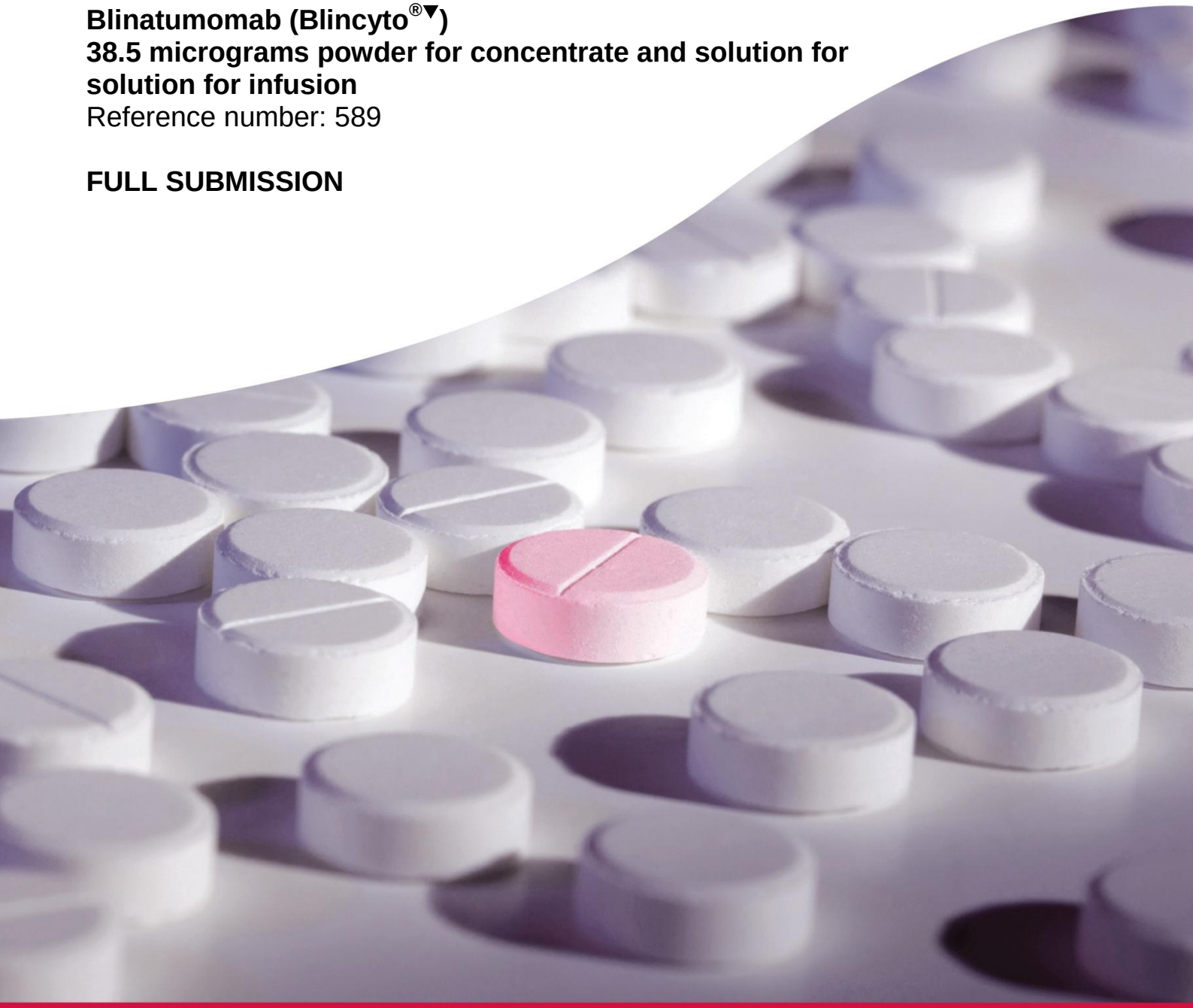
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Blinatumomab (Blincyto®▼)
38.5 micrograms powder for concentrate and solution for solution for infusion

Reference number: 589

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Blinatumomab (Blincyto®▼) 38.5 micrograms powder for concentrate and solution for solution for infusion. Reference number: 589 June 2016.

AWMSG Secretariat Assessment Report
Blinatumomab (Blincyto®▼) 38.5 micrograms powder for concentrate and solution for solution for infusion.

This assessment report is based on evidence submitted by Amgen Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Blinatumomab (Blincyto®▼) for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)[2].
Dosing	Patients may receive two cycles of treatment. A single cycle of treatment is four weeks of continuous infusion. Each cycle of treatment is separated by a two week treatment-free interval. Patients who have achieved complete remission (CR/CRh; see Glossary) after two treatment cycles may receive up to three additional cycles of blinatumomab consolidation treatment, based on an individual benefits-risks assessment. Hospitalisation is recommended for initiation at a minimum for the first nine days of the first cycle and the first two days of the second cycle. For patients at least 45 kg in weight, a starting dose of 9 mcg/day is administered on days 1–7 of cycle one increasing to 28 mcg/day on days 8–28, followed by a two week treatment free interval on days 29-42. For subsequent cycles, 28 mcg/day is administered each day for 28 days followed by a 14 day treatment free period. Refer to the Summary of Product Characteristics for further information [2].
Marketing authorisation date	23 November 2015[2]

2.0 DECISION CONTEXT

2.1 Background

Acute lymphoblastic leukaemia (ALL) is a rare aggressive cancer of the blood with an incidence of 1.2–1.4 per 100,000 population per year in Europe[3]. ALL arises from the unregulated proliferation of a single mutated lymphoid progenitor cell leading to the accumulation of leukemic cells in the bone marrow. Normal haematopoietic cells are ultimately replaced resulting in bone marrow failure and accompanying clinical manifestations such as anaemia, haemorrhage and infections. ALL subtypes of therapeutic importance are B cell precursor ALL, mature B cell ALL and T cell ALL[4], which correspond to different levels of maturation into normal B cell development.

Chemotherapeutic treatments will achieve an initial complete remission (CR) in approximately 90% of newly diagnosed patients with adult ALL however up to 50% will relapse, and need a second line of treatment, known as salvage therapy [5,6]. Allogeneic haematopoietic stem cell transplant (HSCT) is the only potentially curative option in adult patients with relapsed/refractory Ph (-) B-precursor ALL [7]. The goal of therapy in

this population is to induce remission and proceed to HSCT where possible, or to obtain long-term disease free survival and increase overall survival[4].

Blinatumomab is a first in class bispecific T-cell engager antibody construct with dual specificity for the B-lineage surface antigen, CD19, and CD3 which is expressed on the surface of T-cells. Blinatumomab engages the patient's endogenous T-cells to attack and eradicate B-precursor lymphoblastic leukaemia blasts[7,8].

2.2 Comparators

The comparator included in the company submission was standard-of-care treatment which is stated to be the multi-chemotherapy FLAG-IDA regimen[1]. FLAG-IDA is a combination of fludarabine, cytarabine (Ara-C), idarubicin, and granulocyte-colony stimulating factor (G-CSF).

2.3 Guidance and related advice

No specific national guidelines are available for the management of adult patients with relapsed/refractory Ph (-) B-precursor ALL. Local guidelines are available which have included recommendations proposed by the European Working Group for Adult Acute Lymphoblastic Leukaemia (EWALL, 2011)[9] and the Medical Research Council (MRC) UKALL XII/Eastern Cooperative Oncology Group (ECOG) trials.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included evidence from the pivotal open-label, single-arm phase II trial (study MT103-211) in adult patients with relapsed or refractory Ph (-) B-precursor ALL[1]. To provide context for these results, an observational historical comparator study has also been submitted[1]. An additional single-arm, phase II, dose finding study is not discussed in detail. The company also conducted a systematic literature review (SLR) to identify and evaluate evidence from clinical studies of patients with relapsed/refractory patients with Ph (-) B-precursor ALL; however, no formal indirect comparisons were presented in the submission. The company are currently conducting an ongoing confirmatory, randomised, phase III study controlled study (TOWER; NCT02013167) designed to evaluate the efficacy of blinatumomab versus investigator's choice of standard-of-care chemotherapy in adult relapsed/refractory Ph (-) B-precursor ALL patients[1].

3.1 MT103-211

This was an open-label, single arm, phase II trial conducted in Europe and the USA. The efficacy and safety of blinatumomab was evaluated in 189 patients with relapsed or refractory Philadelphia-chromosome negative Ph (-) B-precursor ALL, who were primary refractory after induction or who had relapsed within 12 months of first remission, relapsed within 12 months of receiving allogeneic HSCT, or not responded to or relapsed after first salvage therapy or beyond[7]. Patients received from one to five cycles of blinatumomab as per the SPC. Patients had at least 10% bone marrow blasts, an Eastern Cooperative Oncology Group performance status[10] of two or lower and received pre-phase treatment with dexamethasone. 64 (34%) patients had relapsed after previous allogeneic HSCT. 96 (51%) patients had no previous allogeneic HSCT and one or more previous lines of salvage therapy[7].

The primary endpoint was complete remission (CR) or complete remission with partial haematological recovery (CRh) within the first two treatment cycles of blinatumomab (see Glossary for definitions). After two cycles, 81 (43% [95% CI: 36%–50%]) patients had achieved a CR or CRh, see Table 1[7]. The primary endpoint was met; the 95% lower confidence limit for CR/CRh exceeded the pre-specified efficacy threshold of 30% within two cycles[1]. Of the 81 patients that met the primary endpoint, 40% (32/81) went on to undergo allogeneic HSCT, with an overall 100-day mortality post-allogeneic HSCT of 11% (95% CI: 0–23)[1,7]. The median overall survival (OS) for all patients was 6.1(95% CI: 4.2–7.5) months with a median observation time of 17.7 months[7]. A total of

65 patients (34.4%) achieved a confirmed molecular remission by polymerase chain reaction (PCR) testing. Of those who achieved a CR/CRh response and had evaluable minimal residual disease (MRD) data, 82.2% (60/73) evaluable for MRD achieved molecular remission[4].

Table 1. Response rates and survival among adult relapsed/refractory Ph (-) B-precursor ALL patients treated with blinatumomab in Study MT103-211[7].

Study	Response	n (%, [95% CI])	Median RFS (months [95% CI])
MT103-211 (n = 189)	CR/CRh (primary endpoint)	81 (43% [36–50%])	§5.9 (4.8–8.3)
	CR	63 (33% [27%–41%])	6.9 (4.2–10.1)
	CRh	18 (10% [6%–15%])	5.0 (1.4–6.2)
	*No response to therapy	90 (48%)	n/a
	†Not evaluable	18 (9%)	n/a

CI: confidence interval; RFS: relapse-free survival; CR: complete remission; CRh: complete remission with partial haematological recovery.

* Includes no response to blinatumomab (n = 41), progressive disease (n = 27), blast-free hypocellular bone marrow (n = 17) and partial remission (n = 5).

† Death before assessment (n = 9) and adverse events leading to treatment discontinuation (n =9).

§ An additional patient who had haematological response in cycle two and continued treatment despite the presence of extramedullary leukaemia achieved CR in cycle 3 was included for the RFS calculation.

3.2 Historical Comparator Study 20120310

In the absence of comparable efficacy data an observational, historical comparator study was conducted which provided subject level historical data on haematological remission rates and survival among adult patients with relapsed/refractory Ph (-) B-precursor ALL treated with physician's choice of standard of care chemotherapy[1].

A retrospective pooled analysis of historical data was available from 1990 to 2014 on 1,139 adult relapsed/refractory Ph (-) B-precursor ALL patients, provided by eight research groups in the EU and three in the USA. [Commercial in confidence data removed]. Eligible patients had first relapse or salvage treatment after a first remission duration of < = 12 months, were refractory to initial treatment, or had relapsed/were refractory after first or later salvage (e.g. second or later relapse), or relapsed/refractory within 12 months of allogeneic HSCT.

[Commercial in confidence data removed].

3.3 Comparative safety

Study MT103-211 was a single-arm trial; hence, no head-to-head safety data with standard-of-care chemotherapy are currently available. Due to limitation in the evidence available for comparator safety data obtained from the SLR, the company state direct comparisons and pooling of safety results were not possible. The safety assessment focuses mainly on data from the pivotal Phase II study[4].

Adverse events (AE) in the pivotal MT103-211 study were reported for 188 patients (99%) of the study population with serious AEs and death reported in 64% and 14.8%

of subjects respectively[4,7]. Serious adverse events included neurological events (16.4%), infections (31.7%), cytokine release syndrome (0.5%), tumour lysis syndrome (0.5%), and neutropenia/febrile neutropenia (15.3%). Investigators considered 124 serious AEs in 69 patients to be related to blinatumomab treatment. Of these, 23 patients experienced nervous system disorders, 16 experienced infection and infestations and blood and lymphatic disorders occurred in 13 subjects[4,7].

Nervous system disorders such as confusional state, tremor, encephalopathy, neurotoxicity, aphasia, ataxia and convulsion, were the first cause leading to blinatumomab interruption (12.7%); the majority of AEs were resolved after infusion interruption[4]. 18 patients (10%) discontinued treatment due to adverse events thought to be related to treatment. Fatal AEs occurred in 28 patients (12%), with 17 reporting fatal AEs due to infections and infestations[4].

3.4 AWTTC critique

- ALL is a heterogeneous disease with distinct biologic and prognostic groupings; age, MRD status, and initial response to chemotherapy are relevant prognostic factors[4]. Patients with higher age have a significantly poorer outcome than younger patients. The European Medicines Agency (EMA) highlight that treatments for ALL, accompanied by severe AE, often results in clinical remission; however, for many patients it remains an incurable and fatal disease due to its high rate of relapse. Patients with initial treatment failure have an extremely unfavourable prognosis. Advances in treatment for adult ALL have been slow and no specific national UK guidelines have been identified[4].
- In the relapsed/refractory adult population, the goal of therapy is to induce remission and proceed to allogeneic HSCT, which is the only potentially curative option. Clinical expert opinion sought by the All Wales Therapeutic and Toxicology Centre (AWTTC) confirms current treatment options for the patient population under consideration is limited and where possible patients enter a clinical trial. Blinatumomab is the first therapy licensed specifically for adult patients with relapsed/refractory Ph (-) B-precursor ALL. The company highlight blinatumomab as a novel medication designed to specifically treat a rare, aggressive disease for which no specific guidelines or therapies exist.
- In the pivotal single-arm phase II study, overall CR/CRh rates obtained with blinatumomab (81/189, 43%) was deemed significant by the EMA[4]. It was acknowledged that the expected CR rate with conventional therapy hardly exceeds 30% to 45% after first relapse and 18% to 23% in second or subsequent relapses. The clinical importance of this result was highlighted further since CRs significantly prevailed over CRh and, also, when the rate of CR/CRh is assessed with aplastic bone marrow response (51.9%), especially with MRD negativity, because these criteria are often deemed adequate to proceed to potentially curative HSCT. The EMA concluded that the high rates of negative MRD responses observed throughout the clinical studies supported the clinically significant response rate to blinatumomab in the high risk population under consideration[4]. Furthermore, OS survival was 6.1 months with a 6- and 12-month survival probability of 50% and 28% respectively, which was considered significant compared to the similar patient population enrolled in the historical study (12-month OS rate was 15%)[4].
- Clinical expert opinion confirms that the salvage chemotherapy which may be offered to the patient population under consideration is usually FLAG-IDA. The absence of any direct evidence versus the current standard of care was highlighted as a significant limitation by the EMA. The company conducted an observational historical comparator study in the absence of comparative data. While this was accepted as part of the evidence considered by the EMA in assessing the benefit of blinatumomab, the results should be interpreted with caution due to the inherent limitations of this study including specific baseline characteristics which differed across the studies.

- Furthermore, as a condition of the marketing authorisation, efficacy results from direct comparison with chemotherapy regimens are needed in order to better quantify the magnitude of the effect[4]. The company are currently conducting an ongoing confirmatory, randomised, phase III study controlled study (TOWER; NCT02013167) designed to evaluate the efficacy of blinatumomab versus investigator's choice of standard-of-care chemotherapy in adult relapsed/refractory Ph (-) B-precursor ALL patients[1].
- Overall the nature of the treatment emergent AE in the pivotal study were deemed consistent with what would be expected in the population under consideration but with some exceptions[4]. In particular, neurological events are considered an important risk factor and recommendations are included in the SPC as well as the risk management plan. In addition, target educational brochures are required to increase the awareness and mitigate the risks of medication errors as well as neurological events[4].
- Only 10 patients received all five cycles of blinatumomab in study MT103-211 and the long-term safety analysis was conducted in only 12 patients; five cycle exposure data is still considered very preliminary. Therefore, patients may receive up to two initial cycles of treatment. For those who have achieved complete remission after two cycles they may receive up to three additional cycles of consolidation treatment, based on an individual benefit-risk assessment[4].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission consisted of a cost-utility analysis (CUA) of blinatumomab compared to standard care, consisting of multi-chemotherapy with the FLAG-IDA regimen adopted as representative of this (a combination of fludarabine, cytarabine (Ara-C), idarubicin, and G-CSF), in patients with relapsed or refractory Ph (-) B-precursor ALL.

The economic evaluation consisted of a Markov model using area under the curve (AUC) methods to estimate time in each health state and OS. The model has three states: remission, progressive disease and death. Within the remission health state patients could experience complete remission (CR), complete remission with partial haematological recovery (CRh), or complete remission by study group (CRsg). The model patient cohort has a starting age of 40 years and costs and outcomes are modelled over a lifetime horizon, with a discount rate of 3.5% applied.

As the pivotal clinical evidence for blinatumomab is from a single arm trial, the comparison with standard care was based on an indirect comparison of remission rates and OS. The main source of clinical data for blinatumomab was the single arm MT103-211 study, and for the comparator arm data from a retrospective observational historical comparator study 20120310 was used to reflect standard care efficacy[11]. This study included 1,139 patients with relapsed or refractory disease, and who were receiving a variety of single-agent or combination chemotherapy regimens. FLAG-IDA was used in the economic model as the representative standard care chemotherapy regimen for cost assessment purposes; although in the historical comparator study patients received a range of salvage chemotherapies. Observed Kaplan-Meier OS data was available for 25 months for the blinatumomab arm, and for 60 months for the historical standard care patients. Hence, OS was extrapolated beyond 25 months up to 60 months in the blinatumomab arm using the same monthly survival probabilities as in the control arm. [commercial in confidence data removed]. Based on expert clinical opinion (Delphi panel conducted with 10 European clinicians), patients who remained alive beyond 60 months were assumed cured, with general population mortality based on Welsh life tables[12] applied to extrapolate beyond this time point in both treatment

arms, resulting in predicted mean overall survival over the lifetime horizon of [commercial in confidence data removed] for blinatumomab and historical standard care respectively. Based on data from the MT 103-211 study and the historical comparator study it was assumed that 39.5% of patients achieving CR/CRh in the blinatumomab arm and [commercial in confidence data removed] of patients achieving CRsg in the standard care arm receive HSCT.

The model included the medicine acquisition cost of blinatumomab and comparator, administration costs, and costs associated with adverse events are assumed to be part of hospital inpatient cost estimates included in the model. The medicine acquisition cost of blinatumomab is based on a confidential discount offered to all patients in Wales via a Wales Patient Access Scheme (WPAS). Blinatumomab is administered via a continuous IV infusion using an infusion pump, with patients spending nine days in the hospital during the first cycle, and two days during the second cycle of treatment. Costs of the ambulatory infusion pump have been included, based on use for two cycles per pump. Patients were assumed to receive 1.64 cycles of blinatumomab (mean number of vials used per patient estimated as 42) and 2.05 cycles of FLAG-IDA. Drug acquisition costs for FLAG-IDA were taken from the British National Formulary[13] and the NHS Generic Pharmaceuticals electronic Market Information Tool[14]. Health care resource use estimates for responders and non-responders came from hospital chart review studies conducted in Italy and France[15,16], producing pooled estimates for inpatient stays, day hospital visits, and outpatient hospital visits among adults with relpased/refractory Ph(-) B-precursor ALL treated with current salvage chemotherapies, and palliative care costs were based on data sourced from a published study[17]. The costs of HSCT were included based on NHS Blood and Transplant Service estimates.

A vignette based utility elicitation study was performed to obtain utility values for the model health states using time trade-off (TTO) methods in a sample of the UK general public. The results were combined with response rates from the blinatumomab study to produce weighted utility values of 0.84 for the remission health state and 0.35 for progressive disease. A utility of 0.86 was assumed for long term survivors beyond 60 months based on the CR utility estimate from the TTO study. An assumed disutility associated with AE's was included only in sensitivity analysis, but did not have a large impact on results. Deterministic one-way, scenario, and probabilistic sensitivity analyses (PSA) were conducted. One way sensitivity analysis consisted of varying base values by their estimated 95% CI's for efficacy, utilities, number of vials and resource use and cost parameters. Medicine costs were varied ± 30%. Scenario analysis was performed on time horizon, discount rate, start age of cohort, use/cost of salvage chemotherapy rather than FLAG-IDA, and exclusion of palliative care costs. A scenario adopting an alternative approach to blinamotumab survival extrapolation based on the average hazard ratio (HR) for blinamotumab vs standard care in first 25 months was also tested. PSA was conducted to explore joint parameter uncertainty and included distributions for the following parameters: Number of treatment cycles with standard care, vial use for blinatumomab, healthcare resource use, HSCT and palliative care costs, health state utilities, survival probabilities

4.1.2 Results

The estimated incremental cost per quality-adjusted life-year (QALY) gained for the base case comparison of blinamotumab vs. standard care, taking into account the WPAS, is [commercial in confidence data removed]. This is based on incremental costs of [commercial in confidence data removed] and incremental QALYs of 1.50 (Table 2). Patients receiving blinatumomab gained additional time in remission within the first 5 years (estimated at an average of 10.2 months vs. 3.61 months with standard of care).

The results were most sensitive to changes in the following parameters: time horizon, discount rate, survival probabilities, number of blinatumomab vials used, number of inpatient admissions with standard care. The ICER was not highly sensitive to varying mortality probability over months 26-60 by ±10%. Results for a number of relevant

scenarios are presented in Table 3. Results had relatively low sensitivity to start age, use of salvage chemotherapy instead of FLAG-IDA for comparator costs, exclusion of palliative care costs. Use of an alternative method of blinatumomab survival extrapolation was associated with a lower ICER (see Table 3). Including the WPAS, a probabilistic sensitivity analysis (PSA) indicated a probabilistic ICER of [commercial in confidence data removed] and the probability of cost-effectiveness as approximately 3% and 60% at £30,000/QALY and £50,000/QALY thresholds respectively.

Table 2. Base case analysis results (with WPAS)*[1].

	Blinatumomab	SOC	Increment
Drug costs	¶¶	£3,471	¶¶
Other costs†	£39,595	£34,520	£5,075
Total costs	¶¶	¶¶	¶¶
Total life years (LY) gained	3.35	1.60	1.75
QALYs gained	2.67	1.17	1.50
Incremental cost per LY gained			¶¶
Incremental cost per QALY gained (deterministic)			¶¶

SOC: Standard-of-care; QALY: quality-adjusted life-year
*Costs and benefits discounted at 3.5%
† These cover inpatient and outpatient administration, day hospital costs, pump, CR and HSCT follow-up, HSCT administration and palliative care costs.
¶¶ commercial in confidence data removed.

Table 3. Results of sensitivity/scenario analyses applying WPAS for blinatumomab[1].

Sensitivity & scenario analysis	Incremental cost	Incremental LYG	Incremental QALY	ICER	Plausibility
Time horizon 10 years	¶¶	0.78	0.67	¶¶	Not more plausible than the base case, but indicates the impact of uncertainty associated with long extrapolation.
Time horizon 15 years	¶¶	1.01	0.87	¶¶	
Discount rate 0%	¶¶	3.18	2.73	¶¶	Not more plausible than the base case but indicates sensitivity to discount rate due to long extrapolation of health benefits in a proportion of patients. Typically 6% is adopted for upper rate in sensitivity analysis, which would increase the ICER further.
Discount rate 5%	¶¶	1.44	1.23	¶¶	

Sensitivity & scenario analysis	Incremental cost	Incremental LYG	Incremental QALY	ICER	Plausibility
Discount rate 1.5% for effects, 3.5% for costs	¶¶	2.4	2.06	¶¶	This scenario relates to NICE policy on treatments with long term health benefits (> 30 years) – not more plausible than base case, but provides an indication of sensitivity to discounting of QALYs.
Lower 95% CI for trial based blinatumomab survival probability	¶¶	0.85	0.73	¶¶	Not more plausible than the base case, but indicates the impact of uncertainty associated with long extrapolation.
Upper 95% CI for trial based blinatumomab survival probability	¶¶	2.63	2.26	¶¶	
Lower 95% CI for mean vials blinatumomab used (37.02 vials)	¶¶	1.75	1.5	¶¶	There will be variation in vial use across patients hence this provides an indication of sensitivity to this.
Upper 95% CI for mean vials blinatumomab used (47.29 vials)	¶¶	1.75	1.5	¶¶	
Alternative survival extrapolation method for blinatumomab*	¶¶	1.89	1.63	¶¶	No more plausible than base case method.
Seven years cure time point and 1.5 times general population mortality rate	¶¶	1.50	1.28	¶¶	Potentially plausible alternative to base case but reflects uncertainty in key parameters
Three years cure time point and 1.5 times general population mortality rate	¶¶	1.90	1.63	¶¶	Potentially plausible alternative to base case but reflects uncertainty in key parameters
AWTTC analysis: Discount rate of 6%	¶¶	1.28	1.1	¶¶	Typically 6% is adopted for upper rate in sensitivity analysis.

LYG:Life-year-gained; QALY: quality-adjusted life-year; ICER: Incremental cost-effectiveness ratio
*The average HR for blinatumomab vs. standard care within the first 25 months (HR=0.85) was applied to the monthly mortality probability for standard care in month 25-60 in order to estimate survival in the blinamotumab arm.
¶¶ commercial in confidence data removed.

4.1.3 AWTTC critique

The base case ICER has been estimated at [commercial in confidence data removed] per QALY gained. The model structure that this estimate is based on has the strength of being simple. However, there are several weaknesses and uncertainties in the economic analysis:

- There is only single arm trial data for assessing the efficacy of blinatumomab, and the comparison with standard of care is based on a naïve indirect comparison. This means there is high uncertainty in the relative response and survival benefits associated with blinatumomab. The impact of this is demonstrated in sensitivity

analysis whereby varying the survival probability within 95% CI's of median survival for blinatumomab resulted in an ICER range of [commercial in confidence data removed] with WPAS (Table 3).

- There is extensive extrapolation to a lifetime horizon beyond the observed data for patients predicted to be still alive at five years, and uncertainty associated with this. In particular, the assumption that all patients alive at 60 months can be considered cured is based only on clinical expert opinion, and has the potential to be over-optimistic as some patients may relapse. In addition, these patients are assumed to have a general population life expectancy which also seems optimistic. Additional sensitivity analysis provided demonstrated moderate sensitivity to changing the cure time assumption and increasing mortality rate above that of the general population [commercial in confidence data removed] for scenarios of three years cure time/1.5 times general population mortality rate, and seven years cure time/1.5 times general population mortality rate. The ICER results are upwardly sensitive to a shorter time horizon, increasing to over [commercial in confidence data removed] if truncated at 15 years.
- The utility estimate for progressive disease of 0.35 appears low, and there are concerns over face validity in relation to relatively high utilities of 0.84 for remission and 0.86 for long term survivors. The upper range tested for progressive disease in sensitivity analysis is 0.42 which is still quite low, and the range for remission and long term survival in sensitivity analysis is narrow at only 0.82–0.86, and 0.84–0.88 respectively. For illustration, if a hypothetical progressive disease utility of 0.5 and remission utility of 0.78 and 0.8 were applied for remission/long term survivors the ICER increases to [commercial in confidence data removed].
- The cost of the ambulatory pump may have been underestimated as this is based on an assumption the pump can be re-used which seems unlikely.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Estimates of the incidence of ALL and the proportion of adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL were obtained from several published references specified in the submission, including published papers and cancer websites[1].

Relapsed/refractory Ph (-) B-precursor ALL is a rare (ultra-orphan) disease with an annual incidence of 43 cases in Wales in 2013: 40% of whom will be in adults[18], 87% from B-precursor lineage[19], 77% Ph (-)[20], 50% will be relapsed/refractory after initial treatment[21]. This would result in an eligible patient population of six for blinatumomab in Wales. The company estimates the uptake of blinatumomab will be [commercial in confidence data removed] of those eligible, resulting in [commercial in confidence data removed] treated patients per year. The net medicine cost estimates take account of any potential displacement of standard care (multi-chemotherapy, including FLAG-IDA).

5.1.2 Results

The budget impact estimates provided in Table 4 below are based on an estimate of [commercial in confidence data removed] patients treated with blinatumomab per year. Based on an average of 42 blinatumomab vials per patient the medicine budget impact of [commercial in confidence data removed], and net cost including resource use of [commercial in confidence data removed], with the WPAS applied, is estimated.

Table 4. Estimated budget impact of blinatumomab[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients* (all indications)	6	6	6	6	6
Number of eligible patients (indication(s) covered in this submission)	6	6	6	6	6
Treated patients	¶¶	¶¶	¶¶	¶¶	¶¶
Blinatumomab costs per patient with WPAS	¶¶	¶¶	¶¶	¶¶	¶¶
Administration and monitoring	**£12,660**	**£12,660**	**£12,660**	**£12,660**	**£12,660**
Staffing	**£313**	**£313**	**£313**	**£313**	**£313**
Infrastructure	**£176**	**£176**	**£176**	**£176**	**£176**
Net costs (per patient)	¶¶	¶¶	¶¶	¶¶	¶¶
Cost of comparator displaced	**£3,471**	**£3,471**	**£3,471**	**£3,471**	**£3,471**
Overall net medicine cost	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine and resource cost (with WPAS)	¶¶	¶¶	¶¶	¶¶	¶¶
WPAS: Wales patient access scheme ¶¶ commercial in confidence data removed.					

5.1.3 AWTTC critique

- Costs are broken down into medicine, administration, staffing and infrastructure costs but could be provided in more detail. Follow up costs and HSCT administration costs have not been included.
- No sensitivity analysis has been provided for the budget impact estimates.

5.2 Comparative unit costs

Acquisition costs for blinatumomab (Blincyto®▼) and the comparator FLAG-IDA are shown in Table 5.

Table 5. Acquisition costs for blinatumomab and representative standard care chemotherapy comparator used in the economic analysis[1].

Drug	Doses*	Cost per cycle**
Blinatumomab	Continuous IV infusion† **Cycle 1** Days 1 - 7: 9 micrograms/day Days 8 - 28: 28 micrograms/day **Susequent cycles** (Day 1 - 28): 28 micrograms/day	**Cycle 1** £48,408 **Cycle 2** £56,476
Drug	**Doses***	**Cost per cycle****
FLAG-IDA††	**Fludarabine** 30mg/m² IV infusion over 30 minutes on days 2- 6 **Cytarabine** 2,000mg/m² IV infusion over four hours on days 2 - 6 **G-CSF (Lenograstim)** 263 µg, 263 mg per day, on days 1 -7 **Idarubicin** 8mg/m² IV daily on days 4 - 6	£2,593

*See all relevant Summaries of Product Characteristics for full licensed indications and dosing details.[2]
**Costs are based on current BNF list prices as of March 2016 (except blinatumomab from MIMS).[13]
†Takes account of the bag changes every 96 hours and assumes drug wastage at each bag change.
††For FLAG-IDA the following assumptions are used:

- Body surface area assumed to be 1.8m^2
- Assumes that each patients can reuse medication left over in their vials the following day within their course of treatment.

This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, blinatumomab (Blincyto®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that blinatumomab (Blincyto®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

Blinatumomab is currently being evaluated in an ongoing controlled study in adult patients with relapsed/refractory Ph (-) B-precursor ALL[22]. Study 00103311 (TOWER; NCT02013167) is a confirmatory, randomised, phase III study that was designed to evaluate the efficacy of blinatumomab versus investigator's choice of standard-of-care chemotherapy in adult relapsed/refractory Ph (-) B-precursor ALL patients[22].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 7th March 2016

Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines.
The company submission indicates that the use of blinatumomab in the target patient population meets the end-of-life criteria set by the AWMSG Policy on appraising life-extending, end-of-life medicines[23]. These criteria, together with an assessment of whether they are met by blinatumomab, are provided in Table 6.

Table 6. End of life considerations for New Medicines Group (NMG)/AWMSG.

Criteria for application of the EoL policy (all must apply)[23]	Blinatumomab considerations
The most plausible ICER estimate exceeds £30,000 per QALY	The company selected base case ICER exceeds £30,000 per QALY gained, and there are no more plausible scenarios in which the ICER is below £30,000. The PSA indicates a zero probability of blinatumomab being the most cost-effective treatment at a threshold of £30,000 per QALY.
The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).	The pivotal study (MT103-211)[7] is a phase II open-label single-arm study, and data are not yet available from the active comparator phase III study to determine median survival in a control group. The historical comparator study (Study 20120310)[1] that was mandated for conditional EMA approval of blinatumomab was conducted in 1,139 adult patients with relapsed/refractory Ph (-) B-precursor ALL treated with salvage chemotherapy. Follow up time was sufficient to observe > 90% deaths, and estimated a median OS of 3.3 months[4]. This evidence has been submitted by the company to support that current patient survival for the blinatumomab indication is less than 24 months. The base case estimate of mean survival with extrapolation from the economic model for standard care was 2.68 life years (non-discounted), which is above the 2 year life expectancy, but is heavily skewed by a small proportion of patients [commercial in confidence data removed] assumed to be cured at 5 years and living a normal life expectancy (i.e. additional 36 years).
There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival	There is currently no comparative data to assess the survival benefit associated with blinatumomab, although the company state that median survival data will be available May/June 2016 from the ongoing phase III blinatumomab versus chemotherapy study (MT 103-311)[1]. Median OS was 6.1 months (95%CI: 4.2–7.5) in Study MT103-211 versus 3.3 months in the historical comparator study. This represents an additional 2.8 months median survival benefit for blinatumomab vs standard care. The base case in economic model estimated extrapolated extension to life over standard care based on the same data as above as 1.75 life years (21 months or 3.18 years not discounted). However, this is associated with high uncertainty due to limitations in the extrapolation of survival in the economic model, although even with a short time horizon of 10 years applied in the economic model the additional benefit is estimated >3months (see Table 3 above).
AWMSG: All Wales Medicines Strategy Group; NMG: New Medicines Group; EoL: end-of-life; OS: overall survival; ICER: Incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years	

Should NMG/AWMSG conclude that blinatumomab should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[23]:

NMG/AWMSG will need to consider:

- The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age.
- The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the medicine to fall within the current threshold range.

In addition, NMG/AWMSG will need to be satisfied that:

- The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review) and;
- The assumptions used in the economic modelling are plausible, objective and robust.

6.6 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases.

The applicant company suggests that blinatumomab (Blincyto®▼) in the given population meets the AWMSG criteria for an ultra-orphan medicine. AWMSG defines an ultra-orphan medicine as a medicine that has been granted EMA designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[24].

Blinatumomab (Blincyto®▼) has been granted orphan status by the EMA[4]. In the UK, blinatumomab (Blincyto®▼) is only licensed for the treatment of adults with Ph (-) relapsed or refractory ALL[2]. In 2013 there were 43 cases of ALL in Wales[25]. The EMA report, in Europe, approximately 40 % of cases are in adults, 85 % from B-precursor lineage, 85 % are Ph (-) and 50 % will relapse or be refractory after initial treatment[4,19]. In Wales, this would result in approximately six patients eligible for treatment with blinatumomab.

AWTTC consider blinatumomab (Blincyto®▼) to be eligible to be appraised as an ultra-orphan medicine. Should NMG/AWMSG consider the orphan and ultra-orphan medicines and medicines specifically developed for rare diseases policy to apply to blinatumomab, the same criteria for clinical effectiveness and cost effectiveness of ultra-orphan medicines as those applied to other medicines will be considered, but recognising that the evidence base will necessarily be weaker. NMG/AWMSG would also recognise that the incremental cost effectiveness ratios of many ultra-orphan medicines will exceed the threshold cost-effectiveness range. NMG/AWMSG will consider evidence on the following to inform their decisions (see Table 7).

Table 7. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG.

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	Survival prognosis for patients who relapse or do not respond after initial treatment is poor with standard care (salvage chemotherapy), potentially less than 1-2 years.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	Standard care can be considered to be salvage multi-chemotherapy (as relapsed/refractory patients are generally not fit enough to receive HSCT), hence there is an unmet need for an effective therapy that improves remission and can bridge to HSCT in some patients.
Whether the medicine can reverse, rather than stabilise the condition.	No evidence that blinatumomab can reverse the condition. It does seem to offer additional months of OS (estimated mean overall survival of 14.74 months compared to 8.26 for the comparator). There is also estimated 12.6% survival rate at 60 months for blinatumomab, at which point patients are assumed free of ALL. This compares to 5.4% estimated survival in the FLAG-IDA regimen.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	There is evidence that blinatumomab by improving the complete response rate can bridge to potentially curative HSCT – with a substantial proportion (17%) of patients treated with blinatumomab receiving potentially curative allogeneic HSCT[4].
The innovative nature of the medicine.	The company has presented evidence that blinatumumab has a novel mechanism of action. However, other specific evidence demonstrating innovation has not been presented.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	Evidence has been presented showing adults patients diagnosed with Ph (-) B-precursor ALL (median age of 34 to 39 years) are younger than adults with Ph (+) B-precursor ALL (median range 44 to 53 years)[26-28]. Hence, there are likely to be additional productivity losses relative to Ph (+) B-precursor ALL patients, and relative to many other cancers. However, no specific evidence has been provided that shows added value to patient that may not be adequately be captured in the QALY
Added value to the patient's family (e.g. impact on a carer or family life).	Specific evidence not provided. The submission states ", other losses to the economy and family well-being should be taken into consideration" but it is not clear how this has been done.
OS: overall survival; QALY: quality-adjusted life-year	

GLOSSARY

CR
Complete remission defined as:

- ≤ 5% blasts in bone marrow
- No evidence of disease
- Full recovery of peripheral blood counts (ANC >1,000 cells/µL *and* platelets >100,000/µL)
- Absence of extramedullary disease, including CNS disease

CRh
Complete remission with partial haematologic recovery defined as:

- ≤ 5% blasts in bone marrow
- No evidence of disease
- Partial recovery of peripheral blood counts (ANC >500 cells/µL *and* platelets >50,000/µL)

CRi
Complete response incomplete defined as:

- ≤5 % blasts in bone marrow
- No evidence of disease
- No evidence of extramedullary disease, including CNS disease
- ANC >1,000 cells/µL *or* platelets >100,000/µL

CRsg
Complete response by study group defined as:
the percentage of patients who achieved ≤ 5% blasts in the bone marrow with full (CR) or partial/incomplete (CRh, CRi) haematologic recovery.

Table 8. Eastern Cooperative Oncology Group (ECOG) performance status[10].

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

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