOWER. | Removal of the term 'arbitrary'. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. In particular, the ERG notes that the word 'arbitrary' was used in the CS on p 139 to describe this hazard ratio. |

**Issue 22 Pages 87 and 88**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
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| The ERG report states:<br>*'With this in mind, the ERG considers this method for adjusting the Kaplan-Meier curve to be inaccurate for two reasons. First, the survival function for a Gompertz distribution is given as*<br>*S [t] = exp{ [(λ1 / α] *(1- exp(α * t)) }*<br>*where λ is the scale parameter, and α is the shape parameter.*<br>*Second, the survival function for a Gompertz distribution cannot simply multiplied be by a hazard ratio to derive an adjusted survival distribution. The ERG's approach to adjusting the Kaplan- Meier curve for the historical cohort is:*<br>*S [t] = exp{ [(λ1 *HR / α] *(1- exp(α * t)) }*<br>*where HR is the hazard ratio. This equation assumes that the shape parameter, α, is kept constant in both models' (ERG report, pages 87 and 88)*<br>The approach we used to derive the adjusted historical comparator OS curves consisted in raising the survival curve to the power of HR, and not (as stated by the ERG) in multiplying the survival curve by the HR. This approach is methodologically sound and involved applying a well-accepted standard property of exponential functions:<br>Exp(A*B)=[Exp(A)]^B | Removal of all of the quoted ERG text. | Factual inaccuracy. | The ERG, upon further clarification by the company, agrees that the quoted text should be removed and has submitted an erratum accordingly. |

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| Which means that the exponential of the product of two factors (A and B) is equal to raising the exponential of one of the two factors (e.g. A) to the power of the other factor (e.g. B).<br><br>Specifically, for a Gompertz distribution this means that:<br><br>S [t] = exp{ [(λ1 / α] *(1- exp(α * t)) }<br><br>And that:<br><br>SA[t]=S[t]^HR=( exp{ [(λ1 / α] *(1- exp(α * t)) })^HR=<br>= exp{ [(λ1 *HR / α] *(1- exp(α * t)) }<br><br>Overall this approach is mathematically equivalent to the approach proposed by the ERG. | | | |

## Issue 23 Page 88

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br><br>*'As noted above, the treatment effect is based on fitting a restricted Gompertz parametric model to the blinatumomab arm of the trial, and then assuming proportional hazards for the standard of care arm.' (ERG report, page 88)*<br><br>The survival distributions for the blinatumomab arm and SOC chemotherapy arm were fitted simultaneously, not sequentially. | 'As noted above, the treatment effect is based on fitting a restricted Gompertz parametric model to the blinatumomab **and standard of care** arm**s** of the trial, ~~and then assuming~~ with an assumption of proportional hazards **for blinatumomab versus** ~~the~~ standard of care ~~arm~~.' (ERG report, page 88) | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

## Issue 24 Page 89

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'Also, it should be noted that counterfactual plots for EFS were not presented, unlike the analyses of OS.' (ERG report, page 89)*<br>Counterfactual plots were provided for EFS in Appendix VIII to the company submission (Figure 1-9). | Deletion of the quoted text. | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. Plots were not provided in the main report. No change necessary. |

## Issue 25 Page 89

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'From Figure 6, it can be seen that the fitted curve overestimates EFS in blinatumomab and underestimates EFS in SOC chemotherapy.' (ERG report, page 89)*<br>This statement is not completely accurate and should be reworded. The fitted curves overestimate EFS for the blinatumomab arm from approximately month 10 to approximately month 19. The fitted curves underestimate EFS for the SOC chemotherapy arm from approximately month 6 to approximately month 19. After month approximately 20 months, the fitted curves overestimate EFS for both arms (as the KM curves for both arms go to zero). | 'From Figure 6, it can be seen that the fitted curves overestimate~~s~~ EFS ~~in~~ **for the** blinatumomab **arm (from approximately month 10 to month 19)** and underestimates EFS ~~in~~ for the SOC chemotherapy **arm (from approximately month 6 to month 19)**. **After approximately 20 months, the fitted EFS curves overestimate EFS for both arms (as the KM curves for both arms go to zero).**' | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

### Issue 26 Page 95

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Table 29 in the ERG report appears to have been transcribed from the Table 5-11 in the company submission inaccurately, as the contents of some cells are incorrectly duplicated (e.g. the proportion of patients starting Cycle 1 is quoted as being 98.52%, as is the proportion for Cycle 10). | Correction of cell values per company submission Table 5-11. | Factual inaccuracy. | We have amended Table 29 as requested. |

### Issue 27 Page 95

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'Table 30 shows the unit costs for each component of FLAG-IDA per day, and the total drug acquisition cost, which was estimated to be £1,974.34 per day.' (ERG report, page 95)*<br>The quoted total drug acquisition cost is described as 'per day', but this cost refers to the total drug acquisition cost per cycle. | 'Table 30 shows the unit costs for each component of FLAG-IDA per day, and the total drug acquisition cost, which was estimated to be £1,974.34 per **cycle** ~~day~~.' | Factual inaccuracy. | We have amended the text as requested. |

**Issue 28 Page 96**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'In the model, people in this arm received four cycles of treatment, and it can be seen that people who started FLAG-IDA treatment in that cycle, adhered to treatment.' (ERG report, page 96)*<br>The ERG states that patients received four cycles of FLAG-IDA; this should refer to SOC chemotherapy (not FLAG-IDA), and is the maximum number of cycles patients received (1.49% received four cycles). | 'In the model, people in this arm received **a maximum of** four cycles of treatment, and it can be seen that people who started ~~FLAG-IDA~~ **SOC chemotherapy** treatment in ~~that~~ **each** cycle, adhered to treatment.' | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 29 Page 96**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'In the absence of UK costs, costs where obtained from the Dutch costing study and converted using the Health and Social Care Pay and Price index.' (ERG report, page 96)*<br>*'Additionally, the ERG are not aware of using the Health and Social Care Pay and Price index to convert from one currency to another; using the purchasing power parity would have been more appropriate.' (ERG report, page 96)*<br>The included Dutch costs were from the cited NHS Blood and Transplant Service report. This report states that the Dutch costs were converted using 1999 GBP/EUR exchange rates and inflated to 2012/2013 GBP using the Health and Social Care Pay and Price index. We acknowledge that this was not accurately explained in the company submission. The ERG's statements are consequently inaccurate as costs were not converted using the Health and Social Care Pay and Price index as stated in the ERG report. | 'In the absence of UK costs, costs w~~h~~ere obtained from the Dutch costing study and converted **by the authors of the NHS report** using a 1999 GBP/EUR exchange rates, **before being inflated to 2012/2013 costs using** the Health and Social Care Pay and Price index.'<br>~~'Additionally, the ERG are not aware of using the Health and Social Care Pay and Price index to convert from one currency to another; using the purchasing power parity would have been more appropriate.'~~ | Factual inaccuracy. | Not a factual inaccuracy on the part of the ERG, thus no comment required. No change necessary. |

### Issue 30 Page 100

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'The ERG considers this assumption to be plausible. However, it should be noted that >10% of people in the blinatumomab arm of the TOWER trial received six or more cycles.' (ERG report, page 100)*<br>Reference to > 10% as the proportion of patients who received six or more cycles of blinatumomab is factually inaccurate as this 10.1%. Rounded to 1 decimal place per the ERG report it is 10% exactly. | 'The ERG considers this assumption to be plausible. However, it should be noted that **10%** of people in the blinatumomab arm of the TOWER trial received six or more cycles.' (ERG report, page 100) | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

### Issue 31 Page 116

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The heading for Figure 17 in the ERG report states:<br>*'Figure 17 Event-free survival from TOWER compared to projected event-free survival from the Markov model.' (ERG report, page 116)*<br>This title appears to be an error as the presented plots in the first panel (i.e. left side) of the figure is for EFS specifically amongst responders, whereas the second panel (i.e. right side) is EFS amongst all patients. | Accurate figure labelling and description in heading. | Factual inaccuracy. | We have edited the caption for Figure 17 as requested. |

**Issue 32 Page 119**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'Therefore using shorter time horizons may reduce uncertainty, and allows greater confidence in clinical and cost-effectiveness results.' (ERG report, page 119)*<br>This statement is factually inaccurate as the use of a two-year time horizon does not decrease the uncertainty in model projections as stated by the ERG. Instead, it simply makes an assumption which decreases measurable parameter uncertainty while increasing unmeasurable structural uncertainty.<br>In addition, as highlighted in our response to clarification questions, arbitrarily limiting the time horizon to two years is inappropriate and represents a clinically implausible scenario given the likely long-term benefits associated with blinatumomab based on the compelling efficacy data shown in TOWER and longer-term estimates of OS from Study MT103-211. This also contradicts the NICE reference case which states that 'analyses that limit the time horizon to periods shorter than the expected impact of treatment do not usually provide the best estimates of benefits and costs'. | Removal of quoted text from the ERG report or amendment to e.g.:<br>'Therefore using shorter time horizons may reduce **measurable parameter** uncertainty, **but increases unmeasurable structural uncertainty** and ~~allows greater confidence in clinical and cost-effectiveness results~~ **disregards the long-term impacts of blinatumomab.'** | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

**Issue 33 Page 131**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*They report that based on promising results from non-randomised evidence and provision of data from the TOWER trial, blinatumomab was approved on an accelerated assessment pathway by EMA, reflecting a substantial unmet need.' (ERG report, page 131)*<br><br>The reference to blinatumomab being approved by the EMA based on non-randomised evidence and 'provision of data from the TOWER trial' implies that TOWER formed part of the data package considered by the EMA for the (conditional) approval of blinatumomab. As highlighted in the company submission, the EMA approval was based on non-randomised evidence only, subject to the future conduct and provision of data from TOWER. | 'They report that based on promising results from non-randomised evidence**, and on the condition of subsequent conduct and** provision of data from the TOWER trial, blinatumomab was approved on an accelerated assessment pathway by EMA, reflecting a substantial unmet need.' | Factual inaccuracy. | Not a factual inaccuracy, thus no comment required. No change necessary. |

# Issues with ERG report content leading to misleading and potentially factually inaccurate conclusions

## Issue 34 Misleading statements around anticipated hospitalisation requirements and frequency of bag changes for administration of blinatumomab

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report discusses in several instances the feasibility of outpatient treatment with blinatumomab and concludes that:<br>*'The company states that this does not present any additional burden to healthcare providers as hospitalisation during treatment is standard practice with current treatment options. However, the ERG clinical advisor suggested that in practice, day unit facilities may not be set up to cater for patients coming in to have infusion bags changed and that patients may be hospitalised for the whole of each treatment cycle. Day units catering for these patients would theoretically be possible, but would only be possible at larger specialised centres which would have greater experience in treating these patients; the ERG clinical advisor further noted that any centre would treat between 5 and 8 patients a year with this condition.' (ERG report, page 25)*<br>*'Based on correspondence with the ERG's clinical expert, people receiving blinatumomab treatment are likely to spend eight weeks in care for cycles 1 and 2, which is considerably higher than what the company suggested. The ERG has explored this in a scenario analysis. Additionally, our clinical advisor did note that there is a lack of infrastructure at hospitals to support outpatient care, and as a result these patients are frequently hospitalised for the entirety of the treatment cycle.' (ERG report, page 94)*<br>*'The ERG clinical advisor suggested that 14 days is the minimum days that people are hospitalised whilst receiving treatment. It was further suggested* | Acknowledgement of the substantial uncertainty associated with the ERG's estimates of hospitalisation duration and frequency of bag changes, and subsequent revised base case assumptions. | For clarification and to avoid potentially factually inaccurate conclusions. | This is not a factual inaccuracy. The ERG presented these analyses as plausible scenarios that it believed to be relevant and preferable to the company's base case. |

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| *that people are generally hospitalised for four weeks in both cycles 1 and 2 and consolidation cycles.' (ERG report, page 100)*<br><br>*'The ERG clinical advisor noted that the minimum hospitalisation periods in the marketing authorisation, and thus as used in the company's model, were unlikely to be realistic given the demands of treatment and the infrastructure required to support outpatient treatment, with hospitalisation during the entirety of active treatment in each of the five cycles being possible, if not likely.' (ERG report, page 120)*<br><br>Our understanding based on feedback from UK haemato-oncology nurses is that treatment with blinatumomab is likely to be given in the outpatient setting (either hospital or home visits) after at least the minimum period of hospitalisation recommended by the SmPC. We acknowledge that this is likely to be specifically at larger specialised centres where appropriate facilities and specialised staff are available as highlighted by the ERG's clinical advisor, but anticipate that a substantial proportion of patients would be treated in such a setting given the rarity and severity of the disease.<br><br>In addition, the ERG's clinical advisor suggests that 14 days is the minimum that patients are hospitalised while receiving treatment and '*are generally hospitalised for four weeks in both cycles 1 and 2 and consolidation cycles.*' It is unclear whether this statement refers to treatment with blinatumomab or current practice with SOC chemotherapy. If the latter, it is misleading to generalise this to anticipated treatment with blinatumomab given that hospitalisation requirements for SOC chemotherapy are driven by the highly toxic nature of such treatment.<br><br>Overall, we believe these statements that have contributed to the ERG's decision to amend the base case analysis are potentially misleading, and their revised base case assumption that all patients will be hospitalised for the entire duration of Cycle 1 and Cycle 2 with blinatumomab is highly implausible.<br><br>The ERG also states that: | | | |

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| *'The ERG undertook a scenario analysis assuming daily bag changes for intravenous chemotherapy, instead of every four days as in the base case. We expect that this may represent a more realistic estimate of everyday practice.' (ERG report, page 121)*<br><br>However, no evidence or rationale is provided for the assertion that daily IV infusion bag changes may be a more realistic estimate of clinical practice, in contrast to the availability of additional 48-hour, 72-hour, and 96-hour bag change options as per the blinatumomab SmPC. If the ERG's revised assumption of daily bag changes is a consequence of the revised assumption around hospitalisation duration (daily bag changes may be standard practice in the hospital setting), this bag change assumption is similarly implausible. | | | |

## Issue 35 Misleading statements around assessment of proportional hazards and survival modelling

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'The ERG was concerned that the company's use of parametric curves with the observed data from TOWER represented a set of strong assumptions, given that visual inspection of Kaplan-Meier plots relating to overall survival and event-free survival from TOWER suggests that hazards are not proportional.' (ERG report, page 22)*<br>*'The CS also included a hazard ratio estimated using a stratified Cox regression model. Though this is a standard analysis method, the ERG could not find evidence of testing of the proportional hazards assumption.' (ERG report, page 49)*<br>*'The ERG is concerned that the proportional hazards assumption is invalid, given that the Kaplan-Meier plots (Figure 2) appear to cross from month 15 through the remainder of the trial time horizon. The proportionality assumption leads to overestimating the treatment benefit of blinatumomab.' (ERG report, page 88)*<br>*'OS and EFS have been estimated based on fitting parametric curves to the Kaplan-Meier plots of the observed data in the blinatumomab arm, and assuming proportional hazards to determine the treatment effect. The ERG considers this to be a strong assumption given that the Kaplan-Meier plots do not appear to be proportional. (ERG report, page 91).*<br>*'Among other concerns noted by the ERG, the company's use of parametric curves with the observed data from TOWER represented a set of strong assumptions, given that visual inspection of Kaplan-Meier plots relating to overall survival and event-free survival from TOWER suggests that hazards are not proportional.' (ERG report, page 126)'* | Acknowledgement of the comprehensive analyses conducted to explore the PH assumption which did not provide any strong evidence to reject the PH assumption, and acknowledgement that rejecting the PH assumption based on visual inspection of KM plots with very few patients at risk at the time point after which the curves overlap is an inappropriate reason on its own to reject the PH assumption.<br>Statements of opinion (e.g. 'overestimated treatment benefit') are described as opinion rather than stated as fact. | For clarification and to avoid potentially factually inaccurate conclusions. | These are not factual inaccuracies. They represent the ERG's interpretation of the evidence presented. |

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| The ERG's suggestion that we did not explore the validity of the PH assumption is inaccurate, and its conclusion that assuming PH is a strong and invalid assumption is misleading and fundamentally flawed. The description of this 'overestimating the treatment benefit of blinatumomab is stated as a fact rather than an opinion.<br><br>As described in the company submission, we comprehensively evaluated the PH assumption using counterfactual diagnostic plots, plots of the hazards over time, and examination of Schoenfeld residuals. In addition, the BIC based on models fit to the blinatumomab and SOC chemotherapy arm simultaneously accounts for the information loss associated with the PH assumption, and therefore implicitly provides an assessment of the PH assumption. None of these approaches provided strong evidence to suggest the PH assumption was invalid. It should be noted that NICE DSU TSD 14 suggests that log-cumulative hazard plots be examined to evaluate the PH assumption. This approach is analogous to the counterfactual diagnostic plots reported in the submission (on the natural rather than transformed scale).<br><br>The ERG has provided no evidence to refute the assumption of PH other than the visual inspection of the KM curves, which is not an appropriate evidence source alone from which to reject the assumption given that at 15-months (shortly after which the curves converge) there are just 34 patients (8.3%) of the TOWER FAS at risk. The ERG's statement that the curves 'cross' from month 15 'through the remainder of the trial time horizon' is also inaccurate as the curves 'overlap' rather than cross from 15-months to 19-months only, after which the curve for blinatumomab is again higher than the curve for SOC chemotherapy. The curves never actually cross (i.e. the KM survival estimate for blinatumomab is never less than that for SOC chemotherapy).<br><br>The ERG report also states that:<br><br>*'Fitting individual parametric models to each K-M plot relaxes the assumption of proportional hazards, and it may provide a superior fit.' (ERG report, page 128)'* | | | |

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| This statement is also potentially misleading as our analysis, in which curves were fit jointly using restricted and unrestricted assumptions, suggests that the restricted models tend to provide superior fit. Only one unrestricted model, the unrestricted lognormal, yielded a better statistical fit according to BIC than the restricted Gompertz model. However, the difference in fit was minimal (1634.507 vs. 1635.235) and the unrestricted lognormal distribution failed to accurately match the shape of the historical comparator data.<br><br>*'Though the Gompertz was the best fitting model, it predicted that 20% of people would be immortal apart from additional age-related mortality hazards; this appears to be because it underestimates hazard for death at times beyond 12 months.' (ERG report, page 128)*<br><br>This statement is misleading for several reasons:<br>• The hazard rate beyond approximately 24 months is unknown and the long-term OS with the restricted Gompertz model is 20% not because it overestimates survival between 12 and 24 months. Rather both, of these are findings that are a consequence of the data and the distributional assumptions.<br>• While the Gompertz model underestimates the hazard for OS for blinatumomab and SOC chemotherapy during the period from 12-24 months, it closely matches the hazards for OS from the historical control beyond 12 months.<br><br>*'It is likely that a revision of the optimistic extrapolation methods used in the company submission would cause an increase in the ICER…' (ERG report, page 128)*<br><br>This statement is misleading as 'optimistic' is an opinion and should not be stated as a fact. | | | |

### Issue 36 Misleading statements around baseline utility values in the model

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| The ERG report states:<br>*'Analysis of utility values did not account for baseline differences between arms.' (ERG report, page 22)*<br>*First, the company acknowledged that they had not included baseline values in their analyses.' (ERG report, page 92)*<br>*'Failure to adjust for these imbalances in utility values could result in misleading cost-effectiveness results.' (ERG report, page 92)*<br>The ERG fails to acknowledge that (as described in the company submission) as mean baseline utility values were slightly greater for patients receiving SOC chemotherapy, our approach is likely to be conservative (i.e. biased in favour of SOC chemotherapy). | Acknowledgement that the company submission approach is likely to be conservative. | For clarification and to avoid potentially factually inaccurate conclusions. | Not a factual inaccuracy, thus no comment required. No change necessary. |