CADTH

CADTH OPTIMAL USE REPORT

Axicabtagene Ciloleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report

CADTH

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Abbreviations

AE	adverse event
ASCT	autologous stem cell transplant
BIA	budget impact analysis
BSC	best supportive care
CAR	chimeric antigen receptor
CD19	cluster of differentiation 19
CI	confidence interval
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
ICUR	incremental cost-utility ratio
ITT	intention to treat
IVIG	intravenous immunoglobin
MCM	mixture cure model
NHL	non-Hodgkin lymphoma
OS	overall survival
PFS	progression-free survival
PMBCL	primary mediastinal B-cell lymphoma
PSM	partitioned survival model
QALY	quality-adjusted life-year
r/r	relapsed or refractory
SCT	stem cell transplant
SMR	standardized mortality ratio
TFL	transformed follicular lymphoma

Drug	Axicabtagene ciloleucel (Yescarta)
Indication	The treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Reimbursement Request	As per indication
Dosage Form(s)	Cell suspension in patient-specific single-infusion bag, for intravenous infusion
NOC Date	February 13, 2019
Manufacturer	Gilead Sciences Canada, Inc.

Executive Summary

Background

Axicabtagene ciloleucel (Yescarta) is one of two currently approved cluster of differentiation (CD19)-directed genetically modified autologous T-cell immunotherapies. Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.[1] Treatment consists of leukapheresis, whereby patient's white blood cells are removed from their body and these T cells are genetically modified to express a chimeric antigen receptor (CAR).[2] These anti-CD19 CAR T cells are then expanded and a single infusion is administered back into the patient. Each patient receives lymphodepleting chemotherapy prior to infusion of axicabtagene ciloleucel into the patient's bloodstream. Axicabtagene ciloleucel is recommended as an autologous single infusion of approximately 68 mL suspension with a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells per kg of body weight (range: 1 to 2.0×10^6 cells per kg). The confidentially submitted price of axicabtagene ciloleucel is ▓▓▓▓▓▓ for a one-time therapy.[3]

This report is based on a critical appraisal of the economic evidence submitted by the manufacturer, which consisted of an economic evaluation and a budget impact analysis (BIA). CADTH conducted reanalyses to consider alternative assumptions and inputs where relevant and possible.

Economic

The manufacturer submitted a cost-utility analysis comparing the average life expectancy, quality-adjusted life-years (QALYs), and total health care costs associated with axicabtagene ciloleucel with best supportive care (BSC). A secondary analysis was conducted comparing axicabtagene ciloleucel with tisagenlecleucel (the only other approved CAR T-cell product in Canada). BSC was defined as a combination of salvage mono-chemotherapies, specifically gemcitabine, etoposide, and cyclophosphamide. The target population in the primary analysis was adult patients with large B-cell lymphoma (median age 58), including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, that is refractory or has relapsed after two or

more lines of systemic therapy and who are ineligible for autologous stem cell transplant (ASCT), could not receive one or relapsed following an ASCT.[1] The target population in the secondary analysis was a subset of adult patients with r/r DLBCL, PMBCL, and transformed follicular lymphoma, in which the clinical indications overlap between axicabtagene ciloleucel and tisagenlecleucel. The base-case analysis was taken from the perspective of the Canadian health care system over a 44-year time horizon (i.e., treatment begins at age 58 and extends to a maximum age of 100) with future costs and utilities discounted at a rate of 1.5%. The manufacturer submitted a three-state partitioned survival model (PSM) to estimate the proportion of patients in the states of progression free, progressed, and death. State occupancy was determined by fitting different parametric distributions for the overall survival (OS) and progression-free survival (PFS) curves.

OS and PFS curves for axicabtagene ciloleucel were fitted directly from individual-level data from the ZUMA-1 study using a mixture cure model (MCM).[4,5] To determine relative treatment effects, OS for BSC was estimated by fitting a parametric survival model on selected individual-level data from the SCHOLAR-1 study.[6] OS for tisagenlecleucel was determined by adjusting the axicabtagene ciloleucel OS with a constant hazard ratio (HR) derived through ███████████████████████████. Pre-infusion HRs for both CAR T-cell products were based on SCHOLAR-1, with differences in duration of pre-infusion period assumed between the two CAR T-cell interventions. PFS for both BSC and tisagenlecleucel were derived from the OS curves by applying time-dependent HRs of OS for axicabtagene ciloleucel to PFS.

Health states and adverse events (AEs) utilities were collected from EuroQol 5-Dimensions data from the ZUMA-1 safety cohort. If a patient remained in the PFS state for ██ years, they were assumed thereafter to have equal utility to that of the age- and gender-matched general population.[7,8] For CAR T-cell products, costs include those related to leukapheresis, conditioning chemotherapy, product acquisition cost, infusion, and monitoring. Acquisition costs for both CAR T-cell products were assumed to be equivalent at a one-time cost of ████████. It was assumed that there was no cost of retreatment. BSC costs include drug acquisition and administration. Bridging therapy costs were included only in the case of tisagenlecleucel, as bridging therapy was not permitted in the ZUMA-1 study.

The manufacturer reported that, over a 44-year time horizon, axicabtagene ciloleucel (8.69 QALYs) resulted in a gain of 5.91 QALYs compared with BSC (2.78 QALYs) and a gain of ████ QALYs compared with ████████████ (████). Health care costs associated with axicabtagene ciloleucel were estimated to be $621,149, an additional $496,446 compared with BSC ($124,703). Axicabtagene ciloleucel was estimated to cost $12,549 less than tisagenlecleucel ($633,699). The associated incremental cost-utility ratio (ICUR) was $84,030 per QALY for axicabtagene ciloleucel compared with BSC while, in the secondary analysis, axicabtagene ciloleucel was dominant over tisagenlecleucel (axicabtagene ciloleucel was less costly and provided more QALYs).

The key limitation identified by CADTH with the manufacturer's economic model was uncertainty in the comparability of the treatment populations used to estimate the treatment effects of axicabtagene ciloleucel compared with both BSC and tisagenlecleucel. This resulted in high uncertainty regarding the applicability of the clinical data to inform the reimbursement decision. The economic model was based on non-randomized clinical evidence from two single-arm trials and one international cohort study. Given the small population size and the lack of head-to-head comparisons or any randomization design in the included studies, the uncertainty regarding long-term treatment benefit remains high.

The strict eligibility criteria for level of organ function and functional status in ZUMA-1 may favour more stable patients, and may not be generalizable to many of the typical patients with r/r large B-cell lymphomas who do not meet this criteria for end organ function and performance status. Furthermore, JULIET allowed bridging therapy prior to infusion while ZUMA-1 did not. The differences in the patients studied in each trial introduces uncertainty around the true differences in AEs, need for bridging therapy, time to delivery and infusion, and length of hospital stay in the tisagenlecleucel versus axicabtagene ciloleucel comparison. The clinical expert consulted by CADTH also raised concerns as to whether the salvage chemotherapies regimens used in SCHOLAR-1 adequately reflect current contemporary practice in order to be considered an appropriate historical control. It is unclear if the relative risk, complete response, and OS have changed over the past 10 to 15 years. Use of SCHOLAR-1 data may not be an accurate estimate of OS and PFS for BSC and may have possibly biased the comparative effectiveness results.

Another limitation relates to the generalizability of the patient population. The manufacturer assumed an average patient age of 58 based on the ZUMA-1 baseline patient characteristics; however, the clinical expert consulted by CADTH noted that this is likely a younger age than expected for Canadian recipients of axicabtagene ciloleucel. There was possible underestimation of the long-term mortality rate. Beyond ██ years in the model, it was assumed that the mortality rate for patients without progressed disease would be equal to an age- and gender-matched population based on a study of patients with DLBCL at first diagnosis,[8] which is not comparable with the indicated population for axicabtagene ciloleucel. With this, there is also uncertainty around the timing of long-term remission. The clinical expert consulted by CADTH considered a five-year cure point to be more appropriate.

Methodological concerns remain with the use of a PSM, which has been recognized as a suboptimal modelling approach in the presence of a large proportion of censoring. The use of mixture cure rates into a PSM further limits transparency given that there is no explicitly defined state of cure in PSM. Uncertainty around the modelling of axicabtagene ciloleucel regarding the manufacturers predicted cure rate itself was also of concern. The manufacturer used an MCM to estimate a 52% cure rate for axicabtagene ciloleucel. As such, an estimation of a cure fraction remains highly uncertain given the limited follow-up time of the ZUMA-1 study. The manufacturer further considered cure rate as fixed with no measures of variability (e.g., no standard errors or confidence intervals).

Further, the distributional assumptions for the base case were not selected based on objective criteria like Akaike information criterion / Bayesian information criterion but tended to favour axicabtagene ciloleucel. Selection of an MCM versus a parametric model was not consistent; an MCM was used for OS in axicabtagene ciloleucel, but not BSC, despite evidence of cure in BSC as well. Furthermore, there were limitations in the estimation of PFS for comparator treatments. PFS was assumed to be equivalent to the ratio of OS to PFS in axicabtagene ciloleucel and applied to the generated OS curves for comparators. Key cost components relating to treatment of B-cell aplasia, a side effect of CAR T-cell therapy, and other long-term follow-up costs were not included in the manufacturer's model, leading to an underestimation of the true cost of either CAR T-cell product.

CADTH reanalysis accounted for some of the previously described limitations by increasing the average patient age to 67, redefining the cure point, setting long-term relative risk of death, incorporating costs of a proportion receiving bridging therapy for, and, setting distributional assumptions based on statistical measures of fit. This increased the expected

costs of axicabtagene ciloleucel and decreased the costs of BSC, resulting in the incremental cost of axicabtagene ciloleucel compared with BSC increasing to $519,689. Quality-adjusted life expectancy decreased across all treatments, resulting in an incremental QALY gain for axicabtagene ciloleucel compared with BSC of 2.30. This resulted in an ICUR value of $226,131 per QALY gained compared with BSC. At a willingness-to-pay threshold of $50,000 per QALY, the probability that axicabtagene ciloleucel was the most likely cost-effective intervention was 0%. It should be noted that this is likely a conservative estimate given that the costs of intravenous immunoglobin treatment and other long-term follow-up costs associated with CAR T-cell products were not considered, which would have likely increased the ICUR further. CADTH excluded comparisons with tisagenlecleucel from its base-case reanalysis due to significant concerns around the comparability of the populations and the uncertainty in the assumptions made regarding differences in treatment efficacy and resource use that could not be addressed within the scope of this review. Comparisons to tisagenlecleucel were, however, considered in an exploratory analysis.

Budget Impact

The manufacturer submitted a BIA that assessed the financial impact of the potential reimbursement of axicabtagene ciloleucel for adult patients with r/r DLBCL including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma over a three-year time horizon, based on the Ontario Ministry of Health perspective. This population included patients who were ineligible for an ASCT, who were considered for an ASCT, or who had received an ASCT but had relapsed or been refractory. The submitted BIA used an epidemiology approach and compared two budget scenarios: first, a reference scenario, where patients could access treatment with palliative chemotherapy, tisagenlecleucel, or participate in a clinical trial, and second, a new drug scenario, where axicabtagene ciloleucel joins the market and becomes available. For each scenario, the number of patients likely to receive treatment were multiplied by the relevant per-patient costs to determine the total costs for each therapy. The budget impact was then calculated by subtracting the total cost of the reference scenario from the total cost of the new drug scenario.

The total number of patients expected to receive axicabtagene ciloleucel, tisagenlecleucel, or other treatment under each scenario was estimated by multiplying the total eligible population by the expected marked share of each treatment in each year of the analysis. The total CAR T-cell therapy market share was estimated, based on expert opinion, to be ██%, ██%, and ██% in years 1 through 3, respectively in the reference scenario, all belonging to tisagenlecleucel; while, with the introduction of axicabtagene ciloleucel (new drug scenario), the market share for CAR T-cell therapy would ████████████████████ ███ ███████████████████████). Of the total CAR T-cell therapy market share, ██% was estimated to be captured by axicabtagene ciloleucel, while the remaining ██% would be tisagenlecleucel. Regardless of the scenario evaluated, ███% of patients were assumed to take part in clinical trials rather than use approved therapies in each year, and the remaining proportion of patients were assumed to be on one of three palliative chemotherapy monotherapies. Annual budget costs in the analysis included the cost of therapy (composed of CAR T-cell product cost, conditioning chemotherapy costs, and palliative chemotherapy drug costs) and additional costs (including administration, leukopheresis, hospitalization due to CAR T-cell infusion and monitoring, bridging therapy, stem cell transplant, AE management costs, cytokine release syndrome management costs [considered separately

from other AEs], and health care provider training). The impact of reimbursement on health outcomes was not considered.

The manufacturer reported that the incremental budget impact associated with the reimbursement of axicabtagene ciloleucel in the indicated population in Ontario was expected to be $6.9 million in year 1, and then result in a savings of $1.2 million in year 2 and $1.5 million in year 3, for a total budget impact of $4.1 million over the first three years.

CADTH identified a number of key limitations and sources of uncertainty in the manufacturer's BIA. There remains uncertainty in the generalizability as the population studied in ZUMA-1 is relatively stable and results may not reflect patients who are less stable or who do not meet the strict inclusion criteria of the trial. The clinical expert consulted by CADTH noted that the population was both younger and less severe than the Canadian patient population. As the proportion and the duration of clinical events associated with axicabtagene was sourced from the ZUMA-1 trial, these estimates are subject to uncertainty. Additionally, differences in the population studied in ZUMA-1 and JULIET may further introduce uncertainty in relative costs and resource use between CAR T-cell therapies. The inclusion of patients accessing investigational therapies through future clinical trials as a comparator does not align with those considered in the manufacturer's economic evaluation, nor were costs that would still be borne by public health care payers for patients in these theoretical clinical trials accounted for. The manufacturer further underestimated the eligible patient size. Additionally, the budget impact of axicabtagene may have been underestimated given that it only reported the impact from the perspective of a single province as a proxy (Ontario). Potential system constraints for both axicabtagene ciloleucel and tisagenlecleucel were not considered in the manufacturer's analysis, including the costs of delay of treatment. Further concerns with the cost calculations within the manufacturer's BIA included the inappropriate incorporation of hospitalization and AE costs, and the exclusion of the potential need for IV immunoglobulin treatment as a treatment for B-cell aplasia.

CADTH attempted to account for some of the identified limitations by correcting a series of calculation errors within the model, assuming identical resource consumption (i.e., bridging therapy, hospitalization, and allogeneic stem cell transplant) between CAR T-cell therapies, removing clinical trials as a comparator with market shares adjusted accordingly, assuming that 35% of patients with non-Hodgkin lymphoma would have an indicated type of DLBCL, incorporating two-year prevalence data in year 1 to be consistent with relapse estimates and applying incidence estimates for the years thereafter, increasing the annual probability of relapse from that estimated by the manufacturer, including patients who were refractory to first-line therapy rather than only those who relapsed, and adjusting for the proportion of patients who undergo leukopheresis but who do not receive CAR T.

Although the manufacturer reported the results from a single province, CADTH reanalyses expanded to a national perspective. With these changes, CADTH found that incremental expenditures associated with the reimbursement of axicabtagene ciloleucel in adult patients with r/r DLBCL in Canada are expected to be $51.6 million in year 1, $28.6 million in year 2, and $18.6 million in year 3, with a cumulative budget impact of $98.8 million. The main driver of this result is the expected increase in the number of patients who would access CAR T-cell therapy.

Conclusions

Uncertainty remains in the comparative treatment effects given the heterogeneity between the clinical sources that informed the efficacy and safety of axicabtagene ciloleucel and BSC, as well as tisagenlecleucel. Similar to the conclusion of the clinical report, the critical limitations of the indirect treatment comparisons render the true potential comparative benefits and the true cost-effectiveness of axicabtagene ciloleucel compared with tisagenlecleucel to be unknown. Interpretation of the validity of the manufacturer's model was further challenged by the fact that the clinical trial population upon which the economic results were based consist of relatively stable patients and may not be generalizable to patients who are less stable or who do not meet the strict inclusion criteria of the trials. The results require careful interpretation.

CADTH estimated that the ICUR for axicabtagene ciloleucel compared with BSC was $226,131 per QALY gained. To achieve an ICUR of $50,000 per QALY compared with BSC, the price of axicabtagene ciloleucel would need to be reduced by 83%. The estimated ICUR for axicabtagene ciloleucel compared with BSC was highly sensitive to assumptions regarding the population age and long-term mortality. Little can be elucidated regarding the comparative cost-effectiveness of axicabtagene compared with tisagenlecleucel given the substantial clinical heterogeneity. This was considered in exploratory analyses by CADTH.

In terms of budget impact, CADTH conservatively estimated that, due to uncertainty in the populations studied in the existing clinical trials, it is likely that the additional treatment-related care costs would be similar between CAR T-cell treatments if treating an identical population. Thus, the total cost of treatment with axicabtagene ciloleucel or tisagenlecleucel may be more similar than has been assumed by the manufacturer. CADTH reanalyses estimated that the introduction of axicabtagene ciloleucel could result in an incremental expenditure of $51.6 million in year 1, $28.6 million in year 2, and $18.6 million in year 3. Sensitivity analyses suggest this increase in cost is primarily driven by increased numbers of patients being able to access CAR T-cell therapy due to the availability of multiple products and the increased number of treatment centres. Given that there are no public Canadian prices for tisagenlecleucel, considerable uncertainty in the price of tisagenlecleucel remains. Caution is therefore required in interpreting the budget impact findings as the results were highly sensitive to the cost of CAR T-cell therapy. If the price of tisagenlecleucel is lower than that used in the analysis (where the price of tisagenlecleucel was assumed identical to that of axicabtagene ciloleucel), the likely budget impact of adopting axicabtagene ciloleucel would be higher than currently estimated.

Information on the Economic Submission

Manufacturer's Economic Evaluation

The manufacturer's submitted economic evaluation was a cost-utility analysis from the perspective of a Canadian public health care system. The primary analysis compared axicabtagene ciloleucel with best supportive care (BSC) under the patient population of adults with large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL from follicular lymphoma, that is refractory or has relapsed after two or more lines of systemic therapy. The manufacturer stated that an additional requirement in the primary analysis was that patients in BSC would not be eligible for autologous stem cell transplant (ASCT). BSC reflected a blended comparator consisting of a mixture of palliative mono-chemotherapies (cyclophosphamide, etoposide, and gemcitabine) with the assumption of identical efficacy and safety between treatment regimens. A secondary analysis was performed for the only other Health Canada–approved chimeric antigen receptor (CAR) T-cell product, tisagenlecleucel, for the patient population of relapsed or refractory (r/r) DLBCL, PMBCL, and transformed follicular lymphoma (TFL). The baseline characteristics of patients in the model were derived mainly from the ZUMA-1 trial, in which the median patient age was 58 (23 to 76) years old and 68% male with an average body surface area of 1.7 m^2 assumed.[9] The manufacturer's analysis was conducted over a 44-year time horizon with a discount rate of 1.5% used for both costs and clinical outcomes.

Model Structure

The manufacturer submitted a partitioned survival model (PSM) developed in Microsoft Excel to simulate long-term health (life-years, quality-adjusted life-years [QALYs]) and cost (total health care costs) outcomes. The model assumed three health states: progression free, progressed disease, and death. The proportion of patients with progression free, progressed disease, and death were estimated over time based on the overall survival (OS) and progression-free survival (PFS) curves. At the start of the model, all patients were assumed to be progressed free and, over time, the proportion of patients with progressed disease was estimated as the difference between the proportion of living patients (estimated from the OS curve) and the proportion of progressed-free patients (estimated from the PFS curve). When patients were in PFS for more than two years in any treatment strategy, they were assumed to be in long-term remission.

Model Inputs

Overall and PFS for axicabtagene ciloleucel was based on pooled data of a modified intent-to-treat (ITT) population from the phase II ZUMA-1 trial with data available up to a median 27.1 months of follow-up based on an August 11, 2018, cut-off point. These curves were fitted by different statistical methods (i.e., parametric curves, mixture cure models [MCM]) and employing different parametric functions (i.e., for all statistical methods: gamma, Weibull and log-normal; and, additional to parametric models, exponential, Gompertz, log logistic). The selection of the method and the appropriate parametric function for the manufacturer's base-case analysis were determined based on visual inspection, goodness of fit statistics, and clinical rationale. OS for axicabtagene ciloleucel was estimated using a ███████ MCM. The MCM method first predicts a likelihood of long-term remission, followed by a fitted parametric survival model for patients without long-term remission. This statistical method assumes that patients with long-term remission have different long-term mortality from that

of a disease progressed population. In the manufacturer's economic model, an assumption was made that patients in remission had a probability of death similar to that of the Canadian population.

As ZUMA-1 was a single-arm study, comparative treatment efficacy in terms of OS was obtained from an indirect comparison using the SCHOLAR-1 trial for salvage chemotherapy and the JULIET trial for tisagenlecleucel. SCHOLAR-1 is a large international multi-cohort retrospective study that reported OS data of mixed but unspecified salvage chemotherapy regimens among patients with refractory DLBCL. Specifically, OS for BSC was based on patient-level data with crude adjustments to remove any patients with Eastern Cooperative Oncology Group (ECOG) performance status rating of 2 to 4, aligning with the ZUMA-1 trial's inclusion criteria. The manufacturer did not, however, remove patients with missing ECOG scores. OS for ▮▮▮▮▮▮▮▮▮ was based on the manufacturer's conducted ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮.

For axicabtagene ciloleucel, PFS was estimated from the same data source as OS and fitted to a parametric function similar to the previously described approach for OS. Different statistical distributions were considered; the manufacturer considered the ▮▮▮▮▮ parametric model to provide the best fit. The manufacturer used a time-dependent hazard ratio (HR) of OS to PFS from axicabtagene ciloleucel that was then applied to comparators' OS curves to derive each comparator's PFS curve.

Key adverse events (AEs) included in the manufacturer's economic model for axicabtagene ciloleucel and tisagenlecleucel were grade 3 or more AEs occurring in more than 10% of the ZUMA-1 or JULIET populations. No AEs were modelled for patients on BSC as a conservative assumption. AEs related to conditioning chemotherapy as well as cytokine release syndrome (CRS) were also considered. To incorporate health utility decrements due to AEs, a one-time decrease in health utility was applied during the first cycle after either axicabtagene ciloleucel or tisagenlecleucel infusion for the proportion of patients experiencing an AE. The manufacturer applied the maximum health utility decrement across all non-CRS AEs for which utility values were not available (i.e., ▮▮▮▮). The duration of the AEs, sourced from the ZUMA-1 data, were assumed to be identical for tisagenlecleucel.

Utilities for progression-free and progressed disease were derived from the ZUMA-1 safety management cohort. The same health state utility values were applied across all comparators. In patients achieving long-term remission after ▮ years, utilities were assumed equal to that of the general population.

BSC costs included drug acquisition and administration costs. For CAR T-cell therapy, costs included pre-treatment (i.e., leukapheresis and conditioning) and treatment (i.e., acquisition, cell infusion, and monitoring). It was assumed that acquisition costs would only be reimbursed for those infused. The price of drug acquisition was assumed to be the same for both tisagenlecleucel and axicabtagene ciloleucel. For the proportion of the population in the ZUMA-1 trial that required retreatment, additional costs of conditioning, infusion, and monitoring were included but without additional costs for leukapheresis or drug acquisition as the manufacturer assumed that the first leukapheresis would be able to extract enough cells for two manufacturing rounds and the acquisition costs of retreatment would be included in the initial product cost. Specific to tisagenlecleucel, the JULIET trial allowed for bridging therapy (in which 92% of the trial population received bridging therapy). Therefore, the manufacturer included the costs of bridging therapy for 92% of the modelled cohort who received tisagenlecleucel. One difference between the two CAR T-cell products assumed by the manufacturer was the length of stay for cell infusion and monitoring; for axicabtagene ciloleucel this was assumed to be 15 days, whereas 26 days was assumed for tisagenlecleucel, resulting in total hospitalization costs of $24,409.21 and $43,054.04, respectively. All AE costs were assumed to occur during the hospitalized monitoring period and have no cost impact with the exception of grade 3 or 4 CRS, which were associated with an additional cost of an intensive care unit stay and cytokine inhibitor drugs. CRS was assumed to last six days for patients undergoing treatment via axicabtagene ciloleucel and eight days for those using tisagenlecleucel, per the clinical trial results.[10-12] Progression-free and progressed states included costs associated with physician visits, laboratory tests, radiological tests, and hospitalization. Costs were based on the Ontario Ministry of Health and Long-Term Care Schedule of Benefits. The manufacturer's model included an allogeneic stem cell transplant (SCT) cost of $155,611[13] applied for the proportion of patients in each treatment strategy who received allogenic SCT in either ZUMA-1 or JULIET and in SCOLAR-1. This was 10%, 5%, and 29%, respectively.[3,12] Training costs were also captured in the manufacturer's economic model.

Manufacturer's Base Case

In the manufacturer's primary analysis, axicabtagene ciloleucel was associated with 5.91 additional QALYs and an additional cost of $496,446. This resulted in an incremental cost-utility ratio (ICUR) of $84,030 per QALY gained. The secondary analysis comparing axicabtagene ciloleucel with tisagenlecleucel found axicabtagene ciloleucel to cost $12,549 less than tisagenlecleucel and produced ▮ incremental QALYs. As axicabtagene ciloleucel was both cost savings and resulted in greater QALY gain, axicabtagene was a dominant strategy compared with tisagenlecleucel (Table 1).

Table 1: Summary of Probabilistic Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental cost of Axicabtagene Ciloleucel ($)	Total QALYs	Incremental QALYs of Axicabtagene Ciloleucel	Incremental Cost per QALY of Axicabtagene Ciloleucel ($)
Axicabtagene ciloleucel	621,149	–	8.69	–	–
BSC	124,703	496,446	2.78	5.91	84,030
Tisagenlecleucel	633,698	−12,549	■	■	Axicabtagene ciloleucel dominant

BSC = best supportive care; QALY = quality-adjusted life-years.

Source: Manufacturer economic submission.[3]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer performed scenario and univariate deterministic sensitivity analyses on both the primary and secondary analysis. These related to assumptions around time horizon, health utilities, discount rate, and distributional fits of OS and PFS. They also included:

- testing different parametric forms of the MCM and different parametric survival curves for axicabtagene ciloleucel's OS
- testing the definition of the patient population analyzed for BSC from the SCHOLAR-1 study based on setting different inclusion and exclusion criteria and using other adjustments (i.e., propensity score matching)
- construction of PFS curves for tisagenlecleucel and salvage chemotherapy by using different assumptions on the HR between PFS and OS for axicabtagene ciloleucel.

The manufacturer noted that survival estimates were the most influential parameter impacting ICUR values. When testing the sensitivity of the outcomes on the assumed distribution for axicabtagene ciloleucel PFS, the manufacturer identified that the cost per QALY of axicabtagene ciloleucel increased relative to BSC and tisagenlecleucel when assuming a gamma distribution. Univariate sensitivity analysis further found that the use of a constant value to model PFS for the comparators was highly influential on overall ICUR values. The ICUR of axicabtagene ciloleucel increased by more than 20% when a parametric (Gompertz) distribution was used to model OS in axicabtagene ciloleucel compared with a MCM due predominantly to a decrease in QALYs for axicabtagene ciloleucel.

The manufacturer also performed univariate deterministic sensitivity analyses relating to the primary analysis on the ten most influential parameters. Here, again, the most responsive parameters were those related to the survival of patients in the axicabtagene ciloleucel and BSC arms. Assumptions made regarding PFS and OS significantly changed the overall ICUR. Such analyses were not conducted for the secondary analysis.

Limitations Identified With the Manufacturer's Economic Submission

CADTH identified a number of key sources of uncertainty and potential limitations relating to the manufacturer's economic evaluation:

Lack of head-to-head comparative efficacy and safety of axicabtagene ciloleucel, salvage chemotherapy, and tisagenlecleucel: ZUMA-1 was a single-arm study from which little can be inferred directly on the relative treatment effects between axicabtagene ciloleucel and BSC or tisagenlecleucel. In the absence of comparative two- (or three-) arm randomized controlled studies, the manufacturer conducted an indirect treatment comparison.

To estimate the relative effectiveness of axicabtagene ciloleucel against BSC, the manufacturer used historical data from the SCHOLAR-1 cohort to inform the BSC arm. With regards to this comparison, there was considerable heterogeneity between the SCHOLAR-1 and ZUMA-1 study populations that could not be adequately controlled for in the analyses. CADTH's clinical review noted that SCHOLAR-1 included patients with primary refractory disease who would thus not be eligible for the manufacturer-defined BSC. Furthermore, SCHOLAR-1 pooled across randomized controlled trial and observational studies despite notable differences in their inclusion criteria that may have introduced clinical heterogeneity. Compared with the overall population in the SCHOLAR -1 study, the patient population for ZUMA-1 was older, had a higher number of previous treatments, and patients were more likely to have advanced disease. However, there is limited reporting to compare the population characteristics of the SCHOLAR-1 subgroup in which the economic analysis is based on with the ZUMA-1 population. Although the manufacturer's base case attempted to address this by removing all SCHOLAR-1 patients with ECOG scores greater than 1, they included all patients with missing ECOG scores in deriving OS for BSC. From CADTH's clinical review, when patients with missing ECOG scores were removed from the analysis, reported OS improved for the BSC arm.[6] Although the manufacturer attempted to conduct a propensity score match by ECOG status, International Prognostic Index score, disease stage, and number of lines of chemotherapy as part of a scenario analysis, ██% of the sample had missing data on these factors. This leads to concerns on the precision of the estimates given the reduced sample size. The CADTH clinical review further noted that major confounders remained in the indirect comparison of SCHOLAR-1 and ZUMA-1 and that significant bias in the measures of their comparative efficacy are likely to remain. It was also unclear if SCHOLAR-1 reflected current contemporary practice and whether it could even be considered an appropriate historical control. According to the clinical review, a sizable proportion of patients were diagnosed prior to 2005. Furthermore, the names of the salvage chemotherapy regimens were not reported within the publication. According to the clinical expert consulted by CADTH, survival estimates have likely changed over the past 15 years, impacting the Kaplan-Meier survival curves and HRs used to calculate comparative efficacy. Together, these limitations may have underestimated the OS associated with salvage chemotherapy.

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Given the lack of comparative clinical data and the limitations with the existing data sources in which comparative treatment effects were derived, CADTH was unable to address this limitation. The cost-effectiveness of axicabtagene ciloleucel is thus highly uncertain due the lack of head-to-head comparative evidence for both comparator treatments under consideration.

Generalizability of the patient population: It was noted by the clinical expert that the average age assumed in the model was lower than the expected population to be treated in Canada. The clinical report further noted that the median age of 58 from the ZUMA-1 trial may have reflected the strict eligibility criteria for organ function and functional status and thus tended to favour more stable, younger patients. In the Canadian context, the CADTH clinical expert estimated that the average age for patients with r/r DLBCL would be closer to 67. This is further supported by a Canadian real-world population-based study of a cancer registry.[14] Additionally, as noted in the CADTH clinical review, the high proportion of patients within ZUMA-1 who were identified as white may not be generalizable to a Canadian ethnicity distribution.

Approach to model cured patients is inappropriate: Two key model assumptions specific to cure were made: first, utility reverted to that of healthy age- and sex-matched individuals after ███ years in the progressed-free survival state, and second, mortality following cure was equivalent to the mortality risks of an age- and sex-matched overall population. The definition of cure was largely based on an assumed flattening of the curve at the ███-year mark. It is unclear if this was a reasonable assumption based on the data available. CADTH's clinical expert advised that a more appropriate time point to assess cure would be at five years. In addition, the manufacturer assumed that the fraction of patients that will achieve cure (52% for axicabtagene ciloleucel in the base case), will have utility values and a risk of death that are similar to the age- and sex-matched values of a general Canadian population.[8] With respect to utility values, this may not be appropriate as patients in the real world are likely to remain at risk of recurrence and may experience long-term treatment-

related adverse outcomes, which may impact their perceived quality of life. While utility values may converge to that of the general population for those who are in long-term remission, the clinical expert felt that it may be more reasonable to assume that they do so at a later time of three or five years. For mortality, this was based on one cited paper finding no increased mortality risk, conditional on surviving for ▇ years, for DLBCL at first diagnosis. This would not be a comparable patient population as the indication for CAR T-cell therapy is for r/r patients after two or more lines of systemic therapy. Rather, it is likely that these patients would experience increased mortality risks. A more comparable study reported that the standardized mortality ratio (SMR) for r/r DLBCL treated with ASCT was 3.4 (95% confidence interval [CI], 2.9 to 4.1) for two-year survivors transplanted after the age of 55.[15] A different study estimated that the non-cancer SMR after two-year survival with DLBCL was 1.41 (95% CI, 1.35 to 1.48).[15,16] A third study that focused on a DLBCL population who received ASCT estimated the SMR for five-year survivors at 1.8. Given the mechanics of the mixture cure estimation, and the fact that a large proportion of the benefit estimated from the economic model for axicabtagene ciloleucel accumulated after the end of the trial period, a misspecification of long-term survival has implications on the perceived magnitude of the treatment's benefit.

Inappropriate modelling and distributional assumptions in estimating OS: The manufacturer incorporated an MCM based on the flattening of the survival curve after ▇ years for patients receiving axicabtagene ciloleucel in the ZUMA-1 study. The MCM estimated a 52% cure rate at ▇ years based on the ZUMA-1 results. Such an estimation of a cure fraction remains highly uncertain given the limited follow-up time of the ZUMA-1 study. Given the increased uncertainty with extrapolating survival past the observable trial period, this is an important feature of the model to adequately test through the conduct of appropriate sensitivity analyses. Yet, the cure rate was considered a fixed input in the manufacturer's model. Clinical experts consulted on this review further indicated that the manufacturer's estimated cure fraction is likely higher than would be expected within a Canadian setting following the implementation of axicabtagene ciloleucel to a broader population that goes beyond the selective clinical trial's patient population. Although the manufacturer's model allowed exploration of several distributional fits, significant uncertainty remains around these distributional fits and their impact on the extrapolation of overall comparative costs and effectiveness. More sensitivity analysis in this area would have been warranted.

For non-cured patients treated with axicabtagene ciloleucel, the manufacturer's model was based on the ▇▇▇▇ distributions to describe OS based on the MCM. Based on interpretation of goodness of fit through either Akaike information criterion or Bayesian information criterion, the MCM should have been estimated assuming a log-normal distribution for non-cured patients (Akaike information criterion: 439.33 versus 440.61, respectively). The distributional assumption may have significant impact on the estimated treatment efficacy.

Contrary to axicabtagene ciloleucel, the manufacturer did not rely on an MCM for the estimation of BSC OS, even though the observed survival seems to clearly suggest the possibility of cure. This was further validated by the clinical expert consulted by CADTH on this review, who noted that there may be a small proportion of patients who may be cured with BSC. Although the manufacturer justified that the relative cure fraction was not high in BSC and that a simpler model provided good fit, the decision to not use the MCM for BSC despite some evidence of plateau in OS was considered inconsistent to the approach taken for axicabtagene ciloleucel. The manufacturer's differential approach to model OS (i.e.,

MCM for axicabtagene ciloleucel versus single parametric function for BSC) would favour axicabtagene ciloleucel by increasing the incremental life expectancy between these two treatments.

Approach to censoring due to subsequent treatment or retreatment: The manufacturer's economic model did not censor those patients who were treated with subsequent SCT or chemotherapy or who were retreated with axicabtagene ciloleucel. They noted that this was because no censoring occurred in the progressed disease stage. In the trial, subsequent treatment through allogenic SCT was observed in five patients to sustain response and, for the 22 patients who received subsequent chemotherapy, it was not specified whether it was received while in response or after relapse.The use of retreatment with axicabtagene ciloleucel in the ZUMA-1 trial following relapse, in which retreated patients were not censored from analysis, may introduce bias in the OS estimates for axicabtagene ciloleucel given that some patients may achieve response following retreatment for a relapse.

There were additionally differences in the allowance of retreatment in ZUMA-1 versus JULIET and how these patients would be censored, impacting the ability to directly compare the two treatments further. In ZUMA-1, 9% of patients underwent retreatment while none did in JULIET.[17] For patients that went on to receive SCT, the manufacturer did not include long-term cost implications or the cost of associated AEs (e.g., graft versus host disease). These may have a significant impact on the long-term costs of all treatments evaluated. The impact on the comparative cost is uncertain but may understate the cost of BSC more so given the higher rates of SCT in BSC. CADTH was unable to assess the impact of this limitation.

Inconsistencies in modelling the pre-infusion and infusion period: The pre-infusion periods (i.e., time from leukapheresis to infusion) were assumed to differ between CAR T-cell therapies and reflected deterministic values of 24 days for axicabtagene ciloleucel and ▮▮ days for tisagenlecleucel. In terms of manufacturing time, the median time for axicabtagene ciloleucel delivery was 17 days in the ZUMA-1 study.[10] Although the duration of the pre-infusion period for axicabtagene ciloleucel was justified based on the trial data, the trial setting may reflect optimal condition in terms of manufacturing process. There is no evidence on the length of time between eligibility and availability of a manufacturer's slot in Canada. Although this extended time period for JULIET could be partly explained by the fact that JULIET allowed for bridging therapy, according the clinical expert consulted by CADTH, the wide difference is unlikely to be valid. From the CADTH axicabtagene ciloleucel clinical report, estimates of time from enrolment to infusion had a median time of ▮▮ days (range: ▮▮ to ▮▮ days) to ▮▮ days (range: ▮▮ to ▮▮ days) from screening to infusion. The clinical expert consulted by CADTH did not foresee significant differences in the manufacturing time between the two CAR T-cell products and the proportion of patients requiring bridging therapy was expected to be similar between the two CAR T-cell interventions. In clinical practice, most clinicians would offer bridging chemotherapy to maintain or achieve disease stability during prolonged wait times (e.g., greater than two weeks). The manufacturer's model assumed that 92% of patients received bridging therapy on tisagenlecleucel based on the reported rates from the JULIET trial while no patients received bridging therapy on axicabtagene ciloleucel in reflection of the ZUMA-1 trial. However, emerging evidence from the US have reported 56% of patients required bridging therapy on axicabtagene ciloleucel in clinical practice.[18] CADTH's clinical expert noted that there was limited evidence to suggest that the proportion of patents requiring bridging therapy would differ between the two CAR T-cell therapy regimens. By not including bridging therapy for axicabtagene ciloleucel, results are biased in favour of axicabtagene ciloleucel.

Hospitalization for infusion and subsequent monitoring were similarly assumed to differ between CAR T-cell therapies and reflected deterministic values of 15 days for axicabtagene ciloleucel and 26 days for tisagenlecleucel. The infusion time for axicabtagene ciloleucel is highly variable and, in the ZUMA-1 trial, the reported range was 15 to 72 days. There is not enough evidence to support the differences proposed by the manufacturer in the duration of hospitalization.

Finally, the manufacturer's approach to patients who received leukapheresis but did not receive infusion with axicabtagene ciloleucel was to include the costs but not factor the clinical outcomes. This is not consistent as patients who do not receive CAR T-cell therapy are likely to be managed by BSC.

Uncertainty in PFS in the comparators: As there were no data available on PFS for either comparator arm, the manufacturer assumed that the same ratio for OS to PFS from axicabtagene ciloleucel can be applied to the OS curve for BSC and tisagenlecleucel to construct their respective PFS curves. The manufacturer acknowledged that this is a limitation. In sensitivity analyses, analyses of two extreme cases were conducted to test the sensitivity of the model's findings to this approach: that either everyone alive moves to a progressed state or that no one moves to a progressed state. In the latter, this had significant effects on the comparative cost-effectiveness with tisagenlecleucel. However, as no published data were available reporting the PFS curve of patients on BSC and tisagenlecleucel, CADTH was unable to assess the impact of this limitation on the cost-effectiveness of axicabtagene ciloleucel. Neither the manufacturer's base case or the extreme analyses are likely to produce valid estimates of the proportion of patients who remain progression free and the extreme analyses is likely to inform the potential range of the cost-effectiveness estimates given the uncertainties in the PFS in the comparator arms.

Uncertainty around the costs of tisagenlecleucel: The manufacturer assumed the acquisition cost of tisagenlecleucel to be equal to axicabtagene ciloleucel (████████) given the lack of published Canadian public list prices. The Health Technology Expert Review Panel reviewed tisagenlecleucel and released its recommendation in January 2019. The details of potential negotiations between the manufacturer and the payers and whether value-based pricing or performance pricing is to be employed remain unclear. This has been the case in some private arrangements in the US, whereby the public funder would only pay the drug acquisition costs for those that achieve remission in the first month.[19,20] CADTH conducted scenario analyses to test differences in the price of tisagenlecleucel and the potential impact of a value-based pricing scheme.

Long-term costs and implementation costs underestimated: Other costs uncertainties include the fact that progression-free state only included the costs for palliative care, and, in all states, there was no costs incurred after █ years. This may be optimistic given that follow-up care is likely to occur for some time afterward. The manufacturer further excluded the cost of intravenous immunoglobin (IVIG) treatment for B-cell aplasia. The clinical report noted that rates of B-cell aplasia were at 16% in the ZUMA-1 trial. Treatments for B-cell aplasia may last for several years and are thus important to consider when calculating the total expected costs of axicabtagene ciloleucel and tisagenlecleucel. Given uncertainties to the approach and the duration that patients with B-cell aplasia would be managed, CADTH conducted scenario analyses to address the sensitivity of the model if such costs were included.

Other limitations identified included the following:

- PSM assumes structural independence. A number of limitations stem from the use of a PSM, which have been documented in the past.[21] PSM assumes that the modelled survival end points are structurally independent, which is potentially problematic because PFS and OS are likely dependent outcomes.

- The manufacturer's model included only a limited range of distributions on which to test results in MCM for all alternative treatment options.

- In the conduct of probabilistic analysis, a number of parameters were varied between a range of +/–15%, without any clear justification around this range and whether this range represents true parameter uncertainty.

CADTH Reanalyses

CADTH identified several important limitations relating to the manufacturer's economic evaluation. Before undertaking any reanalyses, CADTH needed to modify the submitted model, as the probabilistic analysis was programmed to return back to the default values regardless of any model modifications. CADTH further incorporated the following adjustments into the base-case reanalysis:

1. The assumed age at infusions was adjusted from age 58 to age 67. By changing the starting age, fewer benefits would be accumulated from extrapolation of the period beyond the trial. As the effectiveness of treatment, stratified by age, was not reported in the clinical studies, the efficacy of axicabtagene ciloleucel or BSC did not change. Thus, this reanalysis may be presenting a more favourable result for axicabtagene ciloleucel, especially if clinical efficacy and safety differs in older populations.

2. Long-term mortality following "cure" was adjusted to be 1.2 times that of the general Canadian age- and sex-adjusted mortality rate. This SMR is based on the study originally used by the manufacturer. This SMR was reported as non-statistically significant; however, its mean value of 1.2 is more in line with the additional evidence identified in the literature.[8] We assumed this SMR would likely be a conservative assumption compared with the identified estimates in the literature.[15,16] Patients would need to survive to five years' progressed free until their health utilities were equalized to that of the age- and sex-matched general population.

3. A log-normal distribution was used for the estimation of OS in non-cured patients who received axicabtagene ciloleucel based on assessment of the goodness of fit criterion.

4. A BSC strategy was modelled through a MCM model. A log-normal distribution for OS was selected for the non-cured population based on best-fit statistics.

5. The full ITT population from the ZUMA-1 trial was incorporated into the estimation of total expected costs and QALYs for axicabtagene ciloleucel. Only 91% of the cohort would undergo infusion and have characteristics similar to the axicabtagene ciloleucel population in the submitted model. The remaining 9% of the population that would undergo leukapheresis but would not receive axicabtagene ciloleucel infusion was modelled similar to the BSC arm. The costs for this proportion of the cohort (9%) were assumed to be similar to the costs incurred in the BSC arm but with the addition of conditioning and leukapheresis costs incurred.

6. The cost of bridging therapy ($19,816.24) was included for axicabtagene ciloleucel in 56% of patients.[18] Hospitalization length of stay costs, CRS duration, proportion treated with SCT, proportion requiring bridging therapy, and proportion of AE events for axicabtagene ciloleucel and tisagenlecleucel were equalized.

The CADTH base case was informed by all of the previously described reanalysis (one to six). In the CADTH reanalysis, the expected costs of axicabtagene ciloleucel increased and the expected costs of BSC decreased, resulting in the incremental cost of axicabtagene ciloleucel compared with BSC to increase to $519,689. QALYs decreased across all treatments, resulting in an incremental QALY for axicabtagene ciloleucel compared with BSC to be 2.30. This resulted in an ICUR value for axicabtagene ciloleucel of $226,131 per QALY gained compared with BSC (see Table 2). At both a willingness-to-pay threshold of $50,000 and $100,000 per QALY, the probability that axicabtagene ciloleucel was the most likely cost-effective intervention was 0%. It should be noted that the CADTH reanalysis values are likely a conservative estimate of the ICUR for axicabtagene ciloleucel given that the costs of IVIG treatment was not considered, which would likely increase the ICUR estimate further. Furthermore, the CADTH reanalysis assumed no clinical effects introduced by bridging therapy given that no data existed at the time of this review.

Table 2: CADTH Revised Base Case

	Total Costs ($)	Incremental cost of Axicabtagene Ciloleucel ($)	Total QALYs	Incremental QALYs of Axicabtagene Ciloleucel	Incremental Cost per QALY of Axicabtagene Ciloleucel ($)
Axicabtagene ciloleucel	626,104	–	4.47	–	–
BSC	106,415	519,689	2.17	2.30	226,131

BSC = best supportive care; QALY = quality-adjusted life-years.

CADTH performed an individual component analysis of each of the six listed key changes made to CADTH's base-case reanalysis (Table 15). These were done to quantify the individual change brought by each of these adjustments. CADTH's base case was highly dependent on the compounded impact of changing the average age of patients to 67 years, altering the distribution on non-cured patients in the OS for axicabtagene ciloleucel to a log-normal distribution, and modifying the analysis to include the full ITT population over a modified ITT. The increased ICURs for the first two factors were due mostly to estimated decreases in QALY gains of axicabtagene ciloleucel. Inclusion of the full ITT population resulted in additional costs from applying BSC costs to patients who did not receive axicabtagene ciloleucel over assigning them a cost of zero, and in a reduction in QALYs as they were now reweighted to account for the population that would undergo leukapheresis but not receive CAR T-cell therapy.

Of note, CADTH found that the model remained unstable when conducting the probabilistic analysis at 5,000 Monte Carlo iterations in the comparison of axicabtagene ciloleucel with both BSC and tisagenlecleucel. CADTH was unable to address the issues on the potential uncertainties in the comparability between axicabtagene ciloleucel and tisagenlecleucel given the underlying clinical differences between the trials' patient populations. This exploratory analysis was unable to address the uncertainties on the relative treatment effects and the differences assumed in the duration of the pre-infusion period (results are reported in Table 15).

Several scenario analyses were performed to observe the effects of structural and parameter assumptions. All scenarios were tested on CADTH's revised base-case model (see Table 3).

To test assumptions around the distributions chosen, the model was re-run using a specification of a "conventional" PSM with the assumption of a Gompertz distribution for OS for axicabtagene ciloleucel (Scenario A). This decreased the estimate of CADTH's base-case reanalysis moderately. In scenarios B and C, the impact of the assumed cure rate on overall results was tested by employing the lower and upper bound of the 95% CI on the cure rate, as estimated from the standard error from the MCM model. Lowering the cure rate increased the ICUR. Using the lower bound on cure decreased the ICUR value to around $150,000.

The manufacturer's analysis used SCHOLAR-1 data where only patients with a 2 to 4 ECOG score were excluded and not patients with missing information on the ECOG score. As noted, this approach would produce a lower estimate of the OS in the BSC strategy. Furthermore, treatments studied in SCHOLAR-1 may not reflect current standards of care and may have underestimated the current survival expected from BSC. To address this concern, a scenario analysis was conducted that assumed a 30% survival for BSC patients over the base case of 21% (Scenario D). This was found to greatly impact the ICUR by increasing the expected QALYs of BSC and thus decreasing the incremental QALY gain of axicabtagene ciloleucel.

To test how the inclusion of the cost of bridging therapy impacted the overall estimated cost for axicabtagene ciloleucel, scenario analyses were conducted assuming 0% and 100% of patients would receive bridging therapy (scenarios E and F). These factors had moderate impact on the revised base-case analysis. Even assuming 0% bridging therapy costs, the ICUR remained more than $200,000 per QALY.

In scenario H, a value-based pricing scheme for axicabtagene ciloleucel was explored. In this analysis, only the proportion achieving response (defined based on investigator assessment; i.e., 82% according to the ZUMA-1 trial[10]) would result in full reimbursement by the public plans. This caused the average cost of axicabtagene ciloleucel to decrease given that only 82% of patients achieving response are required to pay for the product. Under this scheme, the ICUR dropped to around $190,000 per QALY.

The manufacturer's model did not consider the potential impact of IVIG therapy. Scenario I addresses the potential impact of long-term IVIG therapy. It was assumed that patients with persistent B-cell aplasia would require long-term IVIG therapy (16%). Although the clinical review noted that 30% of patients were reported to require IVIG use, the expected duration of IVIG use for this full set of patients was unclear. Therefore, it was assumed that 16% of patients would require long-term IVIG use and it was estimated that this would cost approximately $2,456 a month based on Ontario Drug Formulary pricing and the outlined treatment schedule from a National Institute for Health and Care Excellence technology appraisal report.[22,23] It was assumed that those individuals would require IVIG therapy for an average of one year. Clinical experts indicated that IVIG therapy for B-cell aplasia could be ongoing for more than three years. This cost was crudely incorporated as a bulk cost at model start for the fraction of patients affected. Incorporating these costs resulted in an ICUR of around $231,000 per QALY.

Scenarios J and K show the effects of assuming a lower baseline age on the cost-effectiveness of axicabtagene ciloleucel (average age of 65 and 58 [ZUMA-1 median age],

respectively). Finally, in scenarios L to N, the time horizon for the cost-effectiveness analysis is varied with the reanalysis performed for time horizons of 20, 10, and 5 years, respectively. Using a lower median age increases the expected cost and expected QALYs for both axicabtagene ciloleucel and BSC. Using a median age equal to that reported in the ZUMA-1 trial (i.e., 58 years of age) produces an ICUR of $157,001 per QALY gained. Using a median age of 65 decreases the ICUR from the base-case reanalysis by about $20,000 to $206,126 per QALY gained. Decreasing the time horizon uniformly increases the ICUR due to reductions in the expected QALYs.

Table 3: CADTH Scenario Analysis

Individual Component		Total Costs ($)	Incremental Cost of Axicabtagene Ciloleucel ($)	Total QALYs	Incremental QALYs of Axicabtagene Ciloleucel	Incremental Cost per QALY ($)
Scenario A: AC OS parametric, Gompertz	Axicabtagene ciloleucel	636,768	525,458	4.67	2.51	209,284
	BSC	111,309		2.16		
Scenario B: Cure rate lower 95% CI (35%)	Axicabtagene ciloleucel	610,606	509,486	3.46	1.28	399,146
	BSC	101,119		2.19		
Scenario C: Cure rate upper 95% CI (62%)	Axicabtagene ciloleucel	663,098	528,619	5.67	3.53	154,977
	BSC	116,724		2.14		
Scenario D: Improved SCHOLAR-1 cure to 30%	Axicabtagene ciloleucel	629,131	505,992	4.70	1.23	410,846
	BSC	123,138		3.47		
Scenario F: Bridging therapy 100%	Axicabtagene ciloleucel	634,781	528,446	4.46	2.30	230,113
	BSC	106,335		2.17		
Scenario G: Bridging therapy 0%	Axicabtagene ciloleucel	614,757	508,508	4.47	2.30	221,034
	BSC	106,249		2.17		
Scenario H: Value-based pricing	Axicabtagene ciloleucel	539,242	432,717	4.48	2.31	187,008
	BSC	106,524		2.17		
Scenario I: Including cost of IVIG therapy	Axicabtagene ciloleucel	635,528	529,299	4.47	2.30	231,357
	BSC	106,524		2.17		
Scenario J: Median age 65	Axicabtagene ciloleucel	629,183	520,480.53	4.85	2.53	206,126
	BSC	108,703		2.32		
Scenario K: Median age 58	Axicabtagene ciloleucel	639,477	522,723.14	6.20	3.33	157,001
	BSC	116,754		2.87		
Scenario L: Time horizon 20 years	Axicabtagene ciloleucel	621,458	518,288	4.05	2.06	252,160
	BSC	103,171		2.00		
Scenario M Time horizon	Axicabtagene ciloleucel	613,930	518,970	2.62	1.21	430,361

Individual Component		Total Costs ($)	Incremental Cost of Axicabtagene Ciloleucel ($)	Total QALYs	Incremental QALYs of Axicabtagene Ciloleucel	Incremental Cost per QALY ($)
10 years	BSC	94,960		1.41		
Scenario N: Time horizon 5 years	Axicabtagene ciloleucel	605,215	517,824	1.44	0.51	1,007,024
	BSC	87,391		0.92		

AC = axicabtagene ciloleucel; CI = confidence interval; BSC = best supportive care; IVIG = intravenous immunoglobin; QALY = quality-adjusted life-years; OS = overall survival.

CADTH undertook price reduction analysis based on the manufacturer-submitted and CADTH base-case analyses (see Table 4). Findings revealed that a reduction of 83% in the submitted price would be required for axicabtagene ciloleucel to achieve an ICUR of $50,000 per QALY gained compared with BSC.

Table 4: CADTH Reanalysis Price Reduction Scenarios Compared With Best Supportive Care (Probabilistic)

ICURs of Submitted Drug Versus Comparator		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CADTH**
Submitted	$82,941	$226,131
10% reduction	$75,680	$204,763
15% reduction	$71,784	$194,391
20% reduction	$67,669	$183,093
25% reduction	$63,554	$171,945
30% reduction	$59,559	$161,600
40% reduction	$52,258	$141,852
50% reduction	$42,981	$120,520
60% reduction	$34,751	$99,723
70% reduction	$26,522	$82,318
80% reduction	$18,292	$57,574
90% reduction	$10,063	$48,589

ICUR = incremental cost-utility ratio.

Information on the Budget Impact Analysis

Manufacturer's Budget Impact Analysis

The manufacturer submitted a budget impact analysis (BIA) that assessed the financial impact of the potential reimbursement of axicabtagene ciloleucel for adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. A model was developed from the perspective of a Canadian health care system using Ontario as a proxy for a non-specific BIA. The manufacturer reported all results in terms of impact on the budget, with a time horizon of three years. Model parameters could be switched to provide the results on the budgetary impact of other individual provinces, or aggregated for all provinces (including Quebec).

The submitted BIA was built in Microsoft Excel using an epidemiology approach and compared two budget scenarios: first, a reference scenario, where patients could access treatment with palliative chemotherapy, the alternate approved CAR T-cell product tisagenlecleucel (Kymriah), or participate in a clinical trial, and second, a new drug scenario, where axicabtagene ciloleucel joins the market and becomes available. For each scenario, the number of patients within the population likely to receive the included therapies was multiplied by the relevant per-patient costs to determine the total costs associated with each therapy (see Figure 1). The budget impact was calculated by subtracting the total costs of the reference scenario and the total costs of the new treatment scenario.

The total number of patients eligible for treatment with CAR T-cell therapy in each reimbursement year was estimated using an epidemiological approach (see Figure 6), leading to an estimated CAR T-cell therapy–eligible population of ▇▇ in year 1, ▇▇ in year 2, and ▇▇ in year 3. To arrive at this total population size for a given year, the population of Ontario in 2017 was filtered by the estimated prevalence of DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma. These patients were then further filtered by the proportion expected to relapse per year, and further narrowed down to include only those who would qualify for CAR T-cell therapy, such as for patients:

- ineligible for subsequent ASCT therapy but who were eligible for CAR T-cell therapy
- considered for ASCT but who did not receive it
- relapsed after receiving ASCT.

The sources of data and assumptions made to arrive at the estimated population size are outlined in Appendix 4.

For each scenario, market share (i.e., the number of patients within the estimated eligible population expected to receive each therapeutic regimen) was derived based on expert opinion. The total CAR T-cell therapy market share was estimated to be ▇▇%, ▇▇%, and ▇▇% in years 1 through 3, respectively, in the reference scenario, all belonging to tisagenlecleucel. With the introduction of axicabtagene ciloleucel in the new drug scenario, the market share for CAR T-cell therapy was estimated to expand in the first year to ▇▇ ▇▇▇ ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇). Of the CAR T-cell therapy market share, ▇▇% was estimated to be captured by axicabtagene ciloleucel, while the remaining ▇▇% would be tisagenlecleucel. Regardless of the scenario evaluated, ▇▇% of patients were assumed to

take part in clinical trials rather than use approved therapies in each year, and the remaining proportion of patients were assumed to be on one of three palliative mono-chemotherapies.

Costs considered included treatment-specific costs and event-related costs, including estimates of the costs associated with administering therapies, leukopheresis, bridging therapies, hospitalization, treating AEs, future therapies such as SCTs, and training costs for administering the therapies. Per-patient event costs associated with each therapy were determined by weighting the cost of each event by its treatment-specific probabilities. Training costs were estimated using the expected cost per training centre, divided by the annual number of patients per centre and the expected number of years required prior to retraining.

Figure 1: Manufacturer's Schematic of Budget Impact Analysis Modelling Approach
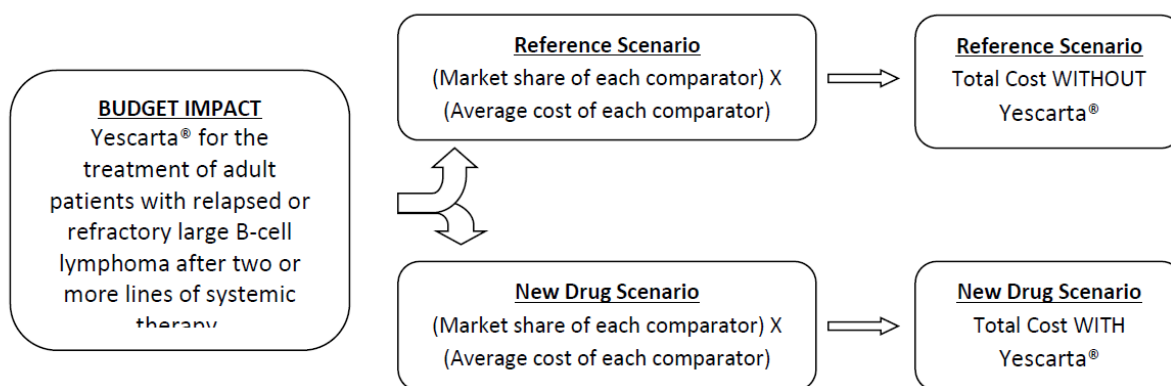
Source: Manufacturer's budget impact analysis submission, Figure 5.[24]

Manufacturer's Base Case

The manufacturer estimated that approximately ▮ patients would be eligible to receive axicabtagene ciloleucel in Ontario for the treatment of r/r DLBCL and other indicated conditions in each of the first three years of its availability, leading to an estimated incremental expenditure of $6.9 million in year 1, and a savings of $1.2 million and $1.5 million in years 2 and 3 when the new drug scenario was compared with the reference scenario, for a total three-year incremental cost of $4.2 million (Table 5). Further details on the methods and results can be found in Appendix 4.

Table 5: Summary of Results of the Manufacturer's Budget Impact Analysis Base Case

Annual Cost Outcomes	Year 1	Year 2	Year 3	3-Year Total[a]
Reference Scenario: Current Treatments Only				
Axicabtagene ciloleucel	$0	$0	$0	$0
Tisagenlecleucel	■	■	■	■
Palliative chemotherapy	■	■	■	■
Investigational therapy	■	■	■	■
Total costs	■	■	■	■
New Treatment Scenario: Axicabtagene Ciloleucel Joins the Market				
Axicabtagene ciloleucel	■	■	■	■
Tisagenlecleucel	■	■	■	■
Palliative chemotherapy	■	■	■	■
Investigational therapy	■	■	■	■
Total costs	■	■	■	■
Budget impact	$6,944,501	($1,224,015)	($1,548,204)	$4,172,282

Note: Budget impact results where the axicabtagene ciloleucel scenario is deemed costs saving are displayed in brackets.[24]

Source: adapted from manufacturer's submission, tables 8, 9, and 10.

The manufacturer also conducted a series of scenario analyses, although the model was found to only be sensitive to incremental differences in the proportion of patients who would be able to access CAR following the addition of axicabtagene ciloleucel to the market (see Table 22 and CAR = chimeric antigen receptor.

Table 23).

Sources of Uncertainty Relating to the Manufacturer's Budget Impact Analysis

CADTH identified a number of key sources of uncertainty and potential limitations relating to the manufacturer's BIA:

Generalizability of population studied in ZUMA-1: Due to inclusion and exclusion criteria within the ZUMA-1 trial, the population assumed within the BIA is reflective of relatively stable patients. For example, the inclusion of patients with an ECOG performance status of only 0 or 1 and the exclusion of patients requiring urgent therapy is likely to favour a younger, more stable set of patients and may not be generalizable to many of the typical patients with r/r large B-cell lymphomas who do not meet the inclusion and exclusion criteria. This is borne out in the median age of people in ZUMA-1, who were predominately American, and 58 years old, while the median age of diagnosis of non-Hodgkin lymphoma (NHL) in the US is 67 years.[25] A 2017 population-based registry study reported that the median age of incident lymphoid neoplasm cases in Manitoba was 67 years of age for men and 71 years of age for women.[14] This was further confirmed as a concern with the clinical expert consulted by CADTH. Additionally, the high proportion of patients within ZUMA-1 who were identified as white may not be generalizable to a Canadian ethnicity distribution. See Critical Appraisal of Pivotal Trial (ZUMA-1) in the clinical report, for more information. A younger, more stable set of patients is likely to experience different effectiveness rates and incur different health care resource use costs than an older and less stable population, leading to increased uncertainty in the budget impact estimated by the manufacturer.

Comparability of the populations studied in the ZUMA-1 and JULIET trials: The ZUMA-1 trial excluded patients who required urgent therapy due to tumour mass effects such as bowel obstruction or blood vessel compression, and did not allow for bridging therapy within its protocol, while 92% of patients in JULIET were given bridging therapy while awaiting infusion. This suggests that the patient populations differed between the two trials, with patients in ZUMA-1 having disease that is sufficiently stable to tolerate the absence of bridging therapy, while those in JULIET and the general population of patients who will be eligible for CAR T-cell therapy in Canada will be able to access bridging therapy if needed. It is inappropriate to assume that 92% of patients using tisagenlecleucel and 0% of patient using axicabtagene ciloleucel will require bridging therapy while simultaneously assuming that axicabtagene ciloleucel would take the market share from those who would otherwise be treated with tisagenlecleucel. The clinical expert consulted by CADTH believed physicians would consider bridging therapy for any patient with a substantial delay in access to CAR T-cell therapy (i.e., more than two weeks). Similarly, as the patients in ZUMA-1 are more likely to be more stable than those of JULIET, differences in the reported length of hospitalization as well as the AE rates are also uncertain.

Inclusion of clinical trials as a relevant comparator: The inclusion of clinical trials as a relevant comparator in the manufacturer's BIA was considered inappropriate as these patients are not receiving approved therapies for the treatment of r/r DLBCL, and allocating ███ of the market share (██ in Alberta) to non-approved therapies artificially restricted the size of the CAR T-cell therapy–eligible population, thereby reducing the estimated budget impact. Moreover, patients entering clinical trials receive investigational therapy from the trial sponsor, but other health care resource use remains reimbursable by the patient's jurisdictional health care payer, which was not accounted for in the manufacturer's model. This does not align to the economic evaluation, which did not consider investigative therapies as an appropriate comparator. The availability of one or more approved CAR T-cell therapies in Canada is likely to change the treatment paradigm over time, making it difficult to predict when and which patients will choose to enter clinical trials rather than seek approved care.

Estimation of the eligible population size: The total number of patients eligible for CAR T-cell therapy was estimated as follows. The five-year prevalence rate of NHL, adjusted by the indicated disease types, was applied to the overall Canadian population. The proportion of patients assumed to have r/r DLBCL each year was then estimated by assuming 30% to 40% of patients would have relapsed within the first two years as reported in the literature, and then further assuming an additional 2% to 3% of these patients would relapse in each of the following three years, in order to align a five-year probability with the five-year prevalence data used. This five-year probability was then converted to an annual probability of approximately 9.5% (this was miscalculated and should reflect approximately 13% after the calculation was corrected). However, these assumptions made by the manufacturer artificially reduced the proportion of patients who would relapse in a given year as it did not adequately account for the increased number of patients who would be eligible for CAR T-cell therapy in the first year of availability (those who relapsed within the past year and those who relapsed in previous years who are still alive; i.e., the prevalent population of r/r patients) and a reduced number of new r/r patients in years 2 and 3 (i.e., the incident population of r/r patients). The manufacturer's calculation further did not account for patients who would be refractory to first-line therapy as it only accounted for those who responded and then relapsed. Together, the manufacturer's approach underestimated the eligible population and thereby reduced the estimated total budget costs associated with axicabtagene ciloleucel.

Uncertainty in the price of tisagenlecleucel: There is currently no publicly available price for tisagenlecleucel in Canada, nor is it known what price will be negotiated by Canadian health care payers. CADTH considered the manufacturer's assumption that tisagenlecleucel will cost the same as the submitted price of axicabtagene ciloleucel to be appropriate for the base case; however, the absence of a true cost for either therapy increases the uncertainty in budget impact estimates.

Inappropriate incorporation of hospitalization and AE costs: The manufacturer calculated the costs of hospitalization associated with initiating CAR T-cell therapy by multiplying the average cost of an elective in-patient stay for a lymphoma intervention (reported as Canadian Institute for Health Information Case Mix Group 614, data not provided) by the median length of stay in the ZUMA-1 and JULIET trials for axicabtagene ciloleucel and tisagenlecleucel, respectively. With the exception of CRS, all AEs were assumed to be treated within this hospitalization period and were thus not included separately within the budget impact model; the clinical expert consulted by CADTH believed it would be plausible that some AEs, particularly infections and central nervous system toxicities, would occur later. The cost of CRS was separately calculated by multiplying the cost of an intensive care unit stay (reported as Canadian Institute for Health Information Case Mix Group 654, Unspecified Sepsis, data not provided) by the time to CRS resolution reported in the clinical trials with the additional cost of tocilizumab treatment also incorporated until resolution. It is unclear why CRS was separated from the costs of other AEs. Due to the hard coding of hospitalization costs into the budget impact model rather than transparent calculations from the source data, the ability to verify, explore, or correct errors within these assumptions is precluded. As previously noted, there are reasons to believe that the populations studied in ZUMA-1 and JULIET were not the same. The assumption of different lengths of stay and AE resolution are unlikely due to differences in CAR T-cell products but rather due to differences in study population baseline health.

Uptake of axicabtagene ciloleucel: The market adoption rates for axicabtagene ciloleucel were based on individually assumed rates within each province, the elicitation of which were not explained within the submission, but appear to be based on the availability of treatment delivery sites for both axicabtagene ciloleucel and tisagenlecleucel. The potential uptake of both CAR T-cell products is uncertain, and market share estimates for each product cannot currently be validated.

Use of Ontario as a proxy: The manufacturer's decision to report the budget impact of Ontario alone, rather than a national perspective, is an issue due to differences in access to CAR T-cell therapy across the country. The availability of treatment centres will vary by province and by CAR T-cell product, as will the proximity of the affected population to a treatment centre within a jurisdiction. The centering of Ontario, a large province that is predicted to have access to both products, may not be representative of the country as a whole.

Exclusion of IVIG therapy costs: Thirty patients in ZUMA-1 (30%) received IVIG therapy following axicabtagene ciloleucel treatment, while 17 (16%) were reported as having B-cell aplasia (see tables 27 and 28 in the Notable Harms section in the clinical report). IVIG therapy is an expensive treatment used to treat B-cell aplasia, which is likely to be required indefinitely for many patients receiving CAR T-cell therapy. While it is unclear why the patient proportions reported as using immunoglobulins and having B-cell aplasia differs so substantially, excluding the cost of IVIG biases the analysis in favour of CAR T-cell therapies when compared with palliative chemotherapy.

Other limitations noted by CADTH included:

Patients who do not receive CAR T-cell infusion: Ten patients within ZUMA-1 underwent leukapheresis but did not receive axicabtagene ciloleucel, including five who had an AE, three who died, and two who had non-measurable disease progression before conditioning chemotherapy. The costs of therapies and treatments these patients did receive were not included within the model.

CADTH Reanalyses of the Budget Impact Analysis

CADTH attempted to account for some of the important shortcomings regarding the manufacturer's BIA. Before undertaking any reanalyses, CADTH corrected modelling errors (appropriate conversion of annual probability of relapse from a multi-year probability of relapse based on methods laid out in Briggs 2006,[26] calculating the five-year prevalence of NHL from 2009 cancer case data using the 2009 population of Canada rather than 2017 to ensure estimates were from the same year, revising the dose of conditioning chemotherapy used prior to tisagenlecleucel treatment to be consistent with the product monograph[27]), as well as incorporating a national level perspective and ensuring consistency in the calculation methods between scenarios. After these modelling errors were corrected, CADTH subsequently conducted the following reanalysis:

1. An assumption of an identical population of patients within the reference and new drug scenarios was incorporated, meaning the same proportion of patients would require bridging therapy (56%)[18] regardless of which CAR T-cell product they are assigned to. Furthermore, CAR T-cell therapy patients would have similar AEs, require similar hospitalization time, and have a similar probability of requiring SCT.

2. The ▮▮▮▮ of patients assigned to participate in clinical trials by the manufacturer are instead proportionally reassigned to axicabtagene ciloleucel, tisagenlecleucel, or palliative chemotherapy.

3. Year 1 incorporates two-year prevalence data of NHL as reported by Canadian Cancer Statistics 2017, rather than the five-year prevalence rate, and years 2 and 3 were informed by the projected annual incidence rate of new NHL cases.[28]

4. Assumption that 35% of NHL cases are DLBCL, PMBCL, or TFL (i.e., the midpoint of the 30% to 40% range estimate by Raut et al. 2014[29] and Lymphoma Canada,[30]) was incorporated rather than the manufacturer's assumption that 85% of NHL cases are B-cell lymphomas, in which 30% to 40% are DLBCL, PMBCL, or TFL.

5. The annual probability of relapsed cases after initial therapy was set to 19.38%. This was derived by converting the reported two-year probability of relapse of 35% (the midpoint of the 30% to 40% estimation from the literature used by the manufacturer).[24,31] These annual probabilities were then applied to the prevalent population of patients in year 1, and the newly incident cases in years 2 and 3.

6. An additional 10% of cases are refractory to initial therapy, consistent with Raut et al. (2014).[29] As refractory cases are known relatively soon after treatment, for the purposes of the individual reanalyses around the manufacturer's base case (i.e., Table 6, scenario 6), this number was transformed to 2% to be consistent with the use of five-year prevalence data (i.e., approximately one-fifth of 10% of total patients would have been treated and become refractory within the previous year, while the remaining four-fifths are likely already deceased). The 10% figure was used in CADTH's base case due to the methodological difference in calculating the overall population of patients.

7. The 9% of patients in ZUMA-1 who underwent leukapheresis but did not subsequently receive axicabtagene ciloleucel treatment were accounted for by inflating the cost of leukapheresis by 8.3% for both CAR T-cell therapies.

The CADTH base case was informed by all of the previously described reanalysis (one to seven) and shown in Table 6. The introduction of axicabtagene ciloleucel to the Canadian market is associated with an additional cost of approximately $51.6 million in year 1, $28.6 million in year 2, and $18.6 million in year 3, for a cumulative total of approximately $98.8 million dollars over the first three years.

Table 6: CADTH Reanalysis of Limitations

Scenario	Annual Cost Outcomes	Scenario	Year 1	Year 2	Year 3	3-Year Total
	Base case, submitted by manufacturer, national population	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$25,534,739**	**$19,913,611**	**$12,403,292**	**$57,851,643**
	Base case, submitted by manufacturer, errors corrected	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$33,184,456**	**$23,243,079**	**$12,364,680**	**$68,792,215**
1	Patient population identical between scenarios, with similar health care use	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$35,787,851**	**$27,713,305**	**$18,188,188**	**$81,689,343**
2	No patients assigned to clinical trials	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$37,454,751**	**$26,463,904**	**$14,379,119**	**$78,297,774**
3	Year 1 NHL population based on 2-year prevalence data, years 2 and 3 based on incidence data	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$15,427,295**	**$7,686,316**	**$4,226,728**	**$27,340,339**
4)	Indicated cancers make up 30% to 40% of NHL cases	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$36,850,641**	**$25,810,951**	**$14,193,519**	**$76,855,111**
5	Annual probability of relapse of 19.38%	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$49,674,161**	**$34,792,810**	**$19,132,671**	**$103,599,642**
6	Additional 10% of patients are refractory to first-line treatment	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$38,311,470**	**$26,834,146**	**$14,756,177**	**$79,901,794**
7	Cost of leukapheresis inflated to account for patients who did not subsequently receive CAR T-cell therapy	Reference	▓	▓	▓	▓
		New drug	▓	▓	▓	▓
		Incremental	**$33,191,981**	**$23,248,904**	**$12,785,258**	**$69,226,142**
1 to 7	CADTH base case	Reference	▓	▓	▓	▓

Scenario	Annual Cost Outcomes	Scenario	Year 1	Year 2	Year 3	3-Year Total
		New drug	███████	███████	███████	███████
		Incremental	**$51,591,760**	**$28,613,942**	**$18,595,522**	**$98,801,223**

CAR = chimeric antigen receptor; NHL = non-Hodgkin lymphoma.

Additionally, due to uncertainty in the confidential price of tisagenlecleucel, as well as the potential for a negotiated confidential reduction in price for axicabtagene ciloleucel, a series of price reduction scenarios were conducted around the CADTH base case, varying the price of both CAR T-cell products (see Table 7).

Table 7: CADTH Reanalysis Price Reduction Scenarios

Three-Year Incremental Budget Impact of Axicabtagene Ciloleucel Under Various Price Reduction Scenarios								
		Price of Tisagenlecleucel ($)						
	Base price: ███████	**Base Price**	**10% Reduction**	**20% Reduction**	**30% Reduction**	**40% Reduction**	**50% Reduction**	**60% Reduction**
Price of Axicabtagene Ciloleucel ($)	Base price	98,801,223	██████	██████	██████	██████	██████	██████
	10% reduction	██████	██████	██████	██████	██████	██████	██████
	20% reduction	██████	██████	██████	██████	██████	██████	██████
	30% reduction	██████	██████	██████	██████	██████	██████	██████
	40% reduction	██████	██████	██████	██████	██████	██████	██████
	50% reduction	██████	██████	██████	██████	██████	██████	██████
	60% reduction	██████	██████	██████	██████	██████	██████	██████

Note: Brackets indicate that the introduction of axicabtagene ciloleucel would be cost saving at the proposed price reductions.

As the CADTH reanalysis assumed most variables are equivalent between axicabtagene ciloleucel and tisagenlecleucel, a series of sensitivity analyses were conducted to explore potential parameter and structural uncertainty. As seen in Table 28, the primary driver of the increase in budget associated with the availability of axicabtagene ciloleucel was the increase in market share for CAR T-cell therapy compared with palliative chemotherapy with the availability of two products rather than one.

Issues for Consideration

- **Travel costs:** Travel costs for patients who do not live near centres or who live in jurisdictions without centres have not been incorporated, regardless of whether they would be reimbursed by the public health care payer. Costs are likely to be required for patients from locations other than major cities, who would be required to stay locally for an extended period of time for leukapheresis, monitoring, and infusion. Although the CADTH base-case analysis was conducted without explicit consideration to which jurisdictions will have centres, there may be differences in both the cost-effectiveness and budgetary impact of CAR T-cell therapy in jurisdictions that do not have a centre or where significant proportions of the population would have to travel to access a centre.

- **Retreatment with axicabtagene ciloleucel:** Eight per cent of patients in ZUMA-1 received a second dose of axicabtagene ciloleucel.[32] Although the Health Canada product monograph states that axicabtagene ciloleucel is available as a one-time treatment,[1] should a second dose of axicabtagene ciloleucel be required, it remains unclear what proportion of the product cost would be borne by public health care payers.

Furthermore, additional hospitalization, bridging therapy, and AE costs would apply and have not been accounted for in the existing BIAs.

- **Capacity constraints:** The availability of CAR T-cell therapy is expected to cause capacity constraints and worsen hospital overcrowding. This concern is supported by the median length of hospitalization observed in both JULIET and ZUMA-1 (23 days and 15 days, respectively). Additionally, this prolonged hospitalization may also impose additional financial burden, such as travel and accommodation costs, to patients and their caregivers.

- **Manufacturing failures or compromised doses:** The manufacturer has specified that, in cases of manufacturing failure, jurisdictions will not pay for the cost of the failed product.[33] However, this does not account for the costs associated with increased hospital stay while a second sample is prepared, if possible and required, nor alternate treatment if initiated, nor the impact on patient outcomes due to treatment delays or compromised doses. Manufacturing failure may be due to losses following equipment failure, while compromised doses within ZUMA-1 included a cracked product infusion bag, failure to maintain optimum temperature during transport, or an improperly sealed apheresis bag that led to cells being exposed to tubing.

- **Place in therapy:** Although CAR T-cell therapies have shown encouraging results in adults with r/r DLBCL who are ineligible for or have relapsed after SCT, it is not yet clear whether CAR T-cell therapy can be used at different stages of therapy, such as first-line use.

- **Long-term clinical impacts:** The limited clinical experience with CAR T-cell products in general and axicabtagene ciloleucel specifically, along with the small sample size and short follow-up of the pivotal trial, cause high uncertainty about the long-term health outcomes and side effects due to the presence of cells that have been genetically manipulated.

- **Unrelated medical costs:** Although the existing CADTH guidelines do not recommend inclusion of unrelated medical costs, potentially curative therapies, such as axicabtagene ciloleucel and tisagenlecleucel, may lead to longer life expectancy in patients and thereby incur future costs to the health care system. This was not considered in the economic analysis.

- **Start-up costs:** Depending on the number of sites that will be offering CAR T-cell therapy in Canada, there may be potential start-up costs associated with new treatment facilities to be able to deliver this novel therapy. Although the manufacturer considered the costs of training, it is unclear what other opportunity costs may be associated with implementing CAR T-cell products in general, and axicabtagene ciloleucel in particular, that will need to be borne by public health care payers.

Patient Input

Two patient groups submitted input regarding axicabtagene ciloleucel — Lymphoma Canada and The Leukemia and Lymphoma Society of Canada. Patients with r/r DLBCL have undergone one or more first-line therapies (chemotherapy, radiation, and SCT) and possibly many years of cancer treatment. Physically, they have experienced a host of side effects, with fatigue, inability to be physically active, hair loss, pain, constipation, nausea, and vomiting reported as treatment-related side effects greatly impacting their lives. Treatment also affected patients' mental health, leading to stressors in the form of fear, anxiety, depression, brain fog, fatigue, and difficulty sleeping.

The financial well-being of patients and their families was strained by patient-borne costs of treatment, and reduced ability to work, both which have not been evaluated in the existing economic review. Oftentimes, a partner or other family member also had to leave or reduce work in order to act as a caregiver. Those patients with children still at home struggled to fulfill their family responsibilities.

CAR T-cell therapies were seen to represent a last resort for many patients with r/r DLBCL. They hoped that these therapies would enable them to go into remission and that they would be able to live longer with fewer side effects. Patients responding to the patient group–input submissions expressed a range of views on the tolerability of CAR T-cell therapy–associated side effects, some considering it as easier than an ASCT, while others described it as a very difficult treatment, although it is unclear whether these patients had prior experience with CAR T-cell therapy. The costs associated with travel for treatment were a significant concern to patients, including having to travel for initial assessment, cell collection, infusion, and then monitoring. These costs are a substantial burden associated with patients' access to CAR T-cell therapy.

Of note, the perspectives of patients who died after receiving therapy and who could therefore not participate in providing input to CADTH are not represented; the experiences of these patients may not be reflected in the input received. See the Summary of Patient Input section of the Ethics and Implementation Report for further information.

Conclusions

Uncertainty remains in the comparative treatment effects given the heterogeneity between the clinical sources that informed the efficacy and safety of axicabtagene ciloleucel and BSC, as well as tisagenlecleucel. Similar to the conclusion of the clinical report, the critical limitations of the indirect treatment comparisons render the true potential comparative benefits and the true cost-effectiveness of axicabtagene ciloleucel compared with tisagenlecleucel to be unknown. Interpretation of the validity of the manufacturer's model was further challenged by the fact that the clinical trial population upon which economic results were based consist of relatively stable patients that may not be generalizable to patients who are less stable or who do not meet the strict inclusion criteria of the trials. The results require careful interpretation.

CADTH estimated that the ICUR for axicabtagene ciloleucel compared with BSC was $226,131 per QALY gained. To achieve an ICUR of $50,000 per QALY compared with BSC, the price of axicabtagene ciloleucel would need to be reduced by 83%. The estimated ICUR for axicabtagene ciloleucel compared with BSC was highly sensitive to assumptions regarding the population age and long-term mortality. Little can be elucidated regarding the comparative cost-effectiveness of axicabtagene compared with tisagenlecleucel given the substantial clinical heterogeneity. This was considered in exploratory analyses by CADTH.

In terms of budget impact, CADTH conservatively estimated that, due to uncertainty in the populations studied in the existing clinical trials, it is likely that the additional treatment-related care costs would be similar between CAR T-cell treatments if treating an identical population. Thus, the total cost of treatment with axicabtagene ciloleucel or tisagenlecleucel may be more similar than has been assumed by the manufacturer. CADTH reanalyses estimated that the introduction of axicabtagene ciloleucel could result in incremental expenditure of $51.6 million in year 1, $28.6 million in year 2, and $18.6 million in year 3. Sensitivity analyses suggest this increase in cost is primarily driven by increased numbers of patients being able to access CAR T-cell therapy due to the availability of multiple products and the increased number of treatment centres. Given that there are no public Canadian prices for tisagenlecleucel, considerable uncertainty in the price of tisagenlecleucel remains. Caution is therefore required in interpreting the budget impact findings as the results were highly sensitive to the cost of CAR T-cell therapy. If the price of tisagenlecleucel is lower than that used in the analysis (where the price of tisagenlecleucel was assumed identical to that of axicabtagene ciloleucel), the likely budget impact of adopting axicabtagene ciloleucel would be higher than currently estimated.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Chimeric Antigen Receptor Modified T-cell Therapies for Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Drug/Comparator	Applicable Indication	Dosage Form	Price ($)	Recommended Dose	Product Cost per Course of Therapy ($)
Axicabtagene ciloleucel (axicabtagene ciloleucel)	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma[a]	Suspension for IV infusion	■■■■[b]	Target of 2×10^6 anti-CD19 CAR T cells/kg body weight (range: 1×10^6 to 2.4×10^6 cells/kg) to a maximum of 2×10^8 anti-CD19 CAR T cells[a]	■■■■
Tisagenlecleucel (Kymriah)	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma[c]	Suspension for IV infusion	No public price available	0.6 to 6.0×10^8 CAR-positive viable T cells (non-weight based)[c]	Unknown

CAR = chimeric antigen receptor; CD19 = cluster of differentiation; DLBCL = diffuse large B-cell lymphoma.

Note: Prices include only the cost of the CAR T-cell therapy infusion and do not include administration, hospitalization, or conditioning chemotherapy costs.

[a] Manufacturer-submitted price.[3]

[b] Axicabtagene ciloleucel product monograph[1]

[c] Tisagenlecleucel is also indicated for pediatric and young adult patients 3 to 25 years of age with B-cell acute lymphoblastic leukemia who are refractory, have relapsed after autologous stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse. Dosages for such patients are different.[27]

Appendix 2: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking "no"	Within the economic evaluation, there were some instances of uncertainty in why certain models and distributions were chosen. There were some instances where assumptions were not backed up by plausible claims, a key one being the assumed long-term mortality rate for patients being equal to that of the general population. The BIA was overall less clear and less transparent than the economic evaluation.		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking "poor"	The manufacturer's model only permitted probabilistic analysis of their default values. CADTH had to shut off certain section of their VBA code to permit probabilistic CADTH reanalyses. Inputs within the BIA were hard-coded rather than calculated from transparent source inputs, making review and exploration of assumptions difficult. Many inputs were inadequately cited.		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking "poor"			

BIA = budget impact analysis; VBA = Visual Basic for Applications.

Table 10: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH
☐ Adaptation of global model/Canadian model done by the manufacturer
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

Appendix 3: Detailed Information — Economic Submission

Table 11: Summary of the Manufacturer's Economic Submission

Drug Product	Axicabtagene Ciloleucel (Yescarta)
Study Question	Primary analysis: What is the cost-effectiveness of axicabtagene ciloleucel compared with best supportive care, including salvage chemotherapy and palliative care, in adult patients relapsed or refractory (r/r) large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (BCL), and DLBCL from follicular lymphoma, after two or more lines of systemic therapy and who are not eligible for autologous SCT from the perspective of provincial health reimbursement authority? Secondary analysis: What is the cost-effectiveness of axicabtagene ciloleucel compared with tisagenlecleucel in adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy from the perspective of provincial health reimbursement authority?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Treatment	Single intravenous infusion of axicabtagene ciloleucel
Outcome(s)	Quality-adjusted life-years, total health care costs
Comparator(s)	Primary analysis: Best supportive care defined as salvage chemotherapy, including gemcitabine, etoposide, and cyclophosphamide Secondary analysis: Tisagenlecleucel
Perspective	Canadian ministry of health
Time Horizon	44 years (maximum age 100)
Results for Base Case	Primary analysis: The ICUR for axicabtagene ciloleucel vs. BSC was $84,030 per QALY gained. Secondary analysis: Axicabtagene ciloleucel was dominant to tisagenlecleucel (i.e., lower costs, higher effectiveness)
Key Limitations	• Lack of head-to-head comparative efficacy and safety of axicabtagene ciloleucel, salvage chemotherapy, and tisagenlecleucel • Generalizability of the patient population as baseline patient characteristics were informed by the ZUMA-1 study that recruited a younger population than would be expected in Canada • Approach to model cured patients would underestimate the long-term mortality and overestimate the utility of these patients, favouring axicabtagene ciloleucel • Inappropriate modelling and distributional assumptions in estimating OS • No censoring due to subsequent treatment or retreatment • Pre-infusion period parameters between the two CAR T-cell therapies, informed by the available clinical data, were not comparable, including the expected duration and the need for bridging therapy • Uncertainty in progression-free survival in the comparators • Uncertainty around the costs of tisagenlecleucel • Long-term costs and implementation costs underestimated

| CADTH Estimate(s)	• Interpretation of the validity of the manufacturer's model is challenged by the fact that the clinical trial population upon which economic results were based consist of a selective population that may not be generalizable to the Canadian population • The ICUR of axicabtagene ciloleucel compared with BSC is estimated to be $226,131 per QALY gained. The probability that axicabtagene ciloleucel is cost-effective was 0% at a willingness-to-pay threshold of $50,000 per QALY • The ICUR comparing axicabtagene ciloleucel with tisagenlecleucel is estimated to be $3,871 per QALY gained. Results for tisagenlecleucel should be interpreted with caution given the significant limitations, including uncertainty in comparative treatment effects and uncertainty in the true price for tisagenlecleucel • A price reduction of 83% (vs. BSC) would be required for axicabtagene ciloleucel to be cost-effective at a threshold value of $50,000 per QALY

BCL = B-cell lymphoma; BSC = best supportive care; DLBCL = diffuse large B-cell lymphoma; ICUR = incremental cost-utility ratio; PMBCL = primary mediastinal B-cell lymphoma; QALY = quality-adjusted life-years; r/r = relapsed or refractory; SCT = stem cell transplant; vs. = versus.

Manufacturer's Model Structure

The cost-utility analysis submitted by the manufacturer compared axicabtagene ciloleucel with best supportive care (BSC) in the primary analysis and with tisagenlecleucel. The model structure was a partitioned survival model (i.e., progression free, progressed disease, and death). The model simulated 5,000 individuals through the partitioned survival model for a period of 44 years (i.e., maximum age of 100). Costs and utilities were applied to each state to calculate total average costs and quality-adjusted life-years (QALYs). All patients enter the model in the event-free state and, for the patients receiving chimeric antigen receptor T-cell therapy, the model had the option of beginning at either leukapheresis or infusion time points. The simple three-state model is presented in Figure 2.

This modelling approach requires two survival curves to estimate state membership over time. Specifically, the overall survival (OS) curve estimated the proportion of patients alive over time with statistical extrapolation to model beyond the clinical study's time horizon. Similarly, progression-free survival (PFS) informed the proportion of patients in the progression-free health state. The proportion of patients with progressed disease was estimated as the difference between the proportion of living patients (estimated from the OS curve) and the proportion of progressed-free patients (estimated from the PFS curve).

Figure 2: Model Structure
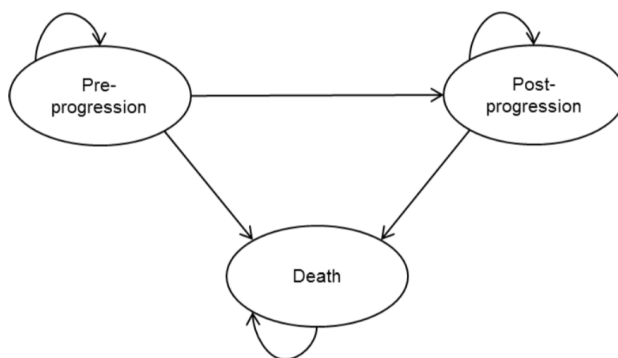
Source: Manufacturer's economic submission.[3]

The OS and PFS curve for axicabtagene ciloleucel were informed directly from the ZUMA-1 clinical trial data. As there are no head-to-head clinical studies comparing the efficacy of axicabtagene ciloleucel with relevant comparators, indirect treatment comparison was conducted to inform OS and PFS for the comparator treatment. The OS curve were informed from SCHOLAR-1 data for BSC while ████████████████████████ ██ ██ ████████████████████ The PFS curve for both comparators were based on applying a time-dependent ratio of PFS to OS from axicabtagene ciloleucel to extrapolate the PFS from the estimated comparator's OS curves.

Table 12: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	ZUMA-1	It was noted by the clinical expert that the median age of 58 is younger than what would be expected within the Canadian context. The estimated average age for patients with r/r DLBCL in Canada is age 67 years.[14] It was noted in the CADTH clinical report that the high proportion (85%) of patients in the sample identified as white in ZUMA-1 may not be generalizable to the ethnicity distribution likely expected in the Canadian context.
Efficacy	• Axicabtagene ciloleucel OS and PFS uses phase II ZUMA-1 (n = 101), August 2018 data cut-off. • BSC OS relies on SCHOLAR-1 data with a crude adjustment of removing all patients with ECOG 2 to 4. ██████████████████████ ██████████████████████ ██████████████████████ ██████████████████ • BSC and tisagenlecleucel PFS are derived from assuming that the fixed ratio between OS and PFS in axicabtagene ciloleucel can be applied to the constructed OS of the BSC and tisagenlecleucel.	Patients in the SCHOLAR-1 study received chemotherapy regimens that may not be reflective of the chemotherapies used in Canadian clinical practice. This may bias results in favour of axicabtagene ciloleucel if older treatments had less durable survival rates. Extrapolation of long-term survival is highly uncertain given limited time horizon of available data and uncertain long-term effects of CAR t-cell treatment. Baseline characteristics between ZUMA-1, SCHOLAR-1, and JULIET were notably different, with heterogeneous factors that cannot be controlled for in analysis. SCHOLAR-1 includes patients with primary refractory disease and a large number who had undergone previous autologous SCT who would thus not be eligible for axicabtagene ciloleucel. The ZUMA-1 patient population was older, had a higher number of previous treatments, and was more likely to have advanced disease. Missing data in SCHOLAR-1 made it difficult to match on these characteristics. Key differences in study design between ZUMA-1 and JULIET related to patient selection, use of bridging chemotherapy in JULIET, and use of retreatment in ZUMA-1. The lack of direct head-to-head comparisons increases the uncertainty on comparative efficacy and safety. Inappropriate due to limited comparability of underlying data for each treatment strategy.
Natural history	• Manufacturer submitted a three-state partitioned survival model (pre-	A number of limitations stem from the use of a partitioned survival model, which have been documented in the

Data Input	Description of Data Source	Comment
	progression, post-progression, and death). OS and PFS curves informed proportion of patients in each health state over time.	past.[21] A partition-survival model assumes that the modelled survival end points are structurally independent. This structural assumption is potentially problematic because PFS and OS are dependent. In addition, the manufacturer assumed the existence of a cure state, which is implicitly assumed in the partitioned survival structure but that would have been more appropriate to be modelled explicitly.
Utilities	• HRQoL data were collected in a safety management cohort of ZUMA-1. A crosswalk algorithm[34] was used to convert EQ-5D-5L to EQ-5D-3L. • A one-off QALY decrement for AEs was applied in the first model cycle. • After two years, individuals were assumed to have equal utility values as the age- and gender-matched general population.[8]	The manufacturer does not appear to differentiate across subsequent treatments, which may have differing utility impacts. Notably, the impact of SCT-related disutility could impact the average utility values across treatments given differing levels of SCT post-treatment. While the manufacturer uses health utility values directly from the ZUMA-1 trial, there is no differentiation across pre-treatment (conditioning) and post-infusion that would likely impact utility and be different across BSC and CAR T-cell treatments. The manufacturer does not include health utility decrements for the portion of the population that is 1) retreated with axicabtagene ciloleucel or tisagenlecleucel; 2) those that receive SCT post-infusion. However, this may not have a large impact on results.
Adverse events	• The manufacturer included treatment-related and chemotherapy-related AEs of grade ≥ 3 and occurring in ≥ 10% of subjects in ZUMA-1/JULIET trials. Grade ≥ 3 treatment-emergent cytokine release syndrome (CRS) occurring in ZUMA- 1/JULIET was also included. • Key AEs were encephalopathy, febrile neutropenia, neutropenia, hypotension, pyrexia, infections, anemia, neutrophil count decreased, platelet count decreased, white blood cell count decreased, thrombocytopenia, and hypophosphatemia.	The impact of AEs on the cost-effectiveness may not have been adequately considered, biasing in favour of CAR T-cell therapies. Previous submissions have included AEs occurring in ≥ 5% of the trial population; this excludes fatigue, hypokalemia, paresthesia, stomatitis, and vomiting. B-cell aplasia was also not considered. The manufacturer did not include AEs for BSC. The manufacturer includes differences in AE onset and duration between the two CAR T-cell therapies, favouring axicabtagene ciloleucel. Differences are not likely in broadened implementation, making this assumption inappropriate.
Mortality	• General Canadian age- and sex-specific mortality rates were used to inform long-term mortality after two years.	Inappropriate. The assumption is backed by a recent paper on mortality of NHL patients that receive standard chemotherapies and are on first diagnosis.[8] It is not reflective of the population of interest. Being that patients are multi-relapsed, and a large portion have received autologous SCT prior to treatment, mortality is likely higher.
Resource Use and Costs		
Drug	• Axicabtagene ciloleucel has a one-time cost of ▮▮▮▮▮▮▮, including all shipping and packaging to and from the manufacturing site, engineering and generation of the CAR T cells. The manufacturer noted that this also	It is unclear if BSC monotherapies were appropriate and reflective of current care. Assuming equal market share is inappropriate. However, this is unlikely to have a large impact on the results of the economic model. Value-based pricing schemes have not been considered.

Data Input	Description of Data Source	Comment
	includes the cost of potential retreatment. • The authors assumed the same price of ▮▮▮▮▮ for tisagenlecleucel. • BSC represented a blended comparator comprised of three mono-chemotherapies. Unit costs for these therapies were taken from a pCODR Economic Guidance Report. Each regimen was assumed to be prescribed 33% of the time.	
Administration	• Administration costs for axicabtagene ciloleucel and tisagenlecleucel include the costs of leukapheresis, conditioning chemotherapy, and cell infusion and monitoring. All costs were assumed to be incurred in the first model cycle. • Analysis included 9.3% of patients receiving retreatment. Additional costs for conditioning chemotherapy, cell infusion, and monitoring were applied to this population but no second manufacturing cost. • BSC administration costs included physician services for an outpatient administration of chemotherapy.	Appropriate. However, it is unclear if retreatment levels are reflective of CAR T-cell product durations (i.e., is axicabtagene ciloleucel less durable than tisagenlecleucel?) and if having differing proportions retreated is appropriate.
SCT	• A cost of SCT was applied to ▮▮ of patients in the axicabtagene ciloleucel arm of the model, 5% in tisagenlecleucel, and 29% of patients in BSC. • SCT costs taken from the Ministry of Health and Long-Term Care Interprovincial Billing Rates for Designated High Cost Transplants, with an assumed cost of $155,611 per allogeneic transplant.	Appropriate.
Bridging therapy	• Bridging therapy is included only in tisagenlecleucel in accordance with the JULIET trial. A one-time cost of $19,816 was applied to 92% of patients.	Inappropriate according to the clinical expert consulted by CADTH. It is unlikely that clinicians would not allow a patient requiring bridging therapy to receive it while waiting for infusion with axicabtagene ciloleucel.
AEs	• AE costs were applied as a one-off cost in the first model cycle to axicabtagene ciloleucel and tisagenlecleucel. Outside of CRS these were assumed to be captured in the hospital stay costs for the first 15 days post-infusion. • For axicabtagene ciloleucel, a CRS hospitalization was costed to be $8,744.77 based on a stay of six days till CRS resolution and $11,659.69 for tisagenlecleucel based on a stay of eight days till CRS resolution. The weighted average cost of CRS	The manufacturers may have underestimated the cost of AEs. According to the clinical expert consulted by CADTH, it is unlikely that there would be a difference in length of stay for acute CRS. Different findings noted from separate one-arm clinical trials are unlikely clinically meaningful. The model may have underestimated resource use cost because it did not include cost of IVIG that may occur for years after infusion in axicabtagene ciloleucel and tisagenlecleucel.

Data Input	Description of Data Source	Comment
	treatment and hospitalization for the axicabtagene ciloleucel treatment arm was $2,678.81 and $5,907.35 for JULIET.	
Health state	• The model also included baseline health resource use in pre-progression and post-progression states. These include physic visits, laboratory fees, radiological tests, and hospitalization. After two years it is assumed that no resource use costs occur. • A cost of death was included at the time of death as an average cost of $31,096.05 to include the use of palliative services by patients in Ontario between 2002 and 2003 for adults who died with cancer.	Appropriate.
Training	• For axicabtagene ciloleucel and tisagenlecleucel treatment arms, a per-patient cost of $123.63 for training health care professionals in the use products was included in the base case. This was based on hours of training at a centre and number of patients expected to be treated at that centre.	The model does not include costs associated with implementing new service delivery methods or facilities. It is unclear who pays for training and whether that occurs at the provincial or hospital level.

AE = adverse event; BSC = best supportive care; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; HRQoL = health-related quality of life; IVIG = intravenous immunoglobin; OS = overall survival; pCODR = CADTH pan-Canadian Oncology Drug Review; PFS = progression-free survival; QALY = quality-adjusted life-years; r/r = relapsed or refractory; SCT = stem cell transplant.

Table 13: Manufacturer's Key Assumptions

Assumption	Comment
A comparison of axicabtagene ciloleucel and BSC can be compared using independent trials/studies: ZUMA-1 and SCHOLAR-1. A comparison of axicabtagene ciloleucel and tisagenlecleucel can be made using two independent trials/studies: ZUMA-1 and JULIET.	Inappropriate. This comparison is likely not valid given key differences in patient characteristics between ZUMA-1, SCHOLAR-1, and JULIET. With limited data on which to match patients, the differences in underlying patient characteristics lead to starkly different outcome that are biased. These lead the comparisons to be of little interpretable use. Without the ability to receive new data on which to measure, scenario analysis adjusting the expected OS and PFS of each treatment can be tested in sensitivity.
The ratio between OS and PFS in the axicabtagene ciloleucel arm can be applied to the BSC OS and tisagenlecleucel OS to estimate progression.	Appropriate. Given the lack of data on PFS for comparator treatments, an imputed PFS was required. It was noted as a limitation. The manufacturer currently tests this assumption through assuming either 100% or 0% of patients remain in event-free. This can be tested in sensitivity at a more granular level.
Cure was defined at two years. Beyond month 24 in the PFS state it is assumed that utility is equal to the age- and gender-matched general population utility values and mortality is equal to the age- and gender-matched general population mortality. No monitoring costs are included.	Inappropriate. It is unclear if a cure point at two years is appropriate given the lack of survival data past this time point. While utility values do appear to converge back to general population age- and sex-adjusted utility,[35] the mortality rate is likely to be higher.[15,36-38] The authors tested this assumption in scenario analyses by using a percentage decrement to the age- and gender-matched general population utility. No monitoring costs after two years in inappropriate given the likelihood of IVIG treatment and monitoring for an indefinite period of time post-treatment.
All grade 3 or 4 AEs for axicabtagene ciloleucel, other than cytokine release syndrome and B-cell aplasia, do not incur treatment costs and are accounted for in the median hospitalization for administration and monitoring of 15 days for axicabtagene ciloleucel and average of 26 days for tisagenlecleucel.	This is a reasonable assumption except for the exclusion of B-cell aplasia with treatment using IVIG replacement that may go on for an undetermined amount of time. Excluding IVIG will decrease the overall costs of CAR T-cell products, biasing resulting in favour of axicabtagene ciloleucel for the primary analysis but having a net zero effect on the secondary analysis.
The comparator regimens that make up the "blended comparator" for the BSC arm are assumed to be used in equal proportions in Canadian clinical practice.	Appropriate. These regimens might not reflect current BSC; however, the cost is not likely to make a large difference in overall comparative cost outcomes.

AE = adverse events; BSC = best supportive care; CAR = chimeric antigen receptor; IVIG = intravenous immunoglobin; OS = overall survival; PFS = progression-free survival.

Manufacturer's Results

The manufacturer ran a Monte Carlo simulation of 5,000 patients through all treatment strategies. For comparisons between axicabtagene ciloleucel and BSC, it reported each simulation as a point on the cost-effectiveness plane (Figure 3). The results reported in Table 14 present the averages of these points to estimate the average incremental cost per incremental QALY. Similar results for axicabtagene ciloleucel compared with tisagenlecleucel can be found in Figure 4. Note that, compared with BSC, axicabtagene ciloleucel was always more costly and resulted in increased QALYs. For the comparison with tisagenlecleucel, there is greater uncertainty as there were instances where axicabtagene ciloleucel cost more or cost less than tisagenlecleucel, and instances where the QALYS associated with axicabtagene ciloleucel were greater or fewer than those of tisagenlecleucel.

Table 14: Summary of Deterministic Results of Manufacturers Base Case

Cost Input	BSC	Axicabtagene Ciloleucel	Tisagenlecleucel	Incremental Vs. BSC	Incremental Vs. Tisagenlecleucel
CAR T-cell therapy costs	■	■	■	■	■
BSC costs	■	■	■	■	■
Stem cell transplant	■	■	■	■	■
Medical resource use costs	■	■	■	■	■
Adverse event costs	■	■	■	■	■
Training costs	■	■	■	■	■
Palliative/death	■	■	■	■	■
Total costs	$123,047.68	$613,305.98	$628,035.08	$490,258.30	–$14,729.11
QALYs in progression-free state	■	■	■	■	■
QALYs in progressed state	■	■	■	■	■
QALY decrements due to AEs	■	■	■	■	■
Total QALYs	■	■	■	■	■
ICUR (cost/QALY gained)	–	–		$82,941.10	–$4,189.28
LYs in progression-free state	■	■	■	■	■
LYs in progressed state	■	■	■	■	■
Total LYs	■	■	■	■	■
ICUR (cost/LY gained)	–	–	–	$61,011.63	–$3,076.73

AE = adverse event; BSC = best supportive care; CAR = chimeric antigen receptor; ICUR = incremental cost-utility ratio; LY = life-years; QALY = quality-adjusted life-years; vs. = versus.

Source: Manufacturer's economic submission.[3]

Figure 3: Base-Case Cost-Effectiveness Plane: Axicabtagene Ciloleucel Versus Best Supportive Care
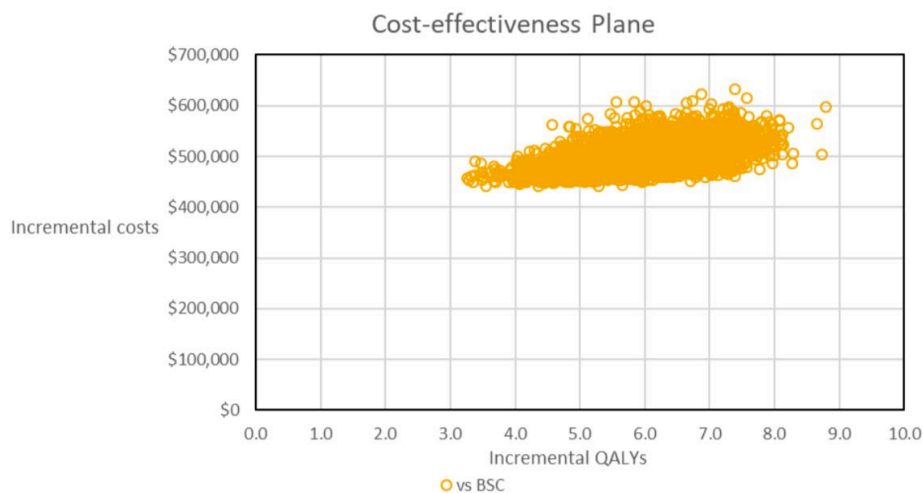
BSC = best supportive care; QALY = quality-adjusted life-years; vs = versus.

Source: Manufacturer's economic submission.[3]

The cost-effectiveness acceptability curve in Figure 4 presents results around the likelihood that axicabtagene ciloleucel is cost-effective given a range of willingness-to-pay thresholds from $0 to $120,000 per QALY gained. From their base-case results, axicabtagene ciloleucel is cost-effective nearly 90% of the time under a $100,000 per QALY willingness-to-pay threshold. Figure 5 plots each simulation on the cost-effectiveness plane for a scenario analysis comparing axicabtagene ciloleucel with tisagenlecleucel.

Figure 4: Cost-Effectiveness Acceptability Curve: Axicabtagene Ciloleucel Versus Best Supportive Care
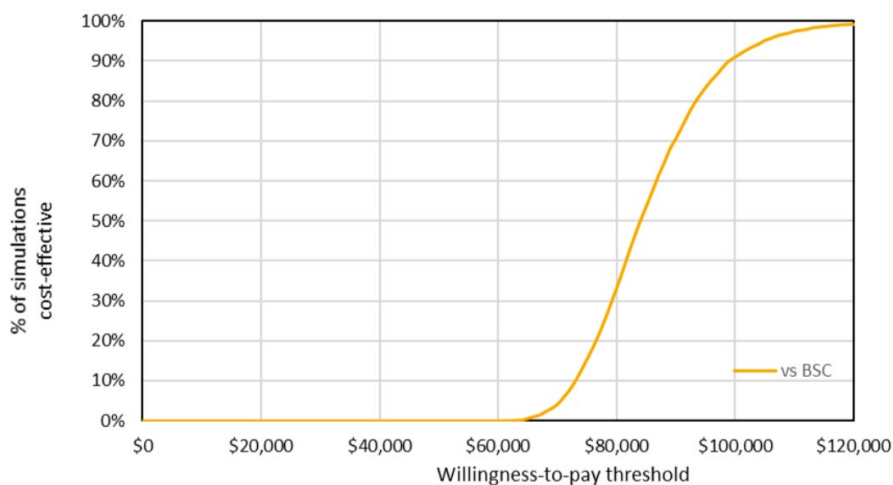
BSC = best supportive care; vs = versus.

Source: Manufacturer's economic submission.[3]

Figure 5: Scenario Analysis Cost-Effectiveness Plane of Axicabtagene Ciloleucel Versus Tisagenlecleucel
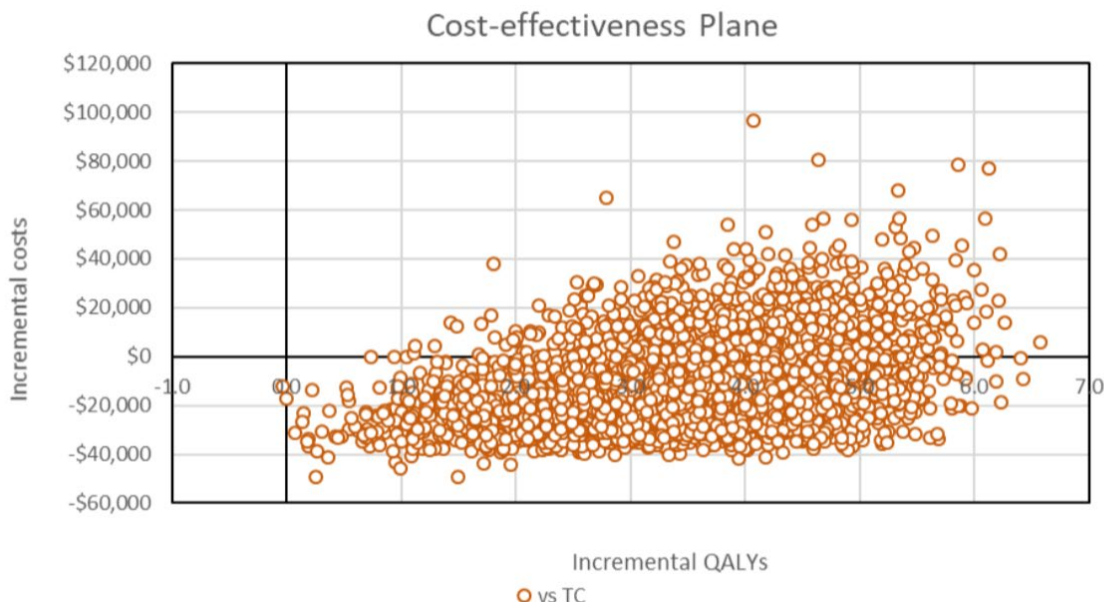
QALY = quality-adjusted life-years; TC = tisagenlecleucel; vs = versus.

Source: Manufacturer's economic submission.[3]

CADTH Reanalyses

The individual component reanalyses conducted to form the CADTH base-case reanalysis outlined in Table 2 can be found in Table 15.

Table 15: CADTH Base-Case Individual Component Analysis

Individual Component		Total Costs ($)	Incremental Cost of Axicabtagene Ciloleucel ($)	Total QALYs	Incremental QALYs of Axicabtagene Ciloleucel	Incremental Cost per QALY ($)
(1) Age 67	Axicabtagene ciloleucel	599,091	479,267	6.05	4.71	101,850
	BSC	113,008		2.12		
(2) SMR 1.2	Axicabtagene ciloleucel	616,253	493,842	8.32	5.63	87,748
	BSC	122,412		2.70		
(3) 5-year cure point	Axicabtagene ciloleucel	620,091	495,670	8.57	5.82	85,181
	BSC	124,421		2.75		
(4) Axicabtagene ciloleucel Log-normal MCM OS	Axicabtagene ciloleucel	596,552	480,360.15	7.73	4.92	97,605.70
	BSC	116,192		2.81		

Individual Component		Total Costs ($)	Incremental Cost of Axicabtagene Ciloleucel ($)	Total QALYs	Incremental QALYs of Axicabtagene Ciloleucel	Incremental Cost per QALY ($)
(5) BSC OS MCM (Log-normal)	Axicabtagene ciloleucel	620,083	490,259	8.67	5.51	88,906
	BSC	129,823		3.15		
(6) ITT population	Axicabtagene ciloleucel	631,325	506,952	8.16	5.38	94,221
	BSC	124,373		2.78		
(7) Bridging therapy for 56% of patients	Axicabtagene ciloleucel	620,012	495,735	8.68	5.90	84,000
	BSC	124,277		2.78		
(8a) CRS costs equal	Axicabtagene ciloleucel	621,551	497,110	8.67	5.89	84,413
	BSC	124,440		2.78		
(8b) Hospitalization costs equal	Axicabtagene ciloleucel	632,917	516,067	8.66	5.88	87,834
	BSC	124,616		2.78		
(8c) SCT retreatment equal	Axicabtagene ciloleucel	612,429	488,082	8.66	5.89	82,936
	BSC	124,347		2.78		
(8d) AE equal	Axicabtagene ciloleucel	620,727	496,244	8.66	5.88	84,417
	BSC	124,483		2.78		

AE = adverse event; BSC = best supportive care; CRS = cytokine release syndrome; ITT = intention to treat; MCM = mixture cure model; OS = overall survival; QALY = quality-adjusted life-year; SCT = stem cell transplant; SMR = standardized mortality ratio.

As CADTH was unable to address the issues related to comparability of axicabtagene ciloleucel with tisagenlecleucel, the comparison to tisagenlecleucel was not included in the base-case analysis. An exploratory analysis was conducted with the same revisions listed previously in which tisagenlecleucel was the comparator (Table 16). This analysis should be interpreted with caution given that CADTH could not control for the underlying differences in patient populations in the ZUMA-1 and JULIET and the uncertainty to the true costs of tisagenlecleucel. This exploratory analysis equalized many parameter inputs that differentiated axicabtagene ciloleucel from tisagenlecleucel (i.e., adverse events, bridging therapy, and manufacturing outcomes).

Table 16: CADTH Exploratory Analysis for Tisagenlecleucel

	Total Costs ($)	Incremental Cost of Axicabtagene Ciloleucel ($)	Total QALYs	Incremental QALYs of Axicabtagene Ciloleucel	Incremental Cost per QALY ($)
Axicabtagene ciloleucel	626,104	–	4.47	–	–
Tisagenlecleucel	617,584	8,520	2.65	1.82	4,681

QALY = quality-adjusted life-years.

# Appendix 4: Detailed Information — Budget Impact Submission

Methods

The eligible patient population was estimated via a top-down, epidemiological approach. Throughout the model, the manufacturer used the perspective of the Ontario Public Drug Programs as a proxy for a non-specific budget impact analysis (BIA). As such, the number of patients was estimated using the population of Ontario[39] as a starting point (Figure 6). To arrive at the size of the model population for a given year, the total projected population of Ontario was first filtered to include the proportion of the population with non-Hodgkin's lymphoma, based on the five-year prevalence rate of non-Hodgkin's lymphoma reported by the Canadian Cancer Society in 2017.[28] This number was then narrowed down to focus on the subset of patients with large B-cell lymphomas, and further filtered to estimate only patients with diffuse large B-cell lymphoma not otherwise specified, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma. The population was further limited to include only patients with relapsed or refractory disease, by transforming a five-year probability of treatment failure to a yearly probability, yielding a total of ▇ patients in the first year.

Fifty per cent of these relapsed or refractory patients were assumed to be eligible for autologous stem cell transplant (ASCT) therapy and it was ▇ of these ASCT-eligible patients would further assumed not achieve to remission (including those who were eligible but did not receive ASCT, and those whose disease relapsed after ASCT). Of these, ▇ were assumed to be eligible for chimeric antigen receptor T-cell therapy. Of those who were not eligible for ASCT, ▇ were also assumed to be eligible for CAR T-cell therapy. In total, the manufacturer calculated that ▇ patients would be eligible to receive CAR T-cell therapy in Ontario in 2017, which was inflated using an assumed population growth rate of 1.2% to reach ▇ patients in 2019 (the first year of potential reimbursement).

Two scenarios were then envisioned: a reference scenario including tisagenlecleucel, palliative chemotherapy, and patients participating in clinical trials, and a new drug scenario, where axicabtagene ciloleucel joins the market, as described in the Information on the Budget Impact Analysis section, and illustrated in Figure 1.

Figure 6: Manufacturer's Estimation of the Size of the Eligible Patient Population
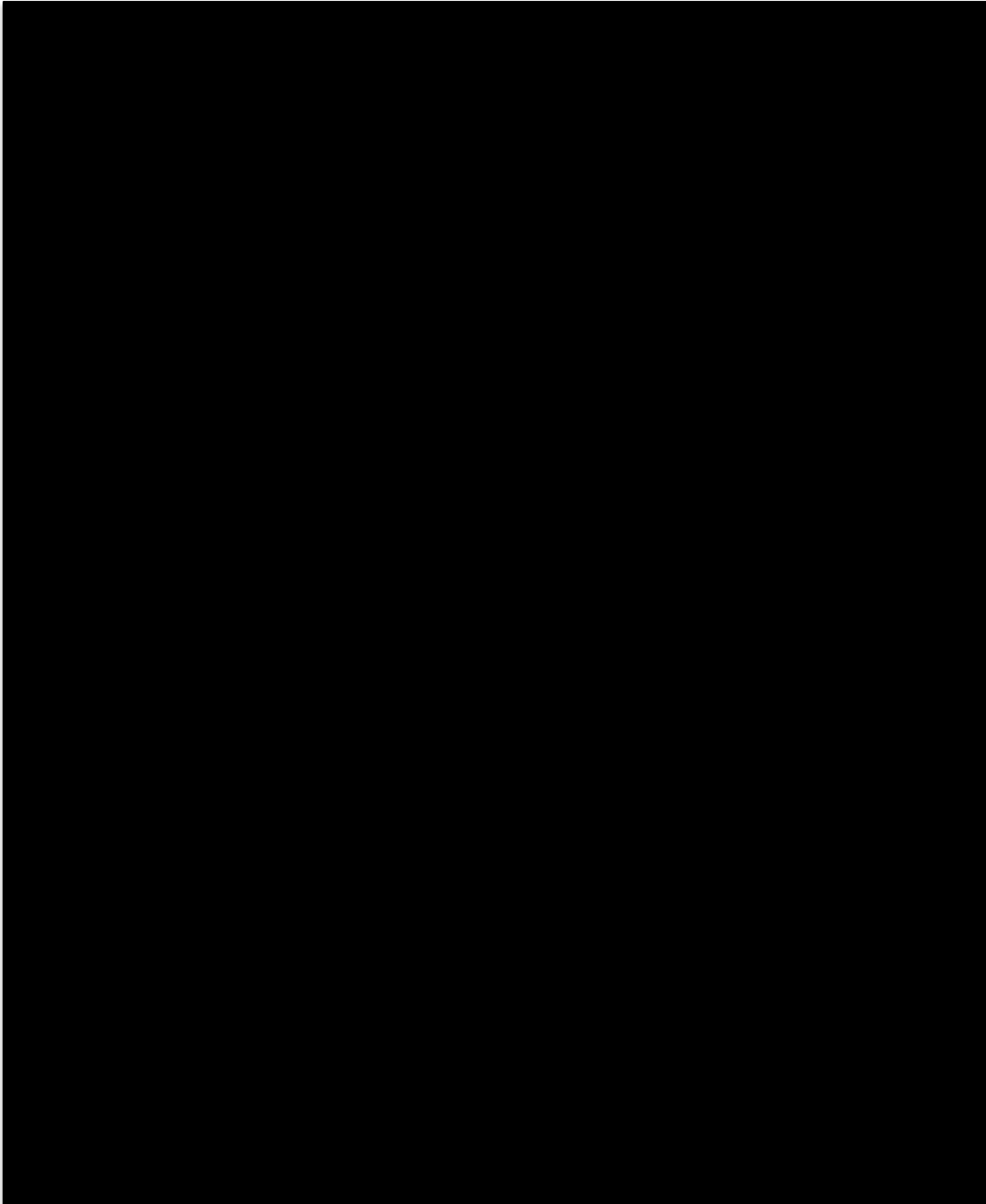
Source: Manufacturer's budget impact analysis submission, Figure 7.[24]

The market shares of treatment options in the reference scenario were based on consultation with experts. A ███% uptake of tisagenlecleucel for eligible patients was assumed in the first year post-funding in Ontario, ████████% in year 2 and ██% in year 3 (see Table 17). A further ███% of CAR T-cell therapy–eligible patients were assumed to be part of clinical trials and thus would not receive approved therapies or incur costs paid by the health care system, while all remaining patients were assumed to receive palliative chemotherapy, which was defined as one-third of patients each receiving 1.5 cycles of monotherapy (gemcitabine, etoposide, or cyclophosphamide).

When axicabtagene ciloleucel was made available in the new drug scenario, it was assumed to capture ██% of the total CAR T-cell therapy market share. Due to the introduction of axicabtagene ciloleucel as a second available CAR T-cell product, the total market share of CAR T-cell therapies was assumed ████████████% in year 1 in the new drug scenario, ███████████████████████% in year 2 and ██% in year 3.

Table 17: Manufacturer's Market Share Summary for Reference and New Drug Scenarios

	Year 1 [N (%)]	Year 2 [N (%)]	Year 3 [N (%)]
Reference Scenario			
Axicabtagene ciloleucel	██████	██████	██████
Tisagenlecleucel	██████	██████	██████
Palliative chemotherapy	██████	██████	██████
Clinical trial	██████	██████	██████
TOTAL	██████	██████	██████
New Drug Scenario			
Axicabtagene ciloleucel	██████	██████	██████
Tisagenlecleucel	██████	██████	██████
Palliative chemotherapy	██████	██████	██████
Clinical trial	██████	██████	██████
TOTAL	██████	██████	██████

Note: Totals may appear off due to rounding. Palliative chemotherapy is defined as monotherapy with gemcitabine, etoposide, or cyclophosphamide.

Source: Manufacturer's budget impact analysis submission, adapted from tables 1 through 4.[24]

Costs in the model were divided into "costs of therapy," which consisted of the cost of the CAR T-cell products themselves and their recommended conditioning therapies as well as the cost of the chemotherapy drugs for patients receiving palliative chemotherapy (see Table 18) and "additional costs," which included administration of conditioning therapy, leukapheresis, cost of hospitalization for administration, and initial adverse event treatment, bridging therapy, ASCT cost, additional medical resource cost (the cost of the progression-free state in the economic model, see Information on the Economic Submission section and Appendix 3), cytokine release syndrome, adverse events requiring tocilizumab usage, and training costs (see Table 19).

Additional costs of therapy were derived from a variety of sources, as outlined in Table 20.

Table 18: Manufacturer's Direct Costs of Therapy Per Patient

Comparator	Dose	Cost Per Unit ($)	Units per Cycle	Share Within Regimen	Total Cost ($)
Axicabtagene Ciloleucel					███
Axicabtagene ciloleucel	NA	██[a]	1	100%	███
Conditioning chemo — fludarabine	30 mg/m² per day for 3 days	5.10[c]	153	100%	780
Conditioning chemo — cyclophosphamide	500 mg/m² per day for 3 days	0.0521[c]	2,550	100%	133
Tisagenlecleucel					███
Tisagenlecleucel	NA	██[b]	1	100%	███
Conditioning chemo — fludarabine	30 mg/m² per day for 3 days	5.10[c]	153	100%	780
Conditioning chemo — cyclophosphamide	500 mg/m² per day for 3 days	0.0521[c]	2,550	100%	133
Palliative Chemotherapy					841
Gemcitabine	1,000 mg/m² on days 1 and 8, 1.5 cycles	0.3084[c]	3,400	33%	524
Etoposide	50 mg/m² to 100 mg/m² for 5 days, 1.5 cycles	0.7500[c]	637.5	33%	239
Cyclophosphamide	300 mg/m² to 400 mg/m² for 5 days, 1.5 cycles	0.0521[c]	2,975	33%	77
Clinical Trial					0

NA = not applicable.

[a] As submitted by manufacturer.[24]
[b] Assumed the same as axicabtagene ciloleucel due to lack of available public price.
[c] Derived from prices reported in a previous CADTH pan-Canadian Oncology Drug Review review.[40]

Table 19: Manufacturer's Additional Costs of Therapy per Patient

Cost Description	Unit Cost ($)	Proportion of Patients	Total Additional Costs ($)
Axicabtagene Ciloleucel			███
Administration cost for conditioning chemotherapy	██	██	██
Leukapheresis cost	███	██	███
Hospitalization cost for administration and initial AE cost	███	██	███
Bridging therapy	███	██	█
ASCT cost	███	██	███
Additional medical resource use (progression-free state in HE model)	███	██	███

Cost Description	Unit Cost ($)	Proportion of Patients	Total Additional Costs ($)
AEs — CRS	███	███	███
AEs requiring tocilizumab usage	███	███	███
Training costs (per patient)	███	███	███
Tisagenlecleucel			███
Administration cost for conditioning chemotherapy	███	███	███
Leukapheresis cost	███	███	███
Hospitalization cost for administration and initial AE cost	███	███	███
Bridging therapy	███	███	███
ASCT cost	███	███	███
Additional medical resource use (progression-free state in HE model)	███	███	███
AEs — CRS	███	███	███
AEs requiring tocilizumab usage	███	███	███
Training costs (per patient)	███	███	███
Palliative Chemotherapy			███
Administration cost	███	███	███
Leukapheresis cost	███	███	███
Hospitalization cost for administration and initial AE cost	███	███	███
Bridging therapy	███	███	███
ASCT cost	███	███	███
Additional medical resource use (progression-free state in HE model)	███	███	███
AEs — CRS	███	███	███
AEs requiring tocilizumab usage	███	███	███
Training costs (per patient)	███	███	███

AE = adverse events; ASCT = autologous stem cell transplant; CRS = cytokine release syndrome; HE = health economic.

Source: Manufacturer's budget impact analysis submission.[41]

Table 20: Manufacturer's Key Assumptions

Assumption	Comment
Persons eligible for treatment with axicabtagene ciloleucel	It was assumed that those eligible for treatment with axicabtagene ciloleucel were diagnosed with DLBCL, PMBCL, or TFL and had relapsed or been refractory to R-CHOP therapy. Of those, ██% were assumed to be eligible for ASCT, with ██% not achieving remission, of which ██% were assumed eligible for CAR T-cell therapy. Of those, ██% of r/r patients who were not eligible for ASCT therapy, ██% were assumed to be eligible for CAR T-cell therapy. These proportions were deemed reasonable by the clinical expert consulted by CADTH.
Proportion of people with NHL	Assumed to be 0.06% of the overall Ontario population, based on the number of reported cases in the five years before 2009 in Canada divided by the 2017 population of Canada. Inappropriate to use the 2017 population as the denominator of 2009-reported data. Additionally, five-year prevalence may be less relevant given the short life expectancy of patients in the indicated population who do not respond to or who do not receive ASCT therapy and the high proportions who relapse within the first two years. CADTH reviewers deemed the two-year prevalence reported within the same document more relevant and easier to apply to the 30% to 40% relapse rate within two years reported in the literature. Additionally, the use of prevalence data where incidence data exists for years 2 and 3 was deemed inappropriate.

Assumption	Comment
Proportion of people with large B-cell lymphoma	Assumed to be ███% of NHL patients. Unclear source. Raut et al. (2014)[29] cites that 30% to 40% of NHL patients have DLBCL, and thus it isn't necessary to first reduce the population to all those with large B-cell lymphoma.
Proportion of people with DLBCL, PMBCL, or TFL	Assumed to be ███% of large B-cell lymphoma cases. Unclear source. Alternate estimate of 30% to 40% of NHL cases being DLBCL available from Raut.
Annual percentage of cases relapsed in previous year	Calculated to be ███%, based on converting an assumed ██% over five years to an annual rate. This ██% was in turn based on statistics from the literature on 30% to 40% of patients failing within the first two years, and assuming a further ███% fail each remaining year in the first five. The equation used to convert a five-year probability to one-year probability was incorrect. Using equations from Briggs et al. (2006)[26] and the manufacturer's assumption of ██% over five years yields a one-year probability of ████%. These assumptions underestimate the proportion of patients who will relapse in a given year by averaging two-year estimates over five years using assumptions. As the majority of cases relapse in the first two years, it is more appropriate in years 2 and 3 of the model to use an annual probability derived from the 35% relapse rate over two years and apply it to incident cases of relapsed disease. The manufacturer did not appear to consider patients who were refractory to their initial therapy, who are not included within the 30% to 40% relapse statistic used, thereby underestimating the eligible population. Per Raut 2014,[29] an additional 10% of patients were estimated to be refractory to first-line therapy and added to the eligible population.
ASCT eligibility	Assumed to be ██% of patients who fail previous treatment annually, no verifiable source given but deemed reasonable by the clinical expert consulted by CADTH.
ASCT patients not achieving remission	Assumed to be ██%, no verifiable source given but deemed reasonable by the clinical expert consulted by CADTH.
Proportion eligible for CAR T-cell therapy	Assumed to be ██% of patients who were eligible for ASCT but did not achieve remission, and ██% of those who were not eligible for ASCT, based on expert opinion.
People entering clinical trials	Assumed to be ███% of all patients who would otherwise be eligible for CAR T-cell therapy, regardless of year, thus removing them from BIA calculations. It is unclear how this proportion was estimated, and given that the availability of two new CAR T-cell therapies will change the patient care paradigm in Canada, it is also unclear why this proportion was assumed to remain stable over time. Unapproved therapies are typically not considered in BIAs unless their use is well established and costs can be estimated. The exclusion of all costs for these patients, including hospitalization, AE, subsequent therapies, treatments after trial withdrawal, and other costs typically borne by public payers, is inappropriate. CADTH reanalyses removed clinical trials as a treatment option and reassigned patients proportionally to the other available therapies.
Market shares in the reference scenario	███% of the CAR T-cell therapy–eligible population would receive tisagenlecleucel in year 1, ██% in year 2, and ██% in year 3, ████████████████████████████████ ████████████████████████████████) in year 1, and expert opinion that CAR T-cell therapy will achieve ██% to ██% of eligible patients within three years. ███% of patients are assumed to participate in clinical trials each year and are thus not considered to have their care covered by public plans. The remainder of the eligible population is assumed to receive palliative chemotherapy, at ███%, ███%, and ███% in years 1 to 3, respectively.
Uptake of axicabtagene ciloleucel in new drug scenario	The addition of axicabtagene ciloleucel would increase the uptake of CAR T-cell therapy in year 1 to ██%, with axicabtagene ciloleucel assumed to have ██% and tisagenlecleucel assumed to have ██%. In years 2 and 3, the market share assumed for CAR T-cell therapy ████████████████████% and █████████████████████████; however, axicabtagene ciloleucel would capture ██% of this market share, with ██% and ██% in years 2 and 3, respectively. Participation in clinical trials would remain unchanged at ███% each year, and palliative chemotherapy would account for the remaining ███%, ███%, and ███% in years 1

Assumption	Comment
	to 3, respectively. Under these assumptions, ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ in the first year.
Conditioning therapy	All patients receiving CAR T-cell therapy were assumed to receive 30 mg/m² per day of fludarabine and 500 mg/m² per day of cyclophosphamide for three days prior to. While consistent with the axicabtagene ciloleucel product monograph, that of tisagenlecleucel specifies 25 mg/m² per day of fludarabine and 250 mg/m² per day of cyclophosphamide for three days for patients with DLBCL.[27] This has a very minor impact on results, but was corrected in CADTH reanalyses.
Palliative chemotherapy	Patients not receiving CAR T-cell therapy or clinical trial therapies are assumed to receive one of three monotherapies in equal proportions: gemcitabine, etoposide, or cyclophosphamide. The clinical expert consulted by CADTH believed more variability exists within Canadian clinical practice, with younger, healthier patients receiving combination chemotherapy regimens in an effort to control their disease, while older or sicker patients would receive palliative monotherapy. By not including combination regimens in the BIA, this biases the model results against CAR T-cell therapy by underestimating the cost of palliative chemotherapies. CADTH explored the impact of assuming palliative chemotherapy patients used one of the three combinations therapies used as comparators in the tisagenlecleucel review [(R)-GDP, (R)-ICE, ((R)-DHAP] in a sensitivity analysis.
Bridging therapy	The manufacturer assumes that 92% of patients using tisagenlecleucel will require bridging therapy, while 0% of axicabtagene ciloleucel patients will require it. This is inappropriate as it assumes two different populations of patients, while simultaneously assuming that market share can be switched between them. ZUMA-1 did not allow bridging therapy in its treatment protocol, thus the patients included in ZUMA-1 may have been more stable (i.e., patients whose disease is sufficiently stable to tolerate the absence of bridging therapy). The Health Canada–approved indication does not limit the population of patients to those who do or do not require bridging therapy for either product.
	As the manufacturer is predicting that axicabtagene ciloleucel will capture ▮▮▮▮▮▮▮ of the market share that would otherwise have gone to treatment with tisagenlecleucel, and 92% of patients receiving tisagenlecleucel were assumed to require bridging therapy, it seems unlikely that ▮% of these would not require it if they were instead treated with axicabtagene ciloleucel. This substantially biases the model results in favour of axicabtagene ciloleucel by including an additional cost of $▮▮▮▮ per patient for those treated with tisagenlecleucel. CADTH reanalyses instead assumed that 56% of patients receiving CAR T-cell therapy in the model would require bridging therapy, consistent with an observational study of axicabtagene ciloleucel patients in clinical practice.[18]
Cost of tisagenlecleucel therapy assumed equivalent to axicabtagene ciloleucel	Acceptable as there is no publicly available price for tisagenlecleucel. CADTH explored the impact of reducing the cost of either or both axicabtagene ciloleucel and tisagenlecleucel in a price reduction analysis.
Hospitalization costs	The manufacturer calculated the cost of hospitalization for CAR T-cell therapy based on the average length of stay during infusion and monitoring from the ZUMA-1 trial for axicabtagene ciloleucel and the JULIET trial for tisagenlecleucel, and multiplied it by the average elective in-patient cost for interventions for lymphoma as reported by CIHI (without providing source inputs). As the inclusion criteria differs between trials, it is likely these differences reflect a different population of patients as well as any true differences in length of stay between treatments due to toxicity or adverse events, and thus this assumption biases the result in favour of axicabtagene ciloleucel. As a conservative assumption, the CADTH base-case reanalysis assumed costs of hospitalization would be similar between CAR T-cell therapies, and that the length of stay in clinical practice was more likely to be reflected by the population of patients in JULIET. Scenario analyses explore alternate assumptions varying hospitalization length of stay.
Costs of AEs	The manufacturer assumed that the cost of most AEs resulting from CAR T-cell therapy would already be reflected in the cost hospitalization during infusion and monitoring. This assumption simplifies the model, but does not adequately reflect potential differences between therapies,

Assumption	Comment
	nor allow for the proper assessment of uncertainty or bias. Additionally, it is unclear why the AE of CRS is treated differently. The model also fails to capture AEs and hospitalizations for patients receiving palliative chemotherapy. The non-transparent nature of AE treatment within the model overall makes assessment of possible biases and the detection of errors such as the double counting of hospitalized days difficult. The clinical expert consulted by CADTH believed that some AEs, such as infections or CNS toxicities, would occur later, further reducing the generalizability of the model to clinical practice.
Cost of CRS AEs	Unlike all other AEs, the cost of treating CRS was considered separately to the initial hospitalization for infusion and monitoring, and calculated as the mean days to resolution of CRS symptoms (█ for axicabtagene ciloleucel, █ for tisagenlecleucel) as reported in the clinical trials and multiplied by the cost of other/unspecified sepsis average cost per day reported by CIHI (only the final result was provided). As the logic behind including all other AEs in the cost of hospitalization for the average trial length of stay was that they would occur simultaneously, it is unclear why the cost of treating CRS would not be double counting the cost of basic hospitalization. Additionally, as with the cost of hospitalization, the differing patient populations within JULIET and ZUMA-1 biases this calculation in favour of axicabtagene ciloleucel. CADTH base-case reanalysis assumes an █ day time to resolution of CRS for both CAR T-cell therapies.
Cost of ASCT	The manufacturer derived the proportion of patients receiving a subsequent allogeneic stem cell transplant from JULIET and ZUMA-1, respectively. Similarly to the logic behind standardizing hospitalization and AE differences between CAR T-cell therapies, a conservative approach in the absence of data within similar populations, is to assume that similar proportions of patients will require ASCT. CADTH reanalyses assume that 5% of all patients receiving CAR T-cell therapy undergo ASCT after CAR T-cell therapy, consistent with JULIET.

AE = adverse event; ASCT = autologous stem cell transplant; BIA = budget impact analysis; CIHI = Canadian Institute for Health Information; CNS = central nervous system; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin lymphoma; PMBCL = primary mediastinal B-cell lymphoma; r/r = relapsed or refractory; TFL = transformed follicular lymphoma.

Manufacturer's Results

The total costs for the approximately █ patients per year estimated to be eligible for CAR T-cell therapy in both the reference and new drug scenarios can be seen in Table 21, which were calculated by multiplying the estimated number of patients by the market share of each category by the per-patient costs per category. The manufacturer estimated that over the first three years of potential reimbursement, the cost of the reference scenario would total █████████, while the addition of axicabtagene ciloleucel to the market would result in a cost of █████████. The incremental cost of the new treatment scenario per year and in total is reported in Table 5.

Table 21: Summary of Results of the Manufacturer's Base Case, Cost by Category, Ontario

	Year 1	Year 2	Year 3	3-Year Total
Reference Scenario: Current Treatment Only				
Axicabtagene ciloleucel total	**$0**	**$0**	**$0**	**$0**
Therapy cost	$0	$0	$0	$0
Additional care cost	$0	$0	$0	$0
Tisagenlecleucel total	████	████	████	████
Therapy cost	████	████	████	████
Additional care cost	████	████	████	████
Palliative chemotherapy total	████	████	████	████

	Year 1	Year 2	Year 3	3-Year Total
Therapy cost	■	■	■	■
Additional care cost	■	■	■	■
Clinical trial total	■	■	■	■
Total costs	■	■	■	■
New Treatment Scenario: Axicabtagene Ciloleucel Joins the Market				
Axicabtagene ciloleucel total	■	■	■	■
Therapy cost	■	■	■	■
Additional care cost	■	■	■	■
Tisagenlecleucel total	■	■	■	■
Therapy cost	■	■	■	■
Additional care cost	■	■	■	■
Palliative chemotherapy total	■	■	■	■
Therapy cost	■	■	■	■
Additional care cost	■	■	■	■
Clinical trial total	■	■	■	■
Total costs	■	■	■	■

Source: Manufacturer's budget impact analysis submission, Table 8.[24]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a series of sensitivity analyses (as described in Table 22), which overall did not have a large impact on results. However, altering assumptions around the proportion of patients who will be able to access CAR T-cell therapy (the total CAR T-cell therapy market share) with the introduction of axicabtagene ciloleucel did have a substantial impact on the incremental budget impact. When axicabtagene ciloleucel was assumed to increase the overall market share, and thus access to, ■■■■■■■■■■■■■■■■■■■■■■■ ■■ ■■■■■■■■■■■■■■■■■■■

Table 22: Summary of Manufacturer's Sensitivity Analyses

Sensitivity Analysis Scenario	Scenario Description	Base-Case Inputs	Sensitivity Analysis Inputs
1	Proportion of ASCT-ineligible patients eligible for CAR T-cell therapy	■	■
2	Axicabtagene ciloleucel has a more optimistic proportion of the CAR T-cell therapy market share	■	■
3	Axicabtagene ciloleucel has a more pessimistic proportion of the CAR T-cell therapy market share	■	■
4	More CAR T-cell therapy–eligible patients participate in other clinical trials	■	■
5	Fewer CAR T-cell therapy–eligible patients participate in other clinical trials	■	■
6	CAR T-cell therapy market share grows with the addition of axicabtagene ciloleucel with the	■	■

Sensitivity Analysis Scenario	Scenario Description	Base-Case Inputs	Sensitivity Analysis Inputs
	reference scenario market share remaining per base-case values		
7	CAR T-cell therapy market share does not change with the addition of axicabtagene ciloleucel	████████████	████████████
8	Proportion of patients receiving ASCT is reduced to 0 for all comparators	████████████	████████████

CAR = chimeric antigen receptor.

Table 23: Manufacturer's Sensitivity Analysis Results — Incremental Budget Impact, Ontario

		Year 1	Year 2	Year 3	3-Year Total[a]
	Base case	$6,944,501	−$1,224,015	−$1,548,204	$4,172,282
1	██% ASCT-ineligible patients eligible for CAR T-cell therapy	$8,422,054	−$1,484,443	−$1,877,609	$5,060,002
2	Axicabtagene ciloleucel larger market share	$6,692,493	−$1,632,020	−$2,064,272	$2,996,202
3	Axicabtagene ciloleucel smaller market share	$7,070,505	−$1,020,012	−$1,290,170	$4,760,323
4	Larger clinical trial population	$6,944,501	−$1,224,015	−$1,548,204	$4,172,282
5	Smaller clinical trial population	$6,944,501	−$1,224,015	−$1,548,204	$4,172,282
6	Axicabtagene ciloleucel increases CAR T-cell therapy access	$11,568,323	$6,262,032	$7,920,575	$25,750,930
7	Axicabtagene ciloleucel does not impact CAR T-cell therapy access	-$453,614	−$1,224,015	−$1,548,204	−$3,225,833
8	No patients receive ASCT after therapy assignment	$7,359,662	−$1,439,451	−$1,820,700	$4,099,511

ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor.

[a] Calculated by CADTH.

While not presented as a scenario analysis in the submission, the manufacturer's model was capable of presenting results on a nationwide scale rather than Ontario alone. These results are presented in Table 24 and Table 25 in order to allow for comparison with CADTH reanalyses, which are based on the national population.

Table 24: Manufacturer's Market Share Summary for Reference and New Drug Scenarios, National Population

	Year 1 [N (%)]	Year 2 [N (%)]	Year 3 [N (%)]
Reference Scenario			
Axicabtagene ciloleucel	0 (0%)	0 (0%)	0 (0%)
Tisagenlecleucel	████████	████████	████████
Palliative chemotherapy	████████	████████	████████

	Year 1 [N (%)]	Year 2 [N (%)]	Year 3 [N (%)]
Clinical trial	■■■■	■■■■	■■■■
TOTAL	■■■■	■■■■	■■■■
New Drug Scenario			
Axicabtagene ciloleucel	■■■■	■■■■	■■■■
Tisagenlecleucel	■■■■	■■■■	■■■■
Palliative chemotherapy	■■■■	■■■■	■■■■
Clinical trial	■■■■	■■■■	■■■■
TOTAL	■■■■	■■■■	■■■■

Note: Totals may appear off due to rounding. Palliative chemotherapy is defined as monotherapy with gemcitabine, etoposide, or cyclophosphamide. National market share of each comparator is based on a weighted average market share across jurisdictions in the reference scenario, but based on Ontario-assumed quantities in the new drug scenario.

Source: Manufacturer's budget impact analysis submission, Excel model set to national population.[41]

Table 25: Summary of Results of the Manufacturer's Base Case, National Population

Annual Cost outcomes	Year 1	Year 2	Year 3	3-Year Total[a]
Reference Scenario: Current Treatments Only				
Axicabtagene ciloleucel	$0	$0	$0	$0
Tisagenlecleucel	■■■■	■■■■	■■■■	■■■■
Palliative chemotherapy	■■■■	■■■■	■■■■	■■■■
Investigational therapy	■■■■	■■■■	■■■■	■■■■
Total costs	■■■■	■■■■	■■■■	■■■■
New Treatment Scenario: Axicabtagene Ciloleucel Joins the Market				
Axicabtagene ciloleucel	■■■■	■■■■	■■■■	■■■■
Tisagenlecleucel	■■■■	■■■■	■■■■	■■■■
Palliative chemotherapy	■■■■	■■■■	■■■■	■■■■
Investigational therapy	■■■■	■■■■	■■■■	■■■■
Total costs	■■■■	■■■■	■■■■	■■■■
Budget impact	$25,534,739	$19,913,611	$12,403,292	$57,851,643

Note: Excel model set to national population. Budget impact results where the axicabtagene ciloleucel scenario is deemed costs saving are displayed in brackets.

Source: Adapted from manufacturer's submission, Excel model.[41]

CADTH Reanalyses

CADTH reanalyses were conducted on at a national perspective, and the changes to assumptions outlined in lead to an estimate of 725 patients eligible for CAR T-cell therapy in year 1, 521 in year 2, and 527 in year 3. Market shares were based on a population-weighted average of the manufacturer's assumptions of CAR T-cell therapy market share within each provincial jurisdiction (see Table 26). These in turn are based on the availability of treatment centres for both axicabtagene ciloleucel and tisagenlecleucel within each jurisdiction (see CADTH Implementation Report for more information). Unlike in the manufacturer's analysis where only Ontario was considered and the market share of CAR T-cell therapies only increased in year 1 with the introduction of axicabtagene ciloleucel, in this analysis, the total market share of CAR T-cell products is higher in the new drug scenario than in the reference scenario for all three years, albeit to a decreasing degree over time.

Table 26: Chimeric Antigen Receptor T-Cell Therapy Market Share by Province as Used in CADTH Base Case

Jurisdiction	Population 2017	Total CAR T-Cell Therapy Market Share Reference Scenario (%)			Total CAR T-Cell Therapy Market Share New Drug Scenario (%)			Axicabtagene Ciloleucel Proportion of Total CAR T-Cell Therapy Market Share (%)		
		Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
National	**36,708,083**	▪	▪	▪	▪	▪	▪	▪	▪	▪
Alberta	4,286,134	▪	▪	▪	▪	▪	▪	▪	▪	▪
British Columbia	4,817,160	▪	▪	▪	▪	▪	▪	▪		▪
Manitoba	1,338,109	▪	▪	▪	▪	▪	▪	▪	▪	▪
New Brunswick	759,655	▪	▪	▪	▪	▪	▪	▪	▪	▪
Newfoundland	528,817	▪	▪	▪	▪	▪	▪	▪	▪	▪
Nova Scotia	953,869	▪	▪	▪	▪	▪	▪	▪	▪	▪
Ontario	14,193,384	▪	▪	▪	▪	▪	▪	▪	▪	▪
Prince Edward Island	152,021	▪	▪	▪	▪	▪	▪	▪	▪	▪
Quebec	8,394,034	▪	▪	▪	▪	▪	▪	▪	▪	▪
Saskatchewan	1,163,925	▪	▪	▪	▪	▪	▪	▪	▪	▪

CAR = chimeric antigen receptor.

Note: Base percentage estimates provided by the manufacturer for total CAR T-cell therapy market share have been inflated by 12.5% to account for the removal of clinical trials as a treatment option in the model. Of note: This analysis does not account for residents of Canada's three territories. National market share is based on a population-weighted average of provincial market shares.

A summary of CADTH's base-case reanalysis can be found in Table 6, and costs by category can be found in Table 27.

Table 27: Summary of Results of the CADTH Base Case, Cost by Category

	Year 1	Year 2	Year 3	3-year total
Reference Scenario: Current Treatment Only				
Axicabtagene ciloleucel total	**$0**	**$0**	**$0**	**$0**
Therapy cost	$0	$0	$0	$0
Additional care cost	$0	$0	$0	$0
Tisagenlecleucel total	▪	▪	▪	▪
Therapy cost	▪	▪	▪	▪
Additional care cost	▪	▪	▪	▪
Palliative chemotherapy total	▪	▪	▪	▪
Therapy cost	▪	▪	▪	▪
Additional care cost	▪	▪	▪	▪
Total costs	▪	▪	▪	▪
New Treatment Scenario: Axicabtagene Ciloleucel Joins the Market				
Axicabtagene ciloleucel total	▪	▪	▪	▪
Therapy cost	▪	▪	▪	▪
Additional care cost	▪	▪	▪	▪

	Year 1	Year 2	Year 3	3-year total
Tisagenlecleucel total	████████	████████	████████	████████
Therapy cost	██████	██████	██████	████████
Additional care cost	██████	█████	██████	██████
Palliative chemotherapy total	██████	██████	███████	██████
Therapy cost	████	████	████	█████
Additional care cost	██████	██████	██████	██████
Total costs	███████	███████	███████	███████
Incremental Budget Impact				
Total	**$51,591,760**	**$28,613,942**	**$18,595,522**	**$98,801,223**
Therapy cost	$48,787,616	$27,058,580	$17,584,562	$93,430,757
Additional care cost	$2,804,144	$1,555,362	$1,010,960	$5,370,466

Additionally, CADTH conducted a series of sensitivity analyses around the base case (as outlined in Table 28 and reported in Table 29). Assuming that axicabtagene ciloleucel takes up 20% more or less of the overall CAR T-cell therapy market share, requires 20% more or less bridging therapy than tisagenlecleucel, requires three days longer or shorter hospitalization than tisagenlecleucel, or that both CAR T-cell products required one year of intravenous immunoglobin therapy for 16% of patients all had minimal impact on results. However, assuming that the addition of axicabtagene ciloleucel to the market has no effect on the overall market share of CAR T-cell products greatly reduces the incremental cost.

Table 28: Summary of Sensitivity Analyses Around CADTH Base Case

Sensitivity Analysis Scenario	Scenario Description	Base Case Inputs	Sensitivity Analysis Inputs
1	Axicabtagene ciloleucel has a more optimistic proportion of the CAR T-cell therapy market share	As in Table 26	+20%
2	Axicabtagene ciloleucel has a more pessimistic proportion of the CAR T-cell therapy market share	As in Table 26	–20%
3	CAR T-cell therapy market share does not change with the addition of axicabtagene ciloleucel	As in new drug scenario of Table 26	As in reference scenario of Table 26
4	Axicabtagene ciloleucel patients require bridging therapy less frequently than tisagenlecleucel patients	56%	36%
5	Axicabtagene ciloleucel patients require bridging therapy more frequently than tisagenlecleucel patients	56%	76%
6	Axicabtagene ciloleucel patients require three-day shorter (less costly) hospitalizations for infusion and AEs than tisagenlecleucel patients	████	████
7	Axicabtagene ciloleucel patients require three-day longer (more costly) hospitalizations for infusion and AEs than tisagenlecleucel patients	████	████

Sensitivity Analysis Scenario	Scenario Description	Base Case Inputs	Sensitivity Analysis Inputs
8	Intravenous immunoglobulin therapy assumed for 16% of CAR T-cell therapy patients for one year	$0	$29,472 for 16% of patients ($4,715 per patient)

AE = adverse events; CAR = chimeric antigen receptor.

Table 29: CADTH's Sensitivity Analysis Results — Incremental Budget Impact

	Scenario	Year 1	Year 2	Year 3	3-Year Total
	Base case	$51,591,760	$28,613,942	$18,595,522	$98,801,223
1	Axicabtagene ciloleucel has 20% more of CAR T-cell therapy market share	$51,597,256	$28,624,438	$18,606,412	$98,828,106
2	Axicabtagene ciloleucel has 20% less of CAR T-cell therapy market share	$51,581,191	$28,605,762	$18,582,570	$98,769,523
3	Axicabtagene ciloleucel does not impact CAR T-cell therapy access	$13,027	$22,917	$31,103	$67,046
4	Axicabtagene ciloleucel patients need less bridging therapy	$51,070,814	$28,037,537	$17,921,204	$97,029,555
5	Axicabtagene ciloleucel patients need more bridging therapy	$52,107,634	$29,192,663	$19,267,778	$100,568,074
6	Axicabtagene ciloleucel patients spend less time in hospital	$50,939,418	$27,891,148	$17,750,553	$96,581,118
7	Axicabtagene ciloleucel patients spend more time in hospital	$52,239,030	$29,339,052	$19,438,429	$101,016,511
8	IVIG assumed for 16% of CAR T-cell therapy patients	$52,065,959	$28,876,826	$18,766,202	$99,708,987

CAR = chimeric antigen receptor; IVIG = intravenous immunoglobin.

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