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SMC2548

brexucabtagene autoleucel 0.4 – 2 × 10^8 cells dispersion for infusion (Tecartus®)

Gilead Sciences Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

brexucabtagene autoleucel (Tecartus®) is accepted for use within NHSScotland.

Indication under review: Treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

In a single-arm, open-label, phase I/II study in patients with relapsed or refractory (R/R) ALL who received brexucabtagene autoleucel, overall complete remission rate was 71%.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Brexucabtagene autoleucel is an advanced therapy medicinal product (ATMP) that comprises of autologous T-cells genetically modified with an anti-CD19 chimeric antigen receptor (CAR). After the anti-CD19 CAR T-cells bind to CD19 on cancer cells and normal B cells, the CD28 and CD3-zeta domains activate signalling cascades that lead to T-cell activation and proliferation. This results in death of CD19-expressing cells.[1]

To manufacture brexucabtagene autoleucel, a patient's own T-cells are genetically engineered to express an anti-CD19 CAR before being returned to the patient, as a single dose for intravenous infusion for autologous use only. The target dose is 1×10^6 CAR-positive viable T cells per kg of body weight, or maximum of 1×10^8 CAR-positive viable T cells for patients 100kg and above. Brexucabtagene autoleucel should be infused 2 to 14 days after completion of the lymphodepleting chemotherapy for acute lymphoblastic leukaemia (ALL) patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.[1]

Brexucabtagene autoleucel is the first CAR T-cell therapy licensed in ALL patients ≥26 years of age.

1.2. Disease background

Acute lymphoblastic leukaemia (ALL) is a diverse group of serious and aggressive lymphoid disorders characterised by the clonal proliferation of immature precursor B- or T-cell lymphocytes in blood, bone marrow and various organs such as, lymph nodes, spleen, central nervous system (CNS) and liver. It is more prevalent in young individuals; approximately 37% of cases are diagnosed in adults aged 25 years and older. Among adult patients, B-cell ALL is the most common subtype. Approximately 25% of adult ALL patients present with Philadelphia chromosome (Ph) positive (Ph+) disease, and have a particularly poor prognosis. Adults with R/R ALL have very low survival rates (with median overall survival likely less than a year).[2]

1.3. Treatment pathway and relevant comparators

For patients with R/R B-cell ALL, there are limited treatment options. Some patients may receive allogeneic-stem cell transplantation (allo-SCT), the only potentially curative option. However, eligibility for allo-SCT is limited due to age, fitness and donor availability. Novel therapies include blinatumomab (accepted for use by SMC for the treatment of adults with Ph negative (Ph-)- R/R B-precursor ALL [1145/16]) and inotuzumab-ozogamicin (accepted for use by SMC as monotherapy for the treatment of adults with R/R CD22-positive B cell precursor ALL; adults with Ph+ disease should have failed treatment with at least one tyrosine kinase inhibitor; and restricted in patients for whom the intent is to proceed to SCT [1328/18]). Ponatinib was also accepted for use by SMC for adults with Ph+ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. Clinical trials are to be considered for patients with R/R B-cell ALL.[2]

According to the submitting company, the relevant comparators are: inotuzumab ozogamicin, fludarabine - cytarabine - granulocyte-colony stimulating factor - idarubicin (FLAG-IDA), blinatumomab in Ph- patients only, and ponatinib in the Ph+ population.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Brexucabtagene autoleucel has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Brexucabtagene autoleucel meets SMC orphan and end-of-life criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of brexucabtagene autoleucel comes from ZUMA-3. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study[2-7]

Criteria	ZUMA-3
Study design	Phase I/II multicentre, open-label, single-arm study

Eligible patients	• Age 18 or older
	• R/R B-precursor ALL defined as one of the following:
	  ○ Primary refractory disease
	  ○ First relapse if first remission ≤12 months
	  ○ R/R disease after two or more lines of systemic therapy
	  ○ R/R disease after allo-SCT ≥100 days before enrolment and off of immunosuppressive medications for ≥4 weeks prior to enrolment
	  ○ Patients with Ph+ disease are eligible if they are intolerant to TKI therapy, or if they have R/R disease despite treatment with at least two different TKIs
	• ECOG performance status of 0 or 1
	• ANC ≥500/microlitre and platelet count ≥50,000/microlitre unless principal investigator this is due to underlying leukaemia and is potentially reversible with leukaemia therapy
	• Absolute lymphocyte count ≥100/ microlitre
	• In patients previously treated with blinatumomab, CD19 tumour expression on blasts obtained from bone marrow or peripheral blood must be documented after completion of the most recent prior line of therapy. If CD19 expression is quantified, then blasts must be ≥90% CD19 positive.

Treatments	In phase II, patients underwent leukapheresis followed by conditioning chemotherapy (intravenous fludarabine 25mg/m^2 on days -4, -3, and -2; and intravenous cyclophosphamide 900mg/m^2 on day -2) and a single intravenous infusion on day 0 of 1 x 10^6 CAR T cells/kg (selected from various doses used in the study Phase I portion). Bridging chemotherapy was recommended for all subjects particularly for those with high disease burden at screening (M3 marrow [>25% leukemic blasts] or ≥1,000 blasts/mm^3 in the peripheral circulation). Following bridging chemotherapy, bone marrow blast levels were re-evaluated by day -4 pre-infusion. Allo-SCT, administered at investigator's discretion, was allowed as subsequent consolidative therapy following brexucabtagene autoleucel, but was not protocol defined. Patients were eligible to receive a second infusion of brexucabtagene autoleucel in limited circumstances.
Randomisation	Not applicable
Primary outcome(s)	In the phase II portion of the study: OCR rate (CR or CR with incomplete haematologic recovery [CRi]) per independent review.

Selected secondary outcomes	• MRD- defined by central assessment. MRD negative remission was defined as MRD $<10^{-4}$ threshold. • DOR: for patients who experience CR or CRi per independent review, defined as the time between their first complete response per independent review to relapse or any death in the absence of documented relapse. • Overall survival, defined as the time from brexucabtagene autoleucel infusion to the date of death from any cause. • RFS by central assessment: defined as the time from the brexucabtagene autoleucel infusion date to the date of disease relapse or death from any cause.
Statistical analysis	Efficacy analyses were to be performed in the modified intent-to-treat (mITT) population consisting of all patients enrolled in the Phase II portion of the study who receive brexucabtagene autoleucel. Key efficacy analyses were also to be presented in the following populations: • FAS consisting of all patients enrolled in the Phase II portion of the study. • combined Phase I and Phase II patients treated at a 1.0 x 10^6 anti-CD19 CAR T cells/kg dose level Hierarchical testing order: • OCR rate was to be tested first versus an OCR historical control rate of 40% or less with a one-sided 2.5% alpha level. • If the testing of the OCR rate reached statistical significance, a step-down test of the MRD- rate was to be performed against an MRD historical control rate of 30% (so that the family-wise type I error will be controlled at one-sided 2.5% level).
Abbreviations: ANC: absolute neutrophil count; DOR: Duration of remission; ECOG: Eastern cooperative oncology group; FAS: full analysis set; MRD-: Minimum residual disease negative remission rate; OCR: overall complete remission; RFS: relapse-free survival; R/R: relapsed or refractory; TKI: tyrosine kinase inhibitor	

There were 71 patients enrolled in the phase II study and underwent leukapheresis; 55 patients received brexucabtagene autoleucel (modified intent-to-treat [mITT] population) and the majority of the mITT patients had received bridging chemotherapy (93%). At the primary efficacy analysis, the overall complete remission (OCR) rate was 71%. OCR and minimum residual disease negative remission rate (MRD-) rates with brexucabtagene autoleucel were significantly greater than the historical control rates. Results are presented below for the primary and selected secondary outcomes. [2-4, 8, 9] Results from the most recent analysis (23 July 2022) seem consistent with results from previous data cut-offs.[10]

Table 2.2. Results for the primary and selected secondary outcomes from ZUMA-3 [2-4, 8, 9]

	Primary analysis[a] 09 September 2020	**Updated analysis 23 July 2021**	
Median follow-up time, months	**16.4**	**26.8**	**29.7**
Population	**Phase II treated patients mITT (n=55)**	**Phase II treated patients mITT (n=55)**	**Pooled phase I + phase II patients treated with licensed dose (N=78)**
Primary outcome			
OCR rate (CR + CRi) (95% CI)	71% (57% to 82%)	71% (57% to 82%)	73% (62% to 82%)
CR	56%	56%	60%
CRi	15%	15%	13%

Selected secondary outcomes			
MRD- rate (95% CI)	76% (63% to 87%)	NR	79%
Median DOR (for patients achieving an OCR), months (95% CI)	12.8 (8.7 to NE)	14.6 (9.4 to NE)	18.6 (9.6 to NE)
Number of deaths	20	*	*
Median overall survival, months (95% CI)	18.2 (15.9 to NE)	25.4 (16.2 to NE)	25.4 (16.2 to NE)
KM estimate at 18 months	59%	-	-
KM estimate at 24 months	-	56%	52%
Number of RFS events	29	*	NR
Median RFS per central assessment, months (95% CI)	11.6 (2.7 to 15.5)	11.6 (2.7 to 20.5)	11.7 (6.1 to 20.5)
KM estimate at 12 months	44%	-	-
KM estimate at 18 months	-	35%	38%

Abbreviations: CI = confidence interval; CR = complete remission. CRi = complete remission with incomplete haematological recovery; KM: Kaplan Meier; MRD-: minimum residual disease negative remission rate; NE: not estimable; NR: not reported; OCR = overall complete remission; RFS; Relapse-free survival.
* Results considered confidential by the company
Notes: a) done when all brexucabtagene autoleucel–treated patients had completed at least the 6-month disease assessment

Results in the subgroup of patients relevant to the licensed indication (n=43), adult patients aged 26 years and above, were consistent with the primary outcome population results.[2]

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the EuroQol 5 Dimension 5 Level (EQ-5D-5L) version. Among patients treated in the phase II part of the study, the majority of patients appear to have experienced improved or stable HRQoL as assessed by the EQ-5D scores.[11]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing brexucabtagene autoleucel with any relevant comparators, the submitting company presented indirect treatment comparisons against inotuzumab, ponatinib, FLAG-IDA (using pooled chemotherapy as a proxy), and blinatumomab. As noted in Table 2.2, some of the comparisons are used in the economic base case and others in sensitivity analyses.

Table 2.2: Summary of indirect treatment comparison

Criteria	Overview
Design	• Naïve comparisons (against blinatumomab, inotuzumab[a], FLAG-IDA [a], and ponatinib[a]) • MAICs (against blinatumomab, inotuzumab, and FLAG-IDA) • Propensity score-matched comparison via retrospective cohort (against blinatumomab[a])
Population	R/R B-cell precursor ALL in adults (defined as for ZUMA-3 in Table 2.1)

Comparators	Inotuzumab, ponatinib, FLAG-IDA (using pooled chemotherapy as a proxy) and blinatumomab
Studies included	Four studies were included: ZUMA-3 using IPD (for brexucabtagene autoleucel), INO-VATE (for inotuzumab), TOWER (for blinatumomab) and PACE (for ponatinib). A synthetic control arm created from IPD from historical clinical trials SCHOLAR-3, was used in the propensity score-matched comparison against blinatumomab.
Outcomes	Overall survival and EFS; only overall survival was compared for ponatinib.
Results	The HRs from the naïve comparison used in the base case for inotuzumab, FLAG-IDA and ponatinib suggest that brexucabtagene autoleucel may: • improve EFS and overall survival compared with inotuzumab and pooled chemotherapy (proxy for FLAG-IDA); and • improve overall survival compared with ponatinib. The HRs from the propensity score-matched comparison via retrospective cohort used in the base case for blinatumomab suggests that brexucabtagene autoleucel may: • improve EFS and overall survival compared with blinatumomab. Although they did not include 1, the HRs' confidence intervals were very wide.
Abbreviations: MAIC: Matching-adjusted indirect comparison; EFS: event-free survival; IPD: individual participant data; R/R: relapsed or refractory; FLAG-IDA: fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin; ALL: acute lymphoblastic leukaemia **Note:** [a]used in economic base case	

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

The important identified risks for brexucabtagene autoleucel in this indication are cytokine release syndrome, neurotoxicity, cytopenias, infections, and hypogammaglobulinemia. Regulators noted these were largely reversible and manageable with supportive care and medical interventions. No new safety signals were identified. The safety profile was similar to that observed with other CAR-T cell therapies and for brexucabtagene autoleucel in the mantle cell lymphoma (MCL) indication. [2]

In ZUMA-3 study at the primary analysis data cut-off (09 September 2020), in phase II treated patients, any treatment-emergent adverse event (AE) was reported by 100% (55/55) of patients treated with brexucabtagene autoleucel and these were considered treatment related in 93% of patients. A grade 3 or higher AE was reported in 95% of patients (in 89% of patients grade 3 or higher AEs were considered treatment related), 18% had a fatal grade 5 AE (in two patients [3.6%] grade 5 AEs were considered treatment related [brain herniation [day 8] and septic shock [day 18]]), 75% of patients had a serious AE and in 62% of patients these serious AEs were considered treatment related. [2, 3] At the 23 July 2021 data cut-off, it was reported that the proportion of patients with grade 3 or higher AEs was unchanged. [4]

At the primary analysis, in phase II treated patients (n=55), the most frequently reported treatment-related AEs of any grade were pyrexia (84%), hypotension (62%), and sinus tachycardia (35%). The most common treatment-related AEs with worst severity Grade 3 or higher were pyrexia (36%), hypotension (29%), and hypoxia (20%). [2]

At the primary analysis, cytokine release syndrome was reported by 89% of patients, but the severity grade was ≥3 in 24% of patients. The most common symptoms of cytokine release syndrome were pyrexia (94%), hypotension (67%), sinus tachycardia (37%), chills (29%), and

hypoxia (29%). Neurologic AEs occurred in 60% of patients and were at least grade 3 severity in 25% of patients. These included tremor (27%), confusional state (25%) and encephalopathy (22%). Infections of at least grade 3 severity developed in 25% of patients, with 32%. Grade 3 or higher cytopenia occurred in 76% of patients and were present on or after day 30 post brexucabtagene autoleucel infusion in 36% of patients Hypogammaglobulinaemia was reported by 7% of patients (none were grade 3 or higher). [2, 3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- At the primary efficacy analysis of the key study, ZUMA-3, the OCR was 71% (with 56% of patients achieving complete remission). [2, 3 4]
- The high complete remission rate achieved with brexucabtagene autoleucel and the duration of response was considered clinically relevant by the regulators. [2]
- Despite significant uncertainties, the observed benefits were regarded by regulators as sufficiently robust to support a favourable benefit-risk in the context of a conditional marketing authorisation. [2]
- The introduction of this medicine would provide the first CAR-T cell therapy for patients with R/R ALL aged 26 years or over and a promising alternative to current treatment options.

4.2. Key uncertainties

- There are no controlled data or direct comparative data available against any comparators. The indirect comparisons have a number of limitations. There was substantial methodological heterogeneity between the studies and clinical heterogeneity in the study populations. Only two selected survival outcomes were compared; event-free survival (EFS) was compared using different outcomes across the studies through a conversion that added uncertainty. There does not appear to be robust evidence to prefer the naïve comparisons over the MAICs. MAIC results are likely unstable, but they benefit from adjustment of key prognostic factors. There is a very high risk of bias in naïve comparisons. The magnitude and direction of bias in both naïve and MAIC analyses are unclear. It appears that the wider confidence intervals obtained with MAIC analyses match the overall uncertainty better. However, these confidence intervals might still not fully capture the uncertainty. For blinatumomab, while the propensity score-matched comparison might be preferable, it is limited by uncertain residual confounding, making the analysis also at high risk of bias. Due to these limitations, conclusions and results drawn from these comparisons are highly uncertain.
- In ZUMA-3, the open-label design, small sample size and heterogeneous population create uncertainty in the size of the treatment effect, the generalisability of the findings and conclusions about QoL.
- Longer follow-up is necessary to assess duration of response and fully capture effects on overall survival. However, updated results (from the 23 July 2022 data cut-off) appear consistent with previous results.[10]

- Regulators noted that brexucabtagene autoleucel, could potentially be a viable option for bridging therapy before allo-SCT, but the follow up from ZUMA-3 is currently too short to determine the exact role of brexucabtagene autoleucel in the overall treatment paradigm. [2] Based on SMC clinical experts' responses, brexucabtagene autoleucel may displace use of allo-SCT in some patients; however this was not included as a comparator by the submitting company.
- Some patients received allo-SCT post infusion with brexucabtagene autoleucel, which could have impacted the results. The impact of subsequent therapies on results is difficult to assess and the long-term efficacy of brexucabtagene autoleucel is challenging to interpret due to the confounding influence of allo-SCT.
- The primary analysis of ZUMA-3 was designed to compare the primary outcome, OCR, and secondary outcome, MRD, with historical control rates. There is uncertainty around these historical control rates and these comparisons.
- Evidence for the licensed population comes from post-hoc subgroup analyses which could have introduced bias and adds uncertainty. Although efficacy seemed generally consistent across the different subgroups, patients with a high disease burden had the lowest response rates. Patients who had previously received blinatumomab or inotuzumab showed numerically lower response rates compared with treatment-naïve patients. [2] However, given the small sample sizes, subgroup analysis results must be interpreted with caution.
- It is unknown whether patients who have previously received CAR T-cell therapy can derive benefits from brexucabtagene autoleucel. In ZUMA-3, re-treatment with brexucabtagene autoleucel was rare (two patients received a second infusion), and the patients who were re-treated did not exhibit a response to the second infusion. [4] The submitting company noted that brexucabtagene autoleucel is intended as a one-time therapy, and no re-treatment is expected in clinical practice.

4.3. EMA conditional marketing authorisation specific obligations

As part of the conditional marketing authorisation, there are specific obligations on the company to confirm efficacy and safety in ALL patients that include longer follow up from the clinical study and data from an observational study based on a registry. [2]

4.4. Clinical expert input

Clinical experts consulted by SMC considered that brexucabtagene autoleucel fills an unmet need in this therapeutic area, as there are limited treatment options. They advised that in the treatment of R/R ALL brexucabtagene autoleucel is a therapeutic advancement, due to its efficacy.

4.5. Service implications

Brexucabtagene autoleucel is likely to be associated with service implications and may have a significant impact on patients as it is administered in specialised treatment centres and is associated with a prolonged period of monitoring. Patients should be monitored daily for the first 10 days post-infusion for signs and symptoms of potential cytokine release syndrome, neurologic events and other toxicities. Physicians should consider hospitalisation for this period or at the first signs of cytokine release syndrome and/or neurologic events. Subsequently the patient should be

monitored at the physician's discretion, but should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion. Patients may need to travel long distances to receive treatment. Due to the rarity of the condition, the number of patients that will be treated in practice will be low.

The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **brexucabtagene autoleucel**, as an **orphan and end-of-life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Relapsed or refractory ALL is an aggressive and devastating condition with severe symptoms and very poor prognosis. Many patients will die within a year.
- With existing treatments, median overall survival remains very poor and the only meaningful prospect of cure is with allogeneic stem cell transplant. Some patients are either ineligible for transplant or have relapsed after transplant, or have already been treated with the current treatment options. There is a significant unmet need for effective treatment options that can control the patient's condition and prolong survival.
- Brexucabtagene autoleucel is an exciting breakthrough therapy that represents a paradigm shift in patient care. This one-time therapy has shown impressive efficacy and it will offer patients hope and prospect of long-term leukaemia control and long-term survival with manageable toxicities.
- Responding patients are expected to quickly recover a good quality of life and experience significant physical and psychological benefits. Patients and their families may be able to return to education, work, and overall a more normal life with fewer hospital visits and reduced care and financial burdens.

Additional Patient and Carer Involvement

We received a joint patient group submission from Leukaemia Care and Anthony Nolan, both organisations are registered charities. Leukaemia Care has received 27% pharmaceutical company funding in the past two years, including from the submitting company. Anthony Nolan has received 6% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (defined as 57 years based on a mean-average starting age of 43 years) with a one-week cycle length.
Population	Adult patients ≥ 26 years of age with R/R B-precursor ALL.
Comparators	For the overall ALL population, the company compared brexucabtagene autoleucel against inotuzumab and FLAG-IDA. Results were also provided for two sub-populations, where different comparators were used. For the Ph negative sub-population blinatumomab was included as an additional comparator, while in the Ph positive sub-population ponatinib was included.
Model description	The model structure used a decision-tree followed by a standard three-state partitioned survival model. The decision-tree component only applied to patients receiving brexucabtagene autoleucel, and captured the pre-treatment costs for patients who do not ultimately receive the infusion. The three states included in the partitioned survival model element were event-free survival (EFS), progressed disease (PD) and death. Patients in the PD health state could receive subsequent therapies, however, patients were assumed not to be re-treated with their initial therapy. Alternatively, patients in the comparator arms could receive allo-SCT in the PD state. Based on clinical feedback received by the company, patients in the brexucabtagene autoleucel arm were assumed not to receive allo-SCT, and no patients would receive a second allo-SCT.
Clinical data	The primary source of clinical data used to inform the clinical efficacy of brexucabtagene autoleucel was the July 2021 mITT data cut of the combined Phase 1 and Phase 2 ZUMA-3 clinical study.[4] These data were used to inform EFS, overall survival, and AEs associated with brexucabtagene autoleucel. ZUMA-3 was a single arm study, and so data for the comparator arms were derived from external sources and used in indirect treatment comparisons. Kaplan Meier curves for inotuzumab, FLAG-IDA and ponatinib were extracted from separate clinical studies and digitised to generate pseudo individual patient data.[12,13,14] The comparison between these medicines and brexucabtagene autoleucel were undertaken through naïve methods in the base case. For the comparison between brexucabtagene autoleucel and blinatumomab a synthetic control arm was created by matching characteristics between the ZUMA-3 study and patient level data from a database of historic clinical studies.[4]
Extrapolation	To extrapolate beyond the observation periods within the studies, independent survival curves were fitted to EFS and overall survival data. The functions used across all the arms are summarized below: **Brexucabtagene autoleucel:** EFS = lognormal, Overall survival = lognormal **Inotuzumab:** EFS = 1-knot spline, Overall survival = 2-knot normal spline **FLAG-IDA:** EFS = generalised gamma, Overall survival = generalised gamma **Blinatumomab:** EFS = 1-knot spline, Overall survival = lognormal **Ponatinib:** EFS = lognormal, Overall survival = Gompertz The company assumed that patients who are alive at 3-years were cured. These cured patients experienced mortality at a slightly higher rate than the general population to account for the impact of toxicity associated with prior treatments. To achieve this the company adjusted Scottish general population mortality data with a standardised mortality ratio (SMR) of 1.09, as reported by Maurer et al.[15]
Quality of life	Health benefits were measured using the EQ-5D-5L questionnaire data collected during Phase 2 of the ZUMA-3 study.[11] These data were 'cross-walked' to EQ-5D-3L data using a published algorithm by van Hout et al[16] before applying UK value set to generate health state utility values. Disutilities associated with AEs were extracted from a variety of published literature sources. Cured patients were assumed to experience a health related quality of life equivalent to their age- and sex-matched equivalents in the general population, based on values from Ara & Brazier.[17]

Costs and resource use	For patients receiving brexucabtagene autoleucel medicine costs included pre-treatment acquisition and administration costs. Subsequently, acquisition, administration and adverse event costs for all treatments and interventions were captured. Other NHS costs included disease monitoring and follow up, and terminal care costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price results can be presented. The results presented do not take account of the PAS discounts for inotunomab, ponatanib and blinatumomab, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS prices for inotunomab, ponatanib and blinatumomab due to commercial confidentiality and competition law issues.

6.2. Results

Base case results for the overall population and sub-populations defined by Ph expression are provided at list price in Table 6.2. Those results were generated using publically available list prices for all medicines.

Disaggregated analysis indicates that brexucabtagene autoleucel is associated with higher incremental quality-adjusted life-years (QALY) and incremental costs versus comparators. Incremental QALY gains were estimated to accrue in both the EFS and PD health states, while higher incremental costs were primarily due to medicine acquisition and administration costs.

Table 6.2: Base case economic results (List prices)

	ICER (£/QALY) – Brexucabtagene autoleucel vs comparator		
Comparator	**Overall population**	***Ph- sub-population***	***Ph+ sub-population***
Inotuzumab	£43,424	£49,568	£42,950
FLAG-IDA	£53,006	£58,072	£52,747
Blinatumomab	N/A	£52,599	N/A
Ponatinib	N/A	N/A	£50,803

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; FLAG-IDA = Fludarabine-Cytarabine-Filgrastim-Idarubicin; Ph = Philadelphia chromosome

6.3. Sensitivity analyses

A number of sensitivity analyses were generated to explore areas of uncertainty. For simplicity, only key scenarios for the overall population at list price are summarised in Table 6.3. These were generated using publically available list prices for all medicines.

Table 6.3: Key scenario analyses – Overall population only (List prices)

#	**Description** **Base-case scenario**	**Alternate scenario**	**Inotuzumab**	**FLAG-IDA**
1	Time-point for cure = 3yrs	Time-point for cure = 5yrs	£54,034	£61,838
2		Time-point for cure = 7.5yrs	£64,368	£71,377
3		Time-point for cure = 10yrs	£71,932	£78,657
4		No cure	£75,183	£82,461
5	SMR applied to cured patients: 1.09	SMR applied to cured patients = 3.00	£51,408	£63,227
6		SMR applied to cured patients = 4.00	£54,658	£67,435
7		v SMR applied to cured patients = 5.00	£57,578	£71,239

8	Naïve ITC for comparison with inotuzumab	MAIC for comparison with inotuzumab	£47,941	N/A
9	Utility for 'cure' patients = General population	Utility for 'cure' patients = post allo-SCT patients[18]	£48,346	£59,306
10	Brexucabtagene autoleucel patients ineligible for allo-SCT	Brexucabtagene autoleucel patients receive allo-SCT at rate observed in ZUMA-3	£49,085	£57,087
11	**Combined scenario:** Time-point for cure = 5yrs, SMR applied to cured patients = 4.00 and Utility for 'cure' patients = post allo-SCT		£71,300	£83,599
12	**Combined Scenario:** Time-point for cure = 5yrs, SMR applied to cured patients = 4.00, MAIC for comparison with inotuzumab and Utility for 'cure' patients = post allo-SCT		£80,673	N/A

Abbreviations: ICER = incremental cost-effectiveness ratio; SCT = stem cell transplant; mITT = modified intention-to-treat; SMR = standardised mortality ratio; ITC = indirect treatment comparison; N/A = not applicable

*Other data were also assessed but remain confidential.**

6.4. Key strengths

- The economic analysis matched the clinical indication under review.
- Various types of sensitivity analysis were reported by the submitting company, facilitating insight into the relative contributions to uncertainty in specific model parameters, the combined effect of multiple parameters, and key structural assumptions used in the analysis on economic results.
- Systematic literature reviews of previously published economic evaluations in similar indications were conducted by the company which facilitated a comparison of both the model types/structures and HRQoL data utilised these economic evaluations versus the company's submission.

6.5. Key uncertainties

- The most relevant comparators within NHSScotland were uncertain. While the comparators included in the analysis were generally considered relevant, SMC clinical experts indicated that brexucabtagene autoleucel might also displace allo-SCT in a proportion of patients. However, allo-SCT was not included as a comparator by the submitting company.
- Direct clinical evidence comparing brexucabtagene autoleucel to the range of other comparators in this population was not available, requiring the use of indirect treatment comparisons. These comparisons were seen as a significant source of uncertainty in the economic evaluation due to methodological and patient heterogeneity between the studies. As an alternative to the naive methods used in the base case, the company explored the use of MAICs to inform the comparisons with inotuzumab and blinatumomab. SMC statistical advice indicated that the MAICs may have been more appropriate, and their use led to a small reduction in the cost-effectiveness of brexucabtagene autoleucel versus this comparator (scenario 8) although also a small improvement in the cost-effectiveness relative to blimatumomab.
- The model assumed all patients alive at 3 years post treatment initiation were cured and

experience long-term survival, even those in the progressed disease state. This assumption may have biased results in favour of brexucabtagene autoleucel. Furthermore, the choice of the cure point at 3 years was a source of uncertainty, with some clinical feedback received by SMC suggesting a later time point may have been appropriate. Scenarios assuming a cure point later than 3 years led to an increased in the incremental cost-effectiveness ratio (see Scenario 1 to 3 in Table 6.3).

- Small sample size of the ZUMA-3 study conferred uncertainty in EFS and overall survival estimates used in the economic evaluation.

7. Conclusion

The Committee considered the benefits of brexucabtagene autoleucel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios. As brexucabtagene autoleucel is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted brexucabtagene autoleucel for use in NHSScotland.

8. Guidelines and Protocols

Relevant guidelines include:

- Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, in 2016.[19]
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Acute Lymphoblastic Leukemia. Version 1.2022, in 2022.[20]

9. Additional Information

9.1. Product availability date

30 November 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
brexucabtagene autoleucel	**Single 1 x 10^6 CAR-T cells intravenous infusion**	**£316,118**

Costs from dmd+d online on 02 June 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 17 patients eligible for treatment with brexucabtagene autoleucel each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 July 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in

determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.