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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Lanadelumab (Takhzyro)

(Shire Pharma Canada ULC)

Indication: For the routine prevention of attacks of hereditary angioedema in adolescents and adults.

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Abbreviations

AE	adverse event
AIC	Akaike information criterion
C1-INH	C1 esterase inhibitor
CUA	cost-utility analysis
EQ-5D	EuroQol 5-Dimensions
ER	emergency room
HAE	hereditary angioedema
ICUR	incremental cost-utility ratio
IV	intravenous
NMA	network meta-analysis
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	rate ratio
SC	subcutaneous
WTP	willingness to pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Lanadelumab (Takhzyro) injection 300 mg
Study Question	What is the cost-effectiveness of lanadelumab compared with C1 esterase inhibitors (C1-INHs) for routine prevention of hereditary angioedema (HAE) attacks in adolescents and adults?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with HAE aged 12 years or older who require prophylactic care
Treatment	Lanadelumab 300 mg subcutaneously every two weeks, or every four weeks if a patient has been attack-free for more than six months
Outcome	QALYs
Comparator	C1-INHs consisting of a single blended comparator: Cinryze IV ([redacted]%), Berinert* IV 20 IU/kg ([redacted]%), Berinert* IV 40 IU/kg ([redacted]%), Berinert* IV 60 IU/kg ([redacted]%) *Berinert IV used as off-label as a prophylactic treatment
Perspective	Canadian publicly funded health care payer
Time Horizon	60 years (lifetime horizon)
Results for Base Case	Lanadelumab dominates C1-INH – C1-INHs were more costly (ΔC = $1,775,242) and associated with fewer QALYs (ΔQALYs = –1.391)
Key Limitations	• There is substantial uncertainty in the comparative efficacy and safety of lanadelumab and C1-INHs. The supporting network meta-analysis should be interpreted with caution, given the substantial differences in trial design, key eligibility criteria, treatment duration, protocols for rescue therapy, and outcome measures. • There are no data to support the manufacturer's assumption that, at six months, 80% of patients will switch from receiving lanadelumab 300 mg every two weeks to every four weeks. • Health utility values used in the manufacturer's model may not reflect the preferences of Canadian patients with HAE in Canada. • Health care utilization used in the model may not reflect health care utilization required by patients in actual clinical practice in Canada. • The manufacturer omitted no prophylaxis as a comparator in its reference-case analysis. It did, however, include it as a scenario analysis upon request. • The effects of long-term safety and efficacy were uncertain, as the economic model was based on a randomized controlled trial with a short treatment duration, i.e., 26 weeks.
CADTH Estimate(s)	• The CADTH reanalysis incorporated no prophylaxis as a comparator. C1-INHs were also disaggregated to consider them as individual comparators. Additionally, Cinryze IV was removed as a rescue therapy, as it has not been approved for this purpose in Canada; the estimate of emergency department cost was replaced by an estimate reported by the OCCI; and the proportion of patients who switch to the every-four-week dosage regimen was changed from 80% to 0%. • When considering no prophylaxis in the CADTH reanalysis, Cinryze IV dominated Berinert IV, but it was extendedly dominated by lanadelumab. Compared with no prophylaxis, the ICUR for lanadelumab was $6,872,940 per QALY. If no prophylaxis was excluded from the CADTH reanalysis, Cinryze IV dominated Berinert IV, and the ICUR for lanadelumab compared with Cinryze IV was $6,981,558 per QALY. • This ICUR of lanadelumab was highly sensitive to the assumption of a health utility improvement due to a more preferential mode of administration for lanadelumab compared with C1-INHs.

	• When the CADTH reanalysis included no prophylaxis, the probability of lanadelumab being cost-effective was 0% at a WTP of $50,000 per QALY. A price reduction of at least 84.7% would be required for lanadelumab to have an ICUR less than $50,000 per QALY. • When the CADTH reanalysis excluded no prophylaxis, the probability of lanadelumab being cost-effective was 0% at a WTP of $50,000 per QALY, and a price reduction of at least 58.6% would be required for lanadelumab to have an ICUR less than $50,000 per QALY.

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; ICUR = incremental cost-utility ratio; IV = intravenous; OCCI = Ontario Case Costing Initiative; QALY = quality-adjusted life-year; WTP = willingness to pay.

Drug	Lanadelumab injection (Takhzyro)
Indication	Routine prevention of attacks of hereditary angioedema in adolescents and adults
Reimbursement request	As per indication
Dosage form(s) and route of administration)/strength(s)	150 mg/mL solution for subcutaneous injection
NOC date	19 September 2018
Manufacturer	Shire Pharma Canada ULC

Executive Summary

Background

Lanadelumab is a human monoclonal antibody with a targeted mechanism of action that provides sustained inhibition of plasma kallikrein, which prevents the subsequent release of bradykinin and attacks of hereditary angioedema (HAE). It is indicated for the routine prevention of attacks of HAE in adolescents and adults aged 12 years or older.[1] The recommended dose of lanadelumab is 300 mg administered via subcutaneous injection every two weeks. A dosage interval of 300 mg every four weeks may be considered if the patient's HAE is well-controlled or the patient has been attack-free for more than six months. Lanadelumab is supplied as a single ready-to-use (300 mg/2 mL) solution at a submitted price of $20,538 per vial. The average annual cost for lanadelumab is $533,988 and $266,994, with dosage intervals every two and four weeks, respectively.

The manufacturer submitted a cost-utility analysis over a lifetime horizon (i.e., 60 years) from a Canadian publicly funded health care payer perspective.[2] The analysis compared total costs and quality-adjusted life-years (QALYs) of lanadelumab and plasma-derived C1 esterase inhibitors (C1-INHs), including both Cinryze intravenous (IV) and Berinert IV as a single blended comparator ([redacted]% Cinryze, [redacted]% Berinert 20 IU/kg, [redacted]% Berinert 40 IU/kg, [redacted]% Berinert 60 IU/kg). The manufacturer also included no prophylaxis as part of a scenario analysis upon the request of CADTH. The manufacturer assumed Berinert IV 20 IU/kg, Berinert IV 40 IU/kg, and Berinert IV 60 IU/kg to have the same efficacy as Cinryze IV 20 IU/kg every three or four days because of the lack of studies assessing the effect of Berinert IV in preventing long-term HAE attacks.

The manufacturer used a cohort Markov model with two health states ("alive with HAE" and "dead") to trace the total costs and QALYs of HAE patients using 28-day cycles. Average attack rates and attack duration for lanadelumab and C1-INHs were obtained from the HELP-03 trial[3] and a network meta-analysis (NMA)[4] that included the HELP-03 and CHANGE trials.[3,5] It was assumed that mortality rates were unaffected by treatment and were the same as those in the general Canadian population. In the manufacturer's base case, health utility values were based on two sources: utility value for patients experiencing HAE attack based on a cohort study of Swedish patients with HAE;[6] and a health utility increment due to a more preferential route of administration and less frequent drug administration, independent of disease area,[7] derived from 1,645 adults in the UK general

population elicited using a time trade-off exercise. The manufacturer considered drug acquisition, resource use associated with HAE attacks, and adverse event costs (such as hospitalization, emergency room visit, and physician visits).

The manufacturer reported that lanadelumab dominated C1-INHs, as it was associated with lower health care costs ($9,091,303 versus $10,866,545) and improved QALYs (24.347 versus 22.955). The probability that lanadelumab is cost-effective was 100% at a willingness-to-pay (WTP) threshold of $50,000 per QALY.

Summary of Identified Limitations and Key Results

CADTH identified a number of limitations as part of its review. The manufacturer excluded no prophylaxis from its reference-case analysis. The manufacturer did, however, include no prophylaxis as a scenario analysis upon the request of CADTH. No prophylaxis is a relevant comparator in patients with a very low frequency of HAE attacks, especially in men, according to a clinical expert consulted by CADTH.

The manufacturer assumed that, after six months, 80% of patients receiving lanadelumab switched from receiving the recommended 300 mg dose administered via subcutaneous injection every two weeks to receiving it every four weeks. However, this assumption was not well-justified. According to a clinical expert consulted by CADTH, the optimal dosage for patients with well-controlled HAE remains unknown, given that the evidence from the HELP-03 trial suggests that 300 mg every four weeks may be less efficacious than 300 mg every two weeks; however, no statistical comparisons were conducted between treatment groups in HELP-03.

C1-INHs were included in the analysis as a single blended comparator. It is inappropriate to combine Cinryze IV and Berinert IV, as it is not possible to compare the cost-effectiveness of lanadelumab with each comparator individually. Additionally, the evidence on the clinical efficacy of Berinert IV for HAE prophylaxis was lacking because it is indicated only as a rescue treatment for HAE, and its safety and efficacy for prophylactic therapy has not been established. The manufacturer therefore assumed that the efficacy of Berinert IV was equal to that of Cinryze IV. The manufacturer reported that Cinryze IV has a small market share ([redacted]%), with off-label Berinert IV accounting for most of the market for prophylactic therapy in Canada. It is, therefore, questionable whether the efficacy data of Cinryze IV can represent the efficacy of all C1-INHs. There is substantial uncertainty in the comparative efficacy and safety of lanadelumab and C1-INHs. The comparative efficacy of lanadelumab and C1-INHs were obtained from a fixed-effects NMA, but the results of the NMA should be interpreted with caution, given the substantial differences in trial design, key eligibility criteria, treatment duration, protocols for rescue therapy, and outcome measures.

The manufacturer estimated the health-related quality of life and health utility values associated with being attack-free from a cohort of patients with HAE in Sweden.[6] The study showed that attack frequency (regression coefficient = –0.0043 per attack; $P < 0.0001$) and older age (regression coefficient = –0.02205 per 10 years of age; $P < 0.0001$) were associated with reduced health utility scores and that the number of days since the last attack had a positive correlation with health utility scores. The manufacturer did not describe why its health utility algorithm did not account for the number of days since the last attack. Furthermore, a health utility increment due to a more preferential mode of drug administration was obtained from an adult UK general population.[7] This value may not reflect the health utility of patients in Canada, and it is uncertain whether this is applicable in the treatment of HAE.

In the manufacturer's base case, it assumed that 10% and 100% of patients with HAE attacks would require hospitalization or emergency room (ER) visits, respectively. The clinical experts consulted by CADTH disagreed with this assumption and noted that only patients with severe attacks would require an ER visit or hospitalization, because most attacks can be self-treated by patients. Additionally, the cost of an ER visit was underestimated, as it included only emergency physician fees but did not include the costs of other health care professionals providing care in ERs and costs that are not directly related to patient care (e.g., general administration, information technology, capital expenses, etc.).

The manufacturer did not account for HAE-specific mortality. Existing evidence shows that laryngeal attacks would lead to a reported mortality rate of 40% if they were left untreated;[2] however, both the HELP-03 and CHANGE trials reported no deaths due to HAE attacks. Excluding HAE-specific mortality may overestimate the life expectancy of HAE patients, but it is likely to have a minimal impact on the incremental cost-utility ratios (ICURs) because the HELP-03 and the CHANGE trials reported no deaths due to HAE attacks or serious treatment-emergent adverse events.

In the revised base case, CADTH considered no prophylaxis as a comparator; considered Cinryze IV and Berinert IV as individual comparators; and added direct and indirect hospital costs to ER physician costs, as reported by the Ontario Case Costing Initiative. Cinryze IV was also removed as a rescue therapy, as it is not approved for the treatment for HAE acute attacks in Canada. Furthermore, the proportion of patients who switch to a less frequent dosage regimen, i.e., every four weeks, from six months onward was reduced from 80% to 0%. Results of the CADTH base case showed that Cinryze IV dominated Berinert IV but was extendedly dominated by lanadelumab. When considering non-dominated options, lanadelumab would be considered an optimal option compared with no prophylaxis if the WTP is less than $6,872,940 per QALY. The cost-effectiveness of lanadelumab compared with no prophylaxis was highly sensitive to assumptions regarding preferences for the mode of administration. If the mode of administration of lanadelumab (subcutaneous injection) has no impact on patients' quality of life, then the ICUR of lanadelumab compared with no prophylaxis would increase to $10,918,255 per QALY.

CADTH also included a scenario analysis and excluded no prophylaxis from a list of comparators. This reanalysis showed that Cinryze IV dominated Berinert IV. Compared with Cinryze IV, the ICUR for lanadelumab was $6,981,558 per QALY. Consistent with the first CADTH reanalysis with no prophylaxis, the cost-effectiveness of lanadelumab compared with Cinryze IV or Berinert IV was highly sensitive to assumptions regarding preferences for the mode of administration. If the mode of administration of lanadelumab (subcutaneous injection) did not improve patients' quality of life, then the ICUR of lanadelumab compared with Cinryze IV would increase to $15,417,069 per QALY.

Conclusions

CADTH's revised base case showed that, when considering no prophylaxis, Cinryze IV dominates Berinert IV but is extendedly dominated by lanadelumab. However, lanadelumab is not cost-effective compared with no prophylaxis, with an ICUR of $6,872,940 per QALY. The probability that lanadelumab is cost-effective was 0% at the WTP value of $50,000 per QALY. A price reduction of 84.7% or greater is required for lanadelumab to be cost-effective at a WTP threshold of $50,000 per QALY.

A scenario analysis that excluded no prophylaxis from CADTH's base case showed that Cinryze IV dominated Berinert IV and that lanadelumab is not cost-effective compared with Cinryze IV, with an ICUR of $6,981,558 per QALY. The probability that lanadelumab is cost-effective was 0% at a WTP value of $50,000 per QALY. A price reduction of 58.6% or greater is required for lanadelumab to be cost-effective at a WTP threshold of $50,000 per QALY if no prophylaxis is excluded as a comparator in the sequential analysis.

The cost-effectiveness of lanadelumab compared with C1-INHs is highly uncertain, given that evidence on the comparative efficacy of lanadelumab and subcutaneous C1-INHs was not included as part of the NMA report submitted by the manufacturer.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis (CUA) comparing lanadelumab 300 mg with C1 esterase inhibitors (C1-INHs) for the routine prevention of hereditary angioedema (HAE) attacks in adolescents and adults aged 12 years or older. No prophylaxis was included as part of a scenario analysis upon request by CADTH. The target population was aligned with the patient population who were part of the HELP-03 study,[8] a pivotal phase III randomized controlled trial (RCT) that assessed the efficacy and safety of subcutaneous lanadelumab 300 mg and placebo in preventing HAE. The CUA was conducted from a Canadian publicly funded health care payer perspective using Ontario as a proxy for all other Canadian provinces and territories. A Markov cohort model with two health states ("alive with HAE" and "dead") was used to simulate total costs and quality-adjusted life-years (QALYs) over a time horizon of 60 years. The model used a 28-day cycle length to be consistent with the intervals used for the follow-up and dosage schedule of lanadelumab in the HELP-03 study. The HELP-03 trial was a multi-centre, parallel-arm, double-blind trial that compared three subcutaneous (SC) lanadelumab regimens (300 mg every two weeks, 300 mg every four weeks, and 150 mg every four weeks) and placebo among 126 patients with a confirmed diagnosis of type I or II HAE. Patients underwent a four-week run-in period and a 26-week treatment period.

In the manufacturer's base case, the efficacy (i.e., a reduction in the number of attacks) of lanadelumab was obtained from the HELP-03 study, while the efficacy of C1-INHs was based on a fixed-effects network meta-analysis (NMA)[4] that estimated the rate ratio (RR) of the attack frequency of lanadelumab versus placebo and C1-INHs versus placebo. The estimated RR for C1-INHs versus placebo was applied to a Poisson regression based on data from a placebo arm of the HELP-03 study to get the number of attacks for C1-INHs. Poisson regression analyses were used to model the number of attacks for each treatment arm, including lanadelumab 300 mg every four weeks, lanadelumab 300 mg every two weeks, and placebo. These Poisson regression models included two covariates: baseline risk and the number of attacks in the previous cycle. The selection of these covariates was guided by clinicians, results of subgroup analyses of the HELP-03 trial, and the goodness of fit of a Poisson model (i.e., Akaike information criterion [AIC]). In the manufacturer's base case, the Poisson regression model by treatment arms was chosen, as it had a slightly better goodness of fit than a pooled model that included all treatment arms (AIC: [redacted] versus [redacted], respectively). The attack rate data from the HELP-03 trial were adjusted for treatment discontinuation, as it was calculated by dividing the number of attacks during the treatment period (26 weeks) by the number of days the patients contributed to the period. Patients who discontinued the therapy were assumed to receive no further prophylactic treatments. Due to a lack of data on the distribution of attack severity for Cinryze IV, the manufacturer assumed that the attack severity distribution of C1-INHs was equal to that of lanadelumab, as reported in the HELP-03 trial. Data on the average duration of attacks were obtained from the HELP-03 and CHANGE trials[5] for lanadelumab/placebo and C1-INHs administered intravenously (IV), respectively. The CHANGE trial was a phase III, double-blind crossover trial that compared Cinryze IV 1,000 unit in 10 mL of sterile water with placebo (10 mL of saline) among 22 patients with a confirmed diagnosis of HAE.

The trial consisted of two consecutive 12-week treatment periods, during which patients received Cinryze IV or placebo IV every three to four days.

Patients who received lanadelumab, C1-INHs, or no prophylaxis (in a scenario analysis) were assumed to have a risk of death that was equal to general population mortality rates in Canada, given that no HAE-specific mortality data were available. In the manufacturer's base case, health utility values for attack-free patients were based on a survey of Swedish patients with HAE who completed EuroQol 5-Dimensions (EQ-5D) questionnaires for the attack-free state and the last HAE attack.[6] This study showed that attack frequency (regression coefficient –0.0043 per attack; $P < 0.0001$) and older age (regression coefficient –0.02205 per 10 years of age; $P < 0.0001$) were associated with reduced health utility scores and that the number of days since the last attack had a positive correlation with health utility scores. The manufacturer's model used health utility values weighted by attack severity distribution shown in the lanadelumab arm of the HELP-03 trial. In the base case, the manufacturer applied a health utility increment of 0.024 to the model to account for the preferential and less frequent administration of lanadelumab compared with C1-INHs IV. Health utility decrements due to adverse events (AEs) were not included in the manufacturer's model.

Severe AE (grade 3 or higher) rates were obtained from the HELP-03 trial for lanadelumab/placebo and the CHANGE trial for C1-INHs. The manufacturer's model considered the costs of drugs, acute attacks, and AEs. Administration and monitoring costs were excluded from the base case, as global clinical experts suggested that patients receiving C1-INH require minimal monitoring visits/tests, and that these visits were likely to be similar across all C1-INH IV treatments. The manufacturer assumed self-administration for all treatments, regardless of route of administration, but applied a 30-minute training fee for the first administration. The proportion of patients who are self-administering the treatment was varied in sensitivity analyses. In the manufacturer's base case, 10% and 100% of patients with HAE attack were assumed to require hospitalization or emergency room (ER) visits, respectively. The manufacturer assumed that 80% of HAE patients receiving lanadelumab switched dosage regimens from every two weeks to every four weeks from six months onwards. AE costs were assumed to be equal to an extra physician visit. Physician costs were obtained from the Ontario Schedule of Benefits.[9] Cost data were reported in 2019 Canadian dollars. A series of scenario analyses were performed to assess the robustness of the cost-effectiveness findings.

Manufacturer's Base Case

The manufacturer reported that, over a 60-year time horizon, lanadelumab was less costly ($9,091,303 versus $10,866,545) but more effective (24.35 versus 22.96 QALYs) than C1-INHs; thus, lanadelumab was dominant. Results from a probabilistic analysis revealed that lanadelumab was cost-saving in 100% of 5,000 simulations. However, there was a 37% chance that lanadelumab would result in fewer QALYs than C1-INHs (Appendix 5, Figure 2). The probability of lanadelumab being cost-effective compared with C1-INHs at a willingness to pay (WTP) of $50,000 per QALY was 100%.

Summary of Manufacturer's Sensitivity Analyses

Results of scenario analyses showed that C1-INHs were dominated by lanadelumab in all scenarios. In a scenario analysis considering no prophylaxis, C1-INHs were also dominated by lanadelumab, as they were more costly and produced fewer QALYs. Compared with no

prophylaxis, lanadelumab was more expensive ($9,097,786 versus $1,934,964) but more effective (24.233 versus 22.393 QALYs), suggesting that lanadelumab was the optimal therapy at a WTP greater than $3,893,812 per QALY (Table 2). The probability that lanadelumab is cost-effective was 0% at a WTP of $50,000 per QALY.

Table 2: Results of the Manufacturer's Scenario Analysis Considering No Prophylaxis

	Total Costs ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	Sequential ICUR ($/QALY)
Non-dominated options					
No prophylaxis	$1,934,964	–	22.393	–	–
Lanadelumab	$9,097,786	$7,162,822	24.233	1.840	$3,893,812
Dominated treatments					
C1-INHs	$11,300,592	$2,202,806	22.976	–1.257	Dominated by lanadelumab

C1-INH = C1 esterase inhibitor; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Limitations of Manufacturer's Submission

CADTH identified the following key limitations with the manufacturer's submission.

Lack of head-to-head comparative efficacy and safety data for lanadelumab and C1-INHs. The manufacturer derived the comparative efficacy of lanadelumab and C1-INHs IV from a fixed-effects NMA. However, findings from the NMA should be interpreted with caution, given the substantial differences in trial design, key eligibility criteria, treatment duration, protocols for rescue treatment, and outcome measures.

Clinical experts consulted by CADTH also raised their concerns about the exclusion of two pivotal RCTs from the NMA ([redacted] and [redacted]), which assessed the efficacy of subcutaneous C1-INHs. Although no subcutaneous C1-INH is currently marketed in Canada, Berinert subcutaneous injection with doses up to 60 IU/kg has been used off-label as long-term prophylactic therapy in Canada for several years. Furthermore, clinical experts consulted by CADTH noted that the C1-INH dosage used in the trial was not weight-based, although the CHANGE trial was a pivotal study for Cinryze IV. Consequently, patients may receive higher doses of Cinryze IV in clinical practice than did the patients who participated in the CHANGE trial.

CADTH also identified issues related to the manufacturer-conducted NMA. There was potential clinical heterogeneity in the characteristics of patients enrolled in the HELP-03 and CHANGE trials, but CADTH was unable to fully assess the appropriateness of the use of the fixed-effects NMA and the heterogeneity in patient populations in the two studies because the CHANGE trial did not report key baseline patient characteristics (i.e., the number of attacks at baseline and the attack sites). Furthermore, the quality of the CHANGE trial was low, as the trial did not appropriately report or conduct randomization, concealment, or blinding of care providers, participants, and outcome assessors.

CADTH noted that the average attack duration for each comparator was based on two RCTs (HELP-03 trial for lanadelumab/placebo and CHANGE trial for C1-INHs). The observed differences in attack duration between the two treatments should be interpreted cautiously, as they were based on a naive direct comparison, and no attempt was made to adjust for any differences in patient baseline characteristics between the trials. The observed

difference in attack duration may be a result of differences in population, trial characteristics, and C1-INH dosage schedules.

Proportion of patients switching to less frequent dosages of lanadelumab. The manufacturer assumed that, after six months, 80% of patients receiving lanadelumab switched from receiving the recommended 300 mg dose administered subcutaneously every two weeks to receiving it every four weeks. The product monograph for lanadelumab does indicate that a dosage interval of 300 mg every four weeks may be considered if the patient's HAE is well-controlled or the patient has been attack-free for more than six months.

However, according a clinical expert consulted by CADTH, there is high uncertainty regarding the switching to a less frequent dosage regimen. According to the clinical expert, the optimal dosage for patients with well-controlled HAE remains unknown, given that the evidence from the HELP-03 trial suggests that 300 mg every four weeks may be less efficacious than 300 mg every two weeks; however, no statistical comparisons were conducted between treatment groups in HELP-03. Given the lack of data to support the reduced dosage frequency, CADTH assumed in its revised base case that zero per cent of patients receiving lanadelumab 300 mg every two weeks switch to receiving it every four weeks.

Using C1-INHs as a single, blended comparator. The manufacturer's approach, which used a single blended comparator to represent C1-INHs (combining Cinryze IV and Berinert IV), was not appropriate. The efficacy of Berinert IV for long-term prophylaxis also remains unknown. More importantly, the manufacturer reported that Cinryze IV has a small market share ([redacted]%), with off-label Berinert IV capturing much of the market for prophylactic therapy in Canada. It is, therefore, questionable to use efficacy data of Cinryze IV to represent the efficacy of all C1-INHs. It would be more appropriate to consider each C1-INH separately. This approach would allow the manufacturer to perform a sequential analysis and test the uncertainty in the comparative efficacy of lanadelumab versus Cinryze IV and versus Berinert IV. CADTH used Cinryze IV and Berinert IV as separate comparators in all reanalyses. Due to the lack of efficacy/safety of Berinert IV for the long-term prevention of HAE, CADTH assumed the efficacy of Berinert IV to be equal to that of Cinryze IV.

Data sources for health utility values. The manufacturer derived health utility values associated with the attack-free health state from the following formula:

> Attack-free utility = 0.825 – 0.02205 × age – 0.0043 × number of attacks in the previous cycle

This equation was part of regression results reported by Nordenfelt et al. (2014)[6] that estimated the burden of HAE and health utility in patients with HAE in Sweden. The study showed that attack frequency (regression coefficient –0.0043 per attack; $P < 0.0001$) and older age (regression coefficient –0.02205 per 10 years of age; $P < 0.0001$) were associated with reduced health utility scores, while days since the last attack had a positive correlation with health utility scores. The manufacturer did not describe why the coefficient of days since the last attack was excluded from the equation and whether the manufacturer contacted the authors to access all regression coefficients that were significantly associated with the health utility values of HAE patients. Moreover, a health utility increment due to more preferential and less frequent drug administration was derived from the adult UK general population.[7] This value may not reflect the health utility of Canadians, and it is uncertain whether this is applicable to patients with HAE.

Health care resources required for HAE acute attack. In the base case, the manufacturer assumed that 10% and 100% of patients who experienced an acute attack would require hospitalization or an ER visit, respectively. The clinical experts consulted by CADTH disagreed with this assumption and suggested that most patients with an acute attack would typically self-administer treatment. Patients visiting the ER would typically be patients with severe and life-threatening HAE attacks, especially laryngeal attacks. Hospital length of stay for an acute attack in Canada was assumed to be one day, based on clinical expert opinion; however, the manufacturer did not describe how expert opinion was elicited. CADTH tested the uncertainty in this estimate by using the hospital length of stay for acute attack, as reported in Wilson et al. (2000).[12] Moreover, the manufacturer's model underestimated ER costs, since it included only emergency physician fees but did not include the costs of other health care professionals providing care in ERs and costs that are not directly related to patient care, such as general administration, information technology, and overhead.

Higher mortality due to HAE. The manufacturer's model did not consider HAE-specific mortality. Existing evidence has shown that laryngeal attacks would lead to a reported mortality rate of 40% if left untreated. A previous study[13] has shown that the life expectancy of patients with undiagnosed HAE who died due to asphyxiation attributable to the disease was shorter than the life expectancy of patients who died as a result of other causes. Excluding HAE-specific mortality may overestimate the life expectancy of HAE patients, but it is likely to have a minimal impact on incremental cost-utility ratios (ICURs), as the HELP-03 and CHANGE trials reported no deaths due to HAE attacks or serious treatment-emergent adverse events.

The omission of key comparators. The manufacturer's base case did not consider no prophylaxis as a comparator. CADTH *Guidelines for the Economic Evaluation of Health Technologies* recommend that "it is crucial to identify all appropriate comparators for the analysis, as the choice will be important in determining the cost-effectiveness of the intervention and the relevance of the study to decision-makers." As a scenario analysis upon the request of CADTH, the manufacturer provided an updated economic model with no prophylaxis as a treatment option. However, the manufacturer claimed that a comparison of lanadelumab with no prophylaxis should be interpreted with caution, as there is little justification to consider a placebo comparison in clinical practice, when considering the patient population that forms the basis of this reimbursement request. Given the serious morbidity and mortality associated with HAE, and the inability to predict when a life-threatening attack may occur, routine prophylaxis is an important component in the management of HAE. Thus, long-term prophylaxis therapy is not an alternative to an on-demand only strategy. The clinical experts consulted by CADTH disagreed with this claim, and believed that no prophylaxis was relevant, especially for patients who experienced few HAE attacks and especially for male patients. According to the clinical experts consulted by CADTH, less than 50% of all HAE patients in Canada receive long-term prophylactic treatment. Additionally, 40.2% of patients in the HELP-03 study had received no prior long-term prophylaxis use at baseline.[3] The manufacturer's market research indicates that 67% of treated HAE patients are receiving prophylactic therapy in Canada. CADTH concluded that there is uncertainty surrounding the proportion of HAE patients receiving prophylactic therapy in Canada, and this could range between half and two-thirds of patients.

Inclusion of inappropriate rescue treatment. CADTH noted that the manufacturer allowed patients to receive Cinryze IV as a rescue treatment. This assumption may not be appropriate, as Cinryze IV is indicated only for HAE prophylaxis in Canada.

CADTH Common Drug Review Reanalyses

For the revised base case, CADTH:

1. considered no prophylaxis as a comparator
2. considered Cinryze IV and Berinert IV as separate comparators but assumed the same efficacy due to the lack of evidence on the efficacy of Berinert IV for HAE prevention
3. replaced the ER costs by what was reported by the Ontario Case Costing Initiative; Cinryze IV was also removed from a list of subsequent rescue therapies, as it is not indicated for the treatment for HAE acute attacks in Canada
4. removed Cinryze IV as from a list of rescue treatments and considered only Firazyr SC or Berinert IV as subsequent rescue treatments; the proportion of patients receiving these treatments was calculated by adjusting the proportion of patients receiving Firazyr SC or Berinert IV observed in the HELP-03 trial to 100%
5. reduced the proportion of patients who switch dosage regimen of lanadelumab from every two weeks to every four weeks from 80% to 0%.

The probabilistic reanalysis was undertaken using the same number of iterations as used in the manufacturer's base case (5,000 iterations), as an increased number of iterations had only a minimal impact on the ICURs (± 2% change).

Results of the CADTH revised base case showed that Cinryze IV dominated Berinert IV but was extendedly dominated by lanadelumab. When considering non-dominated options, lanadelumab would be considered an optimal therapy at an ICUR of $6,872,940 per QALY (Table 3). The probability of lanadelumab being cost-effective was 0% at a WTP of $50,000 per QALY.

When no prophylaxis was excluded from the CADTH revised base-case analysis, Cinryze IV dominated Berinert IV. Compared with Cinryze IV, lanadelumab had an ICUR of $6,981,558 per QALY. The probability of lanadelumab being cost-effective was 0% at a WTP of $50,000 per QALY.

Table 3: CADTH's Revised Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus C1-INHs or No Prophylaxis	Sequential ICUR ($/QALY)
Manufacturer's base case				
C1-INHs IV	$10,866,545	22.955	–	–
Lanadelumab	$9,091,303	24.347	Dominant (less costly but more QALYs compared with C1-INHs IV)	
Reanalysis 1: Considering no prophylaxis as one of the comparators (Manufacturer's scenario analysis)				
Non-dominated options				
No prophylaxis	$1,934,964	22.393	–	–
Lanadelumab	$9,097,786	24.233	$3,893,812 *(versus no prophylaxis)*	$3,893,812 *(versus no prophylaxis)*
Dominated options				
C1-INHs IV	$11,300,592	22.976	Dominated by lanadelumab	
Reanalysis 2: Separating C1-INHs IV to Cinryze IV and Berinert IV				
Non-dominated options				

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus C1-INHs or No Prophylaxis	Sequential ICUR ($/QALY)
Cinryze IV	$5,472,047	22.950	–	–
Lanadelumab	$9,089,594	24.350	$2,584,206 *(versus no prophylaxis)*	$2,584,206 *(versus no prophylaxis)*
Dominated options				
Berinert IV	$11,542,275	22.945	Dominated by lanadelumab	
Reanalysis 3: Replacing ER cost with that reported by the OCCI				
C1-INHs IV	$11,012,647	23.052	–	–
Lanadelumab	$9,159,440	24.449	Dominant (less costly but more QALYs compared with C1-INHs IV)	
Reanalysis 4: Removing Cinryze IV from a list of rescue treatments				
C1-INHs IV	$11,593,060	23.001	–	–
Lanadelumab	$9,135,421	24.328	Dominant (less costly but more QALYs compared with C1-INHs IV)	
Reanalysis 5: Reducing the proportion of patients who switch to a less frequent dosage regimen of lanadelumab (80% to 0%)				
C1-INHs IV	$10,895,145	23.048	–	–
Lanadelumab	$14,888,389	24.349	$3,069,715 (versus C1-INHs IV)	$3,069,715 (versus C1-INHs IV)
CADTH's revised base case (Combining reanalyses 1, 2, 3, 4, and 5)				
Non-dominated options				
No prophylaxis	$2,433,840	22.398	–	–
Lanadelumab	$12,361,630	24.215	$6,872,940 *(versus no prophylaxis)*	$6,872,940 *(versus no prophylaxis)*
Dominated options				
Cinryze IV	$6,288,708	22.978	Extendedly dominated by lanadelumab	
Berinert IV	$14,925,075	22.977	Dominated by Cinryze IV	
CADTH's revised base case without no prophylaxis (Combining reanalyses 2, 3, 4, and 5)				
Non-dominated options				
Cinryze IV	$6,288,708	22.978	–	–
Lanadelumab	$14,925,075	24.215	$6,981,558 (versus Cinryze IV)	$6,981,558 (versus Cinryze IV)
Dominated options				
Berinert IV	$12,361,630	22.977	Dominated by Cinryze IV	

C1-INH = C1 esterase inhibitor; ICUR = incremental cost-utility ratio; IV = intravenous infusion; OCCI = Ontario Case Costing Initiative; QALY = quality-adjusted life-year.

CADTH performed a series of scenario analyses to assess the structural and parameter uncertainty associated with the manufacturer's model. Results from CADTH scenario analyses revealed that the magnitude of health utility increment due to more preferential drug administration was the most important driver of the cost-effectiveness of lanadelumab compared with no prophylaxis. If changing the route and the frequency of drug administration did not improve health utility, the ICUR of lanadelumab compared with no prophylaxis would increase to $10,918,255 per QALY (56% increase). Other determinants of the cost-effectiveness findings consisted of the proportion of patients who switched to a less frequent dosage regimen, the approach used to estimate HAE attack rates for each comparator, the assumption on the variation in health utility values by attack severity, and the source of HAE-specific health utility. Detailed results of CADTH scenario analyses are shown in Appendix 5 (Tables 17 and 18).

CADTH undertook a price-reduction analysis based on the manufacturer's and CADTH's revised base case (Table 4). When no prophylaxis was included as a comparator (CADTH revised base case), Cinryze IV dominated Berinert IV but was extendedly dominated by lanadelumab in most scenarios. A price reduction of at least 84.7% was required for the ICUR of lanadelumab to be lower than a commonly used WTP of $50,000 per QALY. In the CADTH reanalysis that excluded no prophylaxis as a comparator, a price reduction of at least 58.6% was required for the ICUR of lanadelumab compared with Cinryze IV to be lower than a commonly used WTP of $50,000 per QALY.

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICURs of Lanadelumab Versus Comparators			
Price	**Base-Case Analysis Submitted by the Manufacturer**	**Reanalysis by CADTH (Including "No Prophylaxis" – CADTH-Revised Base Case)**	**Reanalysis by CADTH (Excluding "No Prophylaxis")**
Submitted	Lanadelumab is optimal. Lanadelumab dominated C1-INHs IV.	If WTP < $6,872,940/QALY, no prophylaxis is optimal. If WTP > $6,872,940/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $6,981,558 /QALY, Cinryze IV is optimal. If WTP > $6,981,558/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
10% reduction		If WTP < $5,804,444/QALY, no prophylaxis is optimal. If WTP > $5,804,444/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $5,437,386/QALY, Cinryze IV is optimal. If WTP > $5,437,386/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
15% reduction		If WTP < $5,428,956/QALY, no prophylaxis is optimal. If WTP > $5,428,956/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $4,886,425/QALY, Cinryze IV is optimal. If WTP > $4,886,425/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
20% reduction		If WTP < $5,198,438/QALY, no prophylaxis is optimal. If WTP > $5,198,438/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $4,535,432/QALY, Cinryze IV is optimal. If WTP > $4,535,432/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
25% reduction		If WTP < $5,009,981/QALY, no prophylaxis is optimal. If WTP > $5,009,981/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $4,216,935/QALY, Cinryze IV is optimal. If WTP > $4,216,935/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
30% reduction		If WTP < $4,036,575/QALY, no prophylaxis is optimal.	If WTP < $2,974,921/QALY, Cinryze IV is optimal.

ICURs of Lanadelumab Versus Comparators			
		If WTP > $4,036,575/QALY lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP > $2,974,921/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
40% reduction		If WTP < $3,796,048/QALY, no prophylaxis is optimal. If WTP > $3,796,048/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $2,395,906/QALY, Cinryze IV is optimal. If WTP > $2,395,906/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
50% reduction		If WTP < $2,780,890/QALY, no prophylaxis is optimal. If WTP > $2,780,890/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $1,034,690/QALY, Cinryze IV is optimal. If WTP > $1,034,690/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
58.6% reduction		If WTP < $2,024,281/QALY, no prophylaxis is optimal. If WTP > $2,024,281/QALY lanadelumab is optimal. Cinryze IV dominated Berinert IV. Lanadelumab extendedly dominated Cinryze IV.	If WTP < $46,286/QALY, Cinryze IV is optimal. If WTP > $46,286/QALY, lanadelumab is optimal. Cinryze IV dominated Berinert IV.
60% reduction		If WTP < $1,934,724/QALY, no prophylaxis is optimal. If WTP > $1,934,724/QALY, lanadelumab is optimal. Cinryze IV and Berinert IV were dominated by lanadelumab.	Lanadelumab is optimal. Lanadelumab dominated Cinryze IV and Berinert IV.
70% reduction		If WTP < $1,087,842/QALY, no prophylaxis is optimal. If WTP > $1,087,842/QALY, lanadelumab is optimal. Cinryze IV and Berinert IV were dominated by lanadelumab.	Lanadelumab is optimal. Lanadelumab dominated Cinryze IV and Berinert IV.
80% reduction		If WTP < $418,355/QALY, no prophylaxis is optimal. If WTP > $418,355/QALY, lanadelumab is optimal. Cinryze IV and Berinert IV were dominated by lanadelumab.	Lanadelumab is optimal. Lanadelumab dominated Cinryze IV and Berinert IV.
84.7% reduction		If WTP < $47,078 /QALY, no prophylaxis is optimal. If WTP > $47,078 /QALY, lanadelumab is optimal. Cinryze IV and Berinert IV were dominated by lanadelumab.	Lanadelumab is optimal. Lanadelumab dominated Cinryze IV and Berinert IV.

C1-INH = C1 esterase inhibitor; ICUR = incremental cost-utility ratio; IV = intravenous infusion; QALY = quality-adjusted life-year; WTP = willingness to pay.

Issues for Consideration

CADTH identified several issues related to the manufacturer-conducted NMA. First, two important phase III studies, i.e., the [redacted], and [redacted] trials, were excluded from the evidence network. Second, there was potential clinical heterogeneity in the characteristics of patients enrolled in the HELP-03 and CHANGE trials. However, CADTH was unable to fully assess the heterogeneity in patient populations in the two studies because the CHANGE trial did not report key baseline patient characteristics (i.e., the number of attacks at baseline and the attack sites). It is therefore difficult to evaluate the manufacturer's argument for preferring a fixed-effects over a random-effects model based on no systematic differences in study populations. Furthermore, the quality of the CHANGE study was low, as mentioned in the NMA report. Specifically, the study did not appropriately report or conduct randomization, concealment, or blinding of care providers, participants, and outcome assessors. Further descriptions of the critical appraisal have been detailed in the CADTH Clinical Review Report. CADTH's concerns regarding the incomplete evidence network were supported by clinical experts consulted by CADTH who suggested that Berinert SC injection has been used off-label for HAE prophylaxis for several years, although Haegarda has not been marketed in Canada. Additionally, the dose of Cinryze IV used in the CHANGE trial was not based on patient weight. Patients receiving Cinryze IV in clinical practice may therefore receive a higher dose than the patients who participated in the CHANGE trial, which may impact the cost-effectiveness findings. The cost-effectiveness of lanadelumab may be different if results from the [redacted] and [redacted] trials are considered.

Patient Input

One patient group (HAE Canada) provided input for the lanadelumab submission. A total of 73 Canadian type I and II HAE patients and caregivers responded to an online survey. Sixty-eight (92%) were individuals living with HAE, and six (8%) were caregivers. A total of eight survey respondents indicated that they had used (or are using) lanadelumab to treat their HAE. The patient group noted that better preventive treatments are urgently needed for the prevention of attacks, improvement in the acute management of HAE, improvement in patient quality of life, and more convenient methods/modalities of self-administration (versus IV). They noted that patients would have more prophylactic treatment options with the availability of lanadelumab and that lanadelumab is expected to better control HAE attacks, improve the management of acute HAE attacks, offer a more convenient route of administration compared with IV infusion, and improve quality of life. The manufacturer's economic model accounted for the benefit of lanadelumab in reducing HAE attacks and improving patient quality of life due to a more preferential administration.

Conclusions

CADTH's revised base case showed that, when no prophylaxis was considered as a comparator, Cinryze IV dominated Berinert IV but was extendedly dominated by lanadelumab. Compared with no prophylaxis, lanadelumab was associated with higher costs and improved QALYs, with an ICUR of $6,872,940 per QALY. The probability of lanadelumab being cost-effective was 0% at a WTP value of $50,000 per QALY. A price reduction of 84.7% or greater is required for the ICUR of lanadelumab to be lower than the threshold of $50,000 per QALY when no prophylaxis was included in the analysis. The cost-effectiveness of lanadelumab compared with no prophylaxis was highly sensitive to the health utility increment due to more preferential drug administration. When no prophylaxis was excluded from the CADTH revised base case, Cinryze IV dominated Berinert IV and the ICUR for lanadelumab compared with Cinryze IV was $6,981,558 per QALY. The probability of lanadelumab being cost-effective was 0% at a WTP value of $50,000 per QALY. A price reduction of 58.6% or greater is required for the ICUR of lanadelumab to be lower than the threshold of $50,000 per QALY when no prophylaxis is excluded from the analysis.

The ICUR of lanadelumab is highly uncertain, given the concerns about the substantial heterogeneity of the trials included in the NMA submitted by the manufacturer.

Appendix 1: Cost Comparison

The comparators presented in Table 5 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's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table, and, as a result, the table may not represent the actual costs to public drug plans.

Table 5: CADTH Common Drug Review Cost Comparison Table for the Routine Prevention of Hereditary Angioedema Attacks

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Lanadelumab (Takhzyro)	300 mg / 2 mL	Solution for SC injection	20,538.0000[a]	300 mg every 2 weeks 300 mg every 4 weeks may be considered if the patient's HAE is well-controlled for more than 6 months	1,467.00 733.50 once well-controlled for 6 months	533,988 266,994 once well-controlled for 6 months
C1 esterase inhibitor (Cinryze)	500 IU	Two 500 IU vials of powder with diluent per package	[redacted]	1,000 IU every 3 or 4 days[14]	[redacted]	[redacted]
Not indicated for prophylactic use in HAE						
C1 esterase inhibitor (Berinert)	500 IU 1,500 IU	Kit, including powder, diluent, and syringe	[redacted]	20 IU per kg by IV injection Prophylactic use is not indicated, although clinical trials and guidelines specify a dose every 3 to 4 days[14]	[redacted]	[redacted]
Not indicated for use in HAE						
Danazol (Cyclomen)	50 mg 100 mg 200 mg	Capsule	0.9983[c] 1.4816[c] 2.3676[c]	Less than 200 mg per day[14]	2.37 (max)	862 (max)

CDR = CADTH Common Drug Review; HAE = hereditary angioedema; IV = intravenous; SC = subcutaneous.

Note: A year is assumed to be 13 28-week cycles, or 364 days long. Average patient weight assumed to be 75 kg. Costs do not include administration.

[a] Manufacturer's submitted price.[2]

[b] No public price available. Price listed was submitted by manufacturer as part of lanadelumab model.[2] CADTH was unable to confirm accuracy.

[c] Ontario Drug Benefit Formulary (July 2019).[15]

Appendix 2: Summary of Key Outcomes

Table 6: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Lanadelumab Relative to No Prophylaxis?

Lanadelumab Versus C1-Inhibitors	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	According to the CADTH reanalysis, from the perspective of a Canadian publicly funded health care payer, lanadelumab was more expensive ($12,491,235) and associated with improved QALYs (1.817) when compared with no prophylaxis, with an estimated ICUR of $6,872,940/QALY.					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Lanadelumab Relative to Cinryze Intravenous or Berinert Intravenous?

lanadelumab Versus C1-Inhibitors	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	According to the CADTH reanalysis without no prophylaxis, from the perspective of a Canadian publicly funded health care payer, Berinert IV was dominated by Cinryze IV (ΔC = $6,072,922, ΔE= –0.001). Compared with Cinryze IV, lanadelumab incurred higher costs and improved QALYs (ΔC = $8,636,367, ΔE= 1.237), with an ICUR of $6,981,558/QALY).					

CE = cost-effectiveness; IV = intravenous; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 8: 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”	The quality of the submitted economic model and economic report is judged to be fair. The original and updated manufacturer’s models did not include all relevant comparators available in Canada. The methodological quality of the supporting network meta-analysis was poor because it excluded two important phase III RCTs and pooled the results from RCTs that were substantially different in terms of patient characteristics, trial design, protocols for rescue therapy, and outcome measures.		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

RCT = randomized controlled trial.

Table 9: Authors’ Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ 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		

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

The Australia Pharmaceutical Benefits Advisory Committee was scheduled to discuss lanadelumab for a similar but more restricted authorization in July 2019 but had not yet posted the result at the time of this review.[16] The Federal Joint Committee in Germany determined that lanadelumab provided considerable additional benefit for patients 12 years of age and older with recurrent hereditary angioedema (HAE).[17] The Scottish Medicine Consortium is currently working on an unspecified review of lanadelumab, scheduled for completion in the fourth quarter of 2019.[18] The Institut national d'excellence en santé et en services sociaux (INESSS, Quebec)[19] and the Institute for Clinical and Economic Review (ICER, US)[20] have published reviews including lanadelumab, which are outlined in Table 10. The National Institute for Health and Care Excellence (NICE, UK) was currently reviewing lanadelumab and, at the time of this review, had posted a Final Appraisal Document, which was undergoing final consultation and thus not yet final (Table 10).[21] In France, the Haute Autorité de Santé gave a positive opinion in favour of listing lanadelumab in patients experiencing severe and recurrent HAE attacks insufficiently controlled by first-line preventive treatments for three to six months.[22]

Table 10: Other Health Technology Assessment Findings

	INESSS (August 2019)[19]	ICER (November 2018)[20]	NICE (September 2019)[21]
Treatment	Lanadelumab 300 mg every 2 weeks or every 4 weeks when HAE is well-controlled (no crises for at least 6 months)	Lanadelumab 300 mg every 2 weeks	Lanadelumab 300 mg every 2 weeks or every 4 weeks in patients who are stably attack-free on treatment may be considered, especially in patients of low weight
Price	Not reported	List price: US$16,520 per 300 mg (C$21,955)[23]	List price: £12,420 (C$20,463)[23] per 300 mg, not including confidential discount for patient access scheme
Similarities with CDR submission	Unknown; economic evaluation not reported	ICER conducted a two-state Markov CUA, no manufacturer submission. Lifetime time horizon.	Cohort, two-state Markov CUA. Utilities from Nordenfelt study. Comparators included Berinert and Cinryze but did not appear to include no prophylaxis.
Differences from CDR submission	Unknown; economic evaluation not reported. The INESSS clinical assessment did not appear to have access to interim results from the HELP-04 extension or the manufacturer-sponsored ITC included in the CDR submission; thus, INESSS had less access to long-term data than CDR.	Prophylaxis with lanadelumab, Cinryze, or Haegarda (all indicated in the US) were individually compared with no prophylaxis (on-demand treatment).	Unclear; full description of economic analysis was not available
Manufacturer's results	Not reported	None	Lanadelumab dominant compared with C1-INHs
Issues noted by the review group	Economic issues not reported. The committee focused on lack of evidence for long-term safety of lanadelumab, as well	ICER's highlighted limitations: • Long-term comparative clinical effectiveness of prophylaxis uncertain due to lack of data	• Manufacturer used list prices of C1-INHs rather than current NHS prices.

	INESSS (August 2019)[19]	ICER (November 2018)[20]	NICE (September 2019)[21]
	as lack of evidence comparing lanadelumab to active and effective comparators currently used in clinical practice.	on natural history of attack rates over patients' lifetimes and small clinical trials of short duration. • Utilities were from European sources. • Data regarding Haegarda prophylaxis reducing the severity of subsequent attacks were assumed equivalent for lanadelumab and Cinryze due to lack of data.	• Uncertainty in the dosage of Berinert in clinical practice. • The scenario analysis in which 61% of patients reduced lanadelumab dose was preferable to the 77% base case estimate.
Results of reanalyses by the review group (if any)	NA	Prophylactic lanadelumab every two weeks had an ICUR of US$1,108,000 (C$1,472,532)[23] compared with no prophylaxis.	ICURs less than £20,000 (C$32,952)[23] compared with C1-INHs, when confidential pricing of all comparators was considered (exact results confidential).
Recommendation	Adding lanadelumab to the Liste des produits du système du sang du Québec for the prevention of HAE attacks would not constitute a fair and reasonable option.	No direct recommendation. In summary, at current drug prices, no prophylactic treatment for HAE compared with lanadelumab every two weeks meets traditional cost-effectiveness thresholds within the health care system; however, significant uncertainty exists. Most forum members voted that prophylactic lanadelumab represents low value for money compared with no prophylaxis (on-demand treatment).	Recommended for patients age 12 and older with recurring HAE attacks if: • Eligible for C1-INH treatment (i.e., having two or more attacks per 8 weeks despite oral prevention therapy or if oral therapy is contraindicated or not tolerated) • Lowest dosage of lanadelumab is used when condition is stable • Company provides lanadelumab according to patient access scheme.

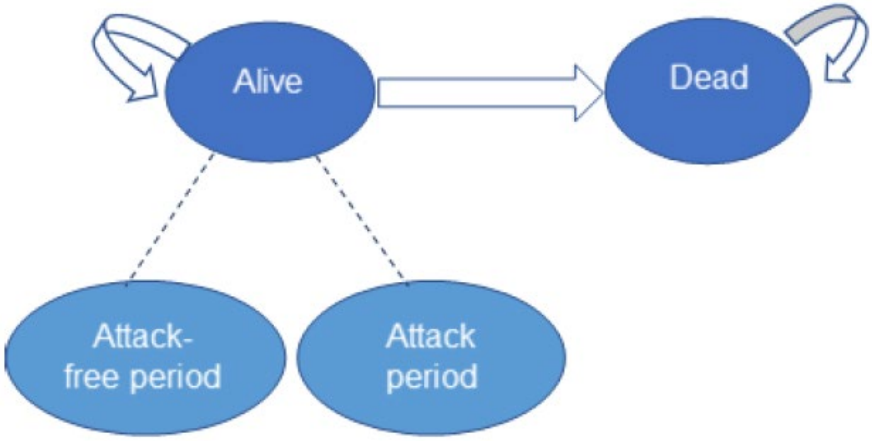
C1-INH = C1 esterase inhibitor; CUA = cost-utility analysis; HAE = hereditary angioedema; ICER = Institute for Clinical and Economic Review; ICUR = incremental cost-utility ratio; INESSS = Institut national d'excellence en santé et en services sociaux; ITC = indirect treatment comparison; NA = not applicable; NICE = National Institute for Health and Care Excellence.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer used a cohort Markov model to simulate total costs and quality-adjusted life-years (QALYs) over a lifetime horizon (60 years). The cohort Markov model consisted of "alive with hereditary angioedema (HAE)" and "dead" health states (Figure 1). Key data sources used in the model are shown in Table 11 and the manufacturer's key assumptions in Table 12.

Figure 1: Model Structure



Source: Manufacturer's pharmacoeconomic submission.[2]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Characteristics of the patient population were based on the HELP-03 trial.	Appropriate. CADTH clinical experts suggested that patients enrolled in the HELP-03 trial might have mild HAE symptoms. In particular, the HELP-03 trial recruited patients who had ≥ 1 investigator-confirmed attack per month. The COMPACT and SAHARA trials, however, recruited HAE patients ≥ 2 attacks requiring immediate treatment or medical attention per month. There was no evidence on the variation in efficacy by HAE attack severity at baseline; its impact on the ICURs is unknown.
Efficacy	Efficacy of lanadelumab (the number of attacks) and no prophylaxis were derived from the Poisson regression on the HELP-03 trial data.	Appropriate. CADTH agrees that it is appropriate to derive the HAE attack rates of patients receiving lanadelumab and placebo from the HELP-03 trial. The manufacturer used a Poisson regression model with two covariates (baseline risk and the number of attacks in the previous cycle) to estimate the number of HAE attacks for each cycle.

Data Input	Description of Data Source	Comment
	The comparative efficacy of lanadelumab and C1-INHs was derived from a fixed-effects NMA. The efficacy of Cinryze IV was used as a proxy for all C1-INHs.	CADTH is concerned about the methodological quality of the NMA, given the substantial clinical and methodological heterogeneity of RCTs included in the NMA (Table 12). More importantly, CADTH clinical experts are concerned by the exclusion of two important RCTs assessing the efficacy of a subcutaneous C1-INH. Although Haegarda has not been marketed in Canada, a subcutaneous C1-INH (Berinert 1,500 IU) has long been used off-label as a long-term prophylaxis treatment. CADTH notes that the average attack duration for each comparator was based on two RCTs (HELP-03 trial for lanadelumab and CHANGE trial for C1-INHs). The observed differences in attack duration between the two treatments should be interpreted cautiously, because they were based on a naive direct comparison in which there is no attempt to adjust for any difference in patient characteristics between the trials.
Mortality	Probabilities that HAE patients transited to death were derived from the weighted average of age-sex–specific mortality rates of Canada's general population.	Inappropriate. The manufacturer assumed that HAE did not affect the risk of death. CADTH clinical experts disagreed with this assumption and suggested that a severe form of HAE attack, such as a laryngeal attack, is life-threatening and may increase the mortality rates of HAE patients. HAE may lead to a laryngeal attack that can be fatal, with a mortality rate of 40% if left untreated. The manufacturer did not account for the potential increased risk of death in the submitted economic model. However, this limitation is not expected to have a large impact on the cost-effectiveness findings, as the mortality rates were assumed to be equal between all prophylactic options.
Utilities	Health utility values for patients experiencing HAE attack were based on a retrospective analysis of a cohort of Swedish patients with HAE. Health utility associated with being attack-free was derived from the following formula: Attack-free utility = 0.825 – 0.02205 × age – 0.0043 × number of attacks in the previous cycle A health utility increment of 0.024 was added to HAE patients receiving	Uncertain. The health utility value associated with HAE attack was appropriate, given the lack of health utility data in HAE Canadian patients. However, CADTH is concerned about the equation used to derive the HAE attack-free health utility value. The Swedish study showed that attack frequency (–0.0043 per attack; $P < 0.0001$) and older age (–0.02205 per 10 years of age; $P < 0.0001$) were associated with reduced health utility scores, while days since last attack has a positive correlation with health utility scores. The manufacturer did not describe the reason

Data Input	Description of Data Source	Comment
	lanadelumab to account for less invasive and less frequent drug administration.	why the coefficient of days since last attack was excluded from the equation and whether the manufacturer contacted the authors to access all regression coefficients that were significantly associated with the health utility values of HAE patients. CADTH notes that a health utility increment due to more preferential drug administration was derived from the adult UK general population. This value may not reflect the health utility of Canadians.
Adverse events	The PE model includes severe treatment-related AEs (grade ≥ 3) occurring in > 2% of patients in any treatment arm. These AEs consisted of the increased liver enzyme for lanadelumab and chest discomfort for Cinryze IV. The manufacturer accounted for the costs of AEs but did not consider health utility decrements due to AEs.	Appropriate. CADTH agrees that it is appropriate to assume no health utility decrement due to AEs due to the absence of studies reporting the impact of increased liver enzyme for lanadelumab and chest discomfort on the health utility of HAE patients.
Resource use and costs		
Drug	Costs of lanadelumab and C1-INHs (Cinryze IV and Berinert IV) were obtained from the manufacturer.	Appropriate
Administration	The manufacturer's base case assumed self-administration. The model only considered a nurse training fee of $20 for the first administration. In scenario analyses, unit costs for drug administration were obtained from the Ontario Schedule of Benefits.	Appropriate
AEs	Costs of AEs (increased liver enzymes and chest discomfort) were assumed to include an extra physician visit.	Appropriate
Health state – acute attack	In the base case, the manufacturer assumed that the proportions of HAE attacks requiring hospitalization and ER visit were 10% and 100%, respectively. As a scenario analysis, the manufacturer used the proportions of patients requiring hospitalization, ER visits, and physician visits during an attack, based on a study conducted by Wilson et al. (2010).[12] Hospital length of stay for the acute attack in Canada was assumed to be one day, based on clinical expert opinion.	Inappropriate. The clinical experts consulted by CADTH noted that the proportions of hospitalizations and ER visit were too high, given that they would be required only for patients with severe attacks. Most attacks would be self-treated at home. The additional hospital day due to HAE attack was based on clinical expert opinion. The manufacturer did not describe how expert opinion was elicited.

AE = adverse event; C1-INH = C1 esterase inhibitor; CDR = CADTH Common Drug Review; ER = emergency room; HAE = hereditary angioedema; IV = intravenous infusion; NMA = network meta-analysis; PE = pharmacoeconomic; RCT = randomized controlled trial.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Characteristics of the patient population (i.e., mean age, % female, and weight) were consistent with patients who enrolled in the HELP-03 trial.	Appropriate
It was assumed that 80% of patients receiving lanadelumab 300 mg every two weeks would switch to receiving it every four weeks.	Inappropriate. According to a clinical expert consulted by CADTH, the optimal dosage for patients with well-controlled HAE remains unknown, given that the evidence from the HELP-03 trial suggests that 300 mg every four weeks may be less efficacious than 300 mg every two weeks; however, no statistical comparisons were conducted between treatment groups in HELP-03.
Efficacy of Cinryze IV was used as a proxy for all C1-INHs, since the efficacy of Berinert IV for long-term prophylaxis is unavailable.	Inappropriate. Although it is reasonable to assume the same efficacy for Cinryze IV and Berinert IV, CADTH believes that it is inappropriate to combine Cinryze IV and Berinert IV as a single blended comparator (C1-INHs), because the efficacy of Berinert IV for long-term prophylaxis remains unknown. It would be more appropriate to consider each C1-INH separately. This approach would allow the manufacturer to perform a sequential analysis and test the uncertainty in the comparative efficacy of lanadelumab versus Cinryze IV versus Berinert IV versus no prophylaxis.
Distribution of attack severity was assumed to be the same among all comparators for HAE patients who experienced an attack.	Appropriate given the lack of severity distribution data for C1-INHs.
The discontinuation rates of lanadelumab and C1-INHs were assumed to be equal. For patients who discontinued the treatment, no subsequent prophylactic treatment was assumed in the long term due to lack of data to inform long-term predictions.	Inappropriate. CADTH clinical experts disagreed with this assumption. CADTH was unable to assess the impact of this assumption on the ICURs due to limited evidence on subsequent prophylactic treatments that patients would receive in practice.
The mortality rates of HAE patients were assumed to be the same as the general Canadian population, given the absence of published HAE-specific mortality rates.	Inappropriate. HAE may lead to a laryngeal attack that can be fatal with a mortality rate of 40% if left untreated. The manufacturer did not account for the potential increased risk of death in the submitted model. Given the model structure, this limitation is, however, expected to have minimal impact on the cost-effectiveness findings, as the mortality rates were assumed to be equal across the prophylactic treatment options.
Patients receiving lanadelumab had a higher health utility increment of 0.024 because patients were assumed to prefer less frequent and invasive administrations.	Uncertain. This health utility increment was based on the UK general population. The value may not reflect the preferences of Canadians.
AEs were assumed to occur in every cycle throughout the treatment duration.	Appropriate, given that the two AEs (increased liver enzyme and chest discomfort) are acute.
The economic model assumed that both prophylactic treatments were self-administered. Regardless of the mode of administration (subcutaneous or intravenous), patients required only 30 minutes of nursing training, provided during the first administration.	Appropriate.
Patients who received C1-INHs were assumed to receive the same rescue treatment when they experienced an acute attack.	Inappropriate. CADTH believes that this assumption is inappropriate for Cinryze IV because this treatment is approved for routine prevention of HAE attacks in adults and adolescents with HAE, not as a rescue treatment.

Assumption	Comment
Patients receiving C1-INHs and lanadelumab were assumed to have a similar number of monitoring tests/visits due to very few and infrequent monitoring tests required.	Appropriate

AE = adverse event; C1-INH = C1 esterase inhibitor; ER = emergency room; HAE = hereditary angioedema; ICUR = incremental cost-utility ratio; IV = intravenous infusion.

Table 13: Characteristics of HELP-03 and CHANGE Trials

	HELP-03 (Banerji et al., 2018)[8]	CHANGE (Zuraw et al., 2010)[5]
Study design	Phase III, parallel-arm RCT	Phase III, crossover, RCT
Key eligibility criteria	Age ≥ 12 years with a confirmed diagnosis of HAE type I or II, ≥ 1 confirmed investigator attack per 4 weeks	Age ≥ 6 years with frequent HAE attack (i.e., ≥ 2 attacks per months)
Outcome definition	Investigator-confirmed HAE attacks	Patient-reported HAE attacks
Treatment duration	26 weeks	12 weeks

HAE = hereditary angioedema; RCT = randomized controlled trial.

Manufacturer's Results

Results of the manufacturer's model are shown in Table 14. Drug acquisition costs accounted for the largest share of cost savings, followed by attack-related costs and administration costs (Table 15).

Table 14: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Lanadelumab ($)	Total QALYs	Incremental QALYs of Lanadelumab	Incremental Cost per QALY
C1-INHs	10,866,545	–	22.955	–	–
Lanadelumab	9,091,303	–1,775,242	24.347	1.391	dominant

C1-INH = C1 esterase inhibitor; QALY = quality-adjusted life-year.

Table 15: Breakdown of Deterministic Results

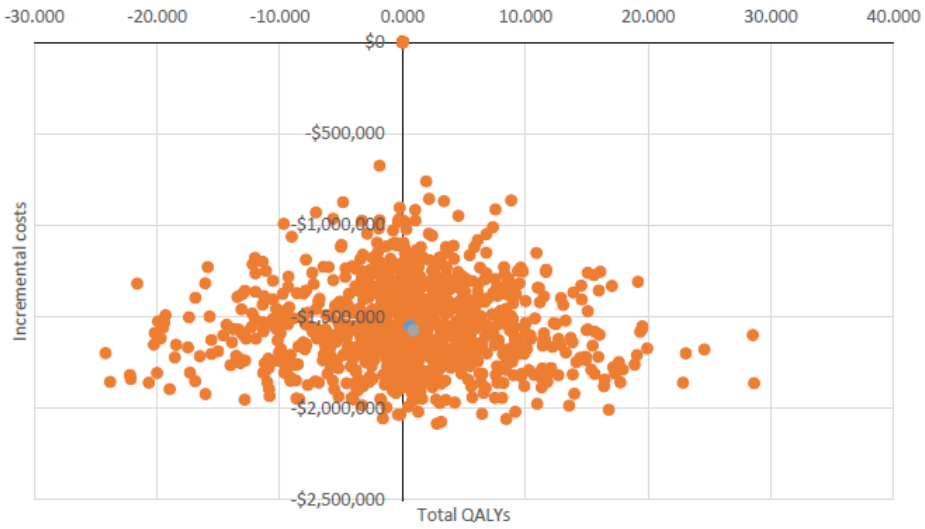
	Lanadelumab	C1-INHs IV	Incremental	% Difference
Total costs ($)	**$9,196,214**	**$10,992,948**	**–$1,796,734**	**100%**
Prophylaxis costs				
Drug acquisition	$8,973,417	$10,587,233	–$1,613,817	90%
Administration	$0	$31,272	–$31,272	2%
AEs	$487	$797	–$310	0%
Attack-related costs				
Treatment	$196,685	$283,841	–$87,156	5%
Hospitalization	$13,998	$49,056	–$35,058	2%
ER visits	$11,627	$40,748	–$29,121	2%
Physician visits	$0	$0	$0	$0

	Lanadelumab	C1-INHs IV	Incremental	% Difference
Societal costs	$0	$0	$0	$0
Monitoring	$0	$0	$0	$0
QALYs	**24.52**	**22.00**	**1.30**	**100%**
Without attack	24.32	22.00	2.33	69%
With attack	0.20	1.23	–1.03	31%

AE = adverse event; C1-INH = C1 esterase inhibitor; ER = emergency room; IV = intravenous; QALY = quality-adjusted life-year.

In all 5,000 iterations of a probabilistic sensitivity analysis, lanadelumab was a cost-saving option compared with C1 esterase inhibitors (C1-INHs). However, there was a 36.8% chance that lanadelumab would lead to fewer QALYs compared with C1-INHs (Figure 2). Lanadelumab was the dominant option compared with C1-INHs in all deterministic analyses. In a scenario analysis in which no prophylaxis was considered, C1-INHs were still dominated by lanadelumab. Compared with no prophylaxis, lanadelumab was associated with an additional cost of $7,162,822 ($9,097,786 versus $1,934,964) and extra 1.840 (24.233 versus 22.393) QALYs, with an incremental cost-utility ratio (ICUR) of $3,893,812 per QALY (Table 16). Under this scenario, the probability that lanadelumab being cost-effective was 0% at a willingness to pay (WTP) of $50,000/QALY.

Figure 2: Cost-Effectiveness Plane Obtained From the Manufacturer's Base Case



Source: Manufacturer's pharmacoeconomic submission.[2]

Table 16: Results of Manufacturer's Scenario Analyses

	Incremental Costs Lanadelumab Versus C1-INHs IV	Incremental QALYs Lanadelumab Versus C1-INHs IV	ICUR Lanadelumab Versus C1-INHs IV
Base-Case Results	**–$1,796,734**	**1.296**	**Dominant**
1. Assuming a steady state + RR applied to placebo arm for lanadelumab	–$446,318	0.919	Dominant
2. Excluding drug wastage	–$64,116	0.930	Dominant
3. Assuming a hospital length of stay of 3.22 days	–$609,941	0.962	Dominant
4. Using the efficacy from the HELP-03 trial regression	–$361,010	0.852	Dominant
5. Deriving the efficacy by applying the risk ratio of lanadelumab to the placebo arm of the HELP-03 trial	–$386,085	0.880	Dominant
6. Using alternative health utility values (Aygören-Pürsün et al., 2006)	–$462,418	0.895	Dominant
7. Varying health utility values by attack severity	–$462,418	0.894	Dominant
8. Combine scenarios (6) and (7)	–$462,418	0.826	Dominant
9. Excluding health utility increment due to drug administration	–$462,418	0.415	Dominant
10. Using alternative health utility values associated with drug administration (Holko et al., 2018)	–$462,418	0.780	Dominant
11. Using alternative health utility values associated with drug administration (Evans et al., 2013)	–$462,418	1.252	Dominant
12. Shorten time horizon to 5 years	–$55,514	0.208	Dominant
13. Shorten time horizon to 10 years	–$147,132	0.378	Dominant
14. Shorten time horizon to 20 years	–$286,326	0.629	Dominant
15. Shorten time horizon to 30 years	–$379,459	0.792	Dominant
16. Considering societal costs	–$490,171	0.930	Dominant
17. Considering no prophylaxis as one of the comparators	–$2,202,806	1.257	Dominant

C1-INH = C1 esterase inhibitor; ICUR = incremental cost-utility ratio; IV = intravenous; QALY = quality-adjusted life-year; RR = rate ratio.

CADTH Common Drug Review Reanalyses

CADTH conducted the following reanalyses:

- As suggested by CADTH clinical experts, CADTH applied the lower proportions of HAE attacks requiring hospitalization, emergency room (ER), or physician visits by assuming that only patients with a severe attack (8%) would require hospitalization or ER visit (scenarios 1 to 3). The proportion of HAE patients with severe attacks was obtained from the HELP-03 trial.
- Instead of using Poisson models by treatment arm, a pooled (dependent) Poisson model that included treatment assignment, baseline risk, and the number of previous attacks in previous 28 days was used to estimate the average number of attacks per cycle (scenario 4).
- CADTH tested the effect of including HAE-specific mortality by adding a constant mortality rate of 0.0022% from asphyxiation due to laryngeal attack (scenario 5). This mortality rate was obtained from the US Institute for Clinical and Economic Review (ICER) report[20] that assessed the effectiveness and value of lanadelumab and C1-INHs as the prophylaxis treatments for HAE.
- The health utility increment for lanadelumab resulting from a more preferential mode was uncertain as it was derived from a UK population. Health utility values may also be dependent upon the severity of HAE attacks and not just their frequency. CADTH excluded the health utility increment (scenario 6) and assumed that health utility values varied by HAE attack severity (scenario 7).
- Because there are no health utility data specific to Canadian patients with HAE, CADTH assessed the uncertainty in this parameter by changing health utility values specific to HAE obtained from Nordenfelt et al. (2014) to those obtained from Aygören-Pürsün et al. (scenario 8). The study by Aygören-Pürsün et al. (2016) included 111 HAE patients from Germany, Denmark, and Spain.
- There was a high uncertainty in the long-term efficacy of lanadelumab, as the manufacturer used data observed from an RCT with a short follow-up period (26 weeks) to extrapolate the efficacy of lanadelumab over patient lifetime (60 years). CADTH assessed the impact of this uncertainty by reducing the time horizon to 40, 20, and 10 years (scenarios 9 to 11).
- CADTH tested the uncertainty in the efficacy of lanadelumab compared with C1-INHs by changing the approach used to estimate HAE attack rates from a regression analysis based on the HELP-03 trial to the application of rate ratios (RRs) estimated from the network meta-analysis (NMA) to the placebo arm of the HELP-3 trial (scenarios 12 and 13).
- CADTH tested the effects of the proportion of HAE patients who switch to a less frequent dosage schedule, i.e., every four weeks, by changing the proportion to 80% (as submitted by the manufacturer) and 44.4% (the proportion of patients receiving lanadelumab 300 mg every two weeks in the HELP-03 study who had attack-free intervals at six months[3]).

Results of CADTH reanalyses are shown in Table 17.

Table 17: Results of CADTH Scenario Analyses (Including No Prophylaxis)

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
CADTH's revised base case					
Non-dominated options					
No prophylaxis	$2,433,840	–	22.398	–	–
Lanadelumab	$14,925,075	$12,491,235	24.215	1.817	$6,872,940
Dominated options					
Cinryze IV	$6,288,708	$3,854,868	22.978	0.580	Extendedly dominated by lanadelumab
Berinert IV	$12,361,630	$9,927,791	22.977	0.579	Dominated by Cinryze IV
Scenario 1: Assuming 8% of HAE attacks require an ER visit					
Non-dominated options					
No prophylaxis	$2,124,016	–	22.353	–	–
Lanadelumab	$14,881,280	$12,757,264	24.195	1.843	$6,923,641
Dominated options					
Cinryze IV	$6,117,096	$3,993,080	22.964	0.612	Extendedly dominated by lanadelumab
Berinert IV	$12,194,176	$10,070,160	22.963	0.610	Dominated by Cinryze IV
Scenario 2: Assuming 8% of HAE attacks require hospitalization					
Non-dominated options					
No prophylaxis	$2,166,196	–	22.395	–	–
Lanadelumab	$14,891,697	$12,725,501	24.335	1.356	$6,561,818
Dominated options					
Cinryze IV	$6,146,484	$10,060,921	22.975	0.583	Extendedly dominated by lanadelumab
Berinert IV	$12,227,117	$10,060,921	22.978	0.583	Extendedly dominated by lanadelumab
Scenario 3: Assuming 8% of HAE attacks require physician visit					
Non-dominated options					
No prophylaxis	$2,106,723	–	22.490	–	–
Lanadelumab	$14,954,526	$12,847,804	24.256	1.766	$7,276,740
Dominated options					
Cinryze IV	$6,138,690	$4,031,968	23.087	0.597	Extendedly dominated by lanadelumab
Berinert IV	$12,245,891	$10,139,168	23.095	0.604	Extendedly dominated by lanadelumab
Scenario 4: Using a pooled Poisson model to predict HAE attack rates					
Non-dominated options					
No prophylaxis	$1,974,620	–	22.7047	–	–
Lanadelumab	$14,781,641	$12,807,022	24.4267	1.722	$7,437,261

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
Dominated options					
Cinryze IV	$6,010,033	$4,035,414	23.2134	0.509	Extendedly dominated by lanadelumab
Berinert IV	$12,101,541	$10,126,921	23.2129	0.508	Dominated by Cinryze IV
Scenario 5: Assuming increased mortality due to asphyxiation following a laryngeal attack					
Non-dominated options					
No prophylaxis	$2,445,579	–	22.460	–	–
Lanadelumab	$14,954,223	$12,508,644	24.266	1.806	$6,927,036
Dominated options					
Cinryze IV	$6,301,999	$3,856,420	23.037	0.577	Extendedly dominated by lanadelumab
Berinert IV	$12,389,046	$9,943,467	23.040	0.579	Extendedly dominated by lanadelumab
Scenario 6: Excluding health utility increment due to the more preferential route of administration					
Non-dominated options					
No prophylaxis	$2,438,789	–	22.417	–	–
Lanadelumab	$14,935,220	$12,496,431	23.561	1.145	$10,918,255
Dominated options					
Cinryze IV	$6,297,731	$3,858,943	23.001	0.584	Extendedly dominated by lanadelumab
Berinert	$12,368,526	$9,929,738	22.997	0.580	Dominated by Cinryze IV
Scenario 7: Assuming health utility values to be varied by the severity of HAE attacks					
Non-dominated options					
No prophylaxis	$2,422,496	–	22.503	–	–
Lanadelumab	$14,921,291	$12,498,794	24.354	1.851	$6,752,288
Dominated options					
Cinryze IV	$6,289,664	$3,867,168	23.019	0.516	Extendedly dominated by lanadelumab
Berinert IV	$12,366,130	$9,943,633	23.021	0.517	Extendedly dominated by lanadelumab
Scenario 8: Using health utility values from Aygören-Pürsün et al. (2016)					
Non-dominated options					
No prophylaxis	$2,451,702	–	20.554	–	–
Lanadelumab	$14,991,872	$12,540,170	22.362	1.808	$6,935,026
Dominated options					
Cinryze IV	$6,316,573	$3,864,871	21.106	0.553	Extendedly dominated by lanadelumab
Berinert IV	$12,417,997	$9,966,296	21.107	0.553	Extendedly dominated by lanadelumab
Scenario 9: Reducing a time horizon to 40 years					
Non-dominated options					
No prophylaxis	$2,199,184	–	20.303	–	–

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
Lanadelumab	$13,459,395	$11,260,211	22.000	1.697	$6,633,715
Dominated options					
Cinryze IV	$5,672,626	$3,473,442	20.841	0.538	Extendedly dominated by lanadelumab
Berinert IV	$11,153,273	$8,954,090	20.842	0.539	Extendedly dominated by lanadelumab
Scenario 10: Reducing a time horizon to 20 years					
Non-dominated options					
No prophylaxis	$1,375,779	–	12.827	–	–
Lanadelumab	$8,374,127	$6,998,348	13.880	1.053	$6,648,861
Dominated options					
Cinryze IV	$3,529,513	$2,153,734	13.174	0.347	Extendedly dominated by lanadelumab
Berinert IV	$6,940,408	$5,564,629	13.175	0.348	Extendedly dominated by lanadelumab
Scenario 11: Reducing a time horizon to 10 years					
Non-dominated options					
No prophylaxis	$755,162	–	7.070	–	–
Lanadelumab	$4,580,313	$3,825,151	7.651	0.581	$6,585,306
Dominated options					
Cinryze IV	$1,931,303	$1,176,141	7.266	0.196	Extendedly dominated by lanadelumab
Berinert IV	$3,797,795	$3,042,633	7.265	0.195	Dominated by Cinryze IV
Scenario 12: Estimating the attack rates for lanadelumab by applying RRs to the placebo arm of the HELP-03 trial and assuming a steady state of attack rates for lanadelumab					
Non-dominated options					
No prophylaxis	$2,348,093	–	22.491	–	–
Lanadelumab	$14,792,833	$12,444,741	24.470	1.979	$6,286,978
Dominated options					
Cinryze IV	$6,132,151	$3,784,059	23.120	0.629	Extendedly dominated by lanadelumab
Berinert IV	$12,214,285	$9,866,193	23.120	0.629	Extendedly dominated by lanadelumab
Scenario 13: Estimating the attack rates for lanadelumab by applying RRs to the placebo arm of the HELP-03 trial and assuming no steady state of attack rates for lanadelumab					
Non-dominated options					
No prophylaxis	$2,346,340	–	22.506	–	–
Lanadelumab	$14,874,819	$12,528,478	24.316	1.810	$6,923,184
Dominated options					
Cinryze IV	$6,134,378	$3,788,038	23.136	0.630	Extendedly dominated by lanadelumab
Berinert IV	$12,229,213	$9,882,872	23.134	0.627	Dominated by Cinryze IV

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
Scenario 14: The proportion of patients who switch to a less frequent dosage regimen, i.e., every four weeks, is 80%					
Non-dominated options					
No prophylaxis	$2,442,890	–	22.500	–	–
Lanadelumab	$9,198,893	$6,756,004	24.171	1.671	$4,043,713
Dominated options					
Cinryze IV	$6,318,279	$3,875,389	23.077	0.578	Extendedly dominated by lanadelumab
Berinert IV	$12,408,549	$9,965,659	23.074	0.574	Dominated by Cinryze IV
Scenario 15: The proportion of patients who switch to a less frequent dosage regimen, i.e., every four weeks, is 44.4%					
Non-dominated options					
No prophylaxis	$2,440,271	–	22.492	–	–
Lanadelumab	$11,767,639	$9,327,368	24.316	1.824	$5,113,723
Dominated options					
Cinryze IV	$6,308,427	$3,868,157	23.064	0.572	Extendedly dominated by lanadelumab
Berinert IV	$12,403,277	$9,963,006	23.065	0.573	Dominated by Cinryze IV

ER = emergency room; HAE = hereditary angioedema; ICUR = incremental cost-utility ratio; IV = intravenous; QALY = quality-adjusted life-year; RR = rate ratio.

[a] Compared with no prophylaxis.

Table 18: Results of CADTH Scenario Analyses (Excluding No Prophylaxis)

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
CADTH's revised base case					
Non-dominated options					
Cinryze IV	$6,288,708	–	22.978	–	–
Lanadelumab	$14,925,075	$8,636,367	24.215	1.237	$6,981,558
Dominated option					
Berinert IV	$12,361,630	$6,072,922	22.977	–0.001	Dominated by Cinryze IV
Scenario 1: Assuming 8% of HAE attacks require an ER visit					
Non-dominated options					
Cinryze IV	$6,117,096	–	22.964	–	–
Lanadelumab	$14,881,280	$8,764,184	24.195	1.231	$7,119,567
Dominated option					
Berinert IV	$12,194,176	$8,764,184	22.963	–0.002	Dominated by Cinryze IV
Scenario 2: Assuming 8% of HAE attacks require hospitalization					
Non-dominated options					
Cinryze IV	$6,146,484	–	22.975	–	–
Lanadelumab	$14,891,697	$8,745,213	24.335	1.356	$6,431,714
Dominated option					
Berinert IV	$12,227,117	$6,080,634	22.978	0.003	Extendedly dominated by lanadelumab

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
Scenario 3: Assuming 8% of HAE attacks require physician visit					
Non-dominated options					
Cinryze IV	$6,138,690	–	23.087	–	–
Lanadelumab	$14,954,526	$8,815,836	24.256	1.169	$7,541,125
Dominated option					
Berinert IV	$12,245,891	$6,107,201	23.095	0.008	Extendedly dominated by lanadelumab
Scenario 4: Using a pooled Poisson model to predict HAE attack rates					
Non-dominated options					
Cinryze IV	$6,010,033	–	23.213	–	–
Lanadelumab	$14,781,641	$3,102,953	24.427	1.214	$7,229,598
Dominated option					
Berinert IV	$12,101,541	$6,091,507	23.213	0.000	Dominated by Cinryze IV
Scenario 5: Assuming increased mortality due to asphyxiation following a laryngeal attack					
Non-dominated options					
Cinryze IV	$6,301,999	–	23.037	–	–
Lanadelumab	$14,954,223	$8,652,224	24.266	1.229	$7,042,913
Dominated option					
Berinert IV	$12,389,046	$6,087,047	23.040	0.002	Extendedly dominated by lanadelumab
Scenario 6: Excluding health utility increment due to the more preferential route of administration					
Non-dominated options					
Cinryze IV	$6,297,731	–	23.001	–	–
Lanadelumab	$14,935,220	$8,637,489	23.561	0.560	$15,417,069
Dominated option					
Berinert IV	$12,368,526	$6,070,795	22.997	–0.004	Dominated by Cinryze IV
Scenario 7: Assuming health utility values to be varied by the severity of HAE attacks					
Non-dominated options					
Cinryze IV	$6,289,664	–	23.019	–	–
Lanadelumab	$14,921,291	$8,631,626	24.354	1.335	$6,464,595
Dominated options					
Berinert IV	$12,366,130	$6,076,465	23.021	0.002	Extendedly dominated by lanadelumab
Scenario 8: Using health utility values from Aygören-Pürsün et al. (2016)					
Non-dominated options					
Cinryze IV	$6,316,573	–	21.106	–	–
Lanadelumab	$14,991,872	$8,675,299	22.362	1.256	$6,908,564
Dominated option					
Berinert IV	$12,417,997	$6,101,425	21.107	0.000	Extendedly dominated by lanadelumab

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
Scenario 9: Reducing a time horizon to 40 years					
Non-dominated options					
Cinryze IV	$5,672,626	–	20.841	–	–
Lanadelumab	$13,459,395	$7,786,769	22.000	1.160	$6,714,581
Dominated option					
Berinert IV	$11,153,273	$5,480,647	20.842	0.001	Extendedly dominated by lanadelumab
Scenario 10: Reducing a time horizon to 20 years					
Non-dominated options					
Cinryze IV	$3,529,513	–	13.174	–	–
Lanadelumab	$8,374,127	$4,844,614	13.880	0.706	$6,865,017
Dominated option					
Berinert IV	$6,940,408	$3,410,895	13.175	0.001	Extendedly dominated by lanadelumab
Scenario 11: Reducing a time horizon to 10 years					
Non-dominated options					
Cinryze IV	$1,931,303	–	7.266	–	–
Lanadelumab	$4,580,313	$2,649,010	7.651	0.385	$6,877,295
Dominated option					
Berinert IV	$3,797,795	$1,866,492	7.265	–0.001	Dominated by Cinryze IV
Scenario 12: Estimating the attack rates for lanadelumab by applying RRs to the placebo arm of the HELP-03 trial and assuming a steady state of attack rates for lanadelumab					
Non-dominated options					
Cinryze IV	$6,132,151	–	23.120	–	–
Lanadelumab	$14,792,833	$8,660,682	24.470	1.350	$6,414,002
Dominated option					
Berinert IV	$12,214,285	$6,082,134	23.120	0.000	Extendedly dominated by lanadelumab
Scenario 13: Estimating the attack rates for lanadelumab by applying RRs to the placebo arm of the HELP-03 trial and assuming no steady state of attack rates for lanadelumab					
Non-dominated options					
Cinryze IV	$6,134,378	–	23.136	–	–
Lanadelumab	$14,874,819	$8,740,440	24.316	1.180	$7,407,954
Dominated option					
Berinert IV	$12,229,213	$6,094,834	23.134	–0.002	Dominated by Cinryze IV
Scenario 14: The proportion of patients who switch to a less frequent dosage regimen, i.e., every four weeks, is 80%					
Non-dominated options					
Cinryze IV	$6,318,279	–	23.077	–	–
Lanadelumab	$9,198,893	$2,880,615	24.171	1.093	$2,635,126
Dominated option					
Berinert IV	$12,408,549	$6,090,271	23.074	–0.003	Dominated by Cinryze IV

	Total Cost	Incremental Cost[a]	Total QALY	Incremental QALY[a]	Sequential ICUR ($/QALY)
Scenario 15: The proportion of patients who switch to a less frequent dosage regimen, i.e., every four weeks, is 44.4%					
Non-dominated options					
Cinryze IV	$6,308,427	–	23.064	–	–
Lanadelumab	$11,767,639	$5,459,211	24.316	1.252	$4,360,881
Dominated option					
Berinert IV	$12,403,277	$6,094,849	23.065	0.001	Dominated by Cinryze IV

ER = emergency room; HAE = hereditary angioedema; ICUR = incremental cost-utility ratio; IV = intravenous; QALY = quality-adjusted life-year; RR = rate ratio.

[a] Compared with Cinryze.

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