CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ECULIZUMAB (SOLIRIS)

Alexion Pharma Canada Corp.

Indication: Neuromyelitis optica spectrum disorder

Service Line	CADTH Common Drug Review
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CADTH

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Abbreviations

AQP4	aquaporin-4
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol 5-Dimensions
ICER	incremental cost-effectiveness ratio
IVIG	intravenous immunoglobulin
NMOSD	neuromyelitis optica spectrum disorder
QALY	quality-adjusted life-year
SOC	standard of care
UK	United Kingdom
WTP	willingness-to-pay

Executive Summary

The executive summary consists of two tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Eculizumab (Soliris), 30 mL parenteral solution (10 mg/mL), for injection
Submitted price	Eculizumab, 300 mg single-use vial for IV injection: $6,742
Indication	For the treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-aquaporin-4 antibody positive Eculizumab is not intended for acute treatment of an NMOSD relapse
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	September 24, 2019
Reimbursement request	As per indication
Sponsor	Alexion Pharma Canada Corp.
Submission history	Previously reviewed: Yes Paroxysmal nocturnal hemoglobinuria: Indication: Treatment of patients with paroxysmal nocturnal hemoglobinuria to reduce hemolysis Recommendation date: February 18, 2010 Recommendation: Do not list at the submitted price Atypical hemolytic uremic syndrome: Indication: Treatment of patients with atypical hemolytic uremic syndrome to reduce complement-mediated thrombotic microangiopathy Recommendation date: July 18, 2013 Recommendation: Do not list

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients who are anti-AQP4 antibody positive
Treatment	Eculizumab plus standard of care (consisting of stable maintenance doses of corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide, either in combination or as monotherapy)
Comparator	SOC
Perspective	Canadian publicly funded health care payer
Outcome	QALYs; life-years
Time horizon	Lifetime (65 years)
Key data source	PREVENT trial, a multi-centre, double-blind, placebo-controlled, phase III, time-to-event randomized controlled trial
Submitted results for base case	ICER = $1,382,186 per QALY gained (incremental costs = $14,991,798; incremental QALYs = 10.85)
Key limitations	• The inclusion criteria in the PREVENT trial identified a highly active disease population more likely to experience a relapse based on their historical relapses. Furthermore, the model's relapse definition required adjudication by an independent committee, which does not reflect Canadian practice. A high rate of major protocol deviations was noted in the trial. Together, these issues impact the generalizability and validity of the clinical efficacy estimates that informed the economic model. • Long-term extrapolation was highly uncertain. The model relies on relapse to predict long-term survival and quality of life, for which no comparative clinical information is available. The exponential distribution of time to first relapse had limited face validity according to the clinical experts consulted by CADTH. The model also fixed an exponential function to model time to subsequent relapse and did not permit flexible exploration of other parametric distributions for this outcome. The majority (99%) of the incremental benefit occurred in the extrapolated period. • Treatment was assumed to be discontinued after the first relapse. This is unlikely to be reflective of clinical management with eculizumab according to the clinical experts. • The long-term disability health state combined patients with either a single disability (i.e., vision or mobility) or those with both disabilities; therefore, this assumes homogeneity in costs and quality of life between these groups. Patients in this health state were further assumed to not be at risk of future relapses. Both assumptions have limited face validity according to the clinical experts. • Health state utility values appear to underestimate the impact of relapse on patient quality of life, increasing the uncertainty of the results. • Under the public health care payer perspective, not all relevant costs (e.g., meningococcal vaccinations and drug administration) were captured in the sponsor's model. In addition, assumptions of drug administration may not reflect how eculizumab would be administered in the Canadian setting according to the clinical experts.
CADTH reanalysis results	• CADTH revised the sponsor's economic analysis by switching the relapse definition to "all on-trial relapse," selecting the gamma distribution to extrapolate time to first relapse, allowing patients to remain on treatment with eculizumab over their lifetime, incorporating both vaccination and drug administration costs, and assuming eculizumab would only be administered in outpatient clinics. CADTH identified other limitations that could not be assessed in reanalyses.

Component	Description
	• ICER = $1,508,152 per QALY compared to SOC alone ($15,569,618 incremental costs and 10.32 incremental QALYs). • Results warrant careful interpretation, since 99% of the incremental benefit for eculizumab plus SOC were accrued in time points for which clinical data were not available. A price reduction of 96% was required for eculizumab plus SOC to achieve an ICER below $50,000 per QALY gained.

AQP4 = aquaporin-4; ICER = incremental cost-effectiveness ratio; QALY= quality-adjusted life-year; SOC = standard of care.

Conclusions

CADTH's findings remained aligned with the sponsor's: the addition of eculizumab to standard of care (SOC) is not a cost-effective option at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY). CADTH accounted for some limitations, including changing the model's relapse definition, selecting an alternate parametric distribution for time to first relapse, assuming lifelong treatment, capturing costs associated with administration and vaccination, and assuming eculizumab would be administered in outpatient clinics. In CADTH's base case, eculizumab plus SOC was associated with an incremental cost-effectiveness ratio (ICER) of $1,508,152 per QALY gained compared with SOC alone in neuromyelitis optica spectrum disorder (NMOSD) patients who are anti-aquaporin-4 (AQP4) antibody positive. A price reduction of 96% would be required for eculizumab plus SOC to achieve an ICER below a WTP threshold of $50,000 per QALY.

The results of CADTH's reanalysis are highly dependent on the treatment effects of eculizumab plus SOC compared to SOC alone. Several limitations were associated with the PREVENT trial (e.g., the absence of relevant outcomes related to subsequent relapses after the first relapse; high rates of major protocol deviation) that could not be addressed by CADTH. In the submitted model, the majority of the incremental clinical benefits were found to occur beyond the trial observed period; there is high uncertainty associated with this extrapolation. The cost-effectiveness of eculizumab compared to rituximab, mitoxantrone, or intravenous immunoglobulin (IVIG) is unknown in the absence of both direct and indirect treatment comparisons. Interpretation of the economic results therefore warrants careful consideration.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

One patient group, the Multiple Sclerosis Society, responded to the call from CADTH to provide input for the review of eculizumab for the treatment of NMOSD.

Patients stated that NMOSD is a rare autoimmune disorder of the central nervous system, characterized by damage to the spinal cord and/or optic nerves. The group noted that NMOSD follows a relapsing-remitting disease course, with subsequent relapse resulting in additional disability and significant impacts to all areas of a patient's life and ability to engage fulsomely in society. The sponsor modelled health states based on relapse counts, and an increase in the number of relapses was associated with a greater reduction in quality of life and increased costs.

NMOSD can result in pain, loss of vision, weakness or paralysis in the legs or arms, loss of sensation, and problems with bladder and bowel function. Additional symptoms include neuropathy, stiffness, and muscle spasms. While most patients described different disease experiences of NMOSD attributed to either its debilitating nature on their vision or mobility, the sponsor's model did not differentiate between these two modes of disability. Instead, the modes were combined into a single, all-encompassing long-term disability health state within the submitted economic model. In addition to physical symptoms, patients further described isolation and loss of independence as having an impact on their quality of life. The sponsor modelled patient's quality of life using the EuroQol 5-Dimensions (EQ-5D) instrument, which considered quality of life in five broad domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.

The patient group identified several off-label agents that are used to treat NMOSD, such as immunosuppressants (e.g., azathioprine, rituximab, or intravenous steroids), IVIG, plasmapheresis, or plasma exchange to prevent further relapses. The sponsor defined SOC within the model as treatment with immunosuppressive therapies, reflective of the treatment seen in the PREVENT trial (i.e., corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide, either in combination or as monotherapy); however, the comparator in the model does not represent patients on off-label treatment with rituximab, mitoxantrone, or IVIG.

Patients suggested that the primary goal of treatment was to reduce severe relapses, and the main treatment efficacy measure in the sponsor's economic evaluation was time-to-relapse data for eculizumab and SOC.

Economic Review

The current review is for eculizumab (Soliris) for adult patients who are anti-AQP4 antibody positive.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis comparing eculizumab plus SOC with SOC alone for the treatment of adult patients who are anti-AQP4 antibody positive.[1] SOC was assumed to consist of a stable dose of immunosuppressive therapies and/or other concomitant medications such as corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, or cyclophosphamide, either in combination or as monotherapy, as administered in the PREVENT trial.[2] The model reflected a population with neuromyelitis optica or NMOSD based on the criteria defined by Wingerchuk et al. in 2006[3] and 2007,[4] respectively, and had similar baseline characteristics to the patients in the PREVENT trial.[2]

The recommended dosage regimen is 900 mg weekly for the first four weeks, followed by 1,200 mg for the fifth week and then 1,200 mg every two weeks thereafter.[5] At the sponsor's submitted price of $6,742 per 300 mg vial, the annual cost of eculizumab was $701,168 within the model.[1] No cost was associated with SOC in the model, as this was assumed to apply equally to both groups.

The sponsor adopted a lifetime time horizon (defined as 65 years) with the analysis conducted from the perspective of the publicly funded health care payer. Costs and clinical outcomes (i.e., QALYs and life-years) were discounted at a rate of 1.5% per annum.[1]

Model Structure

The economic analysis was conducted using a Markov state transition model to capture the long-term costs and effects of a relapsing disease course that may result in long-term disability, with each cycle reflecting 30 days.[1] The model included four unique health states (i.e., relapse-free, relapse, long-term disability, and death [the absorbing health state]). Patients with NMOSD and no presence of long-term disability entered the model in the relapse-free health state. Patients could transition from the relapse-free health state to either a relapse health state (modelled as a series of tunnel states that reflect relapse count) or death.[1] Up to 10 relapses were permitted in the model, and with every subsequent relapse, patients were assumed to be at an increased risk of experiencing long-term disability or dying, thereby entering the long-term disability or death health state, respectively. Long-term disability was defined as being unable to walk without assistance and/or being functionally blind in at least one eye. If a patient entered long-term disability, they remained there until death, and no further relapse recurrence was tracked.[1]

The sponsor's submitted model assumed that patients would stop eculizumab upon experiencing their first relapse event (i.e., median relapse-free survival: 29 years) and that those who discontinued treatment due to relapse would be managed with SOC.[1]

Model Inputs

The patient cohort had a mean age of 44 years, and 91% of the patients were female, as per the PREVENT trial.[1] The patient cohort had a mean of two prior relapses (within 24 months prior to screening).

Transition probabilities in the economic model were estimated from time-to-relapse data for eculizumab and SOC as reported in PREVENT, based on the observed data in the eculizumab and placebo arms, for which the maximum follow-up time was 211 weeks and 208 weeks, respectively. Relapse was defined as an "adjudicated on-trial relapse," which was based on the consensus of an independent relapse adjudication committee rather than the attending physician, and the sponsor assumed an exponential distribution to model the time to the first adjudicated relapse and the time to subsequent relapses.[1] In patients who stopped eculizumab upon first relapse, rates of subsequent relapse reflected those in the SOC arm. All adverse events reported in at least 15% of either arm of the PREVENT trial were included in the model.[1]

Background mortality was taken from age- and sex-specific Canadian life tables.[6] An increased mortality risk based on a US study of NMOSD patients was applied to this background mortality after patients experienced their first relapse in the non-disability health state and was assumed to apply to patients in the long-term disability health state.[1,7]

Patients accrued health state–specific costs and QALYs, as well as treatment-related costs, as they transitioned through the health states in the model. Utility values associated with the relapse-free and relapse health states were derived using a mixed-effect regression model that predicted health-related quality of life outcomes from the EQ-5D data collected in PREVENT and its extension study.[1] Specifically, the mixed-effect regression model included the number of prior relapses and an indicator variable for the acute stage of a relapse (defined as 30 days of a relapse event) as independent variables to predict the long-term decrement and the temporary decrement associated with a relapse. Utility decrements associated with the long-term disability health state were based on a UK study that reported health state utility values for patients with multiple sclerosis.[8] Specifically, the mean utility for the long-term disability state was based on the difference in the weighted average utility score for patients with disability reflected by Expanded Disability Status Scale (EDSS) scores of 6+, compared to an EDSS score between 0 and 5.[1] Utilities associated with adverse events were informed by published literature.[9-12]

The model included costs from drug acquisition and administration, disease management (by health state), and adverse events. The cost of eculizumab was based on the sponsor's submitted price. Drug administration costs were assumed to differ by location (i.e., outpatient centre versus home), in which it was assumed that 50% of patients would receive home-based drug administration and the remainder would receive eculizumab at an outpatient clinic. The meningococcal vaccination and outpatient drug administration costs were assumed to be covered by the sponsor.[1] Adverse event management costs were derived from the Ontario Case Costing Initiative,[13] while other medical costs (e.g., costs of relapse) were estimated by converting a US costing study on relapse (which used an administrative claims database) into Canadian values.[14] Costs associated with long-term disability were based on data from a UK study that examined a cost breakdown of multiple sclerosis[15] in which these costs were reported to be 6.3 times higher than those incurred by patients in the non-disability state. Costs associated with SOC were not included in the sponsor's model, as these were assumed to be equivalent across both groups.[1]

Summary of Sponsor's Economic Evaluation Results

The sponsor's cost-effectiveness analysis was based on 5,000 probabilistic iterations, for which findings are presented below. The results of the deterministic analysis were similar to the results of the probabilistic analysis.

Base Case Results

The sponsor's base case results are presented in Table 3. Compared with SOC alone, eculizumab added to SOC was associated with an incremental cost of $14,991,798 and 10.85 incremental QALYs. The ICER for eculizumab with SOC was $1,382,186 per QALY gained compared to SOC alone. At a WTP threshold of $50,000 per QALY, eculizumab added to SOC would not be considered cost-effective in all iterations.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs, $	Incremental costs, $	Total QALYs	Incremental QALYs	ICER vs. SOC, $/QALY
SOC	590,289	—	5.38	—	—
Eculizumab + SOC	15,582,087	14,991,798	16.23	10.85	1,382,186

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analysis Results

The sponsor conducted several sensitivity and scenario analyses. These included taking a societal perspective (e.g., including disutilities for caregivers); varying the time horizon (i.e., 20 years and 40 years); assuming administration and vaccination costs were not covered by the sponsor; selecting alternative survival distribution for time to first relapses (i.e., gamma and log-normal); applying a different relapse definition (i.e., all on-trial relapses); including the relapse amplification effect (i.e., applying an increased risk of subsequent relapse based on history of relapse events); assuming excess mortality rates in the long-term disability state; allowing patients to remain on treatment for the entire lifetime (i.e., no treatment discontinuation); and exploring different discount rates (0% and 3%).

The model was found to be robust, as eculizumab with SOC was not a cost-effective option at a WTP threshold of $50,000 per QALY. All ICERs were more than $1 million per QALY. Further details of the probabilistic results of the sponsor's sensitivity and scenario analysis are presented in Table 11 in Appendix 3.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **Generalizability and validity of the comparative clinical efficacy is uncertain:** Comparative treatment effects within the submitted model were derived from the PREVENT trial. The clinical experts consulted by CADTH noted that according to the trial's inclusion criteria, the NMOSD patients in the PREVENT trial reflected a highly active disease population with a higher risk of relapse compared with Canadian patients observed in clinical practice. As noted in the CADTH clinical review, this may have contributed to a more pronounced effect of eculizumab on relapse reduction than would be expected in clinical practice. The model's transitions were based on the primary efficacy outcome in the PREVENT trial: time to first adjudicated on-trial relapse. The

adjudication of on-trial relapses was based on the consensus of an independent relapse adjudication committee consisting of two neurologists and one neuro-ophthalmologist, who retrospectively reviewed all cases of the attending physician–determined relapses. The clinical panel consulted by CADTH noted that the use of "adjudicated on-trial relapse" was robust, as this would help to eliminate inter-site variability and reduce over-reporting bias. Although this approach to adjudicate relapse has high internal validity, it has limited external validity, as noted in the CADTH clinical review. In clinical practice, physicians must decide how to manage patients based on their clinical judgment in identifying relapses rather than relying on confirmation from an independent panel. A more clinically representative outcome would be all (non-adjudicated) on-trial relapses defined by the treating physician.

There is further substantial uncertainty in the comparative effectiveness estimates of eculizumab plus SOC compared with SOC alone due to methodological issues with the study. First, major protocol deviations occurred in approximately 40% of patients in each treatment arm, which may have affected study conduct and data integrity (e.g., informed consent and randomization). Time to first adjudicated on-trial relapse was based on a per-protocol analysis that excluded patients with major protocol deviations, which may impact the validity of these estimates. Second, the exclusion of patients receiving commonly used treatments, such as rituximab, mitoxantrone, or IVIG, from the trial impacts the external validity of the study results, given that a large proportion of patients are currently being managed by these interventions according to the clinical experts consulted by CADTH. The cost-effectiveness of eculizumab compared to these other treatments currently used in patients with NMOSD is unknown in the absence of relevant indirect treatment comparisons.

  - CADTH partially addressed this limitation by switching the relapse definition from "adjudicated on-trial" to "all on-trial" relapse, given its applicability to clinical practice. Despite concerns related to the efficacy inputs incorporated into the economic model within a Canadian context, CADTH was unable to conduct reanalysis to address the remaining methodological limitations of the PREVENT trial. The cost-effectiveness findings of the economic model must therefore be interpreted with caution.

- **Uncertainties in the long-term extrapolation of relapses:** The sponsor assumed that first and subsequent relapses occurred at a constant rate by fitting an exponential distribution to time-to-relapse event data. The clinical experts consulted by CADTH expressed that they would not expect the rate of first relapse to be constant over time. Visually, the clinical experts noted that the gamma distribution would be the most clinically plausible curve, as it best reflected their expected clinical trajectory for first relapse in patients typically treated by SOC. The same was noted for the expected clinical trajectory for patients who received eculizumab. Uncertainties in relapse extrapolation could not be further tested in the model as the parametric distribution for time to subsequent relapse for the SOC arm was also fixed to an exponential distribution. This is concerning as the model relies on relapse to predict long-term survival and quality of life, for which no comparative clinical information is available. As the CADTH clinical review noted, the effect of eculizumab was measured only for the first relapse; thus, the impact of eculizumab on subsequent relapses remains unclear. The economic model predicted an incremental survival gain of 11.75 years for patients receiving eculizumab with SOC compared to SOC alone. Furthermore, the majority of the incremental QALY benefits predicted in the sponsor's model (99%) were found to occur outside of the trial observed period.

- CADTH addressed this limitation by switching from an exponential to a gamma distribution for time to first relapse. However, CADTH was unable to revise the distribution for time to subsequent relapse, as the exponential distribution was the only available option in the sponsor's model. CADTH conducted a scenario analysis removing the survival benefits associated with eculizumab.

- **Treatment discontinuation of eculizumab assumed after first relapse:** The sponsor assumed that treatment with eculizumab would be discontinued after the first relapse as it would indicate a lack of treatment efficacy. However, the clinical experts consulted by CADTH did not find this assumption to be appropriate. Furthermore, the clinical panel convened by CADTH noted substantial variability in how discontinuation of treatment may be decided and shared potential discontinuation criteria, but the panel cautioned that the following proposed discontinuation criteria may be applicable on a case-by-case basis: (i) a severe relapse; (ii) two or more relapses after initiating treatment; or (iii) severe adverse events during treatment. As there are no specific guidelines or tools used to classify a severe relapse, the clinical expert panel highlighted that clinician and patient input should be considered, along with the degree of severity and extent of recovery (i.e., residual disability), when assessing treatment discontinuation. Of note, while the sponsor assumed treatment discontinuation after the first relapse in the economic model, patients recruited in the PREVENT trial could remain on eculizumab post-relapse as part of the long-term extension study of PREVENT.
  - CADTH adopted a more conservative estimate by assuming patients would continue on treatment for their lifetime. Thereby, in eculizumab plus SOC, this would increase expected costs (due to drug acquisition costs) and expected QALYs (due to lowered rates of relapse). As it remains highly variable whether and when patients would discontinue treatment, a scenario analysis was conducted that applied a stopping rule in which treatment discontinuation would occur after the first relapse (as per the sponsor's base case).
- **Conceptualization of long-term disability health state is inappropriate:** The long-term disability health state was defined as "being unable to walk without assistance and/or being functionally blind in at least one eye." As each health state within the Markov model is assumed to reflect a homogeneous group of individuals, combining two types of impairments, vision and mobility, into a single state would suggest these impairments — alone or together — are similar. However, the clinical experts consulted by CADTH noted that the impact of visual or mobility disabilities are not the same and, thus, costs and utilities would differ by the type of impairment. Similarly, the costs and quality of life impacts of patients with one of these impairments are likely different than those of patients who have both.

  The model also assumed that patients would not experience any further relapses upon entering the long-term disability health state. According to the experts consulted by CADTH, this has limited face validity as NMOSD patients with long-term disability can continue to experience subsequent relapses.
  - CADTH was unable to address these limitations as part of the reanalysis.
- **Uncertainty in the estimation of utility values associated with relapse in the economic model:** Health state utility values were derived from a mixed-effects regression model to estimate the impact of relapse on the change in EQ-5D utility scores over time. In the economic model, two separate utility decrements were applied to each relapse event to reflect the continual decline in a patient's quality of life: one was applied to capture the temporary (and reversible) quality of life reduction immediately following a relapse ("during" a 30-day period) (0.024; standard error = 0.049), and the other captured

long-term (and non-reversible) effects of worsening disability (0.059; standard error = 0.010). The model assumed that short- and long-term disutilities would be the same for each relapse event. The clinical experts consulted by CADTH noted that, while a patient's quality of life declines with subsequent relapses, relapse effects are typically accelerated with subsequent relapses and that any decline in quality of life would likely be non-linear (and magnified), with subsequent relapses in both the short and long term. The short-term utility impact was further informed by only five observations; therefore, this estimate is associated with a wide confidence interval. Given the probabilistic nature of the model, it is therefore possible that random draws for the short-term disutility could produce a negative value (i.e., a negative disutility can be interpreted as a utility gain or an improvement). This has limited face validity. Despite this, the sponsor's utility regression may have been conservative, with bias in favour of SOC, given that fewer relapses are associated with eculizumab.

  - CADTH was unable to address these limitations as part of the reanalysis.

- **Inappropriate assumptions on administration and meningococcal vaccination costs:** The sponsor assumed half of patients would receive eculizumab at outpatient clinics and the remainder would receive treatment at home. The clinical experts consulted by CADTH stated that eculizumab would primarily be administered in hospitals or infusion clinics and did not expect home-based administration to be a common setting for drug administration. Additionally, in the economic model, vaccination and drug administration costs of eculizumab in outpatient centres were both assumed to be covered by the sponsor. However, the sponsor did not provide supporting documentation that these costs would be covered in their submission materials.

  - CADTH, as part of the reanalysis, changed the proportion of patients who were administered eculizumab from a ratio of 50:50 to 100% outpatient and included vaccination and drug administration costs.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (see Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
In the sponsor's base case, no "amplification effect" was assumed (i.e., HR = 1; no difference in terms of the risk of relapse by number of prior relapses).	Acceptable. The clinical experts consulted by CADTH indicated that while there may be an increased risk of relapse based on the number of prior relapses, there is limited evidence outside of the sponsor's trial that independently confirms this relationship.
Adverse events that occurred in at least 15% of patients in either arm of the PREVENT trial were incorporated into the economic model.	Unacceptable, although unlikely to impact the model. Clinically meaningful adverse events (i.e., serious respiratory infections, serious infusion reactions, hemolysis/low hemoglobin) noted by the clinical experts in which had an event rate less than 15% were not incorporated in the sponsor's model. Only upper respiratory infections which had an event rate greater than 15% in the trial were captured in the economic model. As per CADTH guidelines,[16] researchers should focus on harms that are clinically relevant and not simply those that are experienced by a certain proportion of patients within the trial.
A maximum of 10 relapses could occur over the lifetime time horizon.	Acceptable. The clinical experts indicated that the model's prediction of an average of six relapses over a lifetime was reasonable for patients in the SOC arm.

Sponsor's key assumption	CADTH comment
NMOSD mortality rates reported for the US population were assumed to be relevant to the Canadian population. Specifically, patients were assumed to have an increased mortality rate (7% per year) following their first relapse. This excessive mortality was assumed for individuals with long-term disability.	Uncertain, although unlikely to impact the model.
The sponsor excluded the cost of SOC based on the assumption that these costs would be identical for patients in both arms.	Acceptable. The CADTH clinical review noted that, while concomitant supportive immunosuppressive therapies for NMOSD during the study were generally used similarly between arms in the PREVENT trial, there were some small differences for specific medications.
Long-term disability was defined according to an MS population with an EDSS score ≥ 6 as a proxy for disability in NMOSD patients.	Potentially conservative, though unlikely to impact the model. Long-term disability costs for NMOSD patients with disability may have been underestimated in the model, based on the sponsor's definition of disability. Clinical experts noted that NMOSD patients with disability have a much higher level of disability than MS patients with disability and are expected to require greater resource use. If eculizumab does delay or prevent long-term disability when compared to SOC, this underestimation would bias against eculizumab.

EDSS = Expanded Disability Status Scale; HR = hazard ratio; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; SOC = standard of care.

CADTH Reanalyses of the Economic Evaluation

Base Case Results

CADTH undertook reanalyses that addressed limitations within the model, as summarized in Table 5.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None		
Changes to derive the CADTH base case		
1. The relapse definition applied in the model was not reflective of clinical practice	Relapse was defined as "adjudicated on-trial relapse"	Relapse defined as "all on-trial relapse" to reflect patient management in Canadian clinical practice
2. Inappropriate assumption that long-term extrapolation of time to first relapse would be constant over the lifetime	Exponential distribution	Gamma distribution
3. Treatment discontinuation was not reflective of clinical practice	Eculizumab was discontinued after the first relapse	Eculizumab was assumed to continue over the lifetime time horizon, thereby impacting treatment costs and the effects of treatment on subsequent relapse
4. Inconsistencies in costs assumed to be covered by the sponsor	Excluded vaccination costs or outpatient drug administration costs Eculizumab administered in outpatient and in-home settings (50:50 ratio)	Included vaccination and drug administration costs Eculizumab is administered in outpatient clinics only
CADTH base case	Combine revisions (1 + 2 + 3 + 4)	

CADTH undertook a stepped analysis, incorporating each change to the sponsor's base case detailed in Table 5 to yield the CADTH base case reanalysis. The impact of each change and the summary results of the CADTH reanalysis are presented in Table 6. The

ICER for eculizumab plus SOC compared with SOC alone was $1,508,152 per QALY gained ($15,569,618 incremental costs and 10.32 incremental QALYs). These results suggest that in NMOSD patients, eculizumab plus SOC was not cost-effective at a WTP threshold of $50,000 per QALY or $100,000 per QALY. Of note, the incremental benefit accrued in the extrapolated phase (i.e., beyond the trial observed period) accounted for most of the incremental benefit (99%) (see disaggregated results of the CADTH base case in Appendix 4, Table 14).

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs, $	Total QALYs	ICER, $/QALY
Sponsor's base case	SOC	590,289	5.49	—
	Eculizumab + SOC	15,528,087	16.76	1,382,186
CADTH reanalysis 1	SOC	680,462	4.11	—
	Eculizumab + SOC	7,688,444	9.52	1,543,008
CADTH reanalysis 2	SOC	578,970	6.04	—
	Eculizumab + SOC	17,795,016	18.40	1,421,998
CADTH reanalysis 3	SOC	585,219	5.49	—
	Eculizumab + SOC	18,623,509	17.90	1,454,690
CADTH reanalysis 4	SOC	584,842	5.43	—
	Eculizumab + SOC	15,697,567	16.77	1,383,692
CADTH base case (reanalyses 1 to 4)	**SOC**	**677,302**	**4.43**	**—**
	Eculizumab + SOC	**16,246,919**	**14.75**	**1,508,152**

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.

CADTH identified that the key driver of the model results was the change in relapse definition from "adjudicated on-trial relapses" to "all on-trial relapses." Specifically, under this scenario, the relative risk of relapse between eculizumab plus SOC versus SOC alone was smaller, resulting in smaller incremental costs (due to higher costs attributed to relapse, long-term disability, and other non-disability-related health services) and lower incremental QALYs. Consequently, under this scenario, a higher ICER was observed in the sponsor's base case.

Scenario Analysis Results

CADTH conducted four scenario analyses to examine (i) the impact of assuming a relapse amplification effect, (ii) a scenario in which the sponsor would cover drug administration and vaccination costs, (iii) a scenario where all patients (100%) would receive home-based administration of eculizumab, and (iv) the removal of survival benefits. The ICER for each scenario analysis is presented in Tables 13 to 16. The sponsor reported a post hoc analysis suggesting that the number of previous relapses was associated with an increased risk of on-trial relapse in the PREVENT trial, which trial investigators referred to as the "amplification effect." This was expressed by a hazard ratio of 1.5, which meant that the risk of relapse was 50% higher in those with a prior relapse compared with those without a prior relapse. Although no amplification effect (i.e., hazard ratio = 1; no difference in terms of the risk of relapse by the number of prior relapses) was assumed in the sponsor's or CADTH's base case, a scenario analysis incorporating this amplification effect on the CADTH base

case was conducted with the results reported in Table 13. The results were not sensitive to this scenario analysis.

Similarly, the results were not sensitive to scenario analyses varying either the coverage (i.e., sponsor covers the costs of drug administration and meningococcal vaccination) or the setting for drug administration (i.e., home-based administration). The results are reported in Table 14 and Table 15, respectively, and were found to be similar to those of the CADTH base case. In each scenario, eculizumab plus SOC was not cost-effective.

CADTH also conducted price reduction analyses (Table 7) on both the sponsor's and CADTH's base case. In the CADTH reanalysis, price reductions of at least 96% are required for eculizumab plus SOC to be considered cost-effective at a WTP threshold of $50,000 per QALY.

Table 7: CADTH Price Reduction Analyses

	ICERs for eculizumab + SOC vs. SOC alone	
Price reduction	**Sponsor base case, $**	**CADTH reanalysis, $**
No price reduction	1,382,186	1,508,152
20%	1,090,626	1,201,631
40%	841,141	898,852
60%	541,656	590,843
80%	267,171	286,266
90%	129,929	133,255
91%	114,808	118,361
92%	102,480	104,643
93%	88,756	89,636
95%	59,710	57,613
96%	45,546	42,490
97%	27,206	27,206

ICER = incremental cost-effectiveness ratio; SOC = standard of care; vs. = versus.

Issues for Consideration

- **Drug administration:** Administration of eculizumab entails IV infusion over 35 minutes.[5] Differences were noted between clinical experts regarding the appropriateness of administering eculizumab in a home setting. According to the clinical experts consulted by CADTH, at minimum, the first few injections of eculizumab should be prescribed in outpatient clinics prior to possible transitions to home-based administration. A CADTH scenario analysis was conducted to explore the impact of home administration (see Appendix 4).
- **Rituximab usage:** The approach to treatment for NMOSD differs across Canada in the absence of formal treatment guidelines specifying which interventions should be used as first- or second-line therapies. The clinical experts consulted by CADTH highlighted that rituximab, if available, is considered to be a first-line therapy for patients with NMOSD, followed by treatment with other off-label agents (e.g., azathioprine and mycophenolate mofetil) if rituximab is not available. Given the role and use of rituximab in NMOSD patients, rituximab could be a relevant comparator even though it was not included in the sponsor's economic model. The cost-effectiveness of eculizumab compared to rituximab

is unknown in the absence of both direct and indirect treatment comparisons. See Appendix 1 for the costs associated with rituximab therapy for NMOSD.

Overall Conclusions

CADTH reanalysis of the sponsor's economic model suggested that eculizumab plus SOC compared to SOC alone had an ICER of $1,508,152 per QALY gained and would not be considered a cost-effective option for NMOSD patients within WTP thresholds of $50,000 or $100,000 per QALY. CADTH's findings remained aligned with the sponsor's after accounting for several limitations that included changing the model's relapse definition, selecting an alternate parametric distribution for time to first relapse, assuming lifelong treatment, capturing costs associated with administration and vaccination, and assuming eculizumab would be administered in outpatient clinics. Given that the annual cost of eculizumab is $728,136 and $701,168 per patient in the first and subsequent years, respectively, the probability that eculizumab plus SOC represented the optimal strategy was 0% at WTP thresholds of both $50,000 per QALY and $100,000 per QALY. A price reduction on eculizumab of 96% would be required to achieve an ICER below a WTP threshold of $50,000 per QALY.

Although CADTH was unable to address other important limitations associated with the submitted economic model (i.e., the internal and external validity of the clinical efficacy inputs, the uncertainty in the estimation of the utility values associated with relapse events, and the inappropriate conceptualization of the long-term disability health state), eculizumab plus SOC is not a cost-effective option, given the submitted price of eculizumab. The results of CADTH's reanalysis are highly dependent on treatment effects, specifically relapse, in which several limitations were identified with the PREVENT trial (i.e., the absence of relevant outcomes related to subsequent relapses after the first relapse; enriched study design; high rates of major protocol deviation). The model relies on relapse to predict long-term survival and quality of life, for which no comparative long-term clinical information is available. Most of the clinical benefits associated with eculizumab (99%) in the economic model were found to occur beyond the trial observed period. The health state utility values contribute further uncertainty to the results as they appear to underestimate the impact on patient quality of life following a relapse. All these issues, in addition to structural limitations with the sponsor's model, could not be addressed by CADTH, and interpretation of the economic results therefore warrants careful consideration. The cost-effectiveness of eculizumab compared to rituximab, mitoxantrone, or IVIG is unknown in the absence of both direct and indirect treatment comparisons.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Prescription Drugs Indicated for NMOSD Patients

Treatment	Strength	Form	Price, $	Recommended dosage	Average daily drug cost, $	Average annual drug cost, $
Eculizumab (Soliris)	10 mg/mL	Vial for IV infusion	6,742.0000	900 mg weekly for first 4 weeks, followed by 1,200 mg for fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter	Year 1: 1,994.89 Thereafter: 1,921.01	Year 1: 728,136 Thereafter: 701,168

NMOSD = neuromyelitis optica spectrum disorder.

Table 9: CADTH Cost Comparison Table for Treatments Used Off-Label for NMOSD Patients

Treatment	Strength	Form	Price, $	Recommended dosage	Average daily drug cost, $	Average annual drug cost for duration of treatment, $
Rituximab (Rituxan)	10 mg/mL 100 mg/10 mL 500 mg/50 mL 1,400 mg/11.7 mL 1,600 mg/13.4 mL	Vial for IV infusion	48.2305[a] 337.6135 1,688.0780 198.9867[b] 195.6485[b]	375 mg/m^2/week	28.43	10,173[c]
Tocilizumab (Actemra)	20 mg/mL (4 mL) 20 mg/mL (10 mL) 20 mg/mL (20 mL) 162 mg/0.9 mL	Vial for IV infusion	182.8000[a] 457.0000[a] 914.0000[a] 358.09050[a]	8 mg/kg every month[d]	504.83	184,262[c]
Azathioprine (generic)	50 mg	Tablet	0.2405	2 to 3 mg/kg[e]	0.67 to 1.01	246 to 369
Bortezomib (generic, Velcade)	3.5 mg 10 mL	Single-use vial for SC injection	186.9457[b] 400.6914[b]	4 cycles; 1 mg/m^2 on days 1, 4, 8, and 11 per cycle[f] followed by 10-day treatment-free interval	35.61	(4 cycles, 84 days) 2,991[c]
Cyclophosphamide (Procytox)	25 mg 50 mg	Tablet	0.3520 0.4740	1,000 mg/m^2 every 6 months[g,h]	0.09	32.23
	200 mg/mL 500 mg/mL 1,000 mg/mL 2,000 mg/mL	Solution	0.6163[i] 84.5500[b] 123.5200[b] 217.4700[b]		0.03	11.09
Cyclosporine (generic)	10 mg 25 mg 50 mg 100 mg	Caplet	0.6520 0.9952 1.9400 3.8815	150 mg/day[j]	5.82	2,125

Treatment	Strength	Form	Price, $	Recommended dosage	Average daily drug cost, $	Average annual drug cost for duration of treatment, $
Methotrexate (generic)	2.5 mg	Tablet	0.6325	Initiation: 7.5 mg weekly Maintenance: 7.5 to 15 mg weekly[d]	Initiation: 0.27 Maintenance: 0.27 to 0.54	Initiation: 99 Maintenance: 99 to 198
	50 mg/2 mL 20 mg/2 mL 10 mg/0.2 mL 12.5mg/0.25 mL 17.5 mg/0.35 mL 15mg/0.3 mL 20 mg/0.4 mL 22.5 mg/0.45 mL	Solution	8.9200 12.5000 29.6400 31.2000 32.0000 32.7600 35.0000 35.0000		Initiation: 0.19 Maintenance: 0.19 to 0.38	Initiation: 70 Maintenance: 70 to 140
Mitoxantrone (generic)	2 mg/mL	Vial	63.0370[b]	Initiation: 12 mg/m^2 every 3 to 6 months[d,h] Maintenance: 6 to 12 mg/m^2 every 3 months[d]	Initiation: 7.60 to 19.26 Maintenance: 4.14 to 19.26	Initiation: 1,387 to 2,774 Maintenance: 1,513 to 2,774
Mycophenolate mofetil (Cellcept, generic)	250 mg 500 mg	Caplet	0.3712 0.7423	1,000 to 2,000 mg per day[j]	1.48 to 2.97	541 to 1,084
	200 mg/mL	Solution	1.8644[b]		9.32 to 18.64	3,403 to 6,805
Prednisone (generic, Winpred 1 mg tablet)	1 mg 5 mg 50 mg	Tablet	0.1066 0.0220 0.1735	1 mg/kg[e] daily until taper[j]	0.26	95

SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed March 19, 2020), unless otherwise indicated, and do not include dispensing fees.

[a] Saskatchewan Drug Formulary.

[b] IQVIA DeltaPA.

[c] Assumes drug wastage.

[d] Based on a study by Sherman et al. (2015).[17]

[e] Assumes an average adult body weight of 70 kg.

[f] Based on a study by Zhang et al. (2017).[18]

[g] Based on personal communication with CADTH clinical experts consulted for this review.

[h] Based on a study by Xu et al. (2016), adult dosage.[19]

[i] Assumes a standard body surface area (1.7 m^2) for adults.

[j] Based on a study by Kageyama et al. (2013).[20]

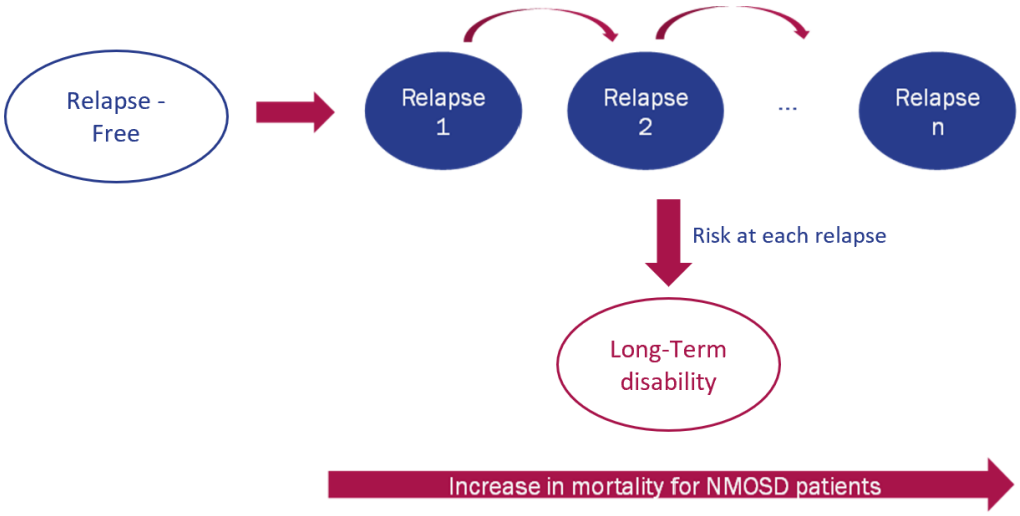
Appendix 2: Submission Quality

Table 10: Submission Quality

	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	
Model has been adequately programmed and has sufficient face validity	☒	☐	
Model structure is adequate for decision problem	☒	☐	
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	Given that the time to subsequent relapse was fixed as an exponential distribution, structural uncertainty was not adequately assessed in the economic model
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough detail)	☒	☐	

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



NMOSD = neuromyelitis optica spectrum disorder.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 11: Sponsor's Scenario Analyses

Stepped analysis	Drug	ICER, $/QALY
Sponsor's base case	SOC	—
	Eculizumab + SOC	1,371,828
Societal perspective	SOC	—
	Eculizumab + SOC	1,348,245
Included disutilities for caregivers (in a societal perspective)	SOC	—
	Eculizumab + SOC	1,348,245
Time horizon: 20 years	SOC	—
	Eculizumab + SOC	1,821,951
Time horizon: 40 years	SOC	—
	Eculizumab + SOC	1,421,717
Administration costs and vaccination cost not covered by manufacturer	SOC	—
	Eculizumab + SOC	1,385,727
Distribution: gamma	SOC	—
	Eculizumab + SOC	1,423,463
Distribution: log-normal	SOC	—
	Eculizumab + SOC	1,818,613
Relapse definition: on-trial data	SOC	—
	Eculizumab + SOC	1,539,431

Stepped analysis	Drug	ICER, $/QALY
Relapse amplification effect considered	SOC	—
	Eculizumab + SOC	1,197,657
Excess mortality in long-term disability state	SOC	—
	Eculizumab + SOC	1,374,173
Discontinuation of eculizumab not considered	SOC	—
	Eculizumab + SOC	1,451,628
Discount rate: 0%	SOC	—
	Eculizumab + SOC	1,283,480
Discount rate: 3%	SOC	—
	Eculizumab + SOC	1,496,376

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 12: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Eculizumab + SOC	SOC	Incremental	Percentage (of total incremental)[a]
Discounted LYs[b]				
Total	22.33	13.01	9.31	—
Week 0 to week 36 (~9 months)	0.74	0.74	0.003	0.033
Week 36 to week 89	0.97	0.94	0.023	0.25
Week 89 to end of lifetime	20.62	11.33	9.29	99.7
Discounted QALYs[b]				
Total	14.79	4.33	10.46	—
Month 0 to week 36 (~9 months)	0.52	0.50	0.02	0.2
Week 36 to week 89	0.67	0.60	0.06	0.6
Week 89 to end of lifetime	13.60	3.23	10.37	99
Discounted costs				
Total	$16,246,919	$677,302	$15,569,618	—
Drugs acquisition	$15,768,753	$0	$15,768,753	100
Drugs administration	$122,108	$0	$122,108	100
Relapse related	$26,142	$175,282	–$149,140	–571
Long-term disability	$120,612	$426,345	–$305,734	–254
Other health services	$196,168	$65,098	$131,070	66.82
Treatment-related adverse event	$13,137	$10,576	$2,561	19.50
ICER, $/QALY	$1,508,152			

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SOC = standard of care.

[a] Deterministic discounted results.

[b] The median follow-up for time to first adjudicated on-trial relapse was 89.43 weeks for eculizumab and 36 weeks for placebo (the max follow-up time in weeks was 211 weeks for eculizumab and 208 weeks for placebo).

Source: Sponsor's pharmacoeconomic submission.[1]

Scenario Analyses

The sponsor reported a post hoc analysis suggesting that the number of previous relapses was associated with an increased risk of on-trial relapse in the PREVENT trial, which trial investigators referred to as the "amplification effect." This was expressed by a hazard ratio of 1.5, which meant that the risk of relapse was 50% higher in those with a prior relapse compared with those without a prior relapse. Although no amplification effect (i.e., hazard ratio = 1; no difference in terms of the risk of relapse by the number of prior relapses) was assumed in both the sponsor's and CADTH's base case analyses, a scenario analysis incorporating this amplification effect on the CADTH base case was conducted, with the results reported in Table 13. The results were not sensitive to this scenario analysis.

Table 13: Scenario Analysis Including the Relapse Amplification Effect

Drug	Total costs, $	Total QALYs	ICER vs. SOC, $
SOC	670,284	4.43	—
Eculizumab + SOC	16,255,949	14.75	1,508,820

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Similarly, the results were not sensitive to scenario analyses varying either the coverage (i.e., sponsor covers the costs of drug administration and meningococcal vaccination) or the setting for drug administration (i.e., home-based administration). Results are reported in Table 14 and Table 15, respectively.

Table 14: Scenario Analysis With the Sponsor Covering Drug Administration and Vaccination Costs

Drug	Total costs, $	Total QALYs	ICER vs. SOC, $
SOC	671,053	4.43	—
Eculizumab + SOC	16,219,491	14.73	1,509,535

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Table 15: Scenario Analysis With 100% Home-Based Administration of Eculizumab

Drug	Total costs, $	Total QALYs	ICER vs. SOC, $
SOC	669,985	4.39	—
Eculizumab + SOC	16,234,050	14.75	1,501,639

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

An additional scenario analysis was undertaken to explore cost-effectiveness results when the survival benefit attributed to eculizumab was removed. Specifically, the sponsor assumed that relapse was associated with an increased risk of mortality in NMOSD patients and applied a constant mortality rate of 7% per year following the first relapse. Given the differences in relapse rates between eculizumab plus SOC versus SOC alone, a survival benefit would be indirectly introduced. By removing this increased mortality rate associated with relapse (i.e., 0%), the gained life-years predicted for eculizumab plus SOC and for SOC alone were identical. The results remained robust in this scenario, highlighting that the major driver in the model is likely the differences in quality of life (i.e., utility weights associated with relapse) rather than the life-year differences between the eculizumab and placebo arms.

Table 16: Scenario Analysis Assuming No Impact of Eculizumab on Mortality

Drug	Total costs, $	Total QALYs	ICER vs. SOC, $
SOC	45,071	1.51	—
Eculizumab + SOC	11,142,479	10.95	1,182,423

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

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