NCPE Assessment

Technical Summary

Brexucabtagene autoleucel (Tecartus®)

23045

23 January 2025

Applicant: Gilead Sciences Ireland UC

For the treatment of adult patients, 26 years of age and above, with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of brexucabtagene autoleucel (Tecartus®) for the treatment of adult patients, 26 years of age and above, with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia.

Following assessment of the Applicant's submission, the NCPE recommends that brexucabtagene autoleucel (Tecartus®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Gilead Sciences Ireland UC) Health Technology Assessment of brexucabtagene autoleucel (Tecartus®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In January 2024, Gilead Sciences Ireland UC submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of brexucabtagene autoleucel (Tecartus®) for the treatment of adult patients, 26 years of age and above, with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). Gilead Sciences Ireland UC is seeking reimbursement of brexucabtagene autoleucel on the Oncology Drug Management System (ODMS).

Brexucabtagene autoleucel (herein 'brexu-cel') is a CD19-targeted CAR T-cell therapy. It is administered as a once-off, single-dose intravenous infusion in a qualified treatment centre. Prior to infusion, a patient will undergo a number of steps. These can include apheresis, bridging therapy, and lymphodepleting therapy. Post-infusion monitoring should occur daily for the first seven days after infusion. Patients should remain within proximity of a qualified treatment centre for up to four weeks post-infusion.

Clinical Opinion, to the Review Group, generally indicates that brexu-cel will be mainly used in patients with relapsed or refractory B-cell precursor ALL, who have relapsed following stem cell transplant (SCT), and those who are ineligible for SCT (some patients 'borderline' eligible for SCT may also be treated). The Review Group note that this expected place in therapy is narrower than the licensed indication, which does not specify requirements regarding SCT status. However, SCT is a well-established treatment for ALL, with evidence to support long-term survival in some patients. This Clinical Opinion indicated that brexu-cel is unlikely to displace SCT; SCT would be the preferred treatment in eligible patients. Clinical Opinion, obtained by the Applicant, indicated that blinatumomab is the comparator of most relevance to the assessment. Inotuzumab is expected to also be displaced but to a lesser extent. This was confirmed by Clinical Opinion obtained by the Review Group. Of note, blinatumomab is reimbursed for patients with Philadelphia chromosome-negative (Ph-) disease only. Inotuzumab is reimbursed for patients with Ph- and Philadelphia chromosome-positive (Ph+) disease. The Applicant also presented comparisons versus ponatinib and chemotherapy; however, as these are not considered key comparators of relevance, no further description is provided in this Report.

1. Comparative effectiveness of brexucabtagene autoleucel

ZUMA-3 Study

The efficacy and safety of brexu-cel was evaluated in the ZUMA-3 study. This is a phase I/II, single-arm, multi-centre study. Participants were required to have relapsed or refractory B-cell precursor ALL, defined as (i) primary refractory disease, (ii) first relapse if first remission ≤12 months, (iii) relapsed or refractory disease after two or more lines of systemic therapy, (iv) relapsed or refractory disease after allogeneic SCT. Patients with Ph+ disease were eligible if they were intolerant to tyrosine kinase inhibitor therapy, or if they had relapsed/refractory disease despite treatment with at least two different tyrosine kinase inhibitors. The trial population included participants aged 18 years and older; however, the EMA licensed indication of brexu-cel is restricted to patients aged 26 years and older. Data were presented for the full enrolled population (i.e., participants aged 18 years and older), and the regulatory-aligned population (i.e., participants aged 26 years and older). For the regulatory-aligned population, the intention-to-treat cohort (ITT) comprised enrolled participants aged 26 years and older (n=81), while the modified ITT (mITT) cohort comprised those aged 26 years and older who received infusion with brexu-cel (n=63). Brexu-cel was administered as a single intravenous infusion at a target dose of $1x10^6$ anti-CD19 CAR T-cells per kilogram of body weight. Bridging therapy and lymphodepleting therapy were permitted prior to brexu-cel infusion.

Results were presented for the 45-month analysis (23 July 2023 data cut). The primary endpoint of phase II was the overall complete remission rate (OCR), defined as the proportion of participants with best response of complete remission or complete remission with incomplete haematologic recovery as per independent review. Relapse-free survival (RFS) and overall survival (OS) were secondary endpoints. Results for the regulatory-aligned population are presented in Table 1.

Table 1 ZUMA-3 clinical outcomes

Date of interim analysis: 23 July 2023
Expected date of final analysis: September 2035

Outcome	Phase I + II ITT ≥26 years[a] (n=81)	Phase I + II mITT ≥26 years[a] (n=63)
Overall complete remission rate[b], n (%)	47 (58)	47 (75)
Median overall survival[c], months (95% CI)	23.5 (13, 61)	NP
48-month overall survival, % (95% CI)	NP	42 (29, 55)
Median relapse-free survival[d], months (95% CI)	7 (3, 13)	12 (3, 15)

ITT: Intention-to-treat population (all those enrolled in ZUMA-3); **mITT:** Modified intention-to-treat population (all those infused with brexu-cel); **NP:** Not provided (data not provided by Applicant).
[a]Participants aged ≥26 years are the regulatory-aligned population.
[b]Defined as complete remission and complete remission with incomplete haematologic recovery as per independent review.
[c]Defined as time from infusion to the date of death from any cause. Participants who had not died by the analysis data cut-off date were censored at their last contact date.
[d]Defined as time from infusion to date of disease relapse or death from any cause.

In single-arm trials, such as ZUMA-3, effects cannot be isolated from time-to-event endpoints (RFS and OS). Interpretation of OCR from the trial is limited by the small sample size and heterogeneous population. Due to the lack of evidence to support the use of OCR as a surrogate for RFS and OS, it cannot be concluded that the treatment effect observed with OCR will translate to an RFS or OS benefit.

Indirect Treatment Comparison

Unanchored indirect treatment comparisons (ITCs) were conducted to generate estimates of relative effectiveness versus the comparators.

In the Applicant base case, the SCHOLAR-3 SCA-3 data set was used to inform efficacy of blinatumomab; ITC results indicated that brexu-cel may be associated with improved RFS and OS versus blinatumomab. The TOWER study was explored as scenario analysis in the comparison versus blinatumomab; ITC results indicated that brexu-cel may be associated with improved RFS/event-free survival (EFS) and OS versus blinatumomab. The INO-VATE study was used to inform efficacy of inotuzumab; ITC results indicated that brexu-cel may be associated with improved RFS/progression-free survival (PFS) and OS versus inotuzumab. However, for all ITCs, the Review Group had major concerns including those regarding heterogeneity of trial populations, differences in the definition of outcomes across studies, inconsistencies in data cuts used, the approach used to select prognostic factors for adjustment, the small effective sample sizes, and the lack of adjustment for some relevant

prognostic factors. All relative treatment effects are highly uncertain due to observed and non-observed differences between the studies, which could not be adjusted for. An unknown degree of bias exists in the relative effectiveness estimates. Thus, the Review Group consider that the relative effectiveness of brexu-cel versus blinatumomab and versus inotuzumab has not been demonstrated.

The positioning of brexu-cel as an option for patients who are ineligible for SCT is not aligned with the comparative clinical evidence available for blinatumomab and inotuzumab. Notably, Clinical Opinion to the Review Group has indicated that this is one of the cohorts, in Irish clinical practice, who would be considered for treatment with brexu-cel. In ZUMA-3, no restriction was implemented regarding SCT eligibility. A cohort of patients in the ZUMA-3 trial were therefore likely to be eligible for SCT. A cohort of patients in the SCHOLAR-3 SCA-3, TOWER and INO-VATE studies received SCT following treatment with blinatumomab and inotuzumab, respectively. Thus, the relative effectiveness of brexu-cel, versus the comparators of relevance, for patients who are ineligible for SCT, has not been investigated.

2. Safety of brexucabtagene autoleucel

The safety profile of brexu-cel was generally consistent with that observed for other CAR T-cell therapies. No new safety signals were identified. The important identified risks associated with CAR T-cell therapies are recognised to be cytokine release syndrome, neurotoxicity, cytopenias, infections, and hypogammaglobulinaemia. In ZUMA-3, these were largely reversible and manageable with supportive care and medical interventions. The toxicity management plan specified for brexu-cel is in line with the general management plans for CAR T-cell therapy.

3. Cost effectiveness of brexucabtagene autoleucel

Methods

A de novo partitioned survival model was used to evaluate the cost effectiveness of brexu-cel. The partitioned-survival model included three mutually exclusive health states; Event-Free Survival, Progressed Disease, and Death. Of note, in the submission, the Applicant used the term EFS to also describe RFS and PFS. In the Applicant base case, parametric survival analyses were used to extrapolate the RFS/EFS/PFS and OS data. This

was conducted by fitting parametric survival distributions to the individual patient-level data (IPD) of ZUMA-3 and SCHOLAR-3 SCA-3, and pseudo-IPD of INO-VATE until Year 3. The SCHOLAR-3 SCA-3 data, used in the model, were partially adjusted using propensity score matching, to better reflect the ZUMA-3 data. Notably, relative effectiveness of brexu-cel versus inotuzumab was based on naïve, unadjusted comparison. For all treatment arms, patients alive from the 3-year timepoint were assumed to be 'cured'. These patients were subject to general population mortality with an increased risk of death (excess mortality). In the brexu-cel arm, for those patients who did not proceed to infusion, it was assumed that those who failed to receive infusion due to adverse events were treated with FLAG-IDA (as informed by the pooled TOWER and INO-VATE chemotherapy arms). Those patients who failed to receive brexu-cel infusion due to other reasons (e.g., manufacturing failure) followed relevant comparators' RFS/EFS/PFS and OS curves based on the subgroup under evaluation. In the absence of long-term and direct comparative evidence, the magnitude and durability of treatment effect of brexu-cel is highly uncertain. The modelled favourable treatment benefit of brexu-cel, sustained over the long-term period, is not supported by the available data. Overall, the Review Group considered the survival estimates in both the Applicant and NCPE-adjusted base case to be highly uncertain, due to the lack of robust data. Results should therefore be interpreted with caution.

Utility data for the Event-Free Survival and Progressed Disease health states were derived from EQ-5D-5L data (mapped to EQ-5D-3L using the algorithm by Van Hout et al.) collected during the ZUMA-3 study. The Applicant assumed that patients alive at the 3-year time point (i.e., 'cured') had utility equivalent to that of the general population. The Review Group considered the values derived from the ZUMA-3 trial to be subject to major limitations, mostly due to the small sample size and methodological weaknesses. Overall, the Review Group considered the utility values used in the model to be implausibly high and lack face validity.

The model included drug acquisition, administration, monitoring, subsequent treatment and adverse event costs. Pre-treatment costs (bridging and conditioning therapy) were also included for brexu-cel. Costs for patients in the brexu-cel arm who did not proceed to infusion were appropriately accounted for.

The Review Group identified a number of limitations in the Applicant's base case, which were addressed, via changes, to develop the NCPE-adjusted base case. The most notable of these changes included using the TOWER study to inform efficacy of blinatumomab, using relative effectiveness estimates derived from matching-adjusted indirect comparisons to inform relative effectiveness versus blinatumomab (TOWER study) and inotuzumab, assuming a 'cure' time point of 5 years, employing alternative health-state and long-term survival utility values, and assuming an alternative subsequent treatment distribution.

Results

Analyses presented in this document are based on the list prices of interventions. The Review Group considered the results of the Applicant and NCPE-adjusted base cases to be highly uncertain, due to uncertainty in comparative effectiveness. Results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 2 for the comparison versus blinatumomab, and Table 3 for the comparison versus inotuzumab.

Table 2 Applicant base case incremental cost-effectiveness results versus blinatumomab (pairwise)[ab]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Blinatumomab	177,465	2.11	-	-	-
Brexu-cel	380,547	5.74	203,082	3.63	55,992

Brexu-cel: Brexucabtagene autoleucel; **ICER:** Incremental cost-effectiveness ratio; **QALYs:** Quality-adjusted life years.
[a]Corresponding probabilistic ICER using 1,000 iterations =€59,841/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]The comparison versus blinatumomab is considered the comparison of most relevance to the assessment.

Table 3 Applicant base case incremental cost-effectiveness results versus inotuzumab (pairwise)[ab]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Inotuzumab	312,309	2.74	-	-	-
Brexu-cel	389,266	6.08	76,957	3.34	23,035

Brexu-cel: Brexucabtagene autoleucel; **ICER:** Incremental cost-effectiveness ratio; **QALYs:** Quality-adjusted life years.
[a]Corresponding probabilistic ICER using 1,000 iterations =€25,306/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]The comparison versus blinatumomab is considered the comparison of most relevance to the assessment.

Results of the NCPE-adjusted base case are presented in Table 4 and Table 5 for the comparison versus blinatumomab and inotuzumab, respectively.

Table 4 NCPE-adjusted base case incremental cost-effectiveness results versus blinatumomab (pairwise)[ab]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Blinatumomab	147,280	1.35	-	-	-
Brexu-cel	396,015	4.15	248,735	2.80	88,687

Brexu-cel: Brexucabtagene autoleucel; **ICER:** Incremental cost-effectiveness ratio; **QALYs:** Quality-adjusted life years.
[a]Corresponding probabilistic ICER using 1,000 iterations =€86,401/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]The comparison versus blinatumomab is considered the comparison of most relevance to the assessment.

Table 5 NCPE-adjusted base case incremental cost-effectiveness results versus inotuzumab (pairwise)[ab]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Inotuzumab	301,107	191	-	-	-
Brexu-cel	439,276	3.98	138,169	2.07	66,808

Brexu-cel: Brexucabtagene autoleucel; **ICER:** Incremental cost-effectiveness ratio; **QALYs:** Quality-adjusted life years.
[a]Corresponding probabilistic ICER using 1,000 iterations =€61,250/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b]The comparison versus blinatumomab is considered the comparison of most relevance to the assessment.

Sensitivity analysis

In the NCPE-adjusted base case, the probability of cost effectiveness versus blinatumomab was 0.0% and 0.2% at the €20,000 per QALY and €45,000 per QALY thresholds, respectively. The probability of cost effectiveness versus inotuzumab was 0.8% and 18.6% at the €20,000 per QALY and €45,000 per QALY thresholds, respectively. Deterministic one-way sensitivity analysis indicated that the most influential parameters in the NCPE-adjusted base case related to the 'cured' utility value, and the proportion receiving allogeneic SCT in the comparator arms. In the Applicant base case, the most influential parameters were the proportion receiving allogeneic SCT in the comparator arms. Of note, the 'cured' utility was not varied in the deterministic one-way sensitivity analysis in the Applicant base case.

A price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that for the comparison versus blinatumomab, a 76% and 52% reduction in the price-to-wholesaler of brexu-cel was required to meet the €20,000 per QALY and €45,000 per QALY thresholds, respectively. For the comparison versus inotuzumab, a 43% and 25% reduction in the price-to-wholesaler of brexu-cel was required to meet the €20,000 per QALY and €45,000 per QALY thresholds, respectively. The Review Group highlight that the results of the price-ICER analysis should be interpreted with caution, due to the high degree of uncertainty in the relative clinical effectiveness and cost-effectiveness estimates.

4. Budget impact of brexucabtagene autoleucel

The price-to-wholesaler per single-dose intravenous infusion of brexu-cel is €368,403. The total cost to the HSE, inclusive of rebate and VAT, is €419,979.42.

Based on data from the National Cancer Registry of Ireland and the literature, the Applicant estimated that there will be 17 cases of B-cell precursor ALL in patients aged 26 years and older in Year One, increasing to 18 from Year Two onwards. Of these, based on Clinical Opinion, the Applicant estimated that 10 patients per year would be eligible for brexu-cel. The Applicant further reduced this estimate, indicating that each year 20% of these patients would be ineligible for CAR T-cell therapy. This resulted in 8 patients per year eligible for treatment. The Applicant estimated that brexu-cel will have a 40% market share in Year One, increasing to 60% from Year Two onwards.

The Review Group considered the proportion of patients expected to be treated with brexu-cel to be potentially underestimated. Therefore, in the NCPE-adjusted base case, it was assumed that 10 patients per year will receive treatment with brexu-cel. This was based on Clinical Opinion obtained by the Review Group. Based on the NCPE-adjusted base case assumptions (50 patients treated with brexu-cel over a five-year period), the cumulative five-year gross and net drug budget impacts, inclusive of VAT, were €20,998,971 (€16,762,337 excluding VAT) and €15,825,028 (€12,632,259 excluding VAT), respectively.

The population of eligible patients and the proportion expected to receive treatment, are very uncertain. The presented estimates assume that brexu-cel will only be used in patients, who have relapsed following SCT, and those who are ineligible for SCT. As highlighted, this is not reflective of the full licensed indication. Therefore, there is considerable uncertainty associated with budget impact estimates.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that brexu-cel not be considered for reimbursement unless

cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.