CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Lanadelumab (Takhzyro)

(Shire Pharma Canada ULC)

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

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Abbreviations

ACE	angiotensin-converting enzyme
ADA	antidrug antibody
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life questionnaire
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
CI	confidence interval
C1-INH	C1 esterase inhibitor
CI	confidence interval
CrI	credible interval
CSEMI	Comité scientifique permanent d'évaluation des médicaments aux fins d'inscription
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
GLM	generalized linear model
HADS	Hospital Anxiety and Depression Scale
HAE	hereditary angioedema
HMWK	high-molecular-weight kininogen
HR	hazard ratio
INESSS	l'Institut national d'excellence en santé et en services sociaux
ITC	indirect treatment comparison
ITT	intention-to-treat population
IV	intravenous
LS	least squares
LTP	long-term prophylactic
MCID	minimal clinically important difference
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PBAC	Pharmaceutical Benefits Advisory Committee
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-12	Short Form (12) Health Survey
STP	short-term prophylactic
TSQM-9	Treatment Satisfaction Questionnaire for Medication
VAS	visual analogue scale
WAO/EAACI	World Allergy Organization and the European Academy of Allergy and Clinical Immunology
WPAI-GH	Work Productivity and Activity Impairment: General Health

Drug	lanadelumab (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
Sponsor	Shire Pharma Canada ULC

Executive Summary

Introduction

Hereditary angioedema (HAE) is a rare autosomal-dominant disorder that is characterized by recurrent attacks of nonpruritic subcutaneous or submucosal edema, most commonly affecting the skin (cutaneous attacks), gastrointestinal tract (abdominal attacks), and respiratory tract (laryngeal attacks).[1-3] The estimated prevalence of HAE is typically cited as 1 in 50,000.[1] There are three types of HAE: type I (85% of patients) is caused by decreased secretion of C1 esterase inhibitor (C1-INH); type II (15% of patients) is characterized by normal or elevated production of functionally impaired C1-INH; and the third type (prevalence is currently uncertain) is characterized by normal C1-INH level and function (formerly referred to as type III, but now known as HAE with normal C1-INH function).[1]

Lanadelumab (Takhzyro) is indicated for the routine prevention of attacks of HAE in adolescents and adults.[4] The recommended dosage of lanadelumab is 300 mg every two weeks; however, a dosage interval of 300 mg every four weeks may be considered if the patient's HAE is well-controlled (e.g., patient is attack free) for more than six months.[4] It is available as a single-use vial containing 300 mg lanadelumab in 2 mL solution for subcutaneous (SC) injection.[4]

The objective of this review is to evaluate the beneficial and harmful effects of lanadelumab for the routine prevention of attacks of HAE in adolescents and adults.

Stakeholder Engagement

Patient Input

One patient group responded to CADTH's call for patient input for the lanadelumab submission. HAE Canada is a patient group that seeks to create awareness about HAE and other related angioedema conditions, to help speed the diagnosis of patients, and to enable patients to become champions for their own quality of life. HAE Canada conducted an online survey of patients and caregivers to assess the challenges they face as a result of HAE and to gain insight into their lived experiences and their expectations for therapies used in the treatment of HAE.

Patients reported that HAE is a severely debilitating and life-threatening disease. For many, the expectation of HAE attacks imposes harsh limits on their activities and plans. Due to the unpredictable nature of the disease, many patients experience high levels of distress and anxiety in everyday life, related to their restricted or disrupted work and social life, and their fear of future attacks.

Patients continue to seek treatments that better control their HAE attacks while offering greater convenience and ease of use. Treatments that eliminate or substantially reduce attacks compared with existing treatments are of critical importance to patients, as any HAE attack can be severely debilitating and, in many cases, life-threatening. Greater control of attacks would also ameliorate the ever-present anxiety and fear many patients experience due to the unpredictable attacks and reduce the negative impact on a patient's ability to work, pursue education, travel, exercise, do household chores, and socialize with family and friends.

Given the burden of illness on patients with HAE and the ever-present risk of experiencing a life-threatening laryngeal attack, patients feel that improved preventive treatments are urgently needed. Further, treatments requiring intravenous (IV) administration require patients to expend much time travelling to treatment and undergoing treatment itself, particularly for those patients who have difficulty administering the infusion in their home. They also find administering IV treatments at home to be difficult and uncomfortable, with some patients reporting damage to their veins or concern about damage to their veins after years of treatment. Respondents also noted that the ability to select a drug based on the route of administration would be valued by patients and that SC administration would be preferred to IV administration.

Clinician Input[1]

The clinical experts consulted by CADTH indicated that many patients who require long-term prophylactic (LTP) therapy find treatment with C1-INH to be inconvenient due to the dosage frequency. In addition, there can be significant challenges with self-administration, particularly for those receiving treatment with an IV formulation. As lanadelumab requires only a single SC injection once every two or four weeks, the drug may offer improvements for patient convenience and for adherence. The experts noted that lanadelumab could be considered as a first-line option for LTP therapy, although it may not be the preferred option for use in women who are pregnant or in patients under 12 years of age, given the limited clinical data for these groups.

Patients could be considered good candidates for treatment with lanadelumab if they experience frequent HAE attacks that require acute treatment. The SC route of administration would be beneficial for patients who are unable to self-administer C1-INH IV (e.g., because of arthritis or problems finding veins). Lanadelumab may also be useful for patients who have to travel, for whom LTP therapy with C1-INH may be impractical. The following patients may not be appropriate candidates for treatment with lanadelumab: those who are misdiagnosed as having HAE but actually have histaminergic chronic urticaria or histaminergic idiopathic angioedema; those with HAE who only have mild and intermittent symptoms (i.e., on-demand therapy is sufficient); those whose HAE is currently well-controlled and who are satisfied with their existing LTP therapy; and any patients who are unable to self-administer SC treatments and do not have a caregiver who can assist.

Prescribing of lanadelumab should be limited to specialists with an expertise in the diagnosis and management of patients with angioedema, including immunologists, allergists, and hematologists. This will help ensure that the correct diagnosis has been

[1] This information is based on information provided by clinical experts consulted by CADTH for the purpose of this review.

made before initiating treatment with lanadelumab and that the response to treatment is appropriately monitored. Response to treatment would be assessed based on a reduction in the frequency, severity, and the duration of attacks. Patients and clinicians would also seek an increase in the ability to perform activities of daily living during attacks, if these were previously affected. The experts noted that the response to treatment with LTP therapy such as lanadelumab would be initially assessed after three months, with subsequently follow-up every six or 12 months. The following were identified as situations in which discontinuing treatment with lanadelumab could be appropriate: pregnancy, since adverse effects during pregnancy are unknown and C1-INH is the preferred option; development of inhibitory antibodies that may require an increased dosage of lanadelumab to maintain the treatment effect; allergic reaction to lanadelumab; or an inadequate response or loss of response (e.g., increase in attacks requiring rescue medication).

Clinical Evidence

The CADTH systematic review included one double-blind, placebo-controlled, randomized controlled trial (RCT; HELP-03).[5-8] In addition, the CADTH review included a long-term extension phase study (HELP-04)[9-11] and an indirect treatment comparison (ITC) submitted by the sponsor.[12,13] CADTH's review focused only on the Health Canada–approved dosage regimens of lanadelumab (i.e., 300 mg every two weeks and 300 mg every four weeks).

Pivotal Studies and Randomized Controlled Trials

Description of Studies

The HELP-03 study was a phase III, multi-centre (41 sites in six countries), double-blind, placebo-controlled RCT (N = 126). The study was conducted in four phases:

- LTP therapy washout phase during which adult patients who were using LTP were required to undergo a washout period of at least two weeks before the start of the run-in period. LTP washout was not permitted in adolescent patients (i.e., between the ages of 12 and 18 years of age).
- A four- to eight-week run-in phase to determine the patient's baseline rate of HAE attacks and to select the patients who would be eligible for randomization (i.e., only those with a baseline HAE attack rate of at least one investigator-confirmed HAE attack per four weeks).
- A 26-week double-blind treatment phase during which eligible patients were randomized (3:2:2:2) to receive subcutaneous injections of placebo (n = 41), lanadelumab 150 mg every four weeks (n = 27), lanadelumab 300 mg every four weeks (n = 29), or lanadelumab 300 mg every two weeks (n = 27). Randomization was stratified by the baseline HAE attack rate that was reported during the run-in period (i.e., one to less than two attacks per four weeks, two to less than three attacks per four weeks, and three or more attacks per four weeks).
- A follow-up phase during which patients who completed the double-blind treatment phase were given the option to enrol in the open-label extension phase study (HELP-04); those who did not participate in HELP-04 underwent an eight-week follow-up period for safety and additional evaluations. Patients were instructed to inform the site of any HAE attack experienced for up to 30 days after the final follow-up visit (i.e., day 238).[5]

The primary end point of HELP-03 was the number of investigator-confirmed HAE attacks from day 0 to day 182.[5] Pre-specified secondary end points that accounted for multiplicity of testing included the number of investigator-confirmed HAE attacks requiring acute treatment; the number of moderate or severe investigator-confirmed HAE attacks; and the number of investigator-confirmed HAE attacks from day 14 to day 182. Exploratory end points identified as being of interest to this CADTH review included the number of high-morbidity HAE attacks; the number of HAE attacks resulting in emergency department visit and/or hospitalization; the number of investigator-confirmed laryngeal attacks; the time to the first investigator-confirmed HAE attack; and the percentage of HAE attack-free days and months.[5] Exploratory patient-report outcomes included the Angioedema Quality of Life questionnaire (AE-QoL) and the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L).[5]

Efficacy Results

Key efficacy results for the HELP-03 study are summarized in Table 1. For the primary end point, the 300 mg every four weeks and every two weeks dosages of lanadelumab were associated with statistically significant and clinically important reductions in the rate of HAE attacks from day 0 to day 182.[5] Compared with placebo, the percentage reductions in the least squares (LS) mean rate with 300 mg lanadelumab were 73.3% (95% confidence interval [CI], –82.379 to –59.456; $P < 0.001$) and 86.9% (95% CI, –92.828 to –76.150; $P < 0.001$) in the every four weeks and every two weeks groups, respectively.[5] Treatment with lanadelumab was also associated with reductions in HAE attack rates when the data were analyzed using alternative time frames (i.e., day 7 to 182, day 14 to 182, and day 70 to 182).[5] Compared with placebo, treatment with 300 mg lanadelumab was associated with a reduction in the following end points: rate of moderate and severe HAE attacks; rate of high-morbidity HAE attacks (i.e., attacks that were severe, resulted in hospitalization, were hemodynamically significant, or were laryngeal); and the rate of HAE attacks that required acute treatment.[5] The sponsor conducted responder analyses based on reductions in HAE attacks of at least 50%, 60%, 70%, 80%, and 90%, with 300 mg lanadelumab being favoured over placebo for all analyses. There were few laryngeal attacks or attacks that resulted in an emergency department visit or admission to hospital.

The median time to first HAE attack was [redacted] in the placebo group, [redacted] in the lanadelumab 300 mg every four weeks group, and [redacted] in the lanadelumab 300 mg every two weeks group.[5]

The differences in AE-QoL total score between the lanadelumab and placebo groups were [redacted] and [redacted] for 300 mg every four weeks and every two weeks groups, respectively.[5] The minimal clinically important difference in the AE-QoL total score of six points was achieved by 37% of patients in the placebo group, 63% of patients in the lanadelumab 300 mg every four weeks group (odds ratio versus placebo 2.91; $P = 0.04$) and by 81% of patients in the lanadelumab 300 mg every two weeks group (odds ratio versus placebo 7.20; $P = 0.01$).[14] There were no differences observed between the 300 mg lanadelumab groups and the placebo group for changes from baseline in the EQ-5D-5L.[5]

Table 1: Summary of Efficacy Results From HELP-03 (Intention-to-Treat Population)

Efficacy End Points[a]	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
HAE Attacks From Day 0 to 182 (Primary End Point)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
LS mean rate per 4 weeks (SE)[b]	1.967 ([redacted])	0.526 ([redacted])	0.257 ([redacted])
Rate ratio (versus placebo) (95% CI)		0.267 (0.176 to 0.405)	0.131 (0.072 to 0.238)
P value (adjusted)[c]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–73.271 (–82.379 to –59.456)	–86.921 (–92.828 to –76.150)
HAE Attacks Requiring Acute Treatment (Secondary End Point)			
Run-in attack rate per 4 weeks; mean (SD)	3.596 (3.485)	3.460 (2.740)	3.110 (2.589)
LS mean rate per 4 weeks (SE)[b]	1.637 ([redacted])	0.423 ([redacted])	0.208 ([redacted])
Rate ratio (versus placebo)		0.258 (0.163 to 0.410)	0.127 (0.065 to 0.248)
P value (adjusted)[c]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–74.169 (–83.733 to –58.983)	–87.299 (–93.494 to –75.204)
Moderate and Severe HAE Attacks (Secondary End Point)			
Run-in attack rate per 4 weeks; mean (SD)	2.341 (2.147)	2.576 (2.396)	2.169 (2.228)
LS mean rate per 4 weeks (SE)[b]	1.216 ([redacted])	0.325 ([redacted])	0.202 ([redacted])
Rate ratio (versus placebo) (95% CI)		0.267 (0.157 to 0.455)	0.166 (0.084 to 0.329)
P value (adjusted)[c]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–73.285 (–84.316 to –54.496)	–83.394 (–91.618 to –67.099)
High-Morbidity HAE Attacks (Exploratory End Point)			
[redacted]	[redacted]	[redacted]	[redacted]
LS mean rate per 4 weeks (SE)[a]	0.219 ([redacted])	0.030 ([redacted])	0.034 ([redacted])
[redacted]		[redacted]	[redacted]
P value (unadjusted)[c]		0.007	0.011
% change in mean rate (versus placebo) (95% CI)		–86.3[redacted]	–84.7[redacted]
HAE Attacks Resulting in an Emergency Department Visit or Admission to the Hospital (Exploratory End Point)			
Run-in attack rate per 4 weeks; mean (SD)	0.057 (0.257)	0.068 (0.253)	0.072 (0.258)
LS mean rate per 4 weeks (SE)[a]	0.032 (0.016)	0.027 (0.017)	0.011 (0.012)
Rate ratio (versus placebo) (95% CI)		0.829 (0.167 to 4.129)	0.354 (0.038 to 3.278)
P value (unadjusted)[d]		0.819	0.360
% change in mean rate (versus placebo) (95% CI)		[redacted]	[redacted]
Laryngeal HAE Attacks (Exploratory End Point)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (versus placebo) (95% CI)		0.184 [redacted]	0.405 [redacted]
[redacted]		[redacted]	[redacted]

Efficacy End Points[a]	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
% change in mean rate (versus placebo) (95% CI)		–81.555 [redacted]	–59.475 [redacted]
Time to First HAE Attack After Day 14 (Exploratory End Point)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

CI = confidence interval; HAE = hereditary angioedema; LANA = lanadelumab; LS = least squares; NE = not estimable; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation; SE = standard error.

[a] All HAE attacks summarized in this table refer to investigator-confirmed HAE attacks.

[b] Poisson regression model with fixed effects for treatment group and normalized baseline HAE attack rate, and logarithm of time in days that the patient was observed during treatment period as an offset variable. Pearson chi-square scaling of standards errors was used to account for potential overdispersion.[5]

[c] *P* value is adjusted for multiple testing.[5]

[d] Unadjusted *P* values are derived from Poisson modelling.[5]

[e] *P* value comparing treatment groups is from a log rank test.[5]

Source: Clinical Study Report for HELP-03.[5]

Harms Results

The proportion of patients who reported at least one adverse event in HELP-03 was greater in the lanadelumab 300 mg groups (96.3% and 86.2% in the every two weeks and every four weeks groups, respectively) compared with the placebo group (75.6%).[5] Injection-site pain was the most commonly reported adverse event in both the lanadelumab 300 mg and placebo groups.[5] The proportion of patients who reported injection-site pain was similar in the placebo and lanadelumab 300 mg every four weeks groups (29.3% and 31.0%, respectively), but was greater in the lanadelumab 300 mg every two weeks group (51.9%).[5] Injection-site erythema and bruising were also more commonly reported in the lanadelumab 300 mg groups than in the placebo groups. Viral upper respiratory tract infection and headache were more commonly reported in the lanadelumab 300 mg every two weeks group (37.0% and 33.3%, respectively) compared with the lanadelumab 300 mg every four weeks group (24.1% and 17.2%, respectively) and the placebo group (26.8% and 19.5%, respectively).[5]

There were no deaths reported in the HELP-03 study.[5] Serious adverse events (SAEs) were reported for three patients in the lanadelumab 300 mg every four weeks group (three events) and one patient in the lanadelumab 300 mg every two weeks group (one event). No SAEs were reported in the placebo group. Events reported in the lanadelumab 300 mg every four weeks group included pyelonephritis (kidney infection), meniscus injury, and bipolar disorder.[5] A single serious event of a catheter site infection was reported in the lanadelumab 300 mg every two weeks group.[5] Withdrawals due to adverse events were rare, with only a single event in both the placebo and lanadelumab 300 mg every four weeks groups, and no events in the lanadelumab 300 mg every two weeks group.[5]

Table 2: Summary of Adverse Events From HELP-03

Adverse Events	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Any TEAE	31 (75.6)	231	25 (86.2)	182	26 (96.3)	235
Any SAE	0 (0.0)	0	3 (10.3)	3	1 (3.7)	1
Any severe TEAE	4 (9.8)	7	4 (13.8)	6	2 (7.4)	2
Deaths due to TEAE	0 (0.0)	0	0 (0.0)	–	0 (0.0)	–
Hospitalizations due to TEAE	0 (0.0)	0	3 (10.3)	3	1 (3.7)	1
WDAE	1 (2.4)	–	1 (3.4)	–	0 (0.0)	–

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse events.

Source: Clinical Study Report for HELP-03.[5]

Indirect Comparisons

Given the absence of head-to-head studies, CADTH reviewed a sponsor-submitted ITC to investigate the comparative efficacy and safety of lanadelumab against other LTP therapies used for management of HAE.[12,13] The ITC consisted of a Bayesian network meta-analysis (NMA) comparing three dosages of lanadelumab (i.e., 150 mg every four weeks, 300 mg every four weeks, and 300 mg every two weeks) against IV-administered C1-INH (1,000 IU twice weekly) and placebo for two end points (reduction in HAE attack rate and time to first HAE attack). The evidence network was limited to two phase III, placebo-controlled trials (i.e., the HELP-03 and CHANGE studies).[7,15] The NMA network was sparse, limited to two studies with small samples, and the results demonstrated considerable variation across the fixed-effects and random-effects analyses. Although the sponsor reported [redacted] for HAE attack rate ([redacted]),[12] important limitations with the indirect comparison prevent drawing any conclusions regarding comparative efficacy of lanadelumab and IV C1-INH. Most notably, there is considerable clinical and methodological heterogeneity across the HELP-03 and CHANGE studies, including different study designs (parallel versus crossover), treatment durations (26 weeks versus 12 weeks), eligibility criteria (e.g., one versus two HAE attacks per month), protocols for rescue therapy and concomitant usage of LTP therapy.

Other Relevant Evidence

Description of Studies

HELP-04 was a phase III, open-label extension study that was designed to evaluate the long-term safety and efficacy of lanadelumab as prophylactic therapy for HAE attacks in patients with type I or II HAE. The HELP-04 study was ongoing at the time the submission for lanadelumab was filed with CADTH, and data were available from the second interim report.[9] Two types of patients were eligible for enrolment in the HELP-04 extension study:

- patients who completed HELP-03 and elected to enter the extension study (referred to as rollover patients; n = 109)
- patients who did not participant in HELP-03 (referred to as non-rollover patients; n = 103).[9]

Patients who completed HELP-03 and enrolled in HELP-04 received a single open-label dose of 300 mg lanadelumab administered SC on day 0. After receiving this dose of 300 mg lanadelumab, they did not receive any additional doses of lanadelumab until they experienced their first investigator-confirmed HAE attack. The purpose of this approach was to evaluate the outer bounds of the 300 mg lanadelumab dosage frequency by assessing the time between a rollover patient's first open-label dose and their first confirmed HAE attack.[9] After receiving the second lanadelumab dose, these patients continued to receive lanadelumab 300 mg every two weeks for up to 66 doses (i.e., up to 132 weeks). Patients who were not enrolled in the HELP-03 study (i.e., non-rollover patients) received an open-label dose of lanadelumab 300 mg on day 0 and every two weeks thereafter for up to 66 doses.[9] In contrast to the HELP-03 study, patients in the HELP-04 study were permitted to self-administer lanadelumab after receiving their first two doses at the study site.[5,9]

Efficacy Results

For those who were treated with placebo in HELP-03 (n = 33), the mean (standard deviation [SD]) HAE attack rate was reduced from [redacted] attacks per four weeks, at the end of HELP-03, to [redacted] attacks per four weeks at the second interim cut-off in the HELP-04 extension study (mean [SD] percentage change [redacted]). The non-rollover population demonstrated reductions in HAE attack rate for all prior LTP therapy groups. The mean (SD) percentage changes were [redacted] for those with no prior LTP therapy ([redacted]); [redacted] for those with prior LTP therapy using only C1-INH ([redacted]); [redacted] for the those with prior exposure to oral LTP therapy ([redacted]); and [redacted] for the two patients with prior exposure to both C1-INH and oral LTP therapy ([redacted]). The proportion of patients with HAE attacks in the HELP-04 study was generally lower in the patients who had already been receiving the recommended dose of lanadelumab 300 mg every two weeks in the HELP-03 study.

The sponsor conducted a series of analyses using Cox proportional hazard models to examine the potential impact of baseline covariates on the time to first HAE attack following the first open-label dose of lanadelumab 300 mg in the rollover population. [redacted] ([redacted]).[9]

Data for the AE-QoL were limited to descriptive reporting.

Harms Results

The proportion of patients who reported at least one adverse event in HELP-04 was 95.4% in the total group (95.1% and 95.3% in the rollover and non-rollover groups, respectively). Similar to the HELP-03 study, the most frequently reported adverse events were injection-site pain (42.9%), viral upper respiratory tract infection (34.0%), headache (22.2%), and upper respiratory tract infection (21.2%). SAEs were reported for a total of 16 patients in the extension study: 10 (9.3%) in the rollover populations and 6 (5.8%) in the non-rollover population. Discontinuations due to adverse events were reported for [redacted] patients, with a greater number of withdrawals occurring in the non-rollover group ([redacted]) compared with the rollover group ([redacted]).

Conclusions

The CADTH review included one phase III, double-blind RCT (HELP-03), one open-label long-term extension phase study (HELP-04), and a Bayesian NMA. HELP-03 demonstrated that administering 300 mg lanadelumab every four weeks and every two weeks was associated with a statistically significant and clinically important reduction in the overall rate of HAE attacks, rate of moderate to severe HAE attacks, and rate of attacks requiring acute treatment with on-demand therapy, compared with placebo. Additional exploratory analyses were aligned with the primary analysis and favoured lanadelumab compared with placebo, including time to first HAE attack, number of attack-free days and months, use of on-demand treatment for HAE attacks, responder analyses, and health-related quality of life. Interim data from the HELP-04 extension trial suggested that the reduction in attack rate persisted beyond the initial 26-week study period of HELP-03.

The most commonly reported adverse events with lanadelumab were injection-site reactions, including pain, erythema, and bruising at the injection-site. Overall, the clinical experts consulted by CADTH indicated that the adverse events associated with lanadelumab were not concerning and were similar to those associated with the other agents currently used as LTP therapy for patients with HAE. There were no direct or indirect comparisons of the adverse events associated with lanadelumab compared with IV or SC administration of C1-INH identified in CADTH's review. However, in their input to CADTH, patients expressed a preference for SC-administered treatments compared with IV-administered treatments, because they are more convenient and have fewer adverse events associated with administration. This lived experience from patients was supported by the clinical experts consulted by CADTH, who also noted that SC administration can help alleviate the adverse events associated with long-term IV administration.

The Bayesian NMA submitted by the sponsor compared lanadelumab against a single regimen of C1-INH (IV 1,000 twice per week). Although the sponsor reported that [redacted] for reducing the rate of HAE attacks, there were important limitations with the indirect comparison that prevent drawing any conclusions regarding the comparative efficacy of lanadelumab and C1-INH. These limitations included the sparse evidence network, differences in the study designs, treatment durations, eligibility criteria, protocols for rescue therapy, and the exclusion of potentially relevant comparators (e.g., SC C1-INH).

Introduction

Disease Prevalence and Incidence

Hereditary angioedema (HAE) is a rare autosomal-dominant disorder that is characterized by recurrent attacks of nonpruritic subcutaneous or submucosal edema, most commonly affecting the skin (cutaneous attacks), gastrointestinal tract (abdominal attacks), and respiratory tract (laryngeal attacks).[1-3] The estimated prevalence of HAE is typically cited as 1 in 50,000.[1] HAE is caused by the deficiency or dysfunction of C1 esterase inhibitor (C1-INH) enzyme, a protease inhibitor that is a key regulator of the complement and contact systems, which leads to the activation of kallikrein and subsequent overproduction of the nanopeptide bradykinin.[1-3] Bradykinin binds to bradykinin type 2 receptors on endothelial cells, causing increased vascular permeability, which may lead to angioedema if present in excessive amounts.[1-3]

There are three types of HAE: type I (85% of patients) is caused by decreased secretion of C1-INH; type II (15% of patients) is characterized by normal or elevated production of functionally impaired C1-INH; and a third type, known as HAE with normal C1-INH (formerly referred to as type III HAE), is characterized by normal C1-INH level and function (prevalence is uncertain).[1] Mutations in the SERPING1 gene, which codes for C1-INH, are inherited in approximately 75% of patients with HAE, but mutations may appear de novo in 25% of patients.[3,16] Although the age of onset in patients with HAE is variable, the majority of patients experience their first attack in childhood or adolescence, with 12 years being the median age of onset.[16]

The diagnosis of type I and type II HAE is based on a detailed history and physical examination, along with confirmatory laboratory diagnostic tests (Table 3). Clinical practice guidelines from the World Allergy Organization and the European Academy of Allergy and Clinical Immunology recommend that all patients suspected of having type I or type II HAE should be assessed for blood levels of C4, C1-INH protein, and C1-INH function.[16]

Table 3: Types of Hereditary Angioedema

Type of HAE	Type I	Type II	HAE with normal C1-INH
Proportion of HAE cases	85%	15%	Uncertain (rare)
C1-INH level	Low	Normal or elevated	Normal
C1-INH function	Low	Low	Normal
C4 level	Low	Low	Normal

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema.

Cutaneous and abdominal attacks are the most frequently type of HAE attack, reported in more than 90% of patients with HAE.[17,18] Cutaneous attacks may involve areas of the face, extremities, and genitals. Facial swelling may involve the lips, tongue, oropharynx, and periorbital tissues, while extremity swelling can progress to affect large areas of the arms or legs. Abdominal attacks involve the gastrointestinal tract and can be extremely painful, accompanied by nausea, vomiting, and diarrhea. Laryngeal attacks are the least frequent type of attack, but 50% of patients may experience one or more episodes in their lifetime.[19] Laryngeal attacks are the primary cause of mortality in patients with HAE owing to the risk of asphyxiation.[20]

The onset of an HAE attack is often unpredictable and can occur without a clear precipitating factor or trigger.[16] Known or suspected triggers for HAE attacks can include accidental trauma, dental and medical procedures, psychological stress, fatigue, febrile illness, and the menstrual cycle.[16] Exposure to some drugs may also trigger HAE attacks, including estrogen-containing contraceptive agents, hormone replacement therapy, and angiotensin-converting enzyme (ACE) inhibitors.[16] The frequency of attacks in patients who are symptomatic but untreated can range from weekly to less than yearly.[3] Without treatment, each attack can last several days.[3]

Standards of Therapy

The clinical management of HAE can be categorized as follows:

- **Long-term prophylactic (LTP) treatment:** ongoing long-term treatment to reduce the frequency and severity of HAE attacks
- **Short-term prophylactic (STP) treatment**: administered to reduce the risk of an attack when exposure to a trigger is anticipated (e.g., before dental or medical procedures)
- **Acute treatment of HAE attacks:** administered acutely to reduce the severity and alleviate the symptoms of an attack.[21]

Therapeutic options available in Canada for LTP treatment include plasma-derived C1-INHs, oral attenuated androgens (e.g., danazol), and antifibrinolytics (e.g., tranexamic acid).[22] The most commonly used treatments in Canada are C1-INHs, which act by replacing the missing or malfunctioning C1-INH protein in patients with HAE. There are currently two C1-INHs marketed in Canada for the treatment of HAE: Cinryze, which is indicated for LTP therapy, and Berinert, which is indicated for the acute treatment of HAE attacks. In addition to usage for the acute management of HAE attacks, Berinert is also routinely administered as an LTP treatment option, although this is beyond the indication approved by Health Canada. Haegarda is a C1-INH product has been approved by Health Canada as a subcutaneous (SC) treatment option for those requiring LTP therapy, but this drug has not been marketed in Canada at the time of this review. Both Berinert and Cinryze are approved for intravenous (IV) administration; however, the clinical experts consulted by CADTH indicated that Berinert 1,500 IU is commonly administered SC, in accordance with the dosages that are recommended in the product monograph for Haegarda (Table 4).

Guidelines from the World Allergy Organization and the European Academy of Allergy and Clinical Immunology (WAO/EAACI) recommend the use of C1-INH as the first-line option for patients who require LTP treatment to manage their condition (see Appendix 4 for a detailed summary of these guidelines).[16] Attenuated androgens are recommended as a second-line option, and antifibrinolytics are not recommended by the WAO/EAACI for LTP therapy.[16] The Canadian Hereditary Angioedema Guideline Committee does not specify particular lines of therapy for those requiring LTP treatment, but recommends that patients should be able to initiate therapy with a C1-INH without having to undergo a trial of any of the other available agents (e.g., oral treatments). The Canadian guidelines recommend that attenuated androgens and antifibrinolytics may be effective for some patients who require LTP treatment. However, the clinical experts consulted by CADTH noted that these are not typically initiated as first-line options, due to the significant adverse events of androgens and limited effectiveness of antifibrinolytics.[1]

Drug Under Review

Lanadelumab is a fully human monoclonal antibody that binds plasma kallikrein and inhibits its proteolytic activity.[4] Plasma kallikrein is a protease that cleaves high-molecular-weight kininogen (HMWK) to generate cleaved HMWK and bradykinin, a potent vasodilator that increases vascular permeability, resulting in the swelling and pain associated with HAE.[4] In patients with HAE due to C1-INH deficiency or dysfunction (i.e., type I or type II), an uncontrolled increase in plasma kallikrein activity leads to an increase in bradykinin and results in angioedema attacks. Lanadelumab decreases plasma kallikrein activity to control bradykinin generation in patients with HAE.[4]

Lanadelumab is indicated for the routine prevention of attacks of HAE in adolescents and adults. The recommended dose of lanadelumab is 300 mg every two weeks; however, a dosing interval of 300 mg every four weeks may be considered if the patient's HAE is well-controlled (e.g., the patient is attack free) for more than six months.[4] It is available as a single-use vial containing 300 mg lanadelumab in 2 mL solution and is administered SC.[4]

Table 4: Key Characteristics of Long-Term Prophylactic Therapies for Hereditary Angioedema

	Lanadelumab	Berinert	Cinryze	Haegarda
Mechanism of Action	• Plasma kallikrein inhibition	• Replace missing or malfunctioning C1-INH protein in patients with HAE	• Replace missing or malfunctioning C1-INH protein in patients with HAE	• Replace missing or malfunctioning C1-INH protein in patients with HAE
Indication[a]	• Indicated for routine prevention of attacks of HAE in adolescents and adults[4]	• Treatment of acute abdominal, facial, or laryngeal attacks of HAE of moderate to severe intensity in pediatric and adult patients[23]	• Routine prevention of angioedema attacks in adults and adolescents with hereditary angioedema[24]	• Routine prevention of HAE attacks in adolescent and adult patients[25]
Route of Administration	• SC	• IV (approved) • SC (not approved)	• IV	• SC
Recommended Dose	• 300 mg q.2.w. • 300 mg q.4.w. can be considered if the patient's HAE is well-controlled (e.g., patient is attack free) for more than six months.[4]	• 20 IU per kg (IV) for acute attack[25] • 20 to 60 IU per kg (IV or SC) for prophylaxis (off-label)[17]	• 1,000 IU every 3 or 4 days[24] • The dosing interval may need to be adjusted according to individual response.[24]	• 60 IU/kg body weight twice weekly (every 3 to 4 days)[25]
Dosage Forms and Strengths	• 300 mg/vial	• 500 IU/vial • 1,500 IU/vial	• 500 IU/vial	• 2,000 IU/vial • 3,000 IU/vial
Monitoring Requirements	• No additional monitoring is required over and above usual clinical practice.	• Patients with known risk factors for thrombotic events should be monitored closely.[23]	• Patients with known risk factors for thrombotic events should be monitored closely.[24]	• Risk of thrombotic events is noted,[25] but there are no specific statements regarding monitoring.
Other	• Non–plasma-derived, recombinant	• Derived from human plasma	• Derived from human plasma	• Derived from human plasma

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; q.2.w. = every two weeks; q.4.w. = every four weeks; SC = subcutaneous.
[a] Health Canada–approved indication.
Sources: Product Monographs for Takzyro,[4] Berinert,[23] Haegarda,[25] Cinzyrze,[24] sponsor's submission.[17]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

Brief Description of Patient Group(s) Supplying Input

One patient group responded to CADTH's call for patient input for the lanadelumab submission. HAE Canada is a patient group that seeks to create awareness about HAE and other related angioedema, to help speed the diagnosis of patients, and to enable patients to become champions for their own quality of life. HAE Canada provides patients, caregivers, family members, and health care providers with the information, tools, and resources to ensure that those living with HAE and other related angioedema can live healthy and productive lives.

HAE Canada has received funding in excess of $50,000 over the past two years from pharmaceutical companies with products used in the treatment of HAE. The patient group did not receive help from pharmaceutical companies in compiling its submission to CADTH.

HAE Canada conducted an online survey of patients and caregivers from June 2, 2019, to June 11, 2019. The objective of the survey was to assess the challenges patients and caregivers face as a result of HAE and to gain insight into their experience and expectation with therapies used to treat HAE, in particular with lanadelumab. The survey contained the use of free-form commentary, scoring options, and limited closed questions. A total of 73 responses were received for the survey (92% were from Canadians living with HAE and 8% were from caregivers). Eight of the survey respondents indicated that they had used (or are using) lanadelumab to treat their HAE. Follow-up telephone interviews, using an interview guide, were conducted with four patients who were using lanadelumab at the time the survey was conducted. In addition to the survey and patient interviews, the input from HAE Canada also reflects information obtained from its experience in patient support and advocacy related to HAE.

Condition-Related Information

HAE is a severely debilitating and life-threatening disease. It manifests as unpredictable, recurrent/intermittent angioedema attacks in different parts of the body, including the gastrointestinal tract, upper respiratory tract, extremities, and face. Gastrointestinal attacks are common in HAE, with severe abdominal pain and other gastrointestinal symptoms. Untreated laryngeal attacks may result in asphyxiation and death. One patient noted "I nearly died from a laryngeal HAE attack, which has profoundly changed all levels of my life." Swelling in other body parts can also significantly interfere with patients' daily pursuits, resulting in severely impaired quality of life.

Patients may still be affected by HAE even after the physical symptoms of an attack abate. For many, the expectation of HAE attacks imposes harsh limits on activities and plans. Due to the unpredictable nature of the disease, many patients experience high levels of distress and anxiety in everyday life, often related to their restricted or disrupted social life, fear of future attacks, concern that HAE will be passed to their children, and disruption/interference in educational and career pursuits. One patient noted they experience "chronic anxiety over the unpredictability of this disease."

Many patients report that they do not pursue higher education due to HAE. When asked how HAE impacted patients with respect to employment, a majority of patients (62%) reported that HAE had caused them to miss time at work or be less productive, 9% reported that HAE has prevented them from securing a job, and 6% reported that HAE had impeded their ability to advance in the workplace. HAE also interferes with patients' daily activities, having substantial negative impacts on many patients' ability to work, travel, exercise, do household chores, and socialize with family and friends. HAE inhibits many patients' ability to pursue higher education or job advancements, and negatively affects their personal finances due to suboptimal employment, interference with employment, and costs related to treatment for HAE.

Current Therapy-Related Information

Given the burden of illness on patients with HAE and the ever-present risk of experiencing a life-threatening laryngeal attack, patients feel that improved preventive treatments are urgently needed. Further, treatments requiring IV administration require patients to expend significant time travelling to treatment and undergoing treatment itself, particularly for those patients who have difficulty administering the infusion in their home. Medical literature states that, despite significant safety measures, there remains the risk of infectious agent transmission with C1-INH inhibitors that are derived from human plasma. Many patients reported experiencing or worrying about damage to their veins. Patients reported having substantial concerns about current treatments to manage acute HAE attacks that require venous access, which require several intricate steps for reconstitution and administration. Such treatments are difficult for the patient to prepare and self-administer during an attack. These therapies can be particularly unmanageable if a patient is travelling or in a work environment that hinders the ability to prepare and administer an IV treatment. These barriers may contribute to amplified risk and, consequently, increased fear and anxiety among patients with HAE, severely compromising their quality of life. Thus, patients with HAE feel that improved prophylactic treatments are urgently required, such as those injected SC, which are anticipated to be easier to administer at home. Patients would also benefit from treatments that have a more convenient and less frequent dosage regimen.

Fifty-nine of the survey respondents reported on their experience with HAE treatments, including Berinert (85%), Firazyr (60%), Cinryze (14%), and Haegarda (5%). Patients/caregivers were asked to rate how important it was for them and their physician to be able to make a choice of drug(s) based upon each different drug's known side effects (from 1 "not important" to 5 "very important"). Respondents indicated that this flexibility is very important, with a weighted average score of 4.7.

Many patients find the treatment schedule for current treatments to be onerous and disrupting. They also find administering IV treatments at home to be difficult and uncomfortable, with some patients reporting damage to their veins or concern about damage to their veins after years of treatment. Respondents also noted that the ability to select a drug based on the route of administration would be valued by patients, with commentary suggesting a preference for SC administration rather than IV administration, for convenience and to reduce the adverse events associated with repeated IV administration.

> "At first it was IV but my veins could not take it anymore. I had to change for subcutaneous. I have to give myself the treatment more often."

> "Giving IVs to yourself can be difficult without any assist and I don't want to hurt my veins for future use."

Expectations About the Drug Being Reviewed

Patients continue to seek treatments that better control attacks while offering greater convenience and ease of use. Treatments that eliminate or substantially reduce attacks compared with existing treatments are of critical importance to patients, as any HAE attack can be severely debilitating and, in many cases, life-threatening. Greater control of attacks would also ameliorate the ever-present anxiety and fear many patients experience due to unpredictable attacks and reduce the negative impact on a patient's ability to work, pursue education, travel, exercise, do household chores, and socialize with family and friends.

Patients with HAE would like a variety of treatment options to address a range of unmet needs, including improvement in prevention of attacks, improvement in the acute management of HAE, and more convenient methods/modalities of self-administration. Patients would benefit from availability of different treatment options to ensure continued access to treatment during drug shortages, with both oral and injectable treatments, which are currently a reality and could be an issue in the future as well.

Patients view lanadelumab as an extremely important addition to the treatment options for HAE and believe that this treatment will greatly improve the quality of life for many patients. Patients with experience with this treatment reported better and, in many cases, complete control of attacks. Patients also reported greatly improved quality of life due to reduced anxiety, easier mode of treatment administration, and reduced dosage frequency.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the lanadelumab review, a panel of four clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel's input is presented below.

Description of the Current Treatment Paradigm for the Disease

Current LTP treatments for HAE include C1-INH replacement therapy, which restores C1-INH in the contact activation system pathway, reducing HAE attacks. It also restores C1-INH in the complement system pathway, restoring C4 levels, which may be important in fighting infection and in destroying autoreactive cells and malignant cells. C1-INH also acts in the coagulation pathway and normalizes the D-dimer, which is often elevated in HAE without any clinical consequence. Additional treatment options include anabolic steroids and tranexamic acid. Anabolic steroids (e.g., danazol) increase the production of endogenous C1-INH from the liver, but their use is limited by masculinizing effects and an increased risk of hepatic tumour. Tranexamic acid reduces the symptoms of HAE attacks, but its mechanism of action is unknown. It increases the risk of thrombosis and may not be tolerated due to gastrointestinal side effects.

Treatment Goals

An ideal treatment for HAE would:

- prolong life by reducing or eliminating life-threatening HAE attacks (e.g., laryngeal attacks)
- reduce the frequency, severity, and duration of HAE attacks
- be associated with minimal or no adverse effects
- improve health-related quality of life for those living with HAE and reduce the burden on their caregivers
- help maintain independence, increasing the ability to maintain employment and attend school
- reduce other health care utilization (e.g., emergency room visits and hospital admissions)
- offer more convenient administration than existing options.

Unmet Needs

Many patients living with HAE find it inconvenient or impossible to self-administer C1-INH intravenously twice weekly (e.g., because it is difficult to find a vein), and some do not like administering C1-INH SC twice weekly, especially since the larger vial sizes of concentrated C1-INH are not yet available in Canada. A treatment that requires only a single SC injection once every two weeks would be more attractive to them. Since all of the C1-INHs currently approved in Canada are derived from human plasma, there is a remote risk of transmitting viral infections. As a result, some patients may not wish to use these products. As previously noted, the other available LTP treatments are less effective (e.g., tranexamic acid) or have significant side effects (e.g., danazol).

Place in Therapy

Lanadelumab may offer advantages over existing treatments for ease of administration and has the potential to shift the current treatment paradigm. It could be considered as a first-line option for LTP treatment, although it may not be the preferred option for use in women who are pregnant or in patients less than 12 years of age, given the limited clinical data for these groups. Patients who experience breakthrough symptoms while using lanadelumab could administer C1-INH IV or icatibant SC to manage the attack. Although not specifically indicated for combination usage in Canada, lanadelumab could potentially be added to C1-INH IV or SC twice weekly prophylaxis or danazol if patients wanted extra assurance that they would not have an attack. However, patients would most likely start this medication and then withdraw their existing LTP therapies completely.

Lanadelumab inhibits the production of bradykinin and does not address the underlying disease process, as it does not replace the C1-INH protein that is deficient or dysfunctional in patients with type I or II HAE, respectively.

Patient Population

HAE can be challenging to diagnose, since patients with chronic urticaria may also develop swelling. Accurate diagnosis of type I and II HAE typically requires testing C1-INH levels, C1-INH function, and C4 levels. It may be challenging to access testing for C1-INH level and function in a timely manner in some areas of Canada. Diagnosis of HAE with normal C1-INH can require genetic testing that is only available in some specialized centres, and patients may be required to pay out-of-pocket for the costs. Acquired angioedema may pose additional challenges for clinicians, as this condition can have many of the same biochemical abnormalities as type I HAE. Although acquired C1-INH deficiency can be differentiated from type I HAE by the presence of low C1q levels, this testing is not currently available in Canada.

Patients could be considered good candidates for treatment with lanadelumab if they experience frequent HAE attacks that require acute treatment. The SC route of administration would be beneficial for patients who are unable to self-administer C1-INH IV (e.g., because of arthritis or problems finding veins). Lanadelumab may also be useful for patients who have to travel, for whom LTP treatment with C1-INH may be impractical. In addition, many patients may prefer the convenience offered by lanadelumab to the existing treatment options.

Based on the available clinical evidence, patients with type I or II HAE are the most likely to respond to treatment with lanadelumab (as other forms of HAE have not been studied). The patients who could benefit most from treatment with lanadelumab (i.e., those in greatest need of an additional intervention) are those who experience frequent and severe attacks, those who have an inadequate response to LTP with C1-INH, and those who require larger amounts of C1-INH to control their attacks. This would be true for patients with any form of bradykinin-mediated angioedema, including patients who have HAE with normal C1-INH or acquired angioedema. The clinical experts believe it would not be necessary to try another LTP treatment before initiating treatment with lanadelumab.

The following patients may not be appropriate candidates for treatment with lanadelumab:

- those who are misdiagnosed as having HAE but actually have histaminergic chronic urticaria or histaminergic idiopathic angioedema
- those with HAE who only have mild and intermittent symptoms (i.e., for whom on-demand therapy is sufficient)
- those whose HAE is currently well-controlled and who are satisfied with their existing LTP therapy
- those who are unable to self-administer SC treatments and do not have a caregiver who can assist
- those who have a significant adverse reaction to lanadelumab.

Assessing Response to Treatment

Assessing a response to LTP treatment in clinical practice is similar to the evaluations conducted in clinical trials. Patients and clinicians are seeking a reduction in the frequency, severity, and the duration of attacks, which, in turn, can result in a reduced need for rescue medications, emergency department visits, and hospital admissions. There should be an increase in the ability to perform activities of daily living during attacks, if these were previously affected. Assessments can vary across individual patients, as a certain level of symptoms may be acceptable to some patients but not to others living with the condition. Initial response to treatment would typically be assessed at three months. Patients would subsequently have clinic visits once every six months, and those with very well-controlled HAE would often be seen only once per year.

Discontinuing Treatment

The following were identified as situations in which discontinuing treatment with lanadelumab could be appropriate:

- pregnancy — adverse effects during pregnancy are unknown, and C1-INH is the preferred option
- development of inhibitory antibodies that may require an increased dose of lanadelumab to maintain effectiveness
- allergic reaction or any significant adverse event to lanadelumab
- inadequate response or loss of response (e.g., increase in attacks requiring rescue medication).

Prescribing Conditions

Prescribing should be limited to specialists with an expertise in the diagnosis and management of patients with angioedema, including immunologists, allergists, and hematologists. This will help ensure that the correct diagnosis has been made before initiating treatment with lanadelumab and that the response to treatment is appropriately monitored. Patients and caregivers who are capable should be trained to administer SC injections to allow patients to receive lanadelumab at home.

Clinical Evidence

The clinical evidence included in the review of lanadelumab is presented in three sections. The first section is a systematic review of pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to a protocol established in advance. The second section includes indirect evidence from the sponsor and/or selected from the literature that met the selection criteria specified in the review. The third section includes long-term extension studies submitted by the sponsor and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of lanadelumab 300 mg every two weeks and 300 mg every four weeks for the routine prevention of attacks of HAE in adolescents and adults.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient Population	Adolescents and adults with HAE **Subgroups:** • HAE type • HAE attack frequency • Primary HAE attack locations • History of laryngeal attack • Prior use of any long-term prophylactic treatment • Age • Body weight
Intervention	Lanadelumab 300 mg SC once every 2 or 4 weeks
Comparators	• Human C1 esterase inhibitor (Berinert, Cinryze, Haegarda) • Placebo (no long-term prophylactic treatment)
Outcomes	**Efficacy outcomes:** • Number of HAE attacks[a] • HAE attacks requiring acute treatment[a] • Time to first HAE attack • Severity of HAE attacks[a] • HAE attacks resulting in an emergency department visit and/or hospitalization[a] • HAE attacks requiring intubation or admission to an intensive care unit • Laryngeal HAE attacks[a] • HAE attack rate responder analysis • Characteristics of HAE attacks (duration, severity, and rescue medication use) • Attack-free days

	• Health-related quality of life[a]
	  ○ Angioedema Quality of Life questionnaire
	  ○ EQ-5D Index Score and EQ-5D VAS
	• Mortality
	
	Harms outcomes:
	• Adverse events
	• Serious adverse events
	• Withdrawals due to adverse events
	• Dosing interruption or adjustment due to adverse events
	• Notable harms/harms of special interest

Study Design	• Published and unpublished phase III and IV RCTs

EQ-5D = EuroQol 5-Dimensions questionnaire; HAE = hereditary angioedema; RCT = randomized controlled trial; SC = subcutaneous; VAS = visual analogue scale.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[26]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Takhzyro (lanadelumab). Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on June 26, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on October 16, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[27] health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials registries, and databases (free). Google was used to search for additional Internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The details of the included study (HELP-03) are summarized in Table 6. There were no excluded studies for this review.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

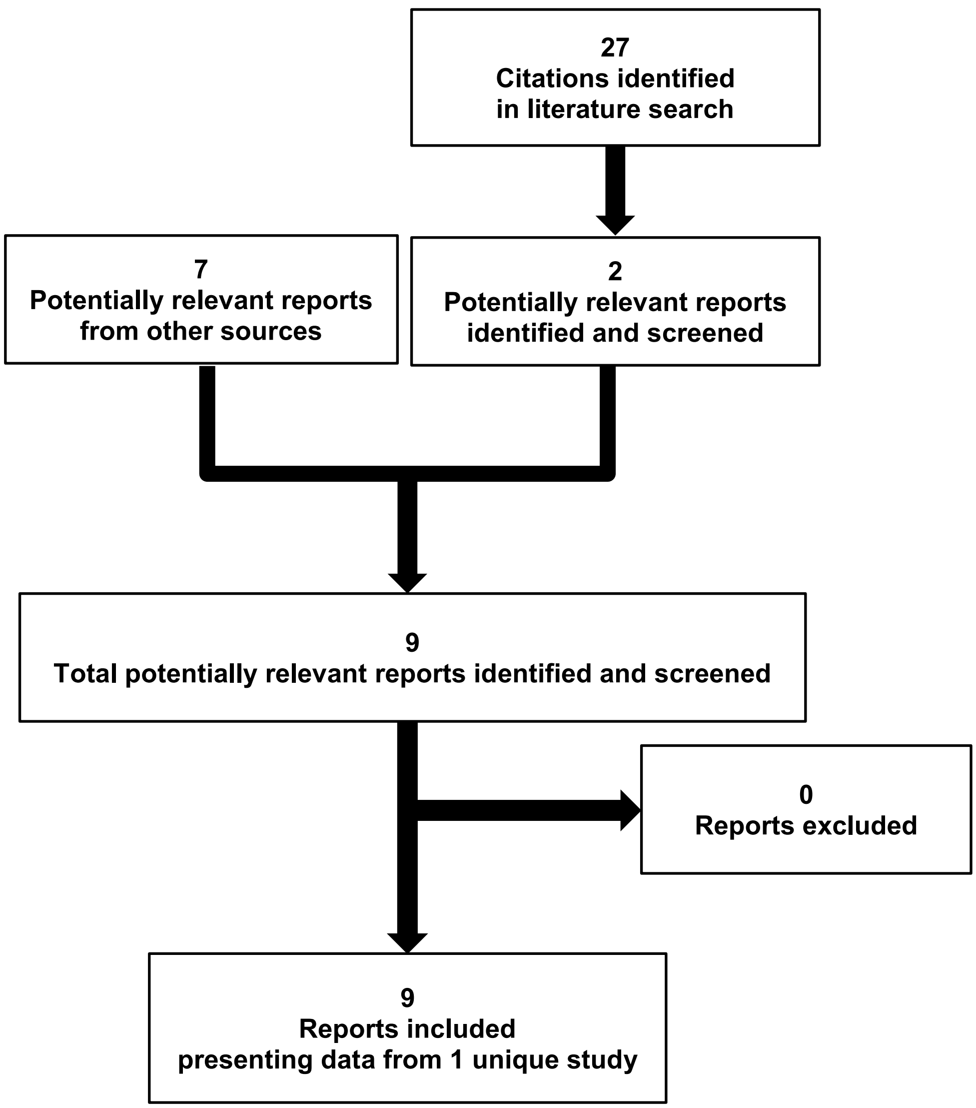


Table 6: Details of the Included Study (HELP-03)

		HELP-03
DESIGNS & POPULATIONS	**Study Design**	Phase III, multi-centre, double-blind, placebo-controlled RCT
	Locations	41 sites in 6 countries: US (32); Germany (3); Italy (1); UK (1); Canada (3); Jordan (1)
	Randomized (N)	125 (3:2:2:2) • 41 placebo • 28 lanadelumab150 mg q.4.w. + matching placebo • 29 lanadelumab 300 mg q.4.w. + matching placebo • 27 lanadelumab 300 mg q.2.w.
	Inclusion Criteria	• Males and females who were at least 12 years of age at screening • Documented diagnosis of type I or II HAE • Baseline rate of ≥ 1 HAE attacks per four weeks during run-in period
	Exclusion Criteria	• Concomitant diagnosis of another form of chronic, recurrent angioedema, such as HAE type III, acquired angioedema, idiopathic angioedema, or recurrent angioedema associated with urticaria • Exposure to ACE inhibitors or any estrogen-containing medications with systemic absorption within 4 weeks before screening • Exposure to androgens within 2 weeks before entering the run-in period • Use of LTP therapy for HAE within 2 weeks before entering the run-in period (i.e., failure to complete the washout period) • Use of short-term prophylaxis for HAE within 7 days before entering run-in period • Any of following liver function test abnormalities: ALT > 3 × ULN, or AST > 3 × ULN, or total bilirubin > 2 × ULN
DRUGS	**Interventions**	• Lanadelumab 150 mg q.4.w. • Lanadelumab 300 mg q.4.w. • Lanadelumab 300 mg q.2.w.
	Comparators	• Placebo
DURATION	**Phase**	
	LTP washout	2 weeks
	Run-in	4 to 8 weeks
	Double-blind	26 weeks
	Follow-up	8 weeks or enrolment in HELP-04 extension study
OUTCOMES	**Primary End Point**	Number of investigator-confirmed HAE attacks
	Other End Points	**Secondary End Points:** • HAE attacks requiring acute treatment • Moderate or severe HAE attacks period • HAE attacks occurring between day 14 and day 182 **Exploratory End Points:** • Time to first HAE attack after day 14 • High-morbidity HAE attacks during the treatment period • HAE attacks resulting in an emergency department visit or hospitalization • HAE attacks resulting in an emergency department visit • HAE attacks resulting in hospitalization • Laryngeal HAE attacks • Reduction in HAE attack rate (i.e., responder analysis) • Characteristics of HAE attacks (duration, severity, and rescue medication use) • Percentage of attack-free days • Achievement of HAE attack-free intervals of 1 month, 3 months, or until day 182 • Angioedema Quality of Life questionnaire • EQ-5D Index Score and EQ-5D VAS

		HELP-03
NOTES	**Publications**	• Banerji et al. 2018[6,7] • Clinical Study Report[5] • Clinicaltrials.gov[8] • Common technical document[28,29] • Regulatory review reports from Health Canada, FDA, and European Medicines Agency[21,30,31]

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAE = hereditary angioedema; LTP = long-term prophylactic treatment; q.2.w. = every two weeks; q.4.w. = every four weeks; RCT = randomized controlled trial; ULN = upper limit of normal.

Source: Clinical Study Report for HELP-03.[5]

Description of Studies

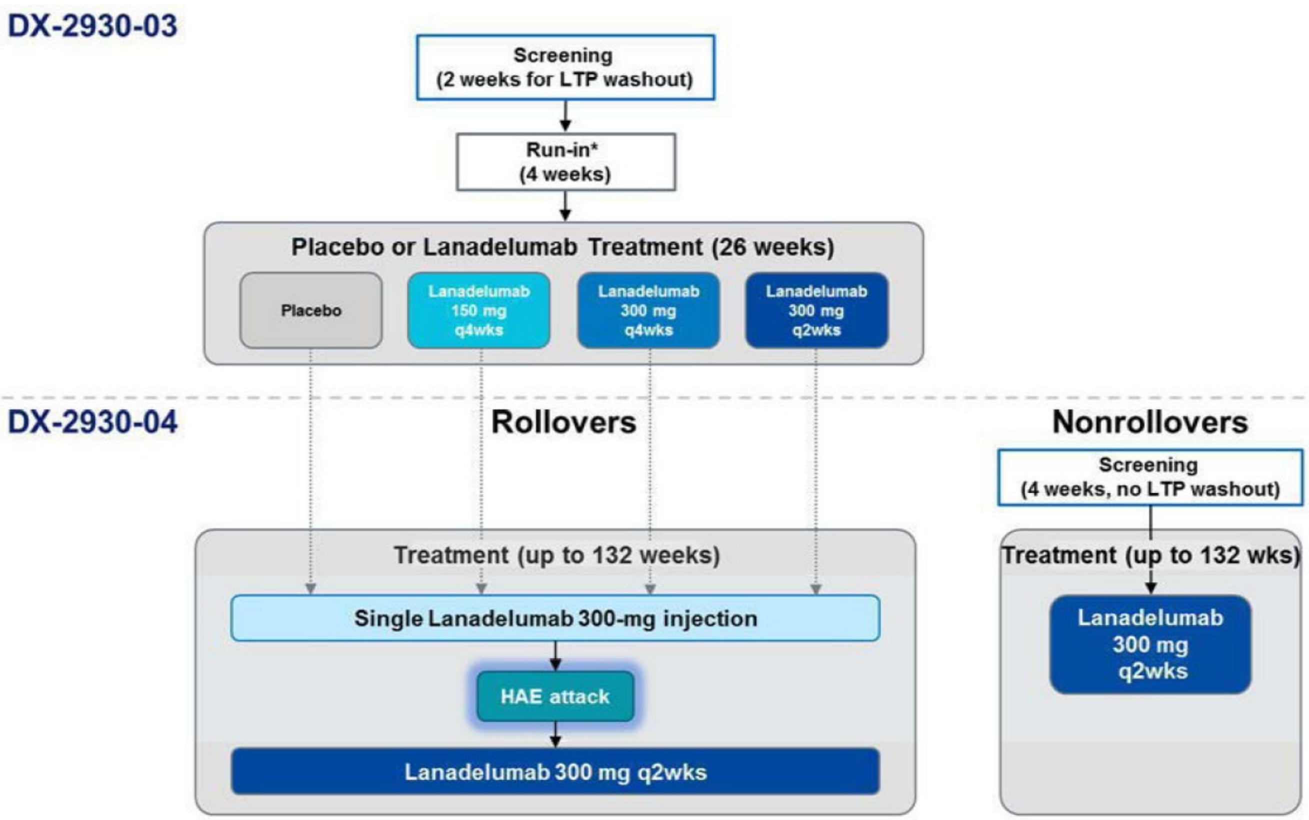
HELP-03 was phase III, multi-centre, double-blind, placebo-controlled randomized controlled trial (RCT) conducted to investigate the safety and efficacy of lanadelumab for the prevention of HAE attacks. The study was carried out at 41 sites in six countries: US (32 sites); Germany (3 sites); Italy (1 site); UK (1 site); Canada (3 sites); Jordan (1 site). There were seven patients enrolled across the three Canadian sites. The HELP-03 study was conducted from March 3, 2016, (first patient enrolled) to April 13, 2017 (last patient completed). The study design involved the following four phases:

- **LTP therapy washout:** Adult patients who were using LTP therapy for HAE were required to undergo a washout period of at least two weeks before the start of the run-in period. LTP washout was not permitted in adolescent patients (i.e., between the ages of 12 and 18 years of age). Study investigators were required to confirm that patients had completed the washout period before entry into the run-in phase. Those not using LTP were entered directly into the run-in period.[5]
- **Run-in phase:** Those who were not using LTP therapy or who completed the LTP washout period were entered into a four- to eight-week run-in phase. The purpose of the run-in phase was to determine the patient's baseline rate of HAE attacks and to select the patients who would be eligible for randomization. To be eligible for randomization, patients were required to have an HAE attack rate of at least one investigator-confirmed HAE attack per four weeks. Any patients who experienced three or more investigator-confirmed HAE attacks before the end of the first four-week period were permitted to end the run-in period early and proceed directly to randomization. Any patients who did not experience at least one investigator-confirmed HAE attack after four weeks of run-in were to have their run-in period extended for another four weeks (i.e., a total of eight weeks). During the additional four-week period, they were required to have at least two investigator-confirmed HAE attacks in order to be eligible for randomization. All patients who did not meet the minimum HAE attack rate during the run-in period were ineligible for randomization and considered to be screening failures.[5]
- **Double-blind treatment phase:** Eligible patients were randomized (3:2:2:2) to receive SC injections of placebo (n = 41), lanadelumab 150 mg every four weeks (n = 27), lanadelumab 300 mg every four weeks (n = 29), or lanadelumab 300 mg every two weeks (n = 27).[5] In accordance with the review protocol, CADTH has focused only on the Health Canada–approved dosage regimens of lanadelumab (i.e., 300 mg every two weeks and 300 mg every four weeks). Randomization was stratified by the baseline HAE attack rate reported during the run-in period (one to less than two attacks per four weeks, two to less than three attacks per four weeks, and three or more attacks per four weeks). The double-blind treatment period was 26 weeks in duration and patients received SC injections of blinded investigational product every two weeks (i.e., a total of 13 injections).[5] The stopping rules in the study protocol stated that any patients who were

discontinued from treatment were followed for the duration of the 26-week treatment period, unless they requested to be discontinued from the study.[5]

- **Open-label extension and follow-up period:** Patients who completed the double-blind treatment phase were given the option to enroll in the open-label extension phase study (DX-2930-04; HELP-04).[5,9] Those who chose to rollover into HELP-04 received an open-label dose of 300 mg lanadelumab at week 26 (visit 14).[9] They did not receive any additional injections of lanadelumab or rescue medications until they experienced their first HAE attack, at which point they began receiving open-label SC doses of 300 mg lanadelumab every two weeks until the end of the treatment period.[9] Details for the HELP-04 study are summarized in the Long-Term Extension Study section of this report.

Figure 2: Schematic Showing Design of HELP-03 (DX-2930-03) and HELP-04 (DX-2930-04)



HAE = hereditary angioedema; LTP = long-term prophylactic treatment; q2wks = every two weeks; q4wks = every four weeks.

Source: Clinical Study Report for HELP-04.[9]

Populations

Inclusion and Exclusion Criteria

Eligible patients included males and females who were at least 12 years of age at the time of screening with a documented diagnosis of type I or II HAE. The diagnosis of HAE had to include all of the following:

- Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
- Diagnostic testing results obtained during screening that confirmed type I or II HAE: C1-INH functional level less than 40% of normal. Those with functional C1-INH levels between 40% and 50% of normal may have enrolled if they also had a C4 level below the normal range.
- At least one of the following: age at reported onset of first angioedema symptoms less than 30 years, a family history consistent with HAE type I or II, or C1q within normal range.[5]

Patients were required to have a baseline rate of at least one investigator-confirmed HAE attack per four weeks during the run-in period.

Key exclusion criteria included concomitant diagnosis of another form of chronic, recurrent angioedema, such as HAE with normal C1-INH (type III), acquired angioedema, idiopathic angioedema, or recurrent angioedema associated with urticaria. Patients were ineligible if they reported exposure to any of the following:

- ACE inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within four weeks before screening
- androgens (e.g., stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within two weeks before entering the run-in period
- use of LTP therapy for HAE within two weeks before entering the run-in period (i.e., failure to complete the washout period)
- use of short-term prophylaxis for HAE within seven days before entering the run-in period.[5]

Patients were also excluded if they had any of following liver function test abnormalities: alanine aminotransferase (ALT) greater than three times the upper limit of normal, or aspartate aminotransferase (AST) greater than three times the upper limit of normal, or total bilirubin greater than twice the upper limit of normal.[5]

Baseline and Demographic Characteristics

Table 7 provides a summary of the baseline demographic characteristics for the patients randomized in the HELP-03 study. The mean age of patients was approximately 40 years across all three groups, and the age ranges were balanced. There few patients under 18 years of age (9.8% in the placebo group and 10.3% and 7.4% in the 300 mg lanadelumab every four weeks and every two weeks groups, respectively). The proportion of female patients differed across the three groups, with a greater proportion in the placebo group (82.9%) compared with the lanadelumab 300 mg every four weeks and every two weeks groups (65.5% versus 55.6%, respectively). The proportion of white patients was lower in the lanadelumab 300 mg every four weeks group (79.3%) compared with the lanadelumab 300 mg every two weeks and placebo groups (96.3% and 95.1%, respectively). Mean body weight and mean body mass index were greater in the lanadelumab 300 mg every two weeks group (90.55 kg and 31.04 kg/m^2) compared with the lanadelumab 300 mg every four weeks group (78.50 kg and 28.09 kg/m^2) and the placebo group (76.33 kg and 27.51 kg/m^2). A greater proportion of patients in lanadelumab 300 mg every four weeks group (79.3%) were enrolled at sites in the US compared with the lanadelumab 300 mg every two weeks and placebo groups (66.7% and 61.0%). Similarly, the proportion of patients enrolled from European sites was lower lanadelumab 300 mg every four weeks group compared with the lanadelumab 300 mg every two weeks and placebo groups (25.9% and 29.3%).[5]

Table 7: Summary of Baseline Demographic Characteristics (Intention-to-Treat Population)

Demographic Characteristics		Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Age (years)	Mean (SD)	40.1 (16.75)	39.5 (12.85)	40.3 (13.35)
	Median (range)	42.4 (12 to 70)	40.7 (12 to 59)	38.4 (15 to 62)
	< 18 years, n (%)	4 (9.8)	3 (10.3)	2 (7.4)
	≥ 18 to < 40	14 (34.1)	10 (34.5)	12 (44.4)
	≥ 40 to < 65	21 (51.2)	16 (55.2)	13 (48.1)
	≥ 65	2 (4.9)	0 (0.0)	0 (0.0)
Sex, n (%)	Male	7 (17.1)	10 (34.5)	12 (44.4)
	Female	34 (82.9)	19 (65.5)	15 (55.6)
Ethnicity, n (%)	Hispanic or Latino	3 (7.3)	2 (6.9)	3 (11.1)
	Not Hispanic	38 (92.7)	27 (93.1)	23 (85.2)
	Unknown	0 (0.0)	0 (0.0)	1 (3.7)
Race, n (%)	White	39 (95.1)	23 (79.3)	26 (96.3)
	African-American	2 (4.9)	6 (20.7)	1 (3.7)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)	Mean (SD)	76.33 (22.669)	78.50 (16.575)	90.55 (25.150)
	Median (range)	70.10 (36.7 to 146.0)	75.70 (46.8 to 121.2)	86.60 (55.2 to 150.0)
	< 50 kg	2 (4.9)	1 (3.4)	0 (0.0)
	50 kg to < 75 kg	24 (58.5)	13 (44.8)	10 (37.0)
	75 kg to < 100 kg	9 (22.0)	11 (37.9)	8 (29.6)
	≥ 100 kg	6 (14.6)	4 (13.8)	9 (33.3)
BMI (kg/m^2)	Mean (SD)	27.51 (7.737)	28.09 (5.158)	31.04 (7.807)
	Median (range)	26.71 (16.8 to 55.0)	27.14 (18.3 to 38.4)	28.09 (21.3 to 47.6)
BMI group: adult, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
BMI group pediatric, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Demographic Characteristics		Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region, n (%)	US	25 (61.0)	23 (79.3)	18 (66.7)
	Canada	3 (7.3)	1 (3.4)	2 (7.4)
	Europe	12 (29.3)	4 (13.8)	7 (25.9)
	Jordan	1 (2.4)	1 (3.4)	0 (0.0)

BMI = body mass index; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

Source: Clinical Study Report for HELP-03.[5]

Table 8 provides a summary of baseline disease characteristics for the patients in the HELP-03 study. The mean age of onset for angioedema symptoms was lower in the placebo group (11.2 years) compared with the lanadelumab 300 mg every four weeks and lanadelumab 300 mg every two weeks groups (14.6 and 15.0 years, respectively). The vast majority of patients had type I HAE, and the proportion of patients with type II HAE was greater in the lanadelumab 300 mg every two weeks group (14.8%) compared with the lanadelumab 300 mg every four weeks and placebo groups (6.9% and 7.3%, respectively). The proportion of patients with a history of laryngeal HAE attacks differed across the three groups, with 58.6% in the lanadelumab 300 mg every four weeks, 65.9% in the placebo group, and 74.1% in the lanadelumab 300 mg every two weeks group. The mean number of attacks in the three-month and 12-month periods before the study were greater in the placebo group (11.46 and 45.46) compared with lanadelumab 300 mg every four weeks group (9.93 and 37.07) and the lanadelumab 300 mg every two weeks group (7.67 and 22.15).[5]

The mean baseline risk of an HAE attack during the run-in period was higher in the placebo group (4.02 attacks per four weeks) compared with the lanadelumab 300 mg every four weeks group (3.71 attacks per four weeks) and the lanadelumab 300 mg every two weeks group (3.52 attacks per four weeks). However, the median baseline risk of HAE attacks was similar across the groups, with approximately three attacks per month in each group. The proportion of patients in each HAE attack rate category (i.e., one to less than two, two to less than three, and three or more per four weeks) was well-balanced across the treatment groups, as this was a stratification factor in randomization.[5]

Prior exposure to LTP therapy for HAE is summarized in Table 8. The proportion of patients who had prior usage of LTP therapy differed across the treatment groups (48.1% with lanadelumab 300 mg every two weeks, 31.0% with lanadelumab 300 mg every four weeks, and 41.5% with placebo).[5] Of those with prior exposure to LTP, the vast majority of patients had received only treatment with C1-INH (lanadelumab 300 mg every two weeks [11/14; 79%]; lanadelumab 300 mg every four weeks [18/20; 90%]; placebo [22/24; 92%]).[5] Prior exposure to androgens or antifibrinolytics were rare in the HELP-03 patient population.

Table 8: Summary of Baseline Disease Characteristics and Prior Prophylactic Treatments

Disease Characteristics		Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Age at onset of symptoms (years)	Mean (SD)	11.2 (8.21)	14.6 (11.16)	15.0 (8.67)
	Median (range)	8.0 (2 to 41)	12.0 (1 to 49)	14.0 (2 to 43)
HAE type, n (%)	Type I	38 (92.7)	27 (93.1)	23 (85.2)

Disease Characteristics		Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
	Type II	3 (7.3)	2 (6.9)	4 (14.8)
History of laryngeal attacks, n (%)	Yes	27 (65.9)	17 (58.6)	20 (74.1)
	No	14 (34.1)	12 (41.4)	7 (25.9)
Primary attack locations, n (%) (combined)	Laryngeal	10 (24.4)	6 (20.7)	5 (18.5)
	Abdominal	35 (85.4)	27 (93.1)	21 (77.8)
	Peripheral	30 (73.2)	22 (75.9)	23 (85.2)
Primary attack locations, n (%)	Laryngeal	0 (0.0)	0 (0.0)	0 (0.0)
	Laryngeal/abdominal	0 (0.0)	0 (0.0)	1 (3.7)
	Laryngeal/peripheral	1 (2.4)	0 (0.0)	1 (3.7)
	Laryngeal/abdominal/peripheral	9 (22.0)	6 (20.7)	3 (11.1)
	Abdominal	11(26.8)	7 (24.1)	3 (11.1)
	Abdominal/peripheral	15 (36.6)	14 (48.3)	14 (51.9)
	Peripheral	5 (12.2)	2 (6.9)	5 (18.5)
Attacks in the last month	Mean (SD)	4.15 (3.978)	3.76 (3.512)	2.96 (2.794)
	Median (range)	3.00 (0.0 to 15.0)	2.00 (0.0 to 14.0)	2.0 (0.0 to 12.0)
Attacks in the last 3 months	Mean (SD)	11.46 (10.824)	9.93 (10.074)	7.67 (7.504)
	Median (range)	8.00 (0.0 to 44.0)	5.00 (1.0 to 42.0)	6.00 (0.0 to 28.0)
Attacks in the last 12 months	Mean (SD)	45.46 (43.441)	37.07 (35.516)	22.15 (18.172)
	Median (range)	30.00 (0.0 to 185.0)	24.00 (1.0 to 140.0)	20.00 (0.0 to 72.0)
Run-in HAE attack rate (attacks/month)	Mean (SD)	4.02 (3.265)	3.71 (2.507)	3.52 (2.327)
	Median (range)	3.00 (1.0 to 14.7)	3.00 (1.0 to 10.5)	3.11 (1.0 to 9.0)
Run-in HAE attack rate category (attacks/month), n (%)	1 to < 2	12 (29.3)	9 (31.0)	7 (25.9)
	2 to < 3	8 (19.5)	5 (17.2)	6 (22.2)
	≥ 3	21 (51.2)	15 (51.7)	14 (51.9)
Prior LTP treatment category n (%)	C1-INH only	22 (53.7)	18 (62.1)	11 (40.7)
	Oral therapy	1 (2.4)	1 (3.4)	0 (0.0)
	C1-INH and oral therapy	1 (2.4)	1 (3.4)	3 (11.1)
	No LTP use	17 (41.5)	9 (31.0)	13 (48.1)
Prior prophylactic treatments n (%)	Androgens	1 (2.4)	0 (0.0)	0 (0.0)
	Androgens, antifibrinolytics, C1-INH	0 (0.0)	0 (0.0)	1 (3.7)
	Androgens, C1-INH	1 (2.4)	1 (3.4)	2 (7.4)
	Antifibrinolytics	0 (0.0)	1 (3.4)	0 (0.0)
	C1-INH	22 (53.7)	18 (62.1)	11 (40.7)
	No LTP use	17 (41.5)	9 (31.0)	13 (48.1)

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; LANA = lanadelumab; LTP = long-term prophylactic; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

Source: Clinical Study Report for HELP-03.[5]

Interventions

Study Medications

Table 9 summarizes the administration schedule for the investigational products in the HELP-03 study. Patients randomized to lanadelumab 300 mg every two weeks received injections of active drug every two weeks. To maintain blinding, those who were randomized to the 300 mg every four weeks alternated between injections of the active drug and placebo.[5] For each 300 mg dose of lanadelumab, each patient received a total of 2 mL, divided into two separate 1.0 mL SC injections of lanadelumab (this was required to maintain blinding, as those in the 150 mg every four weeks group received one 1.0 mL injection of lanadelumab and one 1.0 mL injection of placebo on days they received the active treatment).[5] In the HELP-03 trial, the study treatments were administered by the investigators or designated on-site personnel who were participating in the study.[5] The injections were administered into the patient's upper arm, alternating between the right and left arms at each visit.[5]

Table 9: Administration Schedule for the Investigational Products

Visit	Time	LANA 300 mg q.2.w.	LANA 300 mg q.4.w.	Placebo
1	Week 0	LANA 300 mg	LANA 300 mg	Placebo
2	Week 2	LANA 300 mg	Placebo	Placebo
3	Week 4	LANA 300 mg	LANA 300 mg	Placebo
4	Week 6	LANA 300 mg	Placebo	Placebo
5	Week 8	LANA 300 mg	LANA 300 mg	Placebo
6	Week 10	LANA 300 mg	Placebo	Placebo
7	Week 12	LANA 300 mg	LANA 300 mg	Placebo
8	Week 14	LANA 300 mg	Placebo	Placebo
9	Week 16	LANA 300 mg	LANA 300 mg	Placebo
10	Week 18	LANA 300 mg	Placebo	Placebo
11	Week 20	LANA 300 mg	LANA 300 mg	Placebo
12	Week 22	LANA 300 mg	Placebo	Placebo
13	Week 24	LANA 300 mg	LANA 300 mg	Placebo
14	Week 26	No dose	No dose	No dose

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Clinical Study Report for HELP-03.[5]

Concomitant Treatments

Acute HAE attacks during the HELP-03 study were managed in accordance with the investigator's usual care for their patients, including use of individualized acute therapy that the study investigator considered to be medically appropriate. Use of C1-INH was permitted as an acute attack therapy but not as an LTP treatment. The use of STP treatment for HAE was permitted if considered to be medically indicated. The following concomitant treatments were not permitted during the HELP-03 study: LTP treatment for HAE (e.g., C1-INH, attenuated androgens, or antifibrinolytics); ACE inhibitors; estrogen-containing medications with systemic absorption (e.g., oral contraceptives or hormonal replacement therapy); or androgens (e.g., danazol, methyltestosterone, testosterone).

Outcomes

Table 10 provides a summary of the primary, secondary, and exploratory end points in the HELP-03 study. The number of investigator-confirmed HAE attacks during the treatment period was the primary end point. There were three rank-ordered secondary efficacy end points (i.e., number of investigator-confirmed HAE attacks requiring acute treatment; number of moderate or severe investigator-confirmed HAE attacks; number of investigator-confirmed HAE attacks occurring from day 14 to day 182). All other end points and analyses were exploratory. As shown in Table 10, the exploratory end points included both pre-specified and post hoc analyses.

Table 10: Summary of End Points in HELP-03

End Points	Description	Time Frame	Hierarchy	Pre-specified
Investigator-confirmed HAE attack rate	Overall	Day 0 to 182	Primary	Yes
		Day 7 to 182	Exploratory	Yes
		Day 14 to 182	Secondary	Yes
		Day 70 to 183	Exploratory	Post hoc
	Requiring acute treatment	Day 0 to 182	Secondary	Yes
	Moderate and severe	Day 0 to 182	Secondary	Yes
	High morbidity	Day 0 to 182	Exploratory	Yes
	Resulting in ED visit or hospitalization	Day 0 to 182	Exploratory	Yes
	Resulting in ED visit	Day 0 to 182	Exploratory	Yes
	Resulting in hospitalization	Day 0 to 182	Exploratory	Yes
	Laryngeal attacks	Day 0 to 182	Exploratory	Yes
Time to first attack	After day 0 (single dose)	Day 0 to 182	Exploratory	Post hoc
	After one week	Day 7 to 182		Yes
	After day 14 (50% steady state)	Day 14 to 182		Yes
	After day 28 (2-3 doses)	Day 28 to 182		Post hoc
	After day 70 (steady state)	Day 70 to 182		Post hoc
Responder analyses	≥ 50% reduction in attack rate	Day 0 to 182	Exploratory	Yes
	≥ 60% reduction in attack rate			Yes
	≥ 70% reduction in attack rate			Yes
	≥ 80% reduction in attack rate			Yes
	≥ 90% reduction in attack rate			Yes
Attack-free intervals	One month (starting at day 0)	Day 0 to 28	Exploratory	Yes
	Two months (starting at day 0)	Day 0 to 84		Yes
	Three months (starting at day 0)	Day 0 to 182		Yes
	One month (starting at day 14)	Day 14 to 42		Yes
	Two months (starting at day 14)	Day 14 to 98		Yes
	Three months (starting at day 14)	Day 14 to 182		Yes
AE-QoL	Total score	Day 0 to 182	Exploratory	Yes
	Functioning domain			Yes
	Fatigue/mood domain			Yes
	Fear/shame domain			Yes
	Nutrition domain			Yes

End Points	Description	Time Frame	Hierarchy	Pre-specified
EQ-5D-5L	Utility score	Day 0 to 182	Exploratory	Yes
	VAS			Yes

AE-QoL = Angioedema Quality of Life questionnaire; ED = emergency department; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HAE = hereditary angioedema; VAS = visual analogue scale.

Source: Clinical Study Report for HELP-03.[5]

Investigator-Confirmed Hereditary Angioedema Attacks

Patients or their caregivers (for those less than 18 years of age) were instructed to notify and report the details of an HAE attack to the study site within 72 hours of onset. Patients and caregivers were asked to provide the following information when reporting an attack:

- date and time symptoms of an attack were first experienced
- description of symptoms experienced, including location(s)
- impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- any medications used to treat the attack
- if the attack resolved, date and time when the patient was no longer experiencing symptoms.

To be confirmed as an HAE attack, the event must have had symptoms or signs consistent with an attack in at least one of the following locations:

- peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region
- abdominal angioedema: abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea
- laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx.[5]

Despite the presence of these symptoms, the study protocol indicated that the investigators could have clinically determined that an event did not represent an HAE attack if there were features that strongly refuted such a diagnosis. The examples cited included the following:

- events that were accompanied by symptoms that were not consistent with an HAE attack, such as urticaria
- events that persisted well beyond the typical time course of an HAE attack
- events with a likely alternative etiology (e.g., the patient's abdominal symptoms were attributable to a viral gastroenteritis outbreak in the household).[5]

To be counted as a unique attack distinct from the previous attack, the new symptoms had to occur at least 24 hours after resolution of the symptoms associated with the previous HAE attack.[5]

Moderate and Severe Hereditary Angioedema Attacks

The number of moderate or severe investigator-confirmed HAE attacks was a pre-specified secondary end point of the HELP-03 study. The severity of an HAE attack was assessed the study investigator using the following criteria as reported by the patient:[5]

- **Mild:** transient or mild discomfort
- **Moderate:** mild to moderate limitation in activity — some assistance needed

- **Severe:** marked limitation in activity, assistance required.

High-Morbidity Hereditary Angioedema Attacks

The number of high-morbidity HAE attacks was an exploratory end point of the HELP-03 study. High-morbidity HAE attacks were defined as any attacks that had at least one of the following characteristics: severe, resulted in hospitalization (except hospitalization for observation for a period of less than 24 hours), hemodynamically significant (systolic blood pressure less than 90, required IV hydration, or was associated with syncope or near-syncope), or laryngeal. If the length of hospitalization could not be determined due to missing dates and times, then that hospitalization was conservatively counted as being greater than 24 hours.[5]

Time to First Hereditary Angioedema Attack

The time to the first investigator-confirmed HAE attack after day 14 was a pre-specified exploratory end point of the HELP-03 study. Day 14 was selected because the mean elimination half-life of lanadelumab is approximately 14 days, and it is anticipated that 50% steady state is achieved.[5] Time to event was assessed using Kaplan–Meier methods, and any patients who did not have an HAE attack were censored at the date of discontinuation or completion of the study (i.e., day 182).[5] In addition to the pre-specified analysis for time to event after day 14, the sponsor also conducted the following ad hoc analyses for time to first HAE attack:

- first attack after day 0 (i.e., after a single dose of lanadelumab)
- first attack after day 28 (i.e., after two or three lanadelumab doses for every four weeks and every two weeks, respectively)
- first attack after day 70 (i.e., lanadelumab concentration appeared to reach steady state).[5]

Percentage of Hereditary Angioedema Attack-Free Days

The percentage of HAE attack-free days was an exploratory end point in the HELP-03 study. An attack-free day was defined as a calendar day with no investigator-confirmed HAE attack.[5] The percentage of HAE attack-free days was calculated by counting the number of days in the treatment period without an HAE attack and dividing by the number of days the patient was in the treatment period.[5]

Hereditary Angioedema Attack-Free Intervals

The proportion of patients who did not experience an HAE attack for intervals of one month, three months, or until the end of the study (i.e., day 182) were exploratory end points of the HELP-03 study.[5] The sponsor conducted two types of analysis: one in which the interval began at day 0 and one in which the interval began at day 14. Any patients who discontinued during an interval were considered to be non-responders for that time period.[5]

Angioedema Quality of Life Questionnaire

The Angioedema Quality of Life questionnaire (AE-QoL) was an exploratory end point of the HELP-03 study. The AE-QoL questionnaire is an angioedema-specific, patient-reported, health-related quality of life measure that consists of 17 questions in four domains: functioning, fatigue/mood, fears/shame, and food.[32] Each item has a total of five answers, 1 = never to 5 = very often, with each scored 0 to a maximum of 4 points, respectively. A total score and individual domain scores are generated and converted to a linear scale of 0 to 100, with higher scores representing higher impairment (see Appendix 3 for details).

EuroQol 5-Dimensions 5-Levels Questionnaire

The EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) was an exploratory end point of the HELP-03 study. The EQ-5D-5L consists of two parts (see Appendix 3 for details):

- A series of descriptive questions focused on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the dimensions is further divided into five levels of problems perceived by the patient: no problems, slight problems, moderate problems, severe problems, and extreme problems.
- A visual analogue scale (VAS) that records the patient's self-rated health using a 20 cm vertical scale ranging from "the best health you can imagine" to "the worst health you can imagine."

Safety Outcomes

The HELP-03 included assessment of the following safety parameters:

- Treatment-emergent adverse events: Any untoward medical occurrence, whether or not it appeared to have a causal relationship with the treatment administered; events were considered treatment emergent if the time to onset (or worsening) was after first administration of investigational product.
- Serious adverse events: Any reported death, life-threatening experience, unplanned inpatient hospitalization, or prolongation of existing hospitalization; events resulting in persistent or significant disability or incapacity; any reported congenital anomaly or birth defect; or other important medical events that may jeopardize the patient or require intervention to prevent one of the previously noted outcomes.
- Adverse events of special interest: Hypersensitivity reactions and events of disordered coagulation.
- Clinical laboratory testing (hematology, chemistry, coagulation, and urinalysis); vital signs; physical examination; 12-lead electrocardiogram; and plasma antidrug antibody testing.[5]

Statistical Analysis

Analysis Populations

The analysis populations used in the HELP-03 study were defined as follows:[5]

- **Intention-to-treat (ITT) population:** All randomized patients who received any exposure to the investigational product
- **Safety population**: All patients who received any exposure to the investigational products.

The primary efficacy analyses were performed using the ITT population, and patients were analyzed according to their randomized treatment assignment, regardless of the treatment actually received. Safety analyses were conducted based on the treatment actually received by the patient, regardless of the patient's randomization status.[5]

Hereditary Angioedema Attack Rate End Points

For all HAE attack rate end points (including the primary and secondary end points), the lanadelumab groups were compared with the placebo group using a generalized linear model (GLM) for count data, assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard error (SE) to account for potential overdispersion.[5] The GLM included fixed effects for randomized treatment group and the baseline attack rate, as determined in the run-in period (normalized per 28 days), a random effect for patient, and the logarithm of the number of days the patient was observed during the double-blind treatment period as an offset variable.[5] Table 11 provides a summary of the sensitivity analyses that were conducted for the primary end point in HELP-03.

Table 11: Sensitivity Analyses for the Primary End Point in HELP-03

Sensitivity Analyses	
Pre-specified analyses	• Primary analysis was repeated using the safety population. • Primary analysis was repeated counting HAE attacks occurring on day 7 after administration of study drug to day 182, instead of day 0 to day 182. • Primary analysis was repeated using all patient-reported HAE attacks instead of limiting the analysis to those attacks that were investigator-confirmed. • Primary analysis was repeated using a GEE analysis method, counting HAE attacks occurring on day 14 after administration of study drug to day 182, in order to descriptively compare the results from this study with those from DX2930-02 study. • Tipping-point analysis was conducted to measure the potential effect of missing data on the reliability of efficacy results.
Post hoc analyses	• Use of negative binomial GLM instead of Poisson GLM • Using the primary analysis model, the attack rate was analyzed during steady state (day 70 to 182 visit).

GEE = generalized estimating equation; GLM = generalized linear model; HAE = hereditary angioedema.

Source: Clinical Study Report for HELP-03.[5]

Time to First Hereditary Angioedema Attack

Time to the first HAE attack was summarized using Kaplan–Meier methods.[5] Any patient who did not have an attack was censored at the date of discontinuation or at time of completing the double-treatment period (i.e., day 182).[5] A log rank test was used to compare each of lanadelumab groups with the placebo group.[5]

Responder Analyses

The percentage reduction in HAE attacks from baseline was calculated by subtracting the rate reported in the run-in phase from the rate reported in the double-blind phase divided by the run-in period rate.[5] Descriptive statistics were calculated, but no statistical comparisons were performed for these end points.

Hereditary Angioedema Attack-Free Days and Intervals

A patient was attack-free if there were no investigator-confirmed HAE attacks reported within the time period of interest.[5] Risk differences comparing each of the lanadelumab groups with the placebo group and corresponding 95% CIs were calculated.[5]

Patient-Reported Outcomes (Angioedema Quality of Life Questionnaire and EuroQol 5-Dimensions 5-Levels Questionnaire)

The AE-QoL was administered on days 0, 28, 56, 98, 126, 154, and 182 of the HELP-03 trial, and the EQ-5D-5L was administered on days 0, 98, and 182.[5] Analyses of variance (ANOVA) and analyses of covariance (ANCOVA) were used to test whether there is a difference between the treatment groups in the AE-QoL and EQ-5D-5L change from baseline scores to the final assessment.[5] Post hoc comparisons were included to identify any significant paired differences in mean scores between the treatment groups. Differences were presented as mean difference with 95% confidence interval (CI).[5]

Power Calculations

The sample size calculations in HELP-03 assumed a 10% dropout rate, an HAE attack rate of 0.3 per week in the placebo group, and a one-sided test with a type I error of 0.05.[5] The sponsor reported that having 24 patients in the lanadelumab groups and 36 in the placebo group would provide at least 95% power to detect a 60% reduction in HAE attacks with lanadelumab compared with placebo.[5] The rationale for the 60% reduction in events was not clearly stated in the statistical analysis plan.

Multiplicity Adjustments

The HELP-03 study used a gatekeeping approach with sequential statistical testing to control global family-wise type I error rate at 0.05 for the primary end point (i.e., number of investigator-confirmed HAE attacks during the treatment period) and for the rank-ordered secondary efficacy end points (i.e., [1] number of investigator-confirmed HAE attacks requiring acute treatment; [2] number of moderate or severe investigator-confirmed HAE attacks; [3] number of investigator-confirmed HAE attacks occurring from day 14 to day 182).[5] The gatekeeping approach involved one test for each lanadelumab group compared with placebo (ordered by highest total monthly dose) for the primary end point, followed by each of the rank-ordered secondary end points. Testing continued in sequence until the first test in which statistical significance could not be declared. For each of the end points, a Bonferroni-based procedure was used to adjust for each of the three active treatment comparisons against placebo (i.e., alpha/3 = 1.67% significance level). Testing for the final secondary end point used the Holm–Bonferroni procedure.[5] Statistical tests for the exploratory efficacy end points were conducted without adjustment for multiplicity.[5]

Subgroup Analysis

The sponsor conducted the following exploratory subgroup analyses for the primary end point: age (< 18, 18 to < 40, 40 to < 65, or ≥ 65 years); sex (male or female); race (white, other); body weight (< 50, 50 to < 75, 75 to < 100, or ≥ 100 kg); body mass index (< 18.5 kg/m^2, 18.5 $kg/m^2$to < 25 kg/m^2, 25 kg/m^2 to < 30 kg/m^2, ≥ 30 kg/m^2); run-in period HAE attack rate (one to less than two, two to less than three, or three or more attacks per month); HAE type (type I, type II, or unspecified); region (US, Canada, Jordan, Europe); type of LTP therapy before randomization (C1-INH, oral therapy, C1-INH and oral therapy, none); and history of laryngeal HAE attack (with or without historical laryngeal attack).[5] Statistical tests for the subgroup analyses were conducted without adjustment for multiplicity.[5]

Handling of Missing Data

The statistical analysis plan stated that all available data would be included in the analyses. The length of time that a patient was observed during the double-blind treatment period was included as a variable in the GLM to adjust for any differences in follow-up time.[5] The sponsor conducted a tipping-point analysis to measure the potential effect of missing data on the results for the primary end point. A multiple imputation approach was used to estimate HAE attack rate data for patients who discontinued early from the HELP-03 trial, based on the underlying rate of HAE attacks before withdrawal. Multiplication factors were then applied using progressively more conservative assumptions (i.e., higher post-dropout attack rates) to the patients who withdrew from the lanadelumab groups. Then the plausibility of the tipping point (i.e., the multiplication factor resulting in no significance) was evaluated.[5,30]

Results

Patient Disposition

Patient disposition for the HELP-03 study is summarized in Table 12. A total of 159 patients were screened for inclusion in the HELP-03 study, and 126 were randomized into the four treatment groups: placebo (n = 41), lanadelumab 150 mg every four weeks (n = 28), lanadelumab 300 mg every four weeks (n = 29), and lanadelumab 300 mg every two weeks (n = 27). The ITT and safety populations included all randomized patients. The proportion of patients who completed the double-blind treatment period was greater in the lanadelumab 300 mg every two weeks (93.6%) compared with the lanadelumab 300 mg every four weeks (89.7%) and placebo groups (85.4%). Withdrawn consent was the most commonly cited reason for discontinuation across the placebo group (7.3%) and the 300 mg lanadelumab groups (7.4% [every two weeks] and 3.4% [every four weeks]).[5]

Table 12: Patient Disposition

Disposition, n (%)	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Screened	159		
Randomized	41	29	27
Safety population	41 (100.0)	29 (100.0)	27 (100.0)
ITT population	41 (100.0)	29 (100.0)	27 (100.0)
Completed treatment period	35 (85.4)	26 (89.7)	25 (92.6)
Rolled over to HELP-04	33 (80.5)	25 (86.2)	25 (92.6)
Not rolled over to HELP-04	2 (4.9)	1 (3.4)	0
Completed final follow-up	2 (4.9)	1 (3.4)	0
Did not complete study	6 (14.6)	3 (10.3)	2 (7.4)
Primary reason for withdrawal			
Consent withdrawn	3 (7.3)	1 (3.4)	2 (7.4)
Adverse event	2 (4.9)	1 (3.4)	0
Lost to follow-up	0	1 (3.4)	0
Physician decision	1 (2.4)	0	0
Death	0	0	0
Other	0	0	0

ITT = intention-to-treat; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Clinical Study Report for HELP-03.[5]

Exposure to Study Treatments

Investigational Treatments

In HELP-03, the study drugs were administered under the direct supervision of the investigator or designated site personnel. As shown in Table 13, compliance was high across all of the treatment groups. Approximately 99% of patients received the planned doses.

Table 13: Treatment Compliance and Study Drug Exposure by Treatment Group

Exposure		Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

Source: Clinical Study Report for HELP-03.[5]

Concomitant Treatments

Table 14 summarizes the medications reportedly used in the HELP-03 trial for the acute management of HAE attacks. [redacted]. The study protocol for HELP-03 stated that HAE attacks were to be managed in accordance with individualized standard of care. Patients in HELP-03 were permitted to use C1-INHs for the treatment of an acute HAE attack therapy but were not permitted to use these drugs for LTP treatment after the washout period. Icatibant (Firazyr) was the most commonly used acute treatment for HAE attacks during the HELP-03 study (65.9% in the placebo group and 37.9% and 37.0% in the lanadelumab 300 mg every four weeks and every two weeks groups, respectively).

The use of ecallantide was reported in 12.2% of placebo-treated patients, 20.7% of patients in the lanadelumab 300 mg every four weeks group, and no patients in the lanadelumab 300 mg every two weeks group. Ecallantide (Kalbitor) is a plasma kallikrein inhibitor that is not approved in Canada, but it is marketed in the US as an SC-administered treatment for acute HAE attacks in patients at least 12 years of age.[33] [redacted] conestat alfa (Ruconest), a recombinant C1-INH that is marketed in the US and Europe for the treatment of acute HAE attacks in adults and adolescents with HAE due to C1 esterase inhibitor deficiency.[34,35] Conestat alfa has not been approved for use in Canada.[36]

The use of rescue medication was also assessed an exploratory efficacy end point in HELP-03 (see Table 25).

Table 14: Concomitant Treatments for Hereditary Angioedema Attacks (Safety Population)

Concomitant Medications for HAE Attacks	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Concomitant Medications for HAE Attacks	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; LANA = lanadelumab; LTP = long-term prophylactic; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

Source: Clinical Study Report for HELP-03.[5]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below.

Hereditary Angioedema Attack Rate (Primary End Point)

Table 15 summarizes the results for the rate of investigator-confirmed HAE attacks from day 0 to day 182 (primary end point) and the sensitivity analyses that were conducted for the primary end point. The two doses of lanadelumab that were evaluated by CADTH (i.e., 300 mg every four weeks and 300 mg every two weeks) were associated with a statistically significant reduction in the rate of HAE attacks from day 0 to day 182. Compared with placebo, the percentage reductions in the least squares (LS) mean rate with 300 mg lanadelumab were 73.3% (95% CI, –82.379 to –59.456; *P* < 0.001) and 86.9% (95% CI, –92.828 to –76.150; *P* < 0.001) in the every four weeks and every two weeks groups, respectively.[5] Figure 8 (see Appendix 2; page 111) shows each individual patient's attack duration, severity, and whether or not rescue medication was used.

As shown in Table 15, results for the pre-specified and post hoc sensitivity analyses were considered with the primary analysis. The percentage reduction in investigator-confirmed HAE attacks was slightly higher in the post hoc analysis that focused on events between day 70 to day 182 (i.e., the interval from when lanadelumab concentrations had reached steady state to the end of the HELP-03 study). The tipping-point analysis demonstrated that results in the primary analysis were robust and that the patients with missing data would have had to have HAE attack rates 35-fold higher than those who continued in order to reverse the results.[30]

Subgroup analyses were conducted for the primary end point (Figure 3). The majority of subgroup analyses demonstrated results that were consistent with the primary efficacy analysis in the ITT population. Some of the subgroup analyses contained few patients or no patients for the treatment groups of interest (i.e., the 300 mg lanadelumab groups and placebo); therefore, the estimates of effect are associated with wide CIs or are absent from Figure 3.

Table 15: Hereditary Angioedema Attack Rate (Primary End Point and Sensitivity Analyses)

Efficacy End Points	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Primary End Point			
Investigator-Confirmed HAE Attacks from Day 0 to 182 (ITT Population)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
LS mean rate per 4 weeks (SE)[a]	1.967 ([redacted])	0.526 ([redacted])	0.257 ([redacted])
Rate ratio (versus placebo) (95% CI)		0.267 (0.176 to 0.405)	0.131 (0.072 to 0.238)
P value (adjusted)[b]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–73.271 (–82.379 to –59.456)	–86.921 (–92.828 to –76.150)
Pre-Specified Sensitivity Analyses			
Investigator-Confirmed HAE Attacks from Day 0 to 182 (Safety Population)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
LS mean rate per 4 weeks (SE)[a]	1.967 (0.182)	0.526 (0.103)	0.257 (0.076)
Rate ratio (versus placebo) (95% CI)		0.267 (0.176 to 0.405)	0.131 (0.072 to 0.238)
P value (unadjusted)[c]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–73.271 (–82.379 to –59.456)	–86.921 (–92.828 to –76.150)
Investigator-Confirmed HAE Attacks from Day 7 to 182 (ITT Population)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

Efficacy End Points	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Patient-Reported HAE Attacks from Day 0 to 182 (ITT Population)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
Investigator-Confirmed HAE Attacks from Day 14 to 182 (GEE Poisson Regression; ITT Population)[d]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
Post Hoc Sensitivity Analyses			
Investigator-Confirmed HAE Attacks from Day 70 to 182 (ITT Population)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
LS mean rate per 4 weeks (SE)[a]	1.883 ([redacted])	0.366 ([redacted])	0.161 ([redacted])
Rate ratio (versus placebo) (95% CI)		0.194 (0.115 to 0.327)	0.085 (0.039 to 0.189)
P value (unadjusted)[c]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		[redacted]	[redacted]
Investigator-Confirmed HAE Attacks from Day 0 to 182 (Negative Binomial GLM; ITT Population)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
LS mean rate per 4 weeks (SE)[a]	1.934 ([redacted])	0.481 ([redacted])	0.256 ([redacted])
Rate ratio (versus placebo) (95% CI)		[redacted]	[redacted]
P value (unadjusted)[c]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–75.130 (–84.385 to –60.392)	-86.780 (–92.169 to –77.683)

CI = confidence interval; GEE = generalized estimating equations; GLM = generalized linear model; HAE = hereditary angioedema; ITT = intention-to-treat; LANA = lanadelumab; LS = least squares; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation; SE = standard error.

[a] Poisson regression model with fixed effects for treatment group and normalized baseline HAE attack rate, and logarithm of time in days that the patient was observed during treatment period as an offset variable. Pearson chi-square scaling of standards errors was used to account for potential overdispersion.[5]

[b] *P* value is adjusted for multiple testing.

[c] Unadjusted *P* values are derived from Poisson modelling.

[d] HAE attack rates in the lanadelumab groups were compared with the placebo group using a mixed-model repeated measures analysis of covariance for count data (assuming a Poisson distribution with log link function) using GEEs. The model included a fixed effect for treatment and run-in period attack rate, and a random effect for patient.

Source: Clinical Study Report for HELP-03.[5]

Table 16: Primary Attack Location for Hereditary Angioedema Attacks (Intention-to-Treat Population)

Trial Phase	HAE Attacks	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
		N (%)	Number of events	N (%)	Number of events	N (%)	Number of events
Run-in Period	Attacks	41 (100.0)	127	29 (100.0)	77	27 (100.0)	78
	Abdominal	27 (65.9)	61	19 (65.5)	29	14 (51.9)	21
	Laryngeal	0 (0.0)	0	2 (6.9)	2	2 (7.4)	2
	Peripheral	33 (80.5)	66	22 (75.9)	46	24 (88.9)	55
Treatment Period	Attacks	40 (97.6)	572	20 (69.0)	105	15 (55.6)	46
	Abdominal	35 (85.4)	243	17 (58.6)	77	9 (33.3)	22
	Laryngeal	9 (22.0)	15	2 (6.9)	2	3 (11.1)	4
	Peripheral	37 (90.2)	314	12 (41.4)	26	9 (33.3)	20

HAE = hereditary angioedema; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Clinical Study Report for HELP-03.[5]

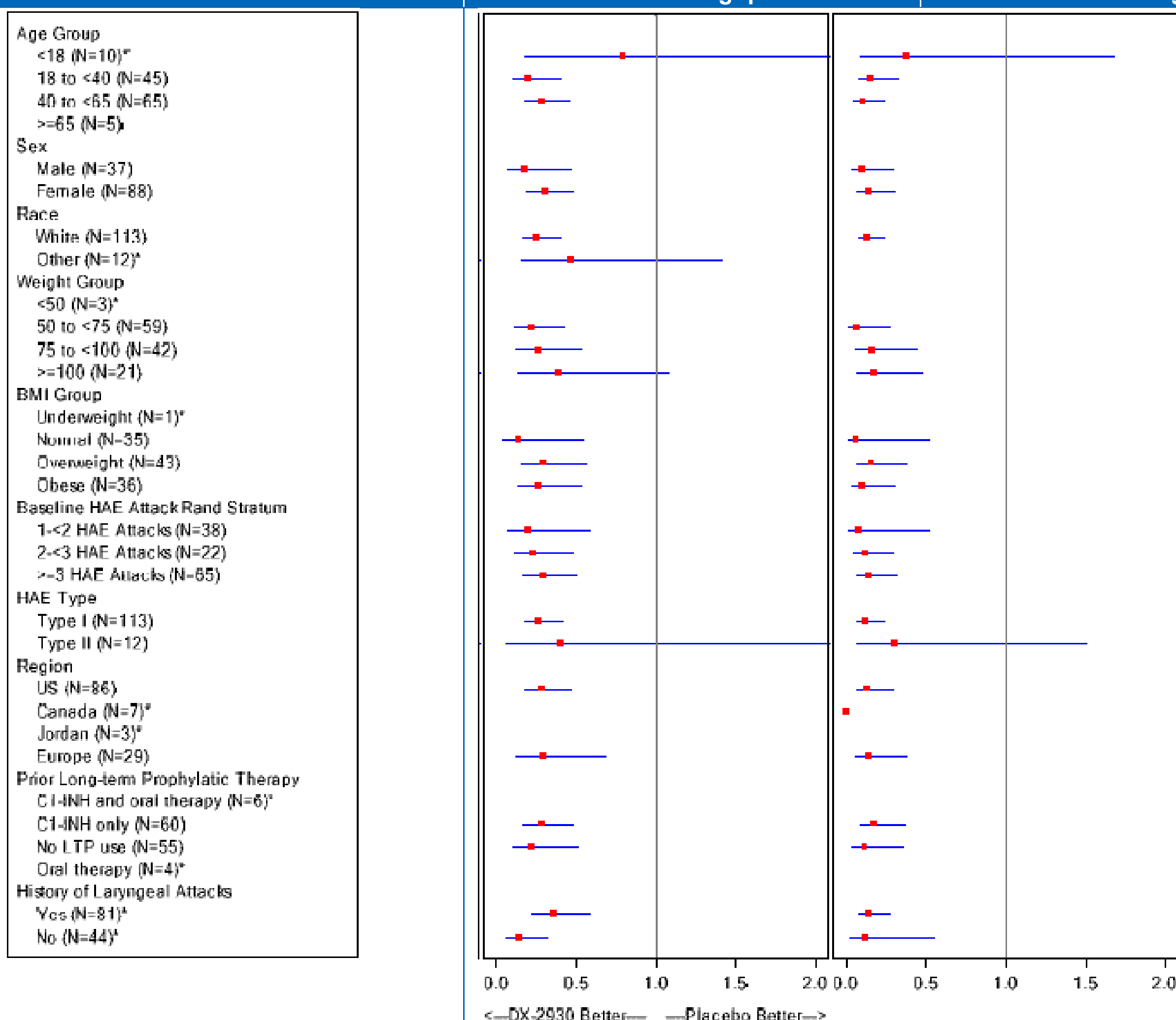
Table 16 provides a summary of the primary attack location for investigator-confirmed HAE attacks in the HELP-03 study in the run-in period and the double-blind treatment period. During the run-in period, peripheral attacks were the most commonly reported across all three treatment groups (80.5% with placebo versus 75.9% and 88.9% with 300 mg lanadelumab every four weeks and every two weeks, respectively), followed by abdominal attacks (65.9% with placebo versus 65.5% and 51.9% with 300 mg lanadelumab every four weeks and every two weeks, respectively), and laryngeal attacks were rarely reported. In the double-blind treatment period, the proportion of patients with events was lower in the two lanadelumab groups compared with the placebo group, irrespective of the attack location.

Hereditary Angioedema Attack Rate (Secondary and Exploratory End Points)

The results for the secondary end point (i.e., HAE attack rate from day 14 to day 182) also demonstrated a statistically significant reduction in HAE attack rate, with LS mean percentage reductions compared with placebo of –75.377% (95% CI, –84.115 to –61.833; *P* < 0.001) and –89.008% (95% CI, –94.325 to –78.707; *P* < 0.001) with 300 mg lanadelumab in the every four weeks and every two weeks groups, respectively.[5] Results for the reduction in HAE attack rate from day 7 to day 182 [redacted].[5]

Figure 3: Subgroup Analyses Hereditary Angioedema Attack Rate in the HELP-03 Study (Rate Ratio)

Subgroup Analyses	LANA Versus Placebo (Rate Ratio [95% CI])	
	LANA 300 mg q.4.w.	LANA 300 mg q.2.w.



BMI = body mass index; C1-INH = C1 esterase inhibitor; CI = confidence interval; DX-2930 = lanadelumab; HAE = hereditary angioedema; LANA = lanadelumab; LTP = long-term prophylactic treatment; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Common Technical Document 2.7.3.[28]

Table 17: Hereditary Angioedema Attack Rate (Secondary and Exploratory End Points) (Intention-to-Treat Population)

Efficacy End Points	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
HAE Attacks from Day 14 to 182 (Secondary End Point)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
LS mean rate per 4 weeks (SE)[a]	1.988 (0.187)	0.489 (0.101)	0.218 (0.071)
[redacted]		[redacted]	[redacted]
P value (adjusted)[b]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–75.377 (–84.115 to –61.833)	–89.008 (–94.325 to –78.707)
HAE Attacks from Day 7 to 182 (Exploratory End Point)			
Run-in attack rate per 4 weeks; mean (SD)	4.022 (3.265)	3.711 (2.507)	3.519 (2.327)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

CI = confidence interval; HAE = hereditary angioedema; LANA = lanadelumab; LS = least squares; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation; SE = standard error.

[a] Poisson regression model with fixed effects for treatment group and normalized baseline HAE attack rate, and logarithm of time in days that the patient was observed during treatment period as an offset variable. Pearson chi-square scaling of standards errors was used to account for potential overdispersion.[5]

[b] *P* value is adjusted for multiple testing.

[c] Unadjusted *P* values are derived from Poisson modelling.

Source: Clinical Study Report for HELP-03.[5]

Severity of Hereditary Angioedema Attacks

Table 18 provides a summary of the results for moderate and severe HAE attacks (a pre-specified secondary end point) and high-morbidity HAE attacks (an exploratory end point). Treatment with lanadelumab was associated with a statistically significant reduction in the rate of moderate and severe HAE attacks from day 0 to day 182. Compared with placebo, the percentage reductions in the LS mean rate with 300 mg lanadelumab were –73.285% (95% CI, –84.316 to –54.496; $P < 0.001$) and –83.394 (95% CI, –91.618 to –67.099; $P < 0.001$) in the every four weeks and every two weeks groups, respectively.[5] Both of the 300 mg lanadelumab groups also demonstrated a reduction in high-morbidity HAE attacks compared with placebo of –86.320% (95% CI, –96.769 to –42.072; $P = 0.007$) and –84.712% (95% CI, –96.398 to –35.106; $P = 0.011$).

Table 18: Severity of Hereditary Angioedema Attacks (Intention-to-Treat Population)

Efficacy End Points	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Moderate and Severe HAE Attacks (Secondary End Point)			
Run-in attack rate per 4 weeks; mean (SD)	2.341 (2.147)	2.576 (2.396)	2.169 (2.228)
LS mean rate per 4 weeks (SE)[a]	1.216 ([redacted])	0.325 ([redacted])	0.202 ([redacted])
[redacted]		[redacted]	[redacted]
P value (adjusted)[b]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–73.285 (–84.316 to –54.496)	–83.394 (–91.618 to –67.099)
High-Morbidity HAE Attacks (Exploratory End Point)			
[redacted]	[redacted]	[redacted]	[redacted]
LS mean rate per 4 weeks (SE)[a]	0.219 ([redacted])	0.030 ([redacted])	0.034 ([redacted])
[redacted]		[redacted]	[redacted]
P value (unadjusted)[c]		0.007	0.011
% change in mean rate (versus placebo) (95% CI)		–86.3 [redacted]	–84.7 [redacted]

CI = confidence interval; HAE = hereditary angioedema; LANA = lanadelumab; LS = least squares; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation; SE = standard error.

[a] Poisson regression model with fixed effects for treatment group and normalized baseline HAE attack rate, and logarithm of time in days that the patient was observed during treatment period as an offset variable. Pearson chi-square scaling of standards errors was used to account for potential overdispersion.[5]

[b] *P* value is adjusted for multiple testing.[5]

[c] Unadjusted *P* values are derived from Poisson modelling.[5]

Source: Clinical Study Report for HELP-03.[5]

Hereditary Angioedema Attacks Requiring Acute Treatment

Table 19 provides a summary of the results for HAE attacks that required acute treatment, a secondary end point of the HELP-03 study. All doses of lanadelumab were associated with a statistically significant reduction in the rate of HAE attacks that required acute treatment from day 0 to day 182. Compared with placebo, the percentage reductions in the LS mean rate with 300 mg lanadelumab were –74.169% (95% CI, –83.733 to –58.983; *P* < 0.001) and –87.299 (95% CI, –93.494 to –75.204; *P* < 0.001) in the every four weeks and every two weeks groups, respectively.[5]

Table 19: Hereditary Angioedema Attacks Requiring Acute Treatment (Intention-to-Treat Population)

Efficacy End Points	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Investigator-Confirmed HAE Attacks Requiring Acute Treatment (Secondary End Point)			
Run-in attack rate per 4 weeks; mean (SD)	3.596 (3.485)	3.460 (2.740)	3.110 (2.589)
LS mean rate per 4 weeks (SE)[a]	1.637 ([redacted])	0.423 ([redacted])	0.208 ([redacted])
Rate ratio (versus placebo)		0.258 (0.163 to 0.410)	0.127 (0.065 to 0.248)
P value (adjusted)[b]		< 0.001	< 0.001
% change in mean rate (versus placebo) (95% CI)		–74.169 (–83.733 to –58.983)	–87.299 (–93.494 to –75.204)

CI = confidence interval; HAE = hereditary angioedema; LANA = lanadelumab; LS = least squares; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation; SE = standard error.

[a] Poisson regression model with fixed effects for treatment group and normalized baseline HAE attack rate, and logarithm of time in days that the patient was observed during treatment period as an offset variable. Pearson chi-square scaling of standards errors was used to account for potential overdispersion.[5]

[b] *P* value is adjusted for multiple testing.[5]

Source: Clinical Study Report for HELP-03.[5]

Hereditary Angioedema Attacks Resulting in Emergency Department Visit or Hospitalization

Table 20 provides a summary of the results for HAE attacks that resulted in a visit to the emergency department and/or hospitalization. There were few investigator-confirmed HAE attacks that resulted in an emergency department visit or admission to hospital in either the run-in period or the double-blind treatment phase.[5] [redacted].

Table 20: Hereditary Angioedema Attacks Resulting in an Emergency Department Visit and/or Hospitalization (Intention-to-Treat Population)

	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
HAE Attacks Resulting in an Emergency Department Visit or Admission to the Hospital (Exploratory End Point)			
Run-in attack rate per 4 weeks; mean (SD)	0.057 (0.257)	0.068 (0.253)	0.072 (0.258)
LS mean rate per 4 weeks (SE)[a]	0.032 (0.016)	0.027 (0.017)	0.011 (0.012)
Rate ratio (versus placebo) (95% CI)		0.829 (0.167 to 4.129)	0.354 (0.038 to 3.278)
P value (unadjusted)[b]		0.819	0.360
% change in mean rate (versus placebo) (95% CI)		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

[a] [redacted].[5]

[b] [redacted].

CI = confidence interval; HAE = hereditary angioedema; LANA = lanadelumab; LS = least squares; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation; SE = standard error.

Source: Clinical Study Report for HELP-03.[5]

Laryngeal Hereditary Angioedema Attacks

Table 21 provides a summary of the results for laryngeal HAE attacks, which was an exploratory end point in the HELP-03 study. There were no laryngeal attacks reported during the run-in period for the placebo group and few events in the lanadelumab groups (i.e., two events in each of the 300 mg lanadelumab groups).[5] There were no differences between the lanadelumab and placebo groups for laryngeal attacks.

Table 21: Laryngeal Hereditary Angioedema Attacks (Intention-to-Treat Population)

Efficacy End Points	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Run-in period HAE attack rate; mean (SD)	0.000 (0.000)	0.068 (0.253)	0.144 (0.544)
LS mean rate per 4 weeks (SE)[a]	0.057 (0.024)	0.011 (0.012)	0.023 (0.018)
Rate ratio (versus placebo) (95% CI)		0.184 (0.019 to 1.834)	0.405 (0.072 to 2.269)
P value (unadjusted)[b]		0.149	0.304
% change in mean rate (versus placebo) (95% CI)		–81.555 (–98.145 to 83.394)	–59.475 (–92.761 to 126.879)

CI = confidence interval; HAE = hereditary angioedema; LANA = lanadelumab; LS = least squares; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation; SE = standard error.

[a] Poisson regression model with fixed effects for treatment group and normalized baseline HAE attack rate, and logarithm of time in days that the patient was observed during treatment period as an offset variable. Pearson chi-square scaling of standards errors was used to account for potential overdispersion.[5]

[b] Unadjusted *P* values are derived from Poisson modelling.

Source: Clinical Study Report for HELP-03.[5]

Responder Analyses

The results for the HAE attack rate responder analyses are summarized in Table 22. The percentage of patients achieving reductions of at least 50%, 60%, 70%, 80%, and 90% was greater in the lanadelumab groups than in the placebo groups.[5] No statistical tests were performed by the sponsor for these end points.[5]

Table 22: Hereditary Angioedema Attack Responder Analysis (Intention-to-Treat Population)

Responder Analysis, n (%)	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
≥ 50% reduction	13 (31.7)	29 (100.0)	27 (100.0)
≥ 60% reduction	9 (22.0)	26 (89.7)	27 (100.0)
≥ 70% reduction	4 (9.8)	22 (75.9)	24 (88.9)
≥ 80% reduction	3 (7.3)	17 (58.6)	22 (81.5)
≥ 90% reduction	2 (4.9)	16 (55.2)	18 (66.7)

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Clinical Study Report for HELP-03.[5]

Time to First Hereditary Angioedema Attack

The results for time to first HAE attack are summarized in Table 23. The time to first HAE attack was longer for both the 300 mg lanadelumab groups compared with the placebo group for all of the analyses (i.e., events after day 0, 7, 14, 28, and 70). Fewer than 50% of patients in the lanadelumab 300 mg every two weeks group had experienced an event in the analyses for day 14 to day 182, day 28 to day 182, and day 70 to day 182; therefore, the median time to first HAE attack could not be estimated. Figure 4 shows the Kaplan–Meier curve for time to first HAE attack from day 0 to day 182.

Table 23: Time to First Hereditary Angioedema Attack (Intention-to-Treat Population)

Time to HAE Attacks (Days)	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Time to First HAE Attack After Day 0			
Events, n (%)	40 (97.56)	20 (68.97)	15 (55.56)
Censored, n (%)	[redacted]	[redacted]	[redacted]
Median days to first HAE attack (95% CI)	8 (6 to 18)	28 (10 to 101)	59 (28 to NE)
P value[a]		< 0.001	< 0.001
Time to First HAE Attack After Day 7			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
Time to First HAE Attack After Day 14			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
Time to First HAE Attack After Day 28			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
Time to First HAE Attack After Day 70			
Events, n (%)	36 (97.30)	16 (55.17)	6 (23.08)

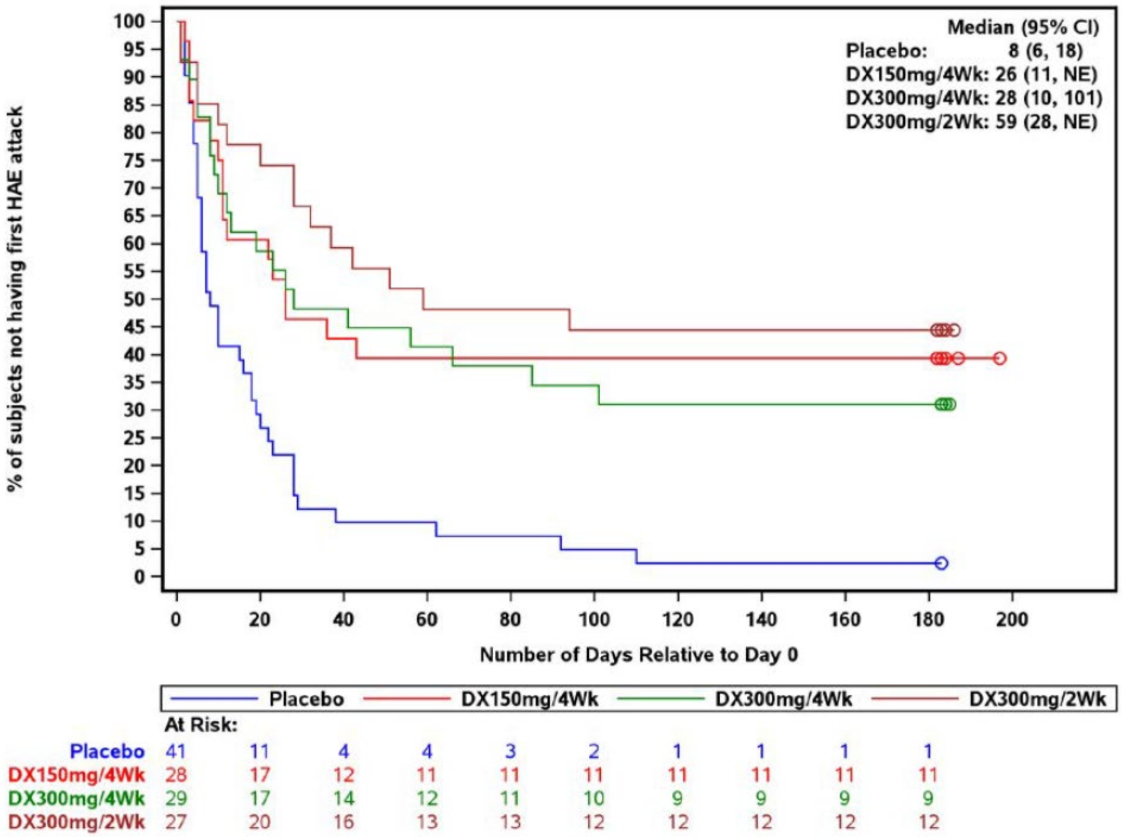
Time to HAE Attacks (Days)	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
Censored, n (%)	[redacted]	[redacted]	[redacted]
Median days to first HAE attack (95% CI)	12 (6 to 16)	61 (25 to NE)	NE (NE to NE)
P value[a]		< 0.001	< 0.001

HAE = hereditary angioedema; LANA = lanadelumab; NE = not estimable; q.2.w. = every two weeks; q.4.w. = every four weeks.

[a] *P* value comparing treatment groups is from a log rank test.

Source: Clinical Study Report for HELP-03.[5]

Figure 4: Time to First Hereditary Angioedema Attack in HELP-03 (Day 0 to Day 182)



CI = confidence interval; DX = lanadelumab; HAE = hereditary angioedema; NE = not estimable; Wk = week.

Source: Common Technical Document 2.7.3.[28]

Hereditary Angioedema Attack-Free Days and Months

The percentage of days without an investigator-confirmed HAE attack (i.e., attack-free days) was an exploratory end point of the HELP-03 study. The mean (SD) percentage of HAE attack-free days was [redacted].

Table 24 provides a summary of the results for the proportion of patients who did not experience an HAE attack for intervals of one month, three months, or until the end of the study (i.e., day 182). The sponsor conducted two types of analysis: one in which the interval began at day 0 and one in which the interval began at day 14. As shown in the table, [redacted]. The proportion of attack-free patients was greater in the lanadelumab 300 mg every two weeks group compared with the every four weeks group for all of the time points. No formal statistical tests were performed for these end points.

Table 24: [redacted]

[redacted]		Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.2.w. (N = 27)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]

CI = confidence interval; HAE = hereditary angioedema; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; RD = risk difference.

[redacted]

Source: Clinical Study Report for HELP-03.[5]

Rescue Medication

Table 25 provides a summary of the rescue medication that was reported in the run-in and treatment periods of the HELP-03 study.

Table 25: Rescue Medication in the HELP-03 Study (Intention-to-Treat Population)

Rescue Medication Use	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Run-In Period						
HAE attacks	41 (100.0)	127	29 (100.0)	77	27 (100.0)	78
Ecallantide	2 (4.9)	2	6 (20.7)	8	1 (3.7)	3
Icatibant	22 (53.7)	38	13 (44.8)	41	13 (48.1)	32
Nano-filtered or plasma-derived C1-INH	22 (53.7)	77	14 (48.3)	28	12 (44.4)	34
Recombinant C1-INH	0 (0.0)	0	1 (3.4)	1	1 (3.7)	2
Fresh frozen plasma	1 (2.4)	1	0 (0.0)	0	0 (0.0)	0
Treatment Period						
HAE attacks	40 (97.6)	572	20 (69.0)	105	15 (55.6)	46
Ecallantide	5 (12.2)	12	6 (20.7)	18	0 (0.0)	0

Rescue Medication Use	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Icatibant	27 (65.9)	172	11 (37.9)	69	10 (37.0)	20
Nano-filtered or plasma-derived C1-INH	27 (65.9)	362	4 (13.8)	7	6 (22.2)	26
Recombinant C1-INH	0 (0.0)	0	1 (3.4)	1	0 (0.0)	0
Fresh frozen plasma	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

C1-INH = C1 esterase inhibitor; LANA = lanadelumab; HAE = hereditary angioedema; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Clinical Study Report for HELP-03.[5]

Angioedema Quality of Life Questionnaire

Change from baseline in AE-QoL score was an exploratory end point of the HELP-03 study, and the results are summarized in Table 26. The differences in AE-QoL total score between the lanadelumab and placebo groups were [redacted] for 300 mg every four weeks and every two weeks groups, respectively.[5] The minimal clinically important difference in the AE-QoL total score of six points was achieved by 37% of patients in the placebo group, 63% of patients in the lanadelumab 300 mg every four weeks group (odds ratio versus placebo 2.91; *P* = 0.04) and by 81% of patients in the lanadelumab 300 mg every two weeks group (odds ratio versus placebo 7.20; *P* = 0.01).[14]

Table 26: Change from Baseline in Angioedema Quality of Life Questionnaire Scores (Intention-to-Treat Population)

Treatment Group	LS Mean Change (SD)				
	Total	Functioning	Fatigue/Mood	Fear/Shame	Nutrition
Placebo	–4.72 (18.75)	–5.42 (22.72)	–1.79 (23.25)	–9 (24.02)	0.51 (22.5)
LANA 300 mg q.4.w.	–17.38 (18.67)	–24.29 (22.66)[a]	–13.86 (23.22)[a]	–16.3 (23.71)	–13.34 (22.32)
LANA 300 mg q.2.w.	–21.29 (18.35)	–35.97 (22.29)[a]	–15.78 (22.79)[a]	–17.59 (23.29)	–18.03 (22.01)
Post Hoc Pairwise Comparisons (Mean Difference [95% CI])					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; CI = confidence interval; LANA = lanadelumab; LS = least squares; NE = not estimable; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

[a] Significant difference between lanadelumab and placebo groups on Tukey–Kramer post hoc pairwise comparison (*P* value < 0.05).

[b] *P* value < 0.05 for the post hoc comparison.

Source: Clinical Study Report for HELP-03.[5]

EuroQol 5-Dimensions 5-Levels Questionnaire Utility and Visual Analogue Scale Scores

Table 27 provides a summary of the results for change from baseline in EQ-5D-5L scores in the HELP-03 study. There were no differences observed between the lanadelumab 300 mg groups and the placebo group.[5]

Table 27: [redacted]

Treatment Group	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ANCOVA = analysis of covariance; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; LANA = lanadelumab; LS = least squares; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

Source: Clinical Study Report for HELP-03.[5]

Harms

Only those harms identified in the review protocol are reported in this section. Table 28 provides a summary of aggregate adverse events outcomes. Compared with the placebo group, a greater proportion of 300 mg lanadelumab-treated patients reported at least one adverse event (96.3% in the every two weeks group and 86.2% in the every four weeks group versus 75.6% in the placebo group), at least one serious adverse event (3.7% in the every two weeks group and 10.3% in the every four weeks group versus 0%), and hospitalization due to an adverse event (3.7% in the every two weeks group and 10.3% in the every four weeks group versus 0% in the placebo group).[5] Withdrawals due to adverse events were rare, with only a single event in the placebo and lanadelumab 300 mg every four weeks groups, and no events in the lanadelumab 300 mg every two weeks group.[5]

Table 28: Summary of Adverse Events (Safety Population)

Adverse Events	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Any TEAE	31 (75.6)	231	25 (86.2)	182	26 (96.3)	235
Any SAE	0 (0.0)	0	3 (10.3)	3	1 (3.7)	1
Any severe TEAE	4 (9.8)	7	4 (13.8)	6	2 (7.4)	2
Deaths due to TEAE	0 (0.0)	0	0 (0.0)	-	0 (0.0)	-
Hospitalizations due to TEAE	0 (0.0)	0	3 (10.3)	3	1 (3.7)	1
WDAE	1 (2.4)	-	1 (3.4)	-	0 (0.0)	-

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse events.

Source: Clinical Study Report for HELP-03.[5]

Adverse Events

Table 29 provides a summary of the treatment-emergent adverse events that were reported in at least 5% of patients within any of the lanadelumab treatment groups in the HELP-03 study. The proportion of patients who reported at least one adverse event was greater in the lanadelumab groups (96.3% and 86.2% in the every two weeks and every four weeks groups, respectively) compared with the placebo group (75.6%).[5] Injection-site pain was the most commonly reported adverse event in both the lanadelumab and placebo groups. The proportion of patients who reported injection-site pain was similar in the placebo and lanadelumab every four weeks groups (29.3% and 31.0%, respectively), but was greater in the lanadelumab every two weeks group (51.9%).[5] Other administration-site events were also more commonly reported in the lanadelumab groups than in the placebo groups. Injection-site erythema was reported in one placebo-treated patient (2.4%) and two patients in both the lanadelumab 300 mg every four weeks (6.9%) and lanadelumab 300 mg every two weeks (7.4%) groups.[5] Injection-site bruising was reported in two patients in the lanadelumab 300 mg every four weeks group (6.9%), one patient in the lanadelumab 300 mg every two weeks group (3.7%), and no placebo-treated patients.[5] Viral upper respiratory tract infection and headache were more commonly reported in the lanadelumab 300 mg every two weeks group (37.0% and 33.3%, respectively) compared with the lanadelumab 300 mg every four weeks group (24.1% and 17.2%, respectively) and the placebo group (26.8% and 19.5%, respectively).[5]

Table 29: Adverse Events in More Than 5% of Patients in the Lanadelumab Groups (Safety Population)

Adverse Events	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Any TEAE	31 (75.6)	231	25 (86.2)	182	26 (96.3)	235
Injection-site pain	12 (29.3)	74	9 (31.0)	74	14 (51.9)	72
Viral URTI	11 (26.8)	16	7 (24.1)	10	10 (37.0)	12
Headache	8 (19.5)	10	5 (17.2)	8	9 (33.3)	18
Injection-site erythema	1 (2.4)	1	2 (6.9)	6	2 (7.4)	7
Injection-site bruising	0 (0.0)	0	2 (6.9)	2	1 (3.7)	1
Dizziness	0 (0.0)	0	3 (10.3)	5	1 (3.7)	1

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; TEAE = treatment-emergent adverse events; URTI = upper respiratory tract infection.

Source: Clinical Study Report for HELP-03.[5]

Serious Adverse Events

SAEs reported in the HELP-03 trial, excluding HAE attacks, are summarized in Table 30. SAEs were reported for three patients in the lanadelumab 300 mg every four weeks group (three events) and one patient in the lanadelumab 300 mg every two weeks group (one event). No SAEs were reported in the placebo group. Events reported in the lanadelumab 300 mg every four weeks group included pyelonephritis (kidney infection), meniscus injury, and bipolar disorder. A single event of a catheter site infection was reported in the lanadelumab 300 mg every two weeks group.[29]

Table 30: Serious Treatment-Emergent Adverse Events (Excluding Hereditary Angioedema Attacks Reported Events) (Safety Population)

SAEs	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Any SAE	0	0	3 (10.3)	3	1 (3.7)	1
Infection and infestations	0	0	1 (3.4)	1	1 (3.7)	1
Catheter site infection	0	0	0		1 (3.7)	1
Pyelonephritis	0	0	1 (3.4)	1	0	0
Injury, poisoning, and procedural complications	0	0	1 (3.4)	1	0	0

SAEs	Placebo (N = 41)		LANA 300 mg q.4.w. (N = 29)		LANA 300 mg q.2.w. (N = 27)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Meniscus injury	0	0	1 (3.4)	1	0	0
Psychiatric disorders	0	0	1 (3.4)	1	0	0
Bipolar II disorder	0	0	1 (3.4)	1	0	0

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; SAE = serious adverse events.

Source: Common Technical Document section 2.7.4.[29]

Withdrawals Due to Adverse Events

Discontinuations from the study due to adverse events were reported for one patient in the lanadelumab 300 mg every four weeks group (non-serious, asymptomatic elevations in ALT and AST) and one patient in the placebo group (non-serious, treatment-emergent adverse event of tension headache).[29]

Mortality

There were no deaths reported in the HELP-03 study.[5]

Notable Harms

Disordered Coagulation

Table 31 provides a summary of adverse events related to bleeding that were reported in the HELP-03 study (based on Standardised MedDRA Query [SMQ]-defined events). The proportions of patients with at least one bleeding-related AE were [redacted].[5] [redacted][5]

Table 31: [redacted]

[redacted]	[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AESI = adverse event of special interest; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; TEAE = treatment-emergent adverse event.

[redacted]

Source: Clinical Study Report for HELP-03.[5]

Hypersensitivity

Table 32 provides a summary of adverse events that were classified as hypersensitivity adverse events (based on SMQ-defined events). The proportion of patients with at least one hypersensitivity adverse event [redacted].[5] None of the events resulted in discontinuation or were classified as serious or severe.[5] The sponsor also included hypersensitivity reactions as a pre-specified adverse event of special interest for the HELP-03 trial; a single patient in the lanadelumab 300 mg every two weeks group had a hypersensitivity reaction that met the criteria as an adverse event of special interest (two events).

Table 32: [redacted]

[redacted]	[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AESI = adverse event of special interest; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; TEAE = treatment-emergent adverse event.

[redacted]

Source: Clinical Study Report for HELP-03.[5]

Immunogenicity

Tests were performed for antidrug antibodies (ADAs) on days 0, 56, 98, 140, and 182 (all ± 3 days).[5] An additional sample was collected during the follow-up period (day 238 ± 3 days) for any patient who elected not to enter the HELP-04 extension study.[5] The proportion of patients who were positive for ADAs was 10.3% and 14.8% in the 300 mg lanadelumab every four weeks and every two weeks groups, respectively, compared with 7.3% in the placebo group. [redacted]. All samples confirmed to be ADA-positive were tested using a neutralizing antibody assay. No patients in the lanadelumab groups of interest for this review tested positive neutralizing antibodies (the only positive tests were two patients in the 150 every four weeks group).[5]

Table 33: Summary of Immunogenicity Response (Safety Population)

Immunogenicity Response n, (%)	Placebo (N = 41)	LANA 300 mg q.4.w. (N = 29)	LANA 300 mg q.4.w. (N = 27)
ADA prevalence[a]	3 (7.3)	3 (10.3)	4 (14.8)
ADA incidence[b]	2 (4.9)	3 (10.3)	2 (7.4)
Pre-existing ADA[c]	1 (2.4)	1 (3.4)	2 (7.4)
Treatment-induced[d]	2 (4.9)	2 (6.9)	2 (7.4)
Treatment-boosted[e]	0 (0.0)	1 (3.4)	0 (0.0)
Non-neutralizing ADA	3 (7.3)	3 (10.3)	4 (14.8)
Neutralizing ADA	0 (0.0)	0 (0.0)	0 (0.0)

ADA = antidrug antibody; q.2.w. = every two weeks; q.4.w. = every four weeks.

[a] Proportion of patients with drug-reactive antibodies at any time point, including pre-existing antibodies.

[b] Proportion of patients found to have seroconverted or boosted their pre-existing ADAs during the study period.

[c] Refers to ADA signals detected before initiating the study treatments.

[d] Responses characterized by a negative pre-treatment sample with at least one positive sample at a subsequent time point.

[e] Responses characterized by a positive pre-treatment sample that are boosted to a higher level following drug administration.

Source: Clinical Study Report for HELP-03.[5]

Critical Appraisal

Internal Validity

Randomization was performed using an appropriate methodology with adequate allocation concealment (i.e., Interactive Web Response System), and stratification was based on a relevant prognostic factor (i.e., four-week baseline HAE risk during the run-in period [one to less than two, two to less than three, and three or more attacks]). Reviewers for Health Canada considered the design of the HELP-03 study to be suitable for minimizing confounding by potentially relevant covariates (i.e., baseline LTP treatment and baseline HAE attack rate).[21] The mean baseline risk of an HAE attack during the run-in period was slightly greater in the placebo group (4.02 attacks per four weeks) compared with the lanadelumab 300 mg every four weeks group (3.71 attacks per four weeks) and the lanadelumab 300 mg every two weeks group (3.52 attacks per four weeks). However, the proportion of patients in each HAE attack rate category (i.e., one to less than two, two to less than three, and three or more attacks) was well-balanced across the treatment groups, as this was a stratification factor in randomization.

Patients in HELP-03 were well-balanced across the treatment groups for age, but there were several notable differences in other demographic and baseline characteristics. The proportion of female patients was greater in the placebo group (82.9%) than in the lanadelumab 300 mg every four weeks and every two weeks groups (65.5% versus 55.6%, respectively). The clinical experts consulted by CADTH and reviewers for the European Medicines Agency (EMA) noted that HAE can be more severe in girls and women compared with boys and men;[31] however, subgroup analyses based on sex did not suggest a differential response to treatment with lanadelumab (Figure 3). Health Canada similarly concluded that the sex imbalance across the groups did not appear to be responsible for the favourable effects of lanadelumab compared with placebo in HELP-03.[21] There were also differences in the mean age at HAE symptom onset and in the proportion of patients with a history of laryngeal HAE attacks. CADTH discussed the nature and magnitude of these differences with Canadian clinical experts, who noted that they were unlikely to be important confounding factors in the study. However, there may be unknown and unmeasured factors that were not balanced and that could have confounded the study results, given observable imbalances in other measured factors.

Mean body mass index was greater in the lanadelumab 300 mg every two weeks group (31.04 kg/m^2) compared with the lanadelumab 300 mg every four weeks group (28.09 kg/m^2) and the placebo group (27.51 kg/m^2). As the recommended dosage regimen for lanadelumab is not weight-based, differences in baseline body weight could potentially be confounding factors in the HELP-03 study. However, greater body weight would likely increase the risk of HAE attacks (both as an independent risk factor and due to a relatively lower concentration of active treatment); therefore, any bias related to body weight is likely to be against the 300 mg lanadelumab every two weeks regimen (which was shown to be the most efficacious regimen in the HELP-03 trial). The clinical experts consulted by CADTH noted the absence of evidence regarding the potential effectiveness of a weight-based dosing regimen for lanadelumab as a research gap.

The study treatments were administered in a double-blind manner, with all groups receiving the same number of injections during the treatment period (i.e., 13 injections of lanadelumab or matching placebo). The active and placebo injections contained the same non-active ingredients and were identical in appearance.[5] Compared with the placebo group (29.3%), the proportion of patients who reported injection-site pain was greater across the lanadelumab groups (42.9%), with the highest rate occurring in the 300 mg every two weeks group (i.e., 51.9%). Injection-site erythema and injection-site bruising were also more commonly reported across the lanadelumab groups (9.5% and 7.1%, respectively) compared with the placebo group (2.4% and 0%, respectively). The clinical experts consulted by CADTH suggested that these differences were unlikely to significantly compromise blinding in the study (i.e., investigators and/or patients were unlikely to have inferred allocation to the active treatment based on the adverse event profile).

The primary outcome of HELP-03 was considered to be appropriate and clinically relevant by the experts consulted by CADTH and regulatory authorities.[21,30,31] The clinical experts noted that the criteria used to define an HAE attack were comprehensive and generalizable to the Canadian setting. There is no commonly accepted threshold for the reduction in HAE attacks that would be considered clinically meaningful; however, the experts consulted by CADTH suggested that reductions in the range of 50% to 70% could be considered meaningful. This aligns with the 60% reduction in HAE attack rate that the hypothesized in the statistical analysis plan for the HELP-03 study.[5,21] As the secondary end points were not independent of the primary end point (i.e., all secondary end points were different types of HAE attacks, all of which would have contributed to the primary end point), Health Canada reviewers noted that the redundancy may inappropriately imply robustness of results from HELP-03.[21] However, they noted that the exploratory end points (e.g., time to first HAE attack and AE-QoL) were distinct from the primary end point and could be supportive of efficacy. The clinical experts consulted by CADTH noted that the secondary end points, most notably HAE attacks requiring acute treatment, are clinically important.

CADTH

Patient disposition in the HELP-03 study was thoroughly documented and well reported. A high proportion of patients in each group completed the double-blind treatment period (range 85.4% to 92.6%).[5] Regulatory authorities noted that there did not appear to be important differences between the treatment groups regarding the rationale for withdrawal from the study.[21] The ITT population included all randomized patients for the placebo, lanadelumab 300 mg every four weeks, and lanadelumab 300 mg every two weeks groups.

Patients in the placebo group had greater usage of on-demand medications for the acute management of HAE attacks. This included the use C1-INH (65.9% in the placebo group versus 13.8% and 22.2% in the 300 mg lanadelumab every four weeks and every two weeks groups, respectively). The clinical experts consulted by CADTH noted that C1-INHs have a longer duration of action than some of the alternative treatments (e.g., icatibant). Therefore, in addition to alleviating symptoms of the acute HAE attack, exposure to these drugs can also provide a protective effect for patients and reduce the risk of further attacks in the period after administration. The expert noted that the protective effects can last three to five days in some patients; therefore, the greater concomitant usage of these drugs in the placebo group could bias the results against lanadelumab (i.e., the rate in the placebo group may have been reduced through the concomitant use of IV C1-INH). In contrast, a trial that was conducted for SC-administered C1-INH in patients with HAE required patients to use icatibant as a first-line treatment (SAHARA).[37]

Regulatory authorities considered the small sample size of the HELP-03 study to be acceptable due to the rarity of HAE.[21,30,31] Statistical power calculations were reported for HELP-03, and a sufficient number of patients were enrolled and completed the study to demonstrate statistical significance for the primary end point. Enrolment exceeded the planned numbers, and the number of withdrawals from the trials was within the 10% proportion assumed in the sponsor's power calculations (i.e., 90.4% of patients completed the study).[30] Events for some of the exploratory end points (e.g., laryngeal attacks and attacks requiring hospitalization) were low in HELP-03, limiting the ability to detect a potential difference between the lanadelumab and placebo groups.

The robustness of the primary efficacy end point was supported by numerous sensitivity analyses, including alternative time points, modelling techniques, and a tipping-point analysis. Statistical analyses for the exploratory end points and subgroup analyses were conducted without adjustment for multiplicity; therefore, the findings should be considered hypothesis-generating because of the risk of type I error. FDA statistical reviewers raised no major objections to any of the approaches used in the analysis of the HELP-03 study.[31] The National Institute for Health and Care Excellence (NICE) in the UK questioned the limited number of covariates that were included in the statistical models, and the sponsor clarified that was due to the small sample size of the study.[38]

Reviewers for Health Canada noted that the AE-QoL questionnaire is a validated instrument for the assessing health-related quality of life in patients living with angioedema.[21] The clinical experts consulted by CADTH noted that the angioedema scale was not specifically designed for patients with HAE and does not have measures that specifically address the impact of gastrointestinal and laryngeal attacks. In their comments on CADTH's draft report, the sponsor noted that AE-QoL is the only validated disease-specific patient-reported outcome tool used in HAE to evaluate quality of life and was the only tool available when the HELP studies were conducted.

HELP-03 was conducted at 41 sites in six countries (i.e., US, Germany, Italy, UK, Canada, and Jordan) and severity of HAE attacks was evaluated by the individual study investigators. Although the study included guidelines for the classification of severity, it is possible that there was variation across regions and/or study sites as to how the criteria were applied in the study, based on differences in clinical judgment.[21] As shown in Table 7, there were differences in the proportion of patients recruited from centres in the US and Europe across some of the treatment groups. Subgroup analyses did not suggest that this had a meaningful impact on the efficacy results for the primary outcome, but similar analyses were not reported for the analyses that included classification of event severity.

The HELP-03 protocol stated that any patient who experienced three or more HAE attacks during the initial four-week run-in period proceeded directly to randomization.[5] As a result, the baseline HAE rate for these patients would not be calculated based on a full four-week assessment (although it is uncertain whether this would over- or underestimate the true frequency in those patients meeting the criteria). Reviewers for the EMA noted that the proportion of patients who exited the run-in phase early was approximately 40% in all of the treatment groups and that any potential bias associated with early completion of the run-in period would be balanced across the treatment groups.[31] [redacted].[21]

External Validity

Reviewers for Health Canada noted that the inclusion criteria for HELP-03 were reasonable, based upon the intended patient population.[21] The diagnostic criteria were similar to the recommendations in the Canadian clinical practice guidelines for HAE[1] and considered to be appropriate by the clinical experts consulted by CADTH. The clinical experts consulted by CADTH and regulatory authorities felt the characteristics of the patient population was generally a good representation of the target population.[21,30,31]

Only patients who demonstrated an HAE attack rate of at least one attack per four weeks during the run-in period were eligible to be randomized in the HELP-03 study. The clinical experts consulted by CADTH indicated that the minimum frequency of attacks for enrolment in HELP-03 (i.e., one attack per four weeks) may be slightly lower than the attack rate at which LTP treatment would typically be initiated in routine practice. The experts indicated that the baseline attack rate in HELP-03 was considerably greater than one per four weeks and is a better reflection of patients who would be good candidates for LTP treatment in Canadian practice. The experts noted that HAE attack rates are not routinely captured by clinicians or patients in Canada outside of a clinical trial setting. Furthermore, it was noted that a patient's HAE attack rate can fluctuate through the year (e.g., owing to exposure to seasonal triggers, hormonal changes, or other factors) and that a four- to eight-week period may not be sufficient to gain insight into the average HAE attack frequency for patients.

The EMA noted that the HELP-03 trial population was enriched with patients who experienced frequent HAE attacks.[31] Patient input provided by HAE Canada for this review emphasized the challenges faced by patients with HAE who have experienced severe attacks, most notably laryngeal attacks, which are life-threatening and can have a lasting emotional impact on patients. The clinical experts consulted by CADTH noted that patients with a history of laryngeal attacks could also be considered good candidates for LTP treatment, even if they experienced a lower overall frequency of HAE attacks.

Enrolment in HELP-03 was limited to patients with a confirmed diagnosis of type I or II HAE; patients with other types of HAE (e.g., HAE with normal C1-INH) were excluded from the study. However, the indication for lanadelumab that was approved by Health Canada and by other regulators (e.g., US FDA, EMA, and the Australia Therapeutic Goods Administration) is not restricted based on HAE type.[39-41] The EMA noted that extrapolation to other forms of HAE is appropriate given the mechanism of action for lanadelumab.[31] The clinical experts consulted by CADTH also noted that there could be interest from patients and clinicians in using lanadelumab for other forms of angioedema, such as HAE with normal C1-INH, acquired angioedema, or non-idiopathic histaminergic angioedema.

The majority of patients in HELP-03 were women, which is reflective of the Canadian HAE population and consistent with other clinical trials conducted in patients with HAE. The clinical experts noted that, in addition to being more common, the symptoms of HAE are often more severe in women; hence, there is often greater enrolment of women in clinical trials, as patients with more severe disease are more likely to actively seek out effective therapies to manage their condition. The mean age of participants in HELP-03 was approximately 40 years of age, which the clinical experts felt is an accurate reflection of the overall Canadian HAE population. There were few patients over the age of 65 years in the study, which was noted as a research gap by the clinical experts consulted by CADTH and is documented in the product monograph for lanadelumab.[4] The majority of patients in the HELP-03 study were also overweight or obese; the clinical experts consulted by CADTH noted that this is reflective of the HAE patient population in Canada. The vast majority of patients in HELP-03 had type I HAE (90.4% overall), and the limited data for type II HAE was initially noted as a potential concern from Health Canada.[21] However, the clinical experts consulted by CADTH indicated that the efficacy and safety is unlikely to be different across type I and II patients.

Compliance was high in HELP-03, with approximately 99% of patients receiving the planned doses.[5] The clinical experts consulted by CADTH indicated that patients in routine practice are generally compliant with their prescribed dosage schedules. In the HELP-03 trial, the study treatments were administered by the investigators or designated on-site personnel who were participating in the study. This is not reflective of routine care in Canada, in which patients and/or caregivers would likely administer the treatment at home following instructions from a physician or other health care professional.[4] However, patients in the HELP-04 extension study were permitted to self-administer lanadelumab, and regulators noted that the efficacy results were similar to those observed in patients who did not self-administer the treatment.[31] The recommended dose of lanadelumab is 300 mg every two weeks; however, the product monograph states that a dosing interval of 300 mg every four weeks may be considered if the patient's HAE is well-controlled (e.g., attack free) for more than six months. The HELP-03 study included three lanadelumab dosage groups (150 mg every four weeks, 300 mg every four weeks, and 300 mg every two weeks). Of these, CADTH's review focused exclusively on the two 300 mg dosage groups, to align with the dosage regimens described in the product monograph. However, neither the HELP-03 or HELP-04 extension studies examined the efficacy of transitioning patients from every two weeks to every four weeks dosage regimens.[5,9]

The HELP-03 study was placebo-controlled, with no active comparator groups included in the trial. Health Canada noted that blinding would not be practical in a head-to-head comparison of lanadelumab and the C1-INH approved for use as LTP treatment in Canada (i.e., Cinryze), due to differences in the route of administration (SC versus IV) and the frequency of administration (every two weeks versus two to three times per week).[21] Limited evidence regarding the comparative efficacy and safety of lanadelumab versus C1-INH has been submitted by sponsor in the form of an indirect treatment comparison (ITC), as described in the Indirect Evidence section of this report.

The use of criteria to confirm HAE attacks by a selected group of study investigators is not reflective of routine care, in which there would be greater diversity in reporting of events patients and physicians. However, Health Canada noted that there was a high correlation between patient-reported and investigator-confirmed HAE attacks in HELP-03 (e.g., 99.3% for the placebo group and 98.3% for lanadelumab groups).[21] Reviewers for the FDA similarly concluded that there is no concern that the rate of investigator-confirmed HAE attacks differed from the actual HAE attack rate in HELP-03.[30] The clinical experts consulted by CADTH also indicated that the correlation would be similar in routine practice.

The severity of HAE attacks in HELP-03 was graded by the study investigators as mild, moderate, or severe (as described in the Outcomes section). The clinical experts consulted by CADTH noted that the criteria were appropriate for the objectives of the HELP-03 trial, but were not necessarily reflective of Canadian practice, in which standardized grading of HAE attack severity would not routinely occur. The experts considered the need for acute treatment and/or a hospital visit to manage the attack to be more relevant measures of HAE attack severity. There were few visits to the emergency department or hospital during the HELP-03 trial. The clinical experts consulted by CADTH noted that, in addition to the severity of the event, the decision to seek treatment at a hospital tends vary across patients and can depend on a number of factors, including ability to self-administer an acute treatment (e.g., difficulty finding or accessing a vein for IV therapy), proximity to the hospital, and individual patient preferences. Overall, the clinical experts suggested that the rate of patients seeking treatment at a hospital would likely be greater in Canadian practice than in the HELP-03 trial.

HAE typically presents during childhood or adolescence, and the HELP-03 trial included a subset of patients (n = 10) who were between the ages of 12 and 18 years of age. Of these 10 patients, only two received 300 mg lanadelumab every two weeks, as recommended in the product monograph. Reviewers for Health Canada noted the importance of including adolescent patients in the trial and acknowledged that the small number of these patients in the study is understandable, given the rarity of HAE. As shown in Figure 3, there is considerable uncertainty in the subgroup analyses for patients less than 18 years of age; however, Health Canada noted that the point estimates favour lanadelumab compared with placebo despite the small sample size.[21] This is reflected in the Canadian product monograph for lanadelumab, which states that the safety and efficacy of lanadelumab was evaluated in a total of 23 patients under the age of 18 and that the results of the subgroup analysis by age were consistent with overall study results.[4] Furthermore, reviewers for Health Canada noted that confirmatory trials conducted with a larger pediatric population would likely be impractical, given that HAE is a rare disease.[21]

Patients enrolled in HELP-03 received extensive contact with health care professionals throughout the study (i.e., 14 clinic visits over six months).[5] The clinical experts consulted by CADTH noted that patients are typically seen once every three to six months in Canada;

those whose HAE is very well-controlled are often only seen once per year. A small subset of patients frequently visit the emergency department for the management of HAE attacks.

Indirect Evidence

Background

Given the lack of head-to-head studies comparing lanadelumab with active prophylactic treatments for HAE, the sponsor conducted a systematic review of the literature followed by an ITC.[12,13] In addition, CADTH conducted a literature search to identify published ITCs that included the patients, interventions, and outcomes identified in the protocol for CADTH's review of lanadelumab. However, no published ITCs were identified. Therefore, this section presents the summary of methods and results as well as critical appraisal of the sponsor-submitted ITC.

Description of the Indirect Treatment Comparison Submitted by the Sponsor

Objectives

The objective of the sponsor-submitted ITC was to compare attack rate and time to first attack for lanadelumab with relevant comparative treatments for HAE type I and type II.[12] The purpose of the ITC was to inform the sponsor's pharmacoeconomic model.

Methods of Indirect Treatment Comparison

Systematic Review Methods

The study selection criteria and methods used in the sponsor-submitted ITC are summarized in Table 34. [redacted].

[redacted]

Table 34: Study Selection Criteria and Methods for the Indirect Treatment Comparison

Population	[redacted]
Intervention	[redacted]
Comparator	[redacted]
Outcome	[redacted]
Study design	[redacted]
Other criteria	[redacted]
Exclusion criteria	[redacted]
Databases searched	[redacted]
Selection process	[redacted]

Data extraction process	[redacted]
Quality assessment	[redacted]

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial.

Source: Sponsor-submitted ITC.[12]

Inclusion Criteria

The inclusion and exclusion criteria for the sponsor-submitted systematic review are summarized in Table 34. The systematic review included [redacted]. The treatments included [redacted].

Outcomes

The search [redacted] (Table 34). However, for ITC, the following outcomes were of interest: (a) attack rate: the number of attacks per 28-day cycle; and (b) time to first attack after day 0, [redacted] and day 70 of treatment.

Indirect Treatment Comparison Analysis Methods

A Bayesian network meta-analysis (NMA) was conducted for the attack rate and time to attack outcomes. For the attack rate outcome, the relative treatment effects were estimated as rate ratios, that is, the rate of attacks per 28-day cycle while on Treatment A divided by the rate of attacks per 28-day cycle on Treatment B. For the time to first attack outcome, the relative treatment effects were estimated as hazard ratios (HRs) comparing time to first attack while on Treatment A relative to Treatment B. Point estimates and 95% credible intervals (CrIs) were estimated for each treatment comparison. For all NMAs, the 95% CrI that excluded the null value was interpreted as statistically significant.

Both fixed- and random-effects models were fitted. Fixed-effects models assume that there is one true effect size that is shared by all of the included studies. Random-effects models allow treatment effects to vary between studies (that is, accounting for between-study heterogeneity). Vague priors were used for the between-trial standard deviation (SD) parameter, to allow the results to be determined by the observed data.

For attack rate, the NMA used log rate ratio and SE of the log rate ratio of each treatment versus placebo were derived using the identified studies. Using these data, one fixed-effects and three random-effects models were run with different vague priors to assess the sensitivity of the results to the choice of prior. The three priors considered were Uniform (0, 5), Uniform (0, 3), and Half-Normal (0, 2).

For time to first attack analysis, the Bayesian NMA followed the method described by Woods (2010)[44] to allow the use of both HRs and count data in a single analysis to estimate the relative effects of treatment on time to first attack after day 0, day 14, and day 70. For those studies that do not report time to first attack directly, the proportion of attack-free patients was used to calculate the proportion of patients experiencing at least one attack.

The cumulative probability of an event (attack) was then used to derive the log cumulative hazard for each treatment in the study. The log cumulative hazard estimates were then included in a treatment effect model with a linear regression structure. This model estimated a relative treatment effect for each treatment (assuming proportional hazards), which is equal to the log HR. The log HR and the corresponding SE are required as inputs to the NMA. Using these data, one fixed-effects and three random-effects models were run with different vague priors to assess the sensitivity of the results to the choice of prior. The three priors considered were Uniform (0, 5), Uniform (0, 3), and Half-Normal (0, 2).

The analysis was conducted with 100,000 iteration initial 'burn-in.' Once convergence was achieved, further 100,000 (for attack rate) and 200,000 (for time to first attack) iterations were conducted for parameter estimation. Convergence was confirmed through the use of three-chain Brooks–Gelman–Rubin plots and inspection of posterior density plots. Autocorrelation was assessed using autocorrelation plots to determine whether samples within each chain were highly correlated.

Table 35: Indirect Treatment Comparison Analysis Methods

	Description
ITC methods	A Bayesian NMA was developed for the attack rate and time to first attack (after day 0, [redacted] and day 70) using data from two studies: • HELP-03 trial comparing lanadelumab and placebo • CHANGE trial comparing C1-INH IV and placebo. Both fixed- and random-effects models were fitted. For the attack rate outcome, the relative treatment effects were estimated as rate ratios (with 95% CrI). For the time to first attack outcome, the relative treatment effects were estimated as hazard ratios (with 95% CrI). For attack rate, log rate ratio and standard error of the log rate ratio of each treatment versus placebo were derived using the two trials. For time to first attack analysis, log hazard ratios were derived using the two trials based on the method described by Woods (2010)[44] to allow the use of both hazard ratios and count data in a single analysis.
Priors	Three random-effects models were run with different vague priors: • Uniform (0,5) • Uniform (0,3) • Half-Normal (0,2)
Assessment of model fit	DIC was not reported. AIC and BIC were used to assess model fit for parametric survival analysis used to derive log hazard ratios, which were used as input parameters in the NMA.
Assessment of consistency	NMA results were consistent with trial results versus placebo. However, no direct head-to-head comparison was available for the two active treatments.
Assessment of convergence	Using the Brooks–Gelman–Rubin statistic and plots of posterior density
Outcomes	Attack rate ratio and hazard ratios for time to first event after day 0, [redacted] and 70 of treatment
Follow-up time points	HELP-03 trial: 26 weeks CHANGE trial: 12 weeks
Sensitivity analyses	Based on choice of priors for the between-trial standard deviation used in the random-effects models
Subgroup analysis	Not conducted

	Description
Methods for pairwise meta-analysis	Not applicable

AIC = Akaike information criterion; BIC = Bayesian information criterion; C1-INH = C1 esterase inhibitor; CrI = credible interval; DIC = deviance information criterion; IV = intravenous; NMA = network meta-analysis.

Source: Sponsor-submitted ITC.[12]

Results

Evidence Network

Data from [redacted]. The review identified [redacted]. Of these, [redacted] compared Cinryze with placebo [redacted] (the [redacted] and the CHANGE study).[15] In the CHANGE study, Cinryze was administered IV [redacted]

[redacted] was compared using two concentrations ([redacted]) against placebo in the [redacted] In addition, the [redacted] trial compared [redacted]

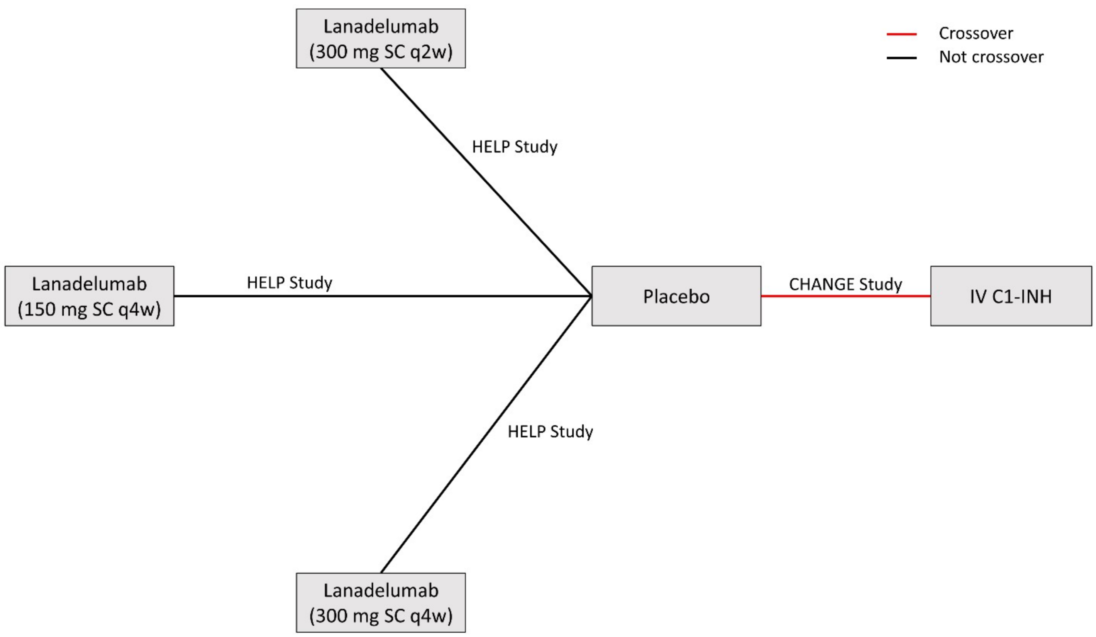
Lanadelumab was assessed in a phase II study,[47] which included 30, 100, 300, and 400 mg doses, and also in the phase III HELP-03 trial, which included 150 mg every four weeks, 300 mg every four weeks, and 300 mg every two weeks dosages.[7] The HELP-03 study was included in the final evidence network. In accordance with protocol for this review, CADTH has reported only the results for the dosages recommended in the Canadian product monograph (i.e., 300 mg every four weeks and 300 mg every two weeks). [redacted]

For the final evidence network, [redacted] were excluded for the following reasons:

- the [redacted] was excluded based on [redacted];
- the [redacted] was excluded based on [redacted];
- [redacted] was excluded because it [redacted];
- [redacted] was excluded because [redacted].
- reason for excluding [redacted].

For the final evidence network, the following two studies were included: the HELP-03 study[7] comparing lanadelumab with placebo and the CHANGE study[15] comparing Cinryze with placebo (Figure 5). The CHANGE study was a crossover study;[15] however, [redacted].

Figure 5: Evidence Network Diagram for the Indirect Treatment Comparison



C1-INH = C1-esterase inhibitor; IV = intravenous; q2w = every 2 weeks; q4w = every 4 weeks; SC = subcutaneous.

Source: Sponsor-submitted ITC.[12]

Summary of Included Studies

Table 36 presents a summary of study characteristics of the two included studies. The HELP-03 study was a phase III, four-arm, 26-week, parallel-group study conducted by the sponsor (N = 125). The characteristics of the HELP-03 study are summarized in detail in the Systematic Review section of this report. The CHANGE study was a phase III, double-blind, crossover trial with two 12-week treatment periods.

Table 36: Study Characteristics of the Trials Included in the Indirect Treatment Comparison

		HELP-03	CHANGE
Study design		Phase III, multi-centre, double-blind, placebo-controlled, parallel RCT	Phase III, multi-centre, double-blind, placebo-controlled, crossover RCT
Locations		US; Germany; Italy; UK; Canada; Jordan	US
Randomized (N)		125 (3:2:2:2) • LANA 150 mg q.4.w. (28) • LANA 300 mg q.4.w. (29) • LANA 300 mg q.2.w. (27) • Placebo (41)	24 (1:1) • Cinryze/Placebo (12) • Placebo/Cinryze (12)
Interventions		• LANA 150 mg q.4.w. • LANA 300 mg q.4.w. • LANA 300 mg q.2.w. • Placebo	• Cinryze 1,000 IU IV twice per week • Placebo
Phases	LTP washout	2 weeks	Not applicable
	Run-in	4 to 8 weeks	Not applicable
	Double-blind	26 weeks	12 weeks
Minimal attack frequency		≥ 1 HAE attacks per month	≥ 2 HAE attacks per month

HAE = hereditary angioedema; IV = intravenous; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; RCT = randomized controlled trial.

Sources: Clinical Study Report for HELP-03[5] and sponsor-submitted ITC.[12]

Table 37 presents baseline patient characteristics of the two included studies. The mean age of patients was similar in the HELP-03 and CHANGE trials. The proportion of female patients was greater in the CHANGE trial than in the HELP-03 trial. The baseline attack frequency ranged from 3.2 to 4.0 attacks per four weeks in the HELP-03 study, but the baseline attack rate was not reported in the publications for the CHANGE study.

Table 37: Patient Characteristics from the Trials Included in the Indirect Treatment Comparison

Trial Name	Treatment Group	Age in Years, (Mean [SD])	Female, n (%)	Baseline Attack Frequency (Mean [SD])
HELP-03	LANA 300 mg q.2.w.	40.3 (13.35)	15 (55.6)	3.5 (2.3) per 4 weeks
	LANA 300 mg q.4.w.	39.5 (12.85)	19 (65.5)	3.7 (2.5) per 4 weeks
	Placebo	40.1 (16.75)	34 (82.9)	4.0 (3.3) per 4 weeks
CHANGE	C1-INH IV (1,000 IU), then placebo	41.7 (19.3)	9 (81.8)	Not reported
	Placebo, then C1-INH IV (1,000 IU)	34.5 (14.8)	11 (100)	Not reported

C1-INH = C1 esterase inhibitor; IV = intravenous; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

Source: Sponsor-submitted ITC.[12]

Attack Rates

Results for both the fixed-effects and random-effects models were reported; the ITC authors argue that the fixed-effects model is the most appropriate approach to use because there does not appear to be any systematic difference between the populations in each trial, and that it is difficult to estimate the uncertainty using a random-effects model due to the small sample size.

Table 38 presents results of indirect comparison of attack rate ratios for lanadelumab and C1-INH IV (1,000 IU) versus placebo, based on the two studies identified in the systematic review (HELP-03 and CHANGE). The rate ratio for lanadelumab 300 mg every two weeks versus placebo was [redacted]. This translated to a point estimate of [redacted] reduction in attack rate compared with placebo. For other dosages of lanadelumab (i.e., 300 mg every four weeks and 150 mg every four weeks), the attack rate ratio was [redacted]). For C1-INH IV (1,000 IU), the fixed-effects analysis found an attack rate ratio of [redacted], implying a rate reduction of [redacted] compared with placebo. The random-effects results were almost unchanged in terms of point estimates but had very large credible intervals.

Table 38: Indirect Evidence for Attack Rate for Active Treatments Versus Placebo

Model	LANA 300 mg q.2.w. (N = 27)	LANA 300 mg q.4.w. (N = 29)	C1-INH IV 1,000 IU (N = 22)
Attack rate ratio (95% CrI) Versus Placebo			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

C1-INH = C1 esterase inhibitor; CrI = credible interval; IV = intravenous; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Sponsor-submitted ITC.[12]

Table 39 presents indirect evidence comparing active treatments against each other. The results show that lanadelumab 300 mg every two weeks has an attack rate ratio of [redacted] compared with lanadelumab 300 mg every four weeks ([redacted]), lanadelumab 150 mg every four weeks ([redacted]) and C1-INH IV (1,000 IU) ([redacted]), with the smallest point estimate against C1-INH IV. For all other pairwise comparisons based on ITC, the rate ratio for lanadelumab was [redacted] when compared against C1-INH IV and the 95% CrI [redacted]. This shows that, compared with C1-INH IV (1,000 IU), lanadelumab was [redacted].

Table 39: Indirect Comparison of Active Treatments for Attack Rate

	LANA 300 mg q.2.w. (N = 27)	LANA 300 mg q.4.w. (N = 29)	C1-INH IV 1,000 IU (N = 22)
Attack Rate Ratio (95% CrI): Fixed-Effects Results			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Attack Rate Ratio (95% CrI): Random Effects: (0,5) Prior			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Attack Rate Ratio (95% CrI): Random Effects: (0,3) Prior			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Attack Rate Ratio (95% CrI): Random Effects: (0,2) Prior			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]

C1-INH = C1 esterase inhibitor; CrI = credible interval; IV = intravenous; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Sponsor-submitted ITC.[12]

Time to First Attack

Table 40 presents results of the ITC for time to first attack for lanadelumab compared with placebo, based on the two studies identified in the systematic review (HELP-03 and CHANGE). The HR for lanadelumab 300 mg every two weeks versus placebo (based on fixed-effects analysis) after day 0 of treatment was [redacted] This translated to a point estimate of [redacted] compared with placebo. For other doses of lanadelumab (i.e., 300 mg every four weeks and 150 mg every four weeks), the HRs [redacted]. For C1-INH IV (1,000 IU), the fixed-effects analysis found an HR of [redacted] after day 0 of treatment, implying a [redacted] in the instantaneous risk of HAE attack compared with placebo (although the CrI [redacted]). The random-effects results were almost unchanged in terms of point estimates but had large CrIs.

The HRs for time to first attack after [redacted] and day 70 of treatment were similar to the HRs after day 0 of treatment, except that the magnitudes of HR for all lanadelumab regimen (compared with placebo) were [redacted] (compared with day 0 of treatment) and [redacted] after day 70 of treatment (Table 40). HRs against C1-INH IV (1,000 IU) remained similar to the HR after day 0 of treatment. These results suggest that, with varying degree of uncertainty, both lanadelumab and C1-INH IV (1,000 IU) were associated with [redacted] compared with placebo; the magnitude of the HR was [redacted].

Table 40: Indirect Evidence for Time to First Attack for Active Treatments Versus Placebo

Model	LANA 300 mg q.2.w. (N = 27)	LANA 300 mg q.4.w. (N = 29)	C1-INH IV 1,000 IU (N = 22)
Time to First Attack After Day 0: Hazard Ratio (95% CrI)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Time to First Attack After [redacted]: Hazard Ratio (95% CrI)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Time to First Attack After Day 70: Hazard Ratio (95% CrI)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

C1-INH = C1 esterase inhibitor; CrI = credible interval; ITC = indirect treatment comparison; IV = intravenous; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Sponsor-submitted ITC.[12]

Table 41 presents indirect evidence comparing active treatments against each other. The results show that, after day 0 of treatment, lanadelumab 300 mg every two weeks has [redacted] compared with lanadelumab 300 mg every four weeks ([redacted]), lanadelumab 150 mg every four weeks ([redacted]), and C1-INH IV (1,000 IU) ([redacted]), with the [redacted] against C1-INH IV; however, [redacted]. Also, HRs for lanadelumab 300 mg every four weeks and 150 mg every four weeks were [redacted] (Table 41).

The HRs for ITC pairwise comparisons after [redacted] and day 70 of treatment were similar in direction to the HRs after day 0 of treatment, except [redacted] (Table 41). In all, except one case (i.e., [redacted]), the HRs [redacted].

Table 41: Indirect Comparison of Active Treatments for Time to First Attack

Fixed-effects results			
	LANA 300 mg q.2.w.	LANA 300 mg q.4.w.	C1-INH IV 1,000 IU
Time to First Attack After Day 0: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After [redacted]: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After Day 70: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Random-effects results: (0,5) prior			
	LANA 300 mg q.2.w.	LANA 300 mg q.4.w.	C1-INH IV 1,000 IU
Time to First Attack After Day 0: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After [redacted]: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After Day 70: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Random-effects results: (0,3) prior			
	LANA 300 mg q.2.w.	LANA 300 mg q.4.w.	C1-INH IV 1,000 IU
Time to First Attack After Day 0: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After [redacted]: Hazard Ratio (95% CrI)			

Random-effects results: (0,3) prior (cont'd)			
	LANA 300 mg q.2.w.	LANA 300 mg q.4.w.	C1-INH IV 1,000 IU
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After Day 70: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Random-effects results: (0,2) prior			
	LANA 300 mg q.2.w.	LANA 300 mg q.4.w.	C1-INH IV 1,000 IU
Time to First Attack After Day 0: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After [redacted]: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]
Time to First Attack After Day 70: Hazard Ratio (95% CrI)			
[redacted]	–	[redacted]	[redacted]
[redacted]	[redacted]	–	[redacted]

C1-INH = C1 esterase inhibitor; CrI = credible interval; IV = intravenous; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Sponsor-submitted ITC.[12]

Critical Appraisal

Systematic Review Methods

The sponsor-submitted ITC used a standard approach for performing and reporting the systematic reviews and indirect comparisons. Inclusion criteria for patients, interventions, comparators, and outcomes (PICO) were well reported and were generally similar to the PICO criteria of interest to this CADTH review. The sponsor conducted a rigorous and comprehensive search of the available literature using several databases and trial registries, and the data sources and search strategy were clearly described. Screening was conducted independently by two reviewers; data extraction was performed by one reviewer and independently checked by a second reviewer. Quality assessment was also performed by two independent reviewers. The NICE submission template was used to assess quality of RCTs, and no trials were excluded based on the assessment. Small study effects and publication bias were not assessed.

Reporting of the Indirect Treatment Comparison

Study-level information, including key trial and patient characteristics, were provided for both of the studies that were included in the ITC (i.e., HELP-03 and CHANGE). Direct pairwise meta-analyses were not feasible using the evidence network; however, the estimates from both the individual studies were reported for comparison with the ITC estimates. Results from both random- and fixed-effects analyses were reported by the sponsor. The ITC did not report the deviance information criterion to justify the choice of model.

Indirect Treatment Comparison Methodology

The ITC included the two end points that were relevant for the pharmacoeconomic analysis (i.e., attack rate and time to attack). No safety outcomes were included in the ITC (although they are discussed in the systematic review). Statistical heterogeneity could not be formally assessed in the ITC, as the evidence network was limited to only the HELP-03 and CHANGE studies. Due to sparsity of the network, the ITC results showed highly uncertain estimates of effect with the random-effects model (i.e., wide credible intervals). However, the fixed-effects models were preferred by the sponsor based on the argument that the included trials were comparable (in terms of patient characteristics and the outcomes measured). As described below, CADTH identified a number of potentially important differences between the HELP-03 and CHANGE trials; therefore, the argument for preferring the fixed-effects over the random-effects model because there were no systematic differences in study populations may not be appropriate.

Two potentially relevant [redacted] studies ([redacted]) were excluded from the ITC evidence network. The [redacted] study was a [redacted] that compared [redacted]. It found that the number of attack rates per month were [redacted] compared with placebo. Similarly, the [redacted] trial was [redacted] that compared [redacted]. It found that the attack rate was [redacted] and was statistically significant. Both studies are larger than the CHANGE study. The [redacted] study was excluded by the sponsor based [redacted]. The [redacted] study was excluded based on [redacted]. However, the clinical experts consulted by CADTH confirmed that C1-INH SC is being currently used in Canada and is a relevant comparator and suggested that these studies could provide useful information. Hence, the exclusion of the [redacted] and [redacted] studies leaves a gap in the comparative efficacy evidence for lanadelumab.

CADTH identified the following additional issues with the methodology of the sponsor's ITC:

- Time to first attack was not reported in all studies; also, the SE for log of attack rate ratio was not reported in the CHANGE trial, and the SE for HR of placebo was not available for the HELP-03 trial. In these cases, the required parameters were calculated post hoc using formulas and used as input in the ITC. The validity of these estimates and their impact on the ITC results is unknown and may have introduced bias into the analysis.
- It is unclear whether pooling of HRs is appropriate when the treatment durations in the two studies are substantially different (i.e., 12 weeks in the CHANGE study and 26 weeks in the HELP-03 study).
- The sponsor did not include any sensitivity or subgroup analyses in the ITC.

Study Characteristics

As shown in Table 42, CADTH identified differences in the design and characteristics of the HELP-03 and CHANGE trials that may limit the comparability of the two studies, particularly with respect to conducting meta-analysis. These included differences in the study design (HELP-03 was a parallel RCT and CHANGE was a crossover RCT); treatment duration (26 weeks in HELP-03 and 12 weeks in CHANGE); time of recruitment (enrolment began in 2016 in HELP-03 and 2005 for CHANGE); sample size (N = 125 for HELP-03; N = 22 for

CHANGE); pre-treatment trial phases (HELP-03 included washout and run-in periods and CHANGE did not); and methodology used to determine baseline attack frequency during screening (a formal run-in period was used in HELP-03 and historical data were used in CHANGE).

The quality of studies in the ITC was assessed using the [redacted] The assessment was performed by the sponsor and further indicated that there may be important differences between the HELP-03 and CHANGE trials. No studies were excluded based on the findings of the risk of bias assessment.

Study Populations

It is challenging to conduct a full assessment and comparison of the patient characteristics across the two trials, due to the limited data available for the patient characteristics of those enrolled in the CHANGE study. Specifically, it was not possible to compare the baseline HAE attack frequencies between the two trials, as this information was not reported in the publications for the CHANGE trial. There were differences in the eligibility criteria with respect to the minimum baseline attack frequency (i.e., one attack or more per month versus two attacks or more per month in HELP-03 and CHANGE, respectively). In addition, there were differences in the mean rate of attacks in the placebo groups of the two trials (approximately two attacks per month in HELP-03 and approximately four attacks per month in CHANGE).

There were also differences between the HELP-03 and CHANGE trials with respect to the prior and concomitant exposure to LTP treatment. The study inclusion criteria in the HELP-03 trial stated that patients using C1-INH as LTP treatment could be eligible for enrolment, provided they completed a two- to three-week washout period for all existing LTP treatment before entering the four- to eight-week run-in period. Prior exposure to LTP treatment was well reported in the HELP-03 study (including both C1-INH and oral treatments), whereas prior exposure to C1-INH as LTP treatment was not reported in the publications for the CHANGE trial. However, patients must not have received any blood products within 90 days of screening to be considerable eligible. In addition, since the CHANGE trial was conducted exclusively in the US and pre-dated the approval and marketing of both blood-derived and recombinant C1-INH in that country (i.e., they were only marketed in Europe in 2005), it is likely that the included patients had no prior exposure to C1-INH as LTP treatment. In contrast, the majority of patients in the HELP-03 trial had prior exposure to LTP treatment with C1-INH. The studies also differed with respect to the use of concomitant LTP treatment during the study. The CHANGE trial pre-dated the HELP-03 study by approximately 10 years, and clinical practice may have evolved over that time period such that the care delivered to patients within the studies and before enrolment in the studies may have been different. Existing LTP therapies had to be discontinued in the HELP-03 trial, whereas patients in the CHANGE trial could be receiving treatment with androgens or antifibrinolytic drugs during the study period.

In both the HELP-03 and CHANGE trials, the study treatments were administered in accordance with recommendations in the Canadian product monographs (as they were pivotal trials). Lanadelumab was administered subcutaneously at doses of 300 mg every four weeks and every two weeks in HELP-03, and C1-INH was administered IV at a dose of 1,000 IU twice per week in the CHANGE trial. The trials differed with respect to the protocols for rescue medication. In HELP-03, treatments for acute attacks were provided in accordance with the routine practice for the individual study investigators. In CHANGE, patients were provided with open-label IV C1-INH for the treatment of acute attacks. The most obvious difference between the two trials is the use of icatibant, which was commonly used in HELP-03, but was not approved or marketed at the time the CHANGE trial was conducted.

Table 42: Appraisal of Heterogeneity in the HELP-03 and CHANGE Trials

Characteristics	CADTH Appraisal of Heterogeneity
Study Characteristics	
Study design	Both the HELP-03 and CHANGE studies were double-blind, placebo-controlled studies; however, there were differences in the study design. HELP-03 was a 26-week, parallel-group study, and CHANGE was a crossover trial with two 12-week periods.
Study setting	Both the HELP-03 and CHANGE studies were multi-centre trials, but there were differences in the locations. HELP-03 was conducted at sites in the US, Canada, Germany, Italy, Jordan, Puerto Rico, and the UK. CHANGE was conducted only at sites in the US. In addition, the trials were conducted at different points in time. Specifically, the CHANGE trial began enrolling patients in 2005 and was completed 2007; the HELP-03 trial began enrolling patients in 2016 and was completed in 2017. As the CHANGE trial pre-dated the HELP-03 study by approximately 10 years, clinical practice may have evolved over that time period, and the care delivered to patients within the study and before enrolment in the study may have been different.
Treatment duration	There were differences in the treatment duration across the two trials. In HELP-03, patients randomized to the lanadelumab groups received 26 weeks of exposure to the active treatment, which is more than twice the duration of the 12-week exposure in the CHANGE trial.
Sample size	There were differences in the overall sample sizes of the two trials (N = 125 for HELP-03; N = 22 for CHANGE) as well as the ratio of patients randomized to the placebo and active treatment groups (3:2:2:2 in HELP-03 and 1:1 in CHANGE).
Run-in period	There were differences in the study designs with respect to the use of a run-in period. All patients in HELP-03 underwent a run-in period to establish their baseline HAE attack frequency and select those who met the minimum frequency for entry into the trial. In contrast, there was no run-in period in the CHANGE trial.
Dosage of comparators	In the included trials, for both lanadelumab and placebo, the study treatments were administered in accordance with recommendations in the Canadian product monographs. Lanadelumab was administered subcutaneously at dosages of 300 mg q.4.w. and q.2.w. in HELP-03. C1-INH was administered IV at a dosage of 1,000 IU twice per week in the CHANGE trial.
Definitions and timing of end point evaluation	The primary end points were similar in the HELP-03 and CHANGE trials, but there were differences in measurement and evaluation. In HELP-03, HAE attacks had to be confirmed by the study investigators; the attack frequency was expressed per 28 days; the rate was determined over the 26-week study period; the placebo and LANA groups were evaluated in parallel. In CHANGE, HAE attacks were based on patient reporting in a diary, and the attack frequency was expressed per 12 weeks and determined over a 12-week treatment period; patients served as their own controls for calculating the difference between C1-INH and placebo.
Rescue medication protocol	There were differences in the protocols for rescue medication. In HELP-03, treatments for acute attacks were provided in accordance with routine practice for the study investigators (e.g., icatibant was used in addition to C1-INH). In CHANGE, patients were provided with open-label IV C1-INH for the treatment of acute attacks (e.g., the trial pre-dated the approval and marketed of icatibant).
Patient Characteristics	
Disease severity	It was not possible to compare the baseline attack frequencies between the two trials, as this information was not reported in the publications for the CHANGE trial. However, there were differences in the eligibility criteria with respect to the minimum baseline attack frequency. In the HELP-03 trial, the minimum attack frequency was ≥ 1 attack per month based on a formal run-in period. In contrast, the minimum attack frequency in the CHANGE trial was ≥ 2 per month and was determined based on the patients' historical data. The proportion of patients with a history of laryngeal attacks was slightly lower in the CHANGE trial (58.3%) than in the HELP-03 trial (64.8%).

Characteristics	CADTH Appraisal of Heterogeneity
Prior LTP treatment usage	There were differences in the study inclusion criteria regarding prior exposure to LTP. In the HELP-03 trial, patients using C1-INH as LTP treatment could be eligible for enrolment provided they completed a 2- to 3-week washout period for all existing LTP before the run-in period. Prior exposure to C1-INH as LTP treatment was not reported in the publications for the CHANGE trial; however, patients could have not received any blood products within 90 days of screening to be considerable eligible. Since the CHANGE trial pre-dated the approval of recombinant C1-INH, it is possible that this criterion would have excluded patients with current or prior exposure to C1-INH as LTP treatment.
Concomitant LTP treatment usage	There were differences in the study protocols for concomitant LTP treatment usage between the two trials. Patients in the CHANGE trial could be receiving treatment with androgens or antifibrinolytic drugs up to and during the study period. In contrast, existing LTP therapies had to be discontinued in adult patients in a 2- to 3-week washout period before entry into the run-in period of HELP-03.
Placebo attack rates	There were differences in the rate of attacks in the placebo groups of the 2 trials. The LS mean (SD) normalized attack frequency during the HELP-03 treatment period was 1.967 (0.182) per 4 weeks. The normalized attack frequency was 12.73 per 12 weeks in CHANGE (e.g., approximately 4.2 attacks per 4-week period).

C1-INH = C1 esterase inhibitor; IV = intravenous; LANA = lanadelumab; LS = least squares; LTP = long-term prophylactic; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

Summary

The sponsor submitted one ITC, which included the patient populations, treatments, and efficacy outcomes of interest to this CADTH review; no other relevant ITCs were identified. The evidence network was sparse and included only two studies (HELP-03 and CHANGE). The sponsor's analysis was conducted using Bayesian methods and compared lanadelumab (300 mg every four weeks and every two weeks), C1-INH (IV 1,000 IU twice per week), and placebo. The ITC focused on two outcomes that informed the pharmacoeconomic model (i.e., attack rate and time to first HAE attack). Results from the fixed-effect analysis showed that lanadelumab 300 mg every four weeks and every two weeks was associated with lower HAE attack rate ratios and lower HRs for time to first attack compared with C1-INH IV (1,000 IU twice per week); however, there was considerable uncertainty in the random-effects analyses due to the sparse evidence network and small sample sizes in the included trials.

CADTH identified a number of potentially important differences in the study and patient characteristics of the HELP-03 and CHANGE trials that may limit the comparability of the two studies. These differences include key factors, such as the HAE attack rate in the placebo group, concomitant usage of LTP and acute treatments, duration of treatment, and the minimal HAE attack frequency for enrolment. Overall, there remains considerable uncertainty regarding the comparative efficacy of lanadelumab versus IV C1-INH for LTP treatment. In addition, the ITC excluded two studies (COMPACT and SAHARA) that compared C1-INH SC with placebo. As C1-INH SC is a comparator of interest for CADTH's review (due to current usage in clinical practice), the exclusion of these studies introduces a gap in the evidence for the comparative efficacy of lanadelumab.

Other Relevant Studies

Long-Term Extension Study

Description of HELP-04 Study

HELP-04 was a phase III open-label extension study that was designed to evaluate the long-term safety and efficacy of lanadelumab as prophylactic therapy for HAE attacks in patients with type I or II HAE. The HELP-04 study was ongoing at the time the submission for lanadelumab was filed with CADTH, and data were available for the second interim report (data cut-off was August 31, 2018; estimated completion date is November 4, 2019).[5,11] As shown in Figure 6, the HELP-04 study consisted of different phases depending on whether patients had previously completed the HELP-03 study (i.e., rollover versus non-rollover patients) and whether the non-rollover patients were using LTP treatment at the time of enrolment.

Figure 6: Schematic Showing Design of HELP-04 (DX-2930-04)

<table>
<tr><td colspan="2"></td><td colspan="5">Treatment Period
[924 Days – Day 0 to Day 910 (last dose)] - (Dosing Will Not Exceed 66 Doses)</td><td>Follow-up Period
4 Weeks – Day 924 to Day 952</td></tr>
<tr><td colspan="2" rowspan="2">Rollover Population</td><td rowspan="2">1st Study Dose
Given on DX-2930-04 Day 0 (300 mg)
(Day 0=Last day of DX-2930-03, Day 182; 2 weeks after most recent dose on DX-2930-03)</td><td rowspan="2">Dose-and-Wait Stage
(No lanadelumab dosing)
Until Subject Has 1st HAE Attack – To Evaluate the Outer Bounds of Dosing Frequency</td><td colspan="2">At 1st Attack</td><td rowspan="2">After 2nd Dose
Regular Dosing Stage
(300 mg q2wks)</td><td rowspan="2">Follow-up Period</td></tr>
<tr><td>Rescue Medication is Allowed per Decision of the Investigator but not required</td><td>Subject Receives 2nd Dose
(300 mg)</td></tr>
<tr><td rowspan="2">Nonrollover Population</td><td>LTP</td><td>Tapering Stage
(300 mg q 2wks)
PLUS
(Tapering of prior LTP – 0 to 3 Weeks)</td><td colspan="4">Non-Tapering Stage (300 mg q2wks)</td><td>Follow-up Period</td></tr>
<tr><td>No LTP</td><td colspan="5">Treatment Period (300 mg q2wks) lanadelumab</td><td>Follow-up Period</td></tr>
</table>

DX-2930-04 = lanadelumab; HAE = hereditary angioedema; LTP = long-term prophylactic treatment; q2wks = every two weeks; wks = weeks.

Source: Clinical Study Report for HELP-04.[9]

Table 43: Details of the HELP-04 Extension Study

		HELP-03
Designs & Populations	**Study design**	Phase III, multi-centre, open-label, extension study
	Locations	41 sites in 6 countries: US (32); Germany (3); Italy (1); UK (1); Canada (3); Jordan (1)
	Sample size	N = 212 • Rollover patients (n = 109) • Non-rollover patients (n = 103)
	Inclusion criteria	**Rollover patients** • Completion of the HELP-03 study **Non-rollover patients** • Boys, men, girls, and women who were at least 12 years of age at screening • Documented diagnosis of type I or II HAE • Baseline rate of ≥ 1 HAE attacks per 12 weeks (historical data)
	Exclusion criteria	**Rollover patients** • Discontinued from HELP-03 study for any reason • Important safety concerns that preclude participation in the extension study **Non-rollover patients** • Concomitant diagnosis of another form of chronic, recurrent angioedema, such as HAE with normal C1-INH, acquired angioedema, idiopathic angioedema, or recurrent angioedema associated with urticaria • Exposure to ACE inhibitors or any estrogen-containing medications with systemic absorption within 4 weeks before screening • Exposure to androgens within 2 weeks before entering the run-in period • Use of LTP therapy for HAE within 2 weeks before entering the run-in period (i.e., failure to complete the washout period) • Use of short-term prophylaxis for HAE within 7 days before entering run-in period • Patients were also excluded if they had any of following liver function test abnormalities: ALT > 3 × ULN, or AST > 3 × ULN, or total bilirubin > 2 × ULN
Drugs	**Interventions**	• **Rollover Patients:** Lanadelumab 300 mg q.2.w. on day 0 with no subsequent treatment until the first reported HAE attack at which point treatment with lanadelumab resumes with 300 mg q.2.w. • **Non-rollover patients:** Lanadelumab 300 mg q.2.w.
Duration	**Rollover**	
	Dose-and-wait phase	Period between first dose and first HAE attack
	Treatment phase	Up to 66 doses of lanadelumab (approximately 132 weeks)
	Safety follow-up	4 weeks
	Non-rollover	
	Tapering phase	2 to 3 weeks for tapering existing LTP treatment (if applicable)
	Treatment phase	Up to 66 doses of lanadelumab (approximately 132 weeks)
	Safety follow-up	4 weeks
Outcomes	**Primary end point**	Safety
	Other end points	**Secondary end points:** • Time from first open-label study dose to the first investigator-confirmed HAE attack for rollover subjects • Number of investigator-confirmed HAE attacks • Number of investigator-confirmed HAE attacks requiring acute treatment • Number of moderate or severe investigator-confirmed HAE attacks • Number of high-morbidity investigator-confirmed HAE attacks **Exploratory end points:**

		HELP-03
		• Angioedema Quality of Life questionnaire • EQ-5D Index Score and EQ-5D VAS • Short Form (12) Health Survey • Hospital Anxiety and Depression Scale • Work Productivity and Activity Impairment: General Health • Treatment Satisfaction Questionnaire for Medication • Global Impression of Treatment Response • Angioedema Control Test
NOTES	**Publications**	• Riedl et al. 2018[10] • Clinicaltrials.gov[11]

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EQ-5D = EuroQol 5-Dimensions questionnaire; HAE = hereditary angioedema; LTP = long-term prophylactic; q.2.w. = every two weeks; q.4.w. = every four weeks; ULN = upper limit of normal; VAS = visual analogue scale.

Source: Clinical Study Report for HELP-04.[9]

Populations

Inclusion and Exclusion Criteria

Two types of patients were eligible for enrolment in the HELP-04 extension study:

- Those who completed HELP-03 and elected to enter the extension study (referred to as rollover patients)
- Patients who did not participate in HELP-03 (referred to as non-rollover patients)

The non-rollover patient population could transition from their existing LTP therapy to lanadelumab without the need for a washout period (as was used in the HELP-03 study). Instead, they underwent an optional two- to three-week tapering period, which the sponsor indicated would be a closer approximation to a real-world clinical setting.[9] The non-rollover patients entering the HELP-04 extension study were required to have a minimum historical baseline HAE attack rate of at least one attack per 12 weeks, which is lower than the baseline rate of at least one attack per four weeks that was required for enrolment in the HELP-03 study.[9]

Baseline and Demographic Characteristics

Table 44 provides a summary of the demographic characteristics for the HELP-04 study. The overall mean age of patients was 40.7 (SD 15.7) years. A majority of the participants were female (67.5%), white (93.4%), [redacted].

Table 44: Demographic Characteristics for the HELP-04 Extension Study (Safety Population)

Characteristics		Rollover (N = 109)	Non-Rollover (N = 103)	Total (N = 212)
Age (years)	Mean (SD)	41.9 (14.74)	39.5 (16.71)	40.7 (15.7)
	Median (range)	43.0 (13 to 74)	39.7 (12 to 76)	42.8 (12 to 76)
Age category n (%)	< 18 years	8 (7.3)	13 (12.6)	21 (9.9)
	18 to < 40 years	38 (34.9)	39 (37.9)	77 (36.3)
	40 to < 65 years	57 (52.3)	46 (44.7)	103 (48.6)
	≥ 65 years	6 (5.5)	5 (4.9)	11 (5.20029)
Sex n (%)	Male	34 (31.2)	35 (34.0)	69 (32.5)
	Female	75 (68.8)	68 (66.0)	143 (67.5)
Ethnicity n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Race n (%)	White	99 (90.8)	99 (96.1)	198 (93.4)
	African-American	8 (7.3)	2 (1.9)	10 (4.7)
	Asian	[redacted]	0 (0.0)	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Race group n (%)	White	99 (90.8)	99 (96.1)	198 (93.4)
	Non-white	10 (9.2)	4 (3.9)	14 (6.6)
Weight (kg)	Mean (SD)	80.08 (21.713)	81.15 (25.558)	80.60 (23.609)
	Median (range)	75.50 (36.7 to 150.0)	76.00 (44.2 to 177.7)	75.60 (36.7 to 177.7)
Weight category n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)	Mean (SD)	28.28 (6.840)	28.42 (7.518)	28.35 (7.161)
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

BMI = body mass index; SD = standard deviation.

Source: Clinical Study Report for HELP-04.[9]

Table 45 provides a summary of the disease characteristics for the HELP-04 extension study. The mean baseline attack rate was lower in the non-rollover group than in the rollover group (2.55 versus 3.52). Exposure to prior LTP treatment was similar between the rollover and non-rollover patient populations.

Table 45: Baseline Hereditary Angioedema Attack Characteristics for HELP-04 (Safety Population)

Baseline Characteristics		Rollover (N = 109)	Non-Rollover (N = 103)	Total (N = 212)
Age at onset of angioedema symptoms (years)	Mean (SD)	13.5 (9.53)	11.6 (7.30)	12.6 (8.55)
	[redacted]	[redacted]	[redacted]	[redacted]
HAE type n (%)	Type I	100 (91.7)	89 (86.4)	189 (89.2)
	Type II	9 (8.3)	12 (11.7)	21 (9.9)
	Unspecified	0 (0.0)	2 (1.9)	2 (0.9)
History of laryngeal attacks n (%)	Yes	67 (61.5)	63 (61.2)	130 (61.3)
	No	42 (38.5)	40 (38.8)	82 (38.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Historical number of attacks in the last month	Mean (SD)	3.8 (4.15)	2.9 (2.89)	3.4 (3.61)
	[redacted]	[redacted]	[redacted]	[redacted]
Historical number of attacks in the last 3 months	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Historical number of attacks in the last 12 months	Mean (SD)	37.7 (45.96)	30.4 (34.16)	34.2 (40.73)
	[redacted]	[redacted]	[redacted]	[redacted]
Baseline HAE attack rate (attacks/4 weeks)	Mean (SD)	3.52 (2.483)	2.55 (2.754)	3.05 (2.657)
	Median (range)	3.00 (1.0 to 14.0)	1.84 (0.0 to 15.4)	2.00 (0.0 to 15.4)
Baseline HAE attack rate group (attacks/4 weeks) n (%)	< 1	0 (0.0)	25 (24.3)	25 (11.8)
	1 to < 2	35 (32.1)	39 (37.9)	74 (34.9)
	2 to < 3	19 (17.4)	11 (10.7)	30 (14.2)
	≥ 3	55 (50.5)	28 (27.2)	83 (39.2)
Prior LTP treatment category	C1-INH only	53 (48.6)	53 (51.5)	106 (50.0)
	Oral therapy	4 (3.7)	8 (7.8)	12 (5.7)
	C1-INH and oral therapy	5 (4.6)	2 (1.9)	7 (3.3)
	No LTP use	47 (43.1)	40 (38.8)	87 (41.0)
Prior LTP treatment	[redacted]	[redacted]	[redacted]	[redacted]

Baseline Characteristics		Rollover (N = 109)	Non-Rollover (N = 103)	Total (N = 212)
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

BMI = body mass index; C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; LTP = long-term prophylactic; SD = standard deviation.

Source: Clinical Study Report for HELP-04.[9]

Interventions

Investigational Treatment

Patients who completed HELP-03 and enrolled in HELP-04 received a single open-label dose of 300 mg lanadelumab administered SC on day 0, irrespective of which study group they were originally assigned to in HELP-03. After receiving this dose of lanadelumab, they did not receive any additional doses of lanadelumab until they experienced their first investigator-confirmed HAE attack. The purpose of this approach was to evaluate the outer bounds of the lanadelumab dosage frequency by assessing the duration of time between a rollover patient's first open-label dose and first confirmed HAE attack.[9] The protocol specified that there had to be a minimum of 10 days between the first and second doses of lanadelumab (irrespective of when the patient experienced the first HAE attack).[9] After receiving the second lanadelumab dose, these patients continued to receive 300 mg lanadelumab every two weeks for up to 66 doses (i.e., up to 132 weeks).[9]

Patients who were not enrolled in the HELP-03 study (i.e., non-rollover patients) received an open-label dose of 300 mg lanadelumab on day 0 and every two weeks thereafter for up to 66 doses.[9]

In contrast to the HELP-03 study, all patients in the HELP-04 study who were considered suitable candidates (i.e., mentally and physically able) were permitted to self-administer lanadelumab after receiving their first two doses at the study site. Before starting to self-administer lanadelumab, the patients were required to complete training and have their understanding confirmed by the study investigator (or a designee).[9] The location of administration was documented as follows: "study staff in clinic;" "self-administration in clinic;" or "self-administration at home."[9] Study personnel called patients within approximately three days after the planned off-site self-administrations to ensure that the administration had occurred.[9]

Concomitant Prophylactic Treatments

The rollover patient population had undergone a washout period for any LTP treatment before randomization in the HELP-03 study.[5] Non-rollover patients who were enrolled in the HELP-04 study were permitted to use LTP treatment with C1-INH, attenuated androgens (e.g., danazol), or antifibrinolytics (e.g., tranexamic acid) during a tapering period of two to three weeks after the start of lanadelumab treatment.[9] The use of STP treatment (i.e., C1-INH) was permitted if the study investigator considered it medically indicated.[9]

Concomitant Treatments for Acute Hereditary Angioedema Attacks

Acute HAE attacks during the HELP-04 extension study were managed in accordance with the study investigators' usual care for their patients, including use of acute attack therapies that the investigator deemed medically appropriate.[9] The use of C1-INH was permitted as an acute attack therapy, but not as an LTP therapy once these drugs had been tapered during the initial two- to three-week period of HELP-04.[9]

Outcomes

The primary end point of the HELP-04 extension study was safety. Secondary efficacy end points included time from the first open-label dose of lanadelumab to the first investigator-confirmed HAE attack in the rollover patient population; the number of investigator-confirmed HAE attacks; the number of investigator-confirmed HAE attacks requiring acute treatment; the number of moderate or severe investigator-confirmed HAE attacks; and the number of high-morbidity investigator-confirmed HAE attacks. Additional exploratory end points include the AE-QoL, EQ-5D-5L, Short Form (12) Health Survey, Hospital Anxiety and Depression Scale, Work Productivity and Activity Impairment: General Health, Treatment Satisfaction Questionnaire for Medication, Global Impression of Treatment Response, and Angioedema Control Test. As noted above, study personnel called patients within approximately three days after the planned off-site self-administrations. These calls were also used to obtain information about adverse events and concomitant medications, and to ensure all HAE attacks had been appropriately documented.[9]

Statistical Analysis

Analysis Populations

Analyses in the HELP-04 extension study were conducted using a safety population, which included all patients who received any open-label lanadelumab.[9] The rollover safety population was the subset of subjects who participated in the HELP-03 study, and the non-rollover safety population was the subset of patients who entered HELP-04 directly.[9]

Multiplicity Adjustments

There were no adjustments for multiple comparisons made for any of the analyses reported for the HELP-04 study.[9]

Subgroup Analysis

The sponsor conducted the following subgroup analyses in the HELP-04 extension study: age group [redacted]); sex ([redacted]); race group ([redacted]); weight group [redacted]); BMI group [redacted]); baseline HAE attack rate group ([redacted]); HAE type ([redacted]); geographic region ([redacted]); lanadelumab administration type [redacted]); history of laryngeal HAE attacks ([redacted]).[9]

Patient Disposition

Patient disposition for the HELP-04 study is summarized in Table 46. A total of [redacted] patients were screened for the HELP-04 extension study, and 212 patients were treated.[9] Only non-rollover patients were screened for enrolment; rollover patients from HELP-03 were not re-screened. A total of 109 patients were enrolled as rollover patients, and 103 were non-rollover patients. A high proportion of patients who completed the HELP-03 study elected to enroll in the extension study (109/113; 96.5%).[9] The majority of patients were still ongoing in the extension study (186/112; 87.7%) at the time of the second interim report. The proportions of patients who [redacted].[9]

Table 46: Patient Disposition for the HELP-04 Extension Study (Safety Population)

Disposition, n (%)	Rollover (N = 109)	Non-Rollover (N = 103)	Total (N = 212)
Patients Treated	109 (100.0)	103 (100.0)	212 (100.0)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Primary Reason for Study Withdrawal			
Adverse event	1 (0.9)	5 (4.9)	6 (2.8)
Death	0	0	0
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report for HELP-04.[9]

Exposure to Study Treatments

Exposure to lanadelumab in the HELP-04 extension study is summarized in Table 47. At the time of the second interim report, patients had received a mean of 37.8 (SD 11.16) doses of lanadelumab during HELP-04. The mean duration of exposure was 20.31 (SD 5.227) months in the rollover population and 19.07 (SD 5.390) in the non-rollover population.[9]

Table 47: Study Drug Exposure in the HELP-04 Extension Study (Safety Population)

Exposure		Rollover (N = 109)	Non-Rollover (N = 103)	Total (N = 212)
Time on study (months)	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
Duration of time on study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

N/A = not applicable; SD = standard deviation.

Source: Clinical Study Report for HELP-04.[9]

Efficacy

Hereditary Angioedema Attack Rate

Table 48 provides a summary of the mean and median HAE attack rates in the HELP-04 extension study. The results are stratified according to the therapy that the patient received before enrolment in the HELP-04 study (i.e., randomized treatment assignment from HELP-03 for the rollover population and prior LTP treatment for the non-rollover population). For those who were treated with placebo in HELP-03, the mean HAE attack rate was reduced from [redacted] attacks per four weeks at the end of HELP-03 to [redacted] attacks per four weeks at the interim cut-off in HELP-04 (mean percentage change [redacted]).[9] Those in rollover group who had previously received lanadelumab 300 mg every two weeks maintained the reduced attack rate frequency.

The non-rollover population demonstrated reductions in HAE attack rate for all prior therapy groups. The mean percentage changes were [redacted] for those with no prior LTP exposure; [redacted] for those with prior LTP exposure with only C1-INH; [redacted] for the those with prior exposure to oral LTP; and [redacted] for the two patients with prior exposure to C1-INH and oral LTP treatment.[9]

Table 48: [redacted]

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; LTP = long-term prophylactic therapy; N/A = not applicable; SD = standard deviation.

Source: Clinical Study Report for HELP-04.[9]

Time to First Hereditary Angioedema Attack

Table 49 summarizes the proportion of patients who had experienced their first HAE attack by weeks 2, 4, 6, 8, and 10 following the single initial 300 mg dose at the outset of the HELP-04 study. The proportion of patients with HAE attacks was [redacted] in the patients who had already been receiving the recommended dose of 300 mg every two weeks lanadelumab in the HELP-03 study.

Table 49: [redacted]

[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Clinical Study Report for HELP-04.[9]

The sponsor conducted [redacted] (Table 50). The sponsor reported that, [redacted].[9]

Table 50: [redacted]

Model	Variable	HR (95% CI)	*P* value
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BMI = body mass index; C1-INH = C1 esterase inhibitor; CI = confidence interval; HAE = hereditary angioedema; HR = hazard ratio; LTP = long-term prophylactic.

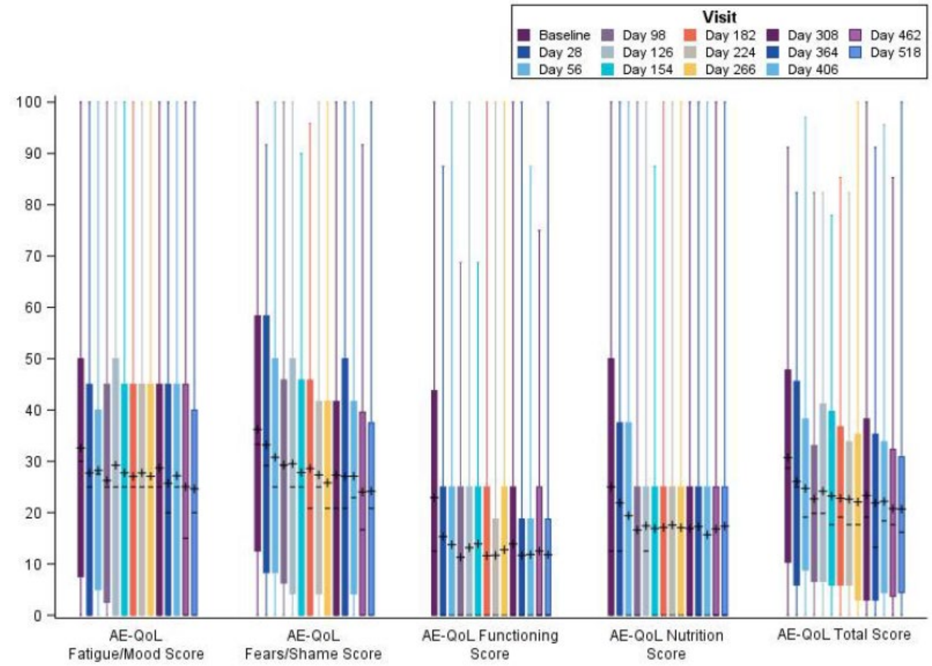
Source: Clinical Study Report for HELP-04.[9]

Patient-Reported Outcomes

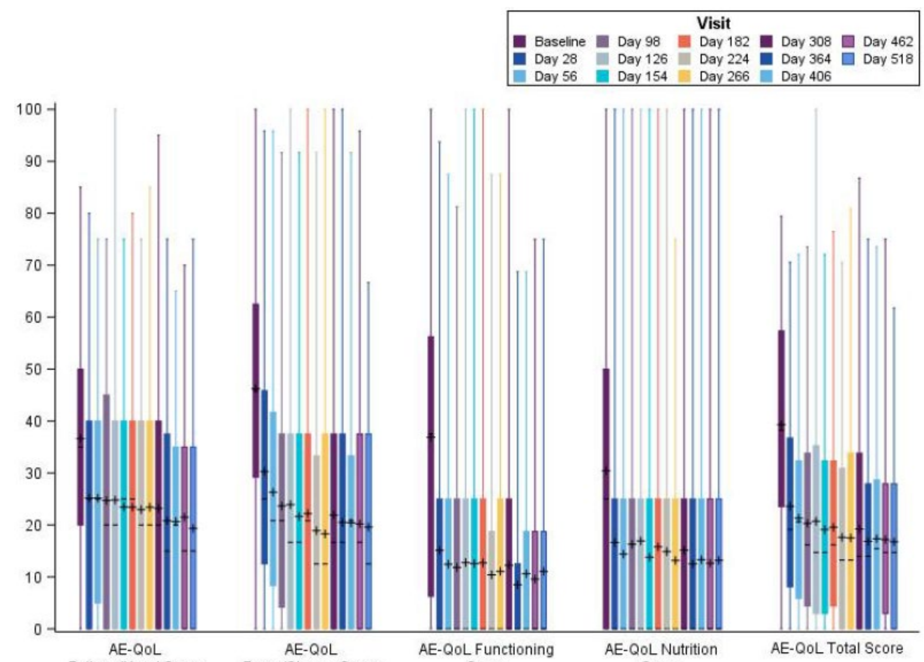
Analyses for patient-reported outcomes are planned for the final analysis of HELP-04. The interim analysis for HELP-04 was limited to descriptive data. There were no analyses or commentary from the sponsor for EQ-5D Index Score and EQ-5D VAS; Short Form (12) Health Survey; Hospital Anxiety and Depression Scale; Work Productivity and Activity Impairment: General Health questionnaire; Treatment Satisfaction Questionnaire for Medication; Global Impression of Treatment Response; or Angioedema Control Test.[9] Data for the AE-QoL were limited to descriptive reporting (Figure 7).

Figure 7: Angioedema Quality of Life Questionnaire Interim Results for HELP-04

Rollover Patient Populations



Non-Rollover Patient Populations



AE-QoL = Angioedema Quality of Life questionnaire.

Source: Clinical Study Report for HELP-04.[9]

Harms

Table 51 provides a summary of aggregate adverse event outcomes reported in the HELP-04 study. Nearly all patients in the HELP-04 study experienced at least one treatment-emergent adverse event (95.3%), with a similar proportion in the both the rollover (95.1%) and non-rollover (95.4%) populations. Serious adverse events were reported for 7.5% of the total population (9.5% and 5.8% in the rollover and non-rollover groups, respectively). The proportion of patients who discontinued as a result of adverse events was 3.3%, with a greater number of withdrawals occurring in the non-rollover group (six patients; 5.8%) compared with the rollover group (one patient; 0.9%).[9]

Table 51: Summary of Adverse Events in HELP-04 (Safety Population)

Adverse Events, n (%)	Rollover (N = 109)		Non-Rollover (N = 103)		Total (N = 212)	
	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events
Any TEAE	104 (95.4)	[redacted]	98 (95.1)	[redacted]	202 (95.3)	[redacted]
Any serious TEAE	10 (9.2)	[redacted]	6 (5.8)	[redacted]	16 (7.5)	[redacted]
Any severe TEAE	14 (12.8)	[redacted]	19 (18.4)	[redacted]	33 (15.6)	[redacted]
Any investigator-reported AESI	4 (3.7)	[redacted]	4 (3.9)	[redacted]	8 (3.8)	[redacted]
Deaths due to TEAE	0 (0.0)	[redacted]	0 (0.0)	[redacted]	0 (0.0)	[redacted]
Hospitalizations due to TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AESI = adverse event of special interest; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse events.

Source: Clinical Study Report for HELP-04.[9]

Adverse Events

Table 52 provides a summary of the treatment-emergent adverse events that were reported in at least 5% of lanadelumab-treated patients in HELP-04. The proportion of patients who reported at least one adverse event was 95.4% in the total group (95.1% and 95.3% in the rollover and non-rollover groups, respectively).[9] Similar to the HELP-03 study (Table 29), the most frequently reported treatment-emergent adverse events were injection-site pain (42.9%), viral upper respiratory tract infection (34.0%), headache (22.2%), and upper respiratory tract infection (21.2%). The proportion of patients who reported treatment-emergent adverse events was generally balanced across the rollover and non-rollover patient populations.[9]

Table 52: Adverse Events Reported in at Least 5% of Patients in HELP-04 (Safety Population)

Adverse Events, n (%)	Rollover (N = 109)		Non-Rollover (N = 103)		Total (N = 212)	
	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events
Any TEAE	104 (95.4)	[redacted]	98 (95.1)	[redacted]	202 (95.3)	[redacted]
Infections and infestations	84 (77.1)	[redacted]	76 (73.8)	[redacted]	160 (75.5)	[redacted]
Viral upper respiratory tract infection	40 (36.7)	[redacted]	32 (31.1)	[redacted]	72 (34.0)	[redacted]
Upper respiratory tract infection	26 (23.9)	[redacted]	19 (18.4)	[redacted]	45 (21.2)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse Events, n (%)	Rollover (N = 109)		Non-Rollover (N = 103)		Total (N = 212)	
	N (%)	Number of events	N (%)	Number of events	N (%)	Number of events
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders/administration site conditions	58 (53.2)	[redacted]	63 (61.2)	[redacted]	121 (57.1)	[redacted]
Injection-site pain	42 (38.5)	[redacted]	49 (47.6)	[redacted]	91 (42.9)	[redacted]
Injection-site erythema	15 (13.8)	[redacted]	16 (15.5)	[redacted]	31 (14.6)	[redacted]
Injection-site bruising	11 (10.1)	[redacted]	12 (11.7)	[redacted]	23 (10.8)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	16 (14.7)	[redacted]	7 (6.8)	[redacted]	23 (10.8)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	26 (23.9)	[redacted]	21 (20.4)	[redacted]	47 (22.2)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LANA = lanadelumab; SAE = serious adverse events; TEAE = treatment-emergent adverse event; WDAE = withdrawals due to adverse event.

Source: Clinical Study Report for HELP-04.[9]

Serious Adverse Events

SAEs reported in the HELP-04 trial, excluding HAE attacks, are summarized in Table 53. SAEs were reported for a total of 16 patients in the extension study: 10 (9.3%) in the rollover populations and 6 (5.8%) in the non-rollover population.

Table 53: Serious Adverse Events Reported in HELP-04 (Safety Population)

Serious Adverse Events, n (%)	Rollover (N = 109)		Non-Rollover (N = 103)		Total (N = 212)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
Any SAE	10 (9.2)	[redacted]	6 (5.8)	[redacted]	16 (7.5)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LANA = lanadelumab.

Source: Clinical Study Report for HELP-04.[9]

Withdrawals Due to Adverse Events

The proportion of patients who discontinued as a result of adverse events was [redacted].[9] [redacted].[9]

Disordered Coagulation

[redacted] of disordered coagulation (vaginal hemorrhage).[9] [redacted].[9] [redacted].[9]

Critical Appraisal

Internal Validity

As with most long-term extension phase studies, the primary limitations of the HELP-04 extension study were the open-label administration of lanadelumab, the absence of an active or placebo comparator group, and the designation of all efficacy end points as exploratory. Open-label administration can bias the reporting of end points, particularly for the patient-reported outcomes and self-reported HAE attack events. Rollover patients and the study investigators remained blinded to the allocated treatments that were administered in the HELP-03 study. The lack of a placebo group may overestimate the magnitude of clinical benefit reported in the interim analysis for the extension study.[21]

All efficacy end points in the HELP-04 extension study were secondary end points and [redacted]. The results are limited to those available from the interim analyses, with final results unavailable at the time of this review. It is possible that the data from the interim analysis may not hold true over the complete duration of the study. In addition, data for the majority of patient-reported outcomes were not available.

As shown in Table 48, there were differences in the baseline HAE attack rate of patients in the rollover and non-rollover patient populations. The historical HAE attack rate was considerably lower in the non-rollover population at baseline (median of 1.84) compared with the baseline rate of the HELP-03 study (median of 3.00). However, the results for these two populations have not been pooled in the analysis and are presented separately in the sponsor's interim report.

As shown in Table 49, the proportion of patients with their first HAE attack [redacted].[4] [redacted].[4] Such variation in the absence of a control group limits the ability to interpret the results of the efficacy results of the HELP-04 study.

Health-related quality of life data for the rollover population may be confounded by differences in the study drug administration protocols in HELP-03 and HELP-04. The ability to self-administer lanadelumab in the extension study would likely be preferred by patients who had previously been required to visit the study site to receive the study drugs (for both placebo and lanadelumab groups).

External Validity

The majority of patients in HELP-04 were women, were overweight, had type I HAE, and had a mean age of approximately 40 years, which is reflective of the Canadian HAE population and consistent with the HELP-03 trial population. The diagnostic criteria used in HELP-04 were considered to be appropriate by regulatory authorities[21] and the clinical experts consulted by CADTH. As in HELP-03, enrolment in HELP-04 was limited to patients with a confirmed diagnosis of type I or II HAE, and patients with all other forms of angioedema were excluded from the study. The enrolment criteria for the non-rollover population stated that patients were required to have a minimum HAE attack frequency of at least one per 12 weeks to be eligible. This is considerably lower than the eligibility criteria of the HELP-03 study (i.e., at least one attack per four weeks). The clinical experts consulted by CADTH noted that patients who experienced only one attack per 12 weeks may not be considered for LTP treatment in clinical practice (depending on the severity of the attacks). The experts also noted that such patients may be unlikely to enroll in a clinical trial; hence, the baseline HAE attack rate in HELP-04 was considerably greater than one per 12 weeks. Approximately 40% (n = 40) of the non-rollover patient population were not receiving LTP treatment at the time of enrolment in HELP-04. Reviewers for Health Canada noted that this could suggest that these patients had not been demonstrating HAE that was sufficiently unmanaged to warrant treatment with an LTP treatment such as lanadelumab.[21]

Administration of lanadelumab in HELP-04 is a better representation of how the product would be used in clinical practice. In contrast to the HELP-03 study, patients in the HELP-04 study were permitted to self-administer lanadelumab after receiving their first two doses at the study site, provided they were mentally and physically able. This may provide a better estimate of the efficacy, compliance, and administration-related adverse events that would occur in actual clinical usage. In addition, all patients received the initial dosage of lanadelumab that is recommended in the product monograph (i.e., 300 mg once every two weeks), with the exception of the dose-and-wait phase of the study for the rollover population. In addition, those using LTP treatment in the non-rollover patient population of HELP-04 were permitted to transition from their existing therapy directly to lanadelumab without the need for the washout period that was applied before randomization in the HELP-03 study. The optional tapering period of two to three weeks was used to provide a closer approximation of how patients with HAE would be transitioned in actual clinical practice.[9]

[redacted].

As in the HELP-03 study, patients enrolled in HELP-04 continued to receive extensive contact with health care professionals throughout the extension study. The clinical experts consulted by CADTH noted that patients are typically seen once every three to six months in Canada; those whose HAE is very well-controlled are often only seen once per year.

Discussion

Summary of Available Evidence

The CADTH systematic review included one RCT (HELP-03; N = 126). In addition, the CADTH review included a long-term extension phase study (HELP-04) and an ITC submitted by the sponsor.

HELP-03 was phase III, multi-centre, double-blind, placebo-controlled RCT conducted to investigate the safety and efficacy of lanadelumab for the prevention of HAE attacks. The study design included four phases: an LTP therapy washout phase of at least two weeks (except in adolescent patients); a four- to eight-week run-in phase to determine the patient's baseline rate of HAE attacks; a 26-week double-blind treatment phase; and a follow-up phase in which patients were given the option to enroll in the open-label extension phase study (HELP-04). Enrolment in HELP-03 was limited to patients with type I or II HAE who demonstrated an HAE attack rate of at least one per four weeks during the run-in period. Eligible patients were randomized (3:2:2:2) to receive investigator-administered SC injections of placebo, lanadelumab 150 mg every four weeks, lanadelumab 300 mg every four weeks, or lanadelumab 300 mg every two weeks. The HELP-03 study included a range of clinically relevant end points related to HAE attacks, including overall attack rates, attacks requiring acute treatment, high-morbidity attacks, attacks required a visit to the emergency department and/or hospitalization, laryngeal attacks, attack-free days and intervals, responder analyses, and health-related quality of life (i.e., AE-QoL and EQ-5D-5L). HELP-03 was a well-designed, well-conducted, placebo-controlled trial, and the study population is a reasonable reflection of the target population in Canada. The primary limitations of the HELP-03 study are the absence of an active comparator and the imbalances between the groups for some of the baseline disease characteristics (although this is common in studies involving rare diseases and small sample sizes).

HELP-04 was a phase III, open-label, extension study that was designed to evaluate the long-term safety and efficacy of lanadelumab in patients with type I or II HAE. The HELP-04 study was ongoing at the time the submission was filed with CADTH, and data were available for the second interim report.[9] The HELP-04 study enrolled patients who had completed HELP-03 (rollover patients) as well as another cohort of patients who did not participate in HELP-03 (non-rollover patients). The key differences between the rollover and non-rollover populations were that the non-rollover patients could transition from their existing LTP therapy to lanadelumab following an optional two- to three-week tapering period rather than a strict washout period, and they were only required to have a minimum historical baseline HAE attack rate of at least one attack per 12 weeks.[30] All patients in HELP-04 received open-label treatment with 300 mg lanadelumab every two weeks. However, after a single dose, those in the rollover population did not receive a subsequent dose until they experienced their first HAE attack in the extension phase. This was performed in an attempt to characterize the outer bounds of lanadelumab dosage frequency in the rollover patients.[9]

Given the absence of head-to-head studies, CADTH reviewed a sponsor-submitted ITC conducted to evaluate the comparative effectiveness of lanadelumab against a single regimen of C1-INH (IV 1,000 twice per week).[12,13]

In accordance with the review protocol, CADTH has focused only on the Health Canada–approved dosage regimens of lanadelumab (i.e., 300 mg every two weeks and 300 mg every four weeks).

Interpretation of Results

Efficacy

In the HELP-03 study, the two doses of lanadelumab that were evaluated by CADTH (i.e., 300 mg every four weeks and 300 mg every two weeks) were associated with statistically significant reductions in the overall rate of HAE attacks, rate of moderate to severe HAE attacks, and rate of attacks requiring acute treatment with on-demand therapy. The clinical experts consulted by CADTH and regulatory authorities concluded that the reduced rate of HAE attacks observed with lanadelumab compared with placebo is clinically relevant for patients with HAE.[21,30,31] The efficacy of lanadelumab relative to placebo was further demonstrated with improvements in a number of exploratory outcomes, including time to first HAE attack; number of attack-free days and months; use of on-demand treatment for HAE attacks; responder analyses; and health-related quality of life as assessed by the AE-QoL. Although none of the exploratory outcomes were adjusted for multiplicity, the results are in alignment with and supportive of the primary analysis.

Treatment with lanadelumab reduced the frequency of HAE attacks across all of the different locations where they typically occur (i.e., abdominal, laryngeal, or peripheral attacks).[21] In its input to CADTH, the patient group (HAE Canada) emphasized that laryngeal HAE attacks have a tremendous impact on the emotional well-being of those living with HAE (e.g., persistent fear of recurrence). There was no statistically significant difference between the lanadelumab and placebo groups in the number of laryngeal HAE attacks in HELP-03; however, these events were rare, and the study was likely underpowered to detect a difference. Due to the severe nature of these attacks, the numerical reduction observed with lanadelumab treatment was considered to be clinically meaningful by Health Canada[21] and the clinical experts consulted by CADTH.

The sponsor conducted responder analyses based on reductions in HAE attacks of at least 50%, 60%, 70%, 80%, and 90%, with lanadelumab being favoured for all analyses. There is no commonly accepted threshold for the reduction in HAE attacks that would be considered clinically meaningful; however, the experts consulted by CADTH suggested that reductions in the range of 50% to 70% could be considered meaningful. This aligns with the 60% reduction in HAE attack rate that was hypothesized in the statistical analysis plan for the HELP-03 study.[5,21] Patients treated with lanadelumab also demonstrated a greater number of attack-free days and months during the HELP-03 trial. Reviewers for the FDA noted that, although an exploratory end point, the proportion of patients who were free of attacks during the study was among the most clinically meaningful outcomes. They noted that, in the absence of a cure, the goal of treatment for patients with HAE is cessation of all attacks.[30]

As stated in the patient group input, HAE has a major detrimental impact on the quality of life of those with living the condition. Although statistical significance cannot be concluded due to the absence of multiplicity adjustment and the use of post hoc analyses, treatment with lanadelumab was associated with clinically relevant improvements in health-related quality of life, as measured using the AE-QoL scale, a validated, reliable instrument for evaluating changes in the quality of patients with angioedema.[21] The change from baseline in the lanadelumab groups exceeded the minimal clinically important difference for the AE-QoL of six points. Similar changes were not observed for the EQ-5D-5L analyses. NICE noted that the largest changes observed with the AE-QoL involved the functioning and fatigue domains, where it may be reasonable to expect that the differences would have been detected by the EQ-5D-5L. In response to this commentary from NICE, the sponsor stated that the EQ-5D-5L is a generic instrument and may be insensitive to some of the disease-specific improvements.

The HELP-04 extension study is currently ongoing. Reviewers for the FDA noted that the treatment effect of lanadelumab did not appear to wane over time in the majority of patients in the rollover group of HELP-04.[30] The reduction in HAE attack rates observed in the non-rollover patients was similar to results observed in the HELP-03 trial (albeit uncontrolled), and clinical experts consulted by CADTH suggested that the effects were clinically relevant. Reviewers for Health Canada acknowledged that the results are suggestive of a durable treatment effect.[21] The interim data from HELP-04 also suggested that self-administration of lanadelumab was effective for reducing HAE attack frequency in the non-rollover patient population and maintaining the reduction achieved in the rollover population who had previously had study personnel administer the treatment.[21]

The clinical experts consulted by CADTH noted that one of the potential disadvantages of lanadelumab is that it does not replace the endogenous C1-INH that is absent or non-functional in patients with type I or II HAE, respectively. This novel approach lacks long-term data to evaluate the comparative safety and effectiveness against the currently available products that simply replace the body's C1-INH. This was one of the reasons given by Quebec's l'Institut national d'excellence en santé et en services sociaux (INESSS) Comité scientifique permanent d'évaluation des médicaments aux fins d'inscription (CSEMI) for not recommending reimbursement of lanadelumab.[51]

Indirect Comparison

Given the absence of head-to-head studies, CADTH reviewed a sponsor-submitted ITC to investigate the comparative efficacy of lanadelumab against other drugs used for management of HAE.[12,13] The NMA compared lanadelumab versus IV-administered C1-INH (1,000 IU twice weekly), with placebo as the common comparator. The sponsor used a Bayesian NMA to compare the treatments for two end points (reduction in HAE attack rate and time to first HAE attack). The evidence network was limited to two phase III, placebo-controlled trials: the HELP-03 study was used for lanadelumab and the CHANGE study was used for C1-INH. There is considerable clinical and methodological heterogeneity across the HELP-03 and CHANGE studies, including different study designs (parallel versus crossover), treatment durations (26 weeks versus 12 weeks), eligibility criteria (e.g., one versus two attacks per month), and protocols for rescue therapy and concomitant LTP treatment. In addition, the NMA network was sparse, limited to two studies with small samples (although this is common with rare diseases). The results demonstrated considerable variation across the estimates of effect that were derived from different modelling approaches (i.e., fixed-effects versus random-effects), and comparators that were considered to be interest for this review (i.e., SC C1-INH) were excluded.

Although the sponsor reported that [redacted] for HAE attack rate (rate ratio [redacted]), important limitations of the ITC prevent drawing any conclusions regarding comparative efficacy of lanadelumab and IV C1-INH. The Institute for Clinical and Economic Review conducted a review of the clinical effectiveness and cost-effectiveness of lanadelumab and C1-INH for prophylaxis of HAE attacks and also concluded that there was insufficient evidence to determine whether any of the agents were superior to the others.[52,53] In its review of lanadelumab, Health Canada noted that the magnitude of reduction in HAE attacks with lanadelumab is consistent with the C1-INHs approved for use as LTP treatment in Canada (i.e., Cinryze and Haegarda).[21] The regulatory reviewers did not suggest that lanadelumab offered superior efficacy in comparison with C1-INHs.

Harms

Treatment with lanadelumab was generally well tolerated by the patients, and withdrawals due to adverse events were rare in HELP-03 and HELP-04. The most commonly reported adverse events in the HELP-03 and HELP-04 studies were injection-site reactions, including pain, erythema, and bruising at the injection site. The majority of these events were graded as mild and had resolved within one day of onset.[4] Clinical experts consulted by CADTH noted that the injection-site adverse events were not concerning and generally consistent with expectations for an SC-administered product. Both of the clinical experts consulted by CADTH and HAE Canada noted that long-term use of IV-administered products for HAE can be associated with adverse events for patients (e.g., damage to veins). There were no direct or indirect comparisons of the adverse events associated with lanadelumab compared with IV administration of C1-INH identified in CADTH's review. However, the clinical experts consulted by CADTH noted that SC administration can help alleviate the adverse events associated with long-term IV administration.

In the HELP-03 study, a greater proportion of lanadelumab-treated patients experienced at least one hypersensitivity adverse event compared with placebo; however, none of the events were severe or resulted in discontinuation of treatment.[5] Regulators noted that these events were generally mild, localized to the injection site, and self-limited (i.e., resolved without the need for concomitant treatment).[30] Hypersensitivity reactions were a pre-specified adverse event of special interest in the HELP-03 and HELP-04 studies.[5,9,29] Only a single patient in the lanadelumab 300 mg every two weeks group was reported to have experienced a hypersensitivity reaction that met the adverse event of special interest criteria. The Canadian product monograph includes a warning that hypersensitivity reactions were observed in the clinical trials for lanadelumab and that treatment should be discontinued in any patient who experiences a severe hypersensitivity reaction.[4]

In the HELP-03 study, [redacted] of lanadelumab-treated patients had at least one ADA-positive sample ([redacted] in the placebo-treated patients). Neutralizing ADAs were reported in only two patients who received 150 mg lanadelumab every four weeks over the 26-week study period. The product monograph for lanadelumab states that ADA (including neutralizing antibodies) did not appear to adversely affect the pharmacokinetics, pharmacodynamics, safety, or clinical response.[4]

HAE is more prevalent in women than men, and the onset of symptoms typically begins before or during child-bearing years. Four patients who were using lanadelumab became pregnant during the HELP-04 study and discontinued treatment immediately upon notification of the pregnancy (no adverse effects have been reported to date). The Canadian product monograph notes that there have been no studies investigating the use of lanadelumab on human fertility, and the drug has not been studied in pregnant or lactating women.[4] Similar warnings are currently included in the product monographs for other C1-INHs (Berinert, Cinryze, and Haegarda);[23-25] however, the WAO/EAACI guidelines recommend C1-INHs as first-line therapy for pregnant or breastfeeding patients.[16] The recommendation is based on a registry study that was conducted in patients using Berinert for acute and/or prophylactic treatment who became pregnant (n = 11) and suggested that Berinert was safe and effective during pregnancy.[54] The clinical experts consulted by CADTH noted that the absence of safety data in patients who are or become pregnant while using lanadelumab is an important research gap.

All of the C1-INHs currently approved for use in Canada are derived from human plasma.[23-25] A fully recombinant C1-INH is currently marketed in the US (Ruconest)[35] but is not currently available in Canada or listed as being under review by Health Canada.[36] As such, all of the C1-INHs available in Canada carry a serious warning in their product monographs stating that the drugs are made from human plasma and may contain infectious agents such as viruses and, theoretically, the agent responsible for the Creutzfeldt–Jakob disease.[23-25] As lanadelumab is not derived from human plasma, it is not associated with a similar risk.[4] The clinical experts consulted by CADTH indicated that patients with HAE and clinicians who treat the condition are generally not concerned with the warnings associated with the available C1-INHs, and the products are considered to be safe and effective treatment options. It is possible that some patients or caregivers could object to the use of a plasma-derived product for religious reasons.[55] Unlike in the US and Europe, recombinant C1-INH is not approved or marketed in Canada;[36] therefore, there may be an unmet need for an effective LTP treatment option that is not derived from human blood for a subset of Canadian patients (particularly if the patient had a contraindication to or inadequate control with oral prophylactic therapy). However, this issue was not identified by the clinical experts or patient groups as an area of significant unmet need in Canada.

Overall, the clinical experts consulted by CADTH indicated that the adverse events associated with lanadelumab were not concerning and were similar to the other agents currently used as LTP treatment for patients with HAE. Given the favourable adverse event profile in the HELP-03 and HELP-04 studies, the FDA did not recommend any additional risk management strategies for lanadelumab, beyond standard considerations for labelling and post-marketing pharmacovigilance.[30,56]

Other Considerations

In its input to CADTH, HAE Canada indicated that patients have strong preference for treatment options that can be administered SC. In addition to the potential for fewer adverse events associated with administration, the patients cited convenience and increased quality of life as benefits of SC administration. Lanadelumab is currently the only LTP treatment marketed in Canada that is approved for SC administration. Haegarda is a C1-INH product approved by Health Canada as an SC treatment option for those requiring LTP therapy; however, this drug has not been marketed in Canada at the time of this review. The clinical experts consulted by CADTH noted that, in lieu of Haegarda, Berinert is also commonly administered SC as an off-label option for patients requiring LTP treatment and seeking a SC option. Therefore, it is uncertain whether lanadelumab would fulfill an unmet need based solely on its SC route of administration. Lanadelumab is currently only available as a single-use vial. The clinical experts consulted by CADTH noted that alternative dosage formats, such as a pre-filled syringe, would be more convenient for patients. The sponsor is currently conducting an open-label, phase I study to determine the bioavailability of SC lanadelumab administered with a pre-filled syringe as well as an autoinjector (SHP643-102; NCT03918239).[57] It is unclear if and when these dosage formats could be made available in Canada.

The recommended dosage regimen for lanadelumab (i.e., every two weeks) is considerably less frequent than the recommended frequency for C1-INHs used as LTP treatment (i.e., two to three times per week).[4,24,25] There were no comparative data available for this review to assess the impact of reduced dosage frequency on the quality of life of patients with HAE; however, reviewers for Health Canada noted that is generally accepted that quality of life, and in some cases compliance, can be improved by reducing the administration burden on patients.[21] Lanadelumab is indicated for use only as a prophylactic therapy and not for the acute treatment of attacks. The clinical experts consulted by CADTH indicated that lanadelumab would not be considered as an off-label option for the acute management of HAE attacks, due to its SC route of administration and slow onset of action. In the clinical development program, it was estimated that steady state was achieved approximately 70 days after initiating treatment. The dosage section of product monograph for lanadelumab does not recommend the use of loading doses as mechanism to reduce the time to steady state, and the clinical experts consulted by CADTH noted that this not something that would likely be routinely performed in clinical practice.

The Canadian product monograph states that a reduced dosage frequency of lanadelumab (i.e., 300 mg every four weeks) could be considered for patients whose HAE is well-controlled on the 300 mg every two weeks dosage regimen;[4] however, there is no specific definition of "well-controlled," and guidance is limited to a patient being "attack-free" as the lone example. Reviewers for Health Canada noted that the inclusion of this dosage option would harmonize the Canadian label for lanadelumab with the approved labels in other jurisdictions (e.g., FDA and EMA)[39,41] and allow greater individualization of therapy for patients, noting the potential quality-of-life gains with reduced administration frequency.[21] The product label approved by the EMA also states that a reduced dose frequency could be relevant for responders with a low body weight, but no further guidance is provided.[39] No evidence was submitted by the sponsor to CADTH to demonstrate the effectiveness of switching from 300 mg every two weeks to every four weeks. NICE also encountered a lack of evidence to evaluate the efficacy of the switching to the reduced dosage regimen.[55] The sponsor is currently conducting post-marketing studies that may provide insight into the real-world effectiveness of lanadelumab, including the reduced dosage regimen (e.g., EMPOWER study).[58] The clinical experts consulted by CADTH noted that the evidence for the every four weeks regimen suggested that it may be less efficacious than the every two weeks regimen in HELP-03; however, no statistical comparisons were conducted between the treatment groups in HELP-03.

In its submission to CADTH, the sponsor has requested reimbursement in accordance with the full indication approved by Health Canada. This is different than the submissions that were filed with NICE and the Australian Pharmaceutical Benefits Advisory Committee (PBAC), in which the reimbursement requests were more restricted. In its submission to NICE, the target population was narrowed to focus on those who would be eligible for LTP treatment with C1-INHs, which is more restricted in the UK National Health Service (NHS) than it is in Canada. Specifically, to receive reimbursement from the NHS, a patient must demonstrate failure of or intolerance to oral prophylaxis and experience at least two clinically significant HAE attacks per week, despite oral prophylaxis, over a period of at least 56 days requiring acute treatment (i.e., on-demand C1-INH or icatibant); or have a contraindication to oral prophylaxis (e.g., pregnancy).[59] According to the clinical experts consulted by CADTH, access to LTP C1-INH in Canada is not subject to similar criteria, and the decision is made at the discretion of the treating physician and patient. In its submission to PBAC, the sponsor requested reimbursement for the prevention of recurrent HAE attacks (specifically for those C1-INH deficiency or dysfunction) for adolescents and adults for whom the use of danazol is not clinically appropriate or not effective. The clinical experts consulted by CADTH indicated that patients should not require a trial of danazol before receiving therapy with alternative LTP treatments because of the adverse events associated with the treatment. At the time of this review, reimbursement of lanadelumab has not been recommended by the Australian PBAC or INESSS. NICE initially issued a draft recommendation that lanadelumab not be reimbursed for use within the NHS, but its final recommendation was in favour of reimbursement if the following conditions are met: the patient is eligible for preventive C1-INH treatment in line with NHS England's commissioning policy (i.e., two or more clinically significant attacks per week over eight weeks despite oral preventive therapy, or oral therapy is contraindicated or not tolerated); the lowest dosing frequency of lanadelumab is used in line with the summary of product characteristics, that is, when the condition is in a stable, attack-free phase; and the company provides lanadelumab in accordance with the commercial arrangement (i.e., a confidential price discount).[60]

Conclusions

The CADTH review included one phase III, double-blind RCT (HELP-03), one open-label long-term extension phase study (HELP-04), and a Bayesian NMA. HELP-03 demonstrated that administering 300 mg lanadelumab every four weeks and every two weeks was associated with a statistically significant and clinically important reduction in the overall rate of HAE attacks, rate of moderate to severe HAE attacks, and rate of attacks requiring acute treatment with on-demand therapy, compared with placebo. Additional exploratory analyses were aligned with the primary analysis and favoured lanadelumab compared with placebo, including time to first HAE attack, number of attack-free days and months, use of on-demand treatment for HAE attacks, responder analyses, and health-related quality of life. Interim data from the HELP-04 extension trial suggested that the reduction in attack rate persisted beyond the initial 26-week study period of HELP-03.

The most commonly reported adverse events with lanadelumab were injection-site reactions, including pain, erythema, and bruising at the injection site. Overall, the clinical experts consulted by CADTH indicated that the adverse events associated with lanadelumab were not concerning and were similar to the other agents currently used as LTP treatment for patients with HAE. There were no direct or indirect comparisons of the adverse events associated with lanadelumab compared with IV or SC administration of C1-INH identified in CADTH's review. However, in its input to CADTH, patients expressed a preference for SC-administered treatments compared with IV treatments, because they are more convenient and have fewer adverse events associated with administration. This lived experience from patients was supported by the clinical experts consulted by CADTH, who also noted that SC administration can help alleviate the adverse events associated with long-term IV administration.

The Bayesian NMA submitted by the sponsor compared lanadelumab against a single regimen of C1-INH (IV 1,000 twice per week). Although the sponsor reported that [redacted] for reducing the rate of HAE attacks, there were important limitations of the ITC that prevent drawing any conclusions regarding the comparative efficacy of lanadelumab and C1-INH. These limitations included the sparse evidence network; differences in the study designs, treatment durations, eligibility criteria, and protocols for rescue therapy; as well as the exclusion of potentially relevant comparators (e.g., SC C1-INH).

CADTH

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–present) Embase (1974–present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 26, 2019
Alerts:	Weekly search updates until project completion
Study Types:	No filters were applied to limit retrieval by study type
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot .hw	Original title Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn .nm .dq	Registry number Name of substance word Candidate Term Word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	2372V1TKXK.rn,nm.
2	(Takhzyro* or lanadelumab* or DX 2930 or DX2930 or SHP643 or SHP 643).ti,ab,kf,ot,hw,nm,rn.
3	or/1-2
4	3 use medal
5	*lanadelumab/
6	(Takhzyro* or lanadelumab* or DX 2930 or DX2930 or SHP643 or SHP 643).ti,ab,kw,dq.
7	or/5-6
8	7 use oemezd

MULTI-DATABASE STRATEGY	
9	(conference review or conference abstract).pt.
10	8 not 9
11	4 or 10
12	remove duplicates from 11

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Takhzyro, lanadelumab, DX 2930, DX2930, SHP643, SHP 643	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Takhzyro, lanadelumab, DX 2930, DX2930, SHP643, SHP 643	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

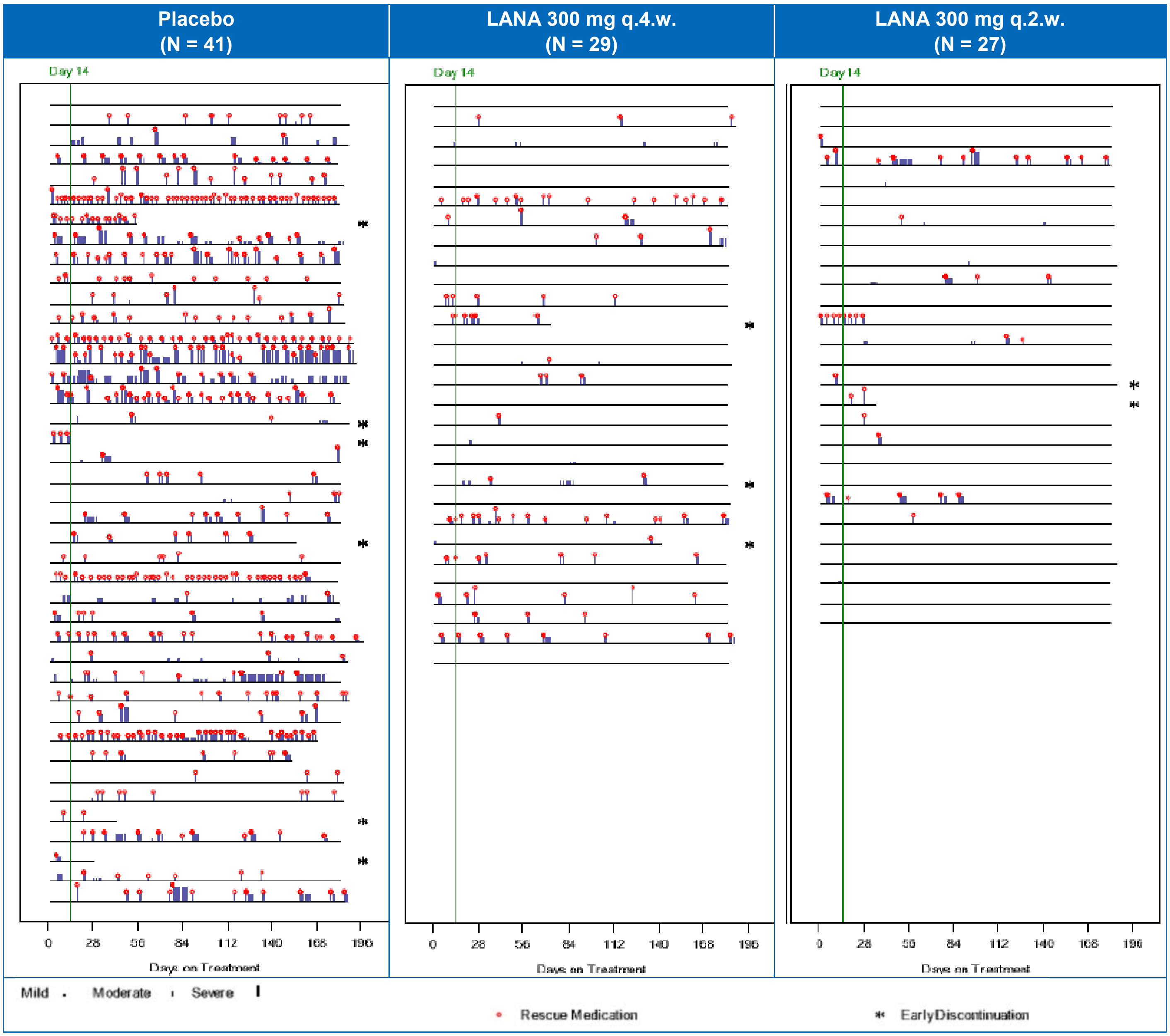
Dates for Search:	June 2019
Keywords:	Search terms: Takhzyro, lanadelumab, hereditary angioedema
Limits:	Publication years: none

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- Internet search.

Appendix 2: Detailed Outcome Data

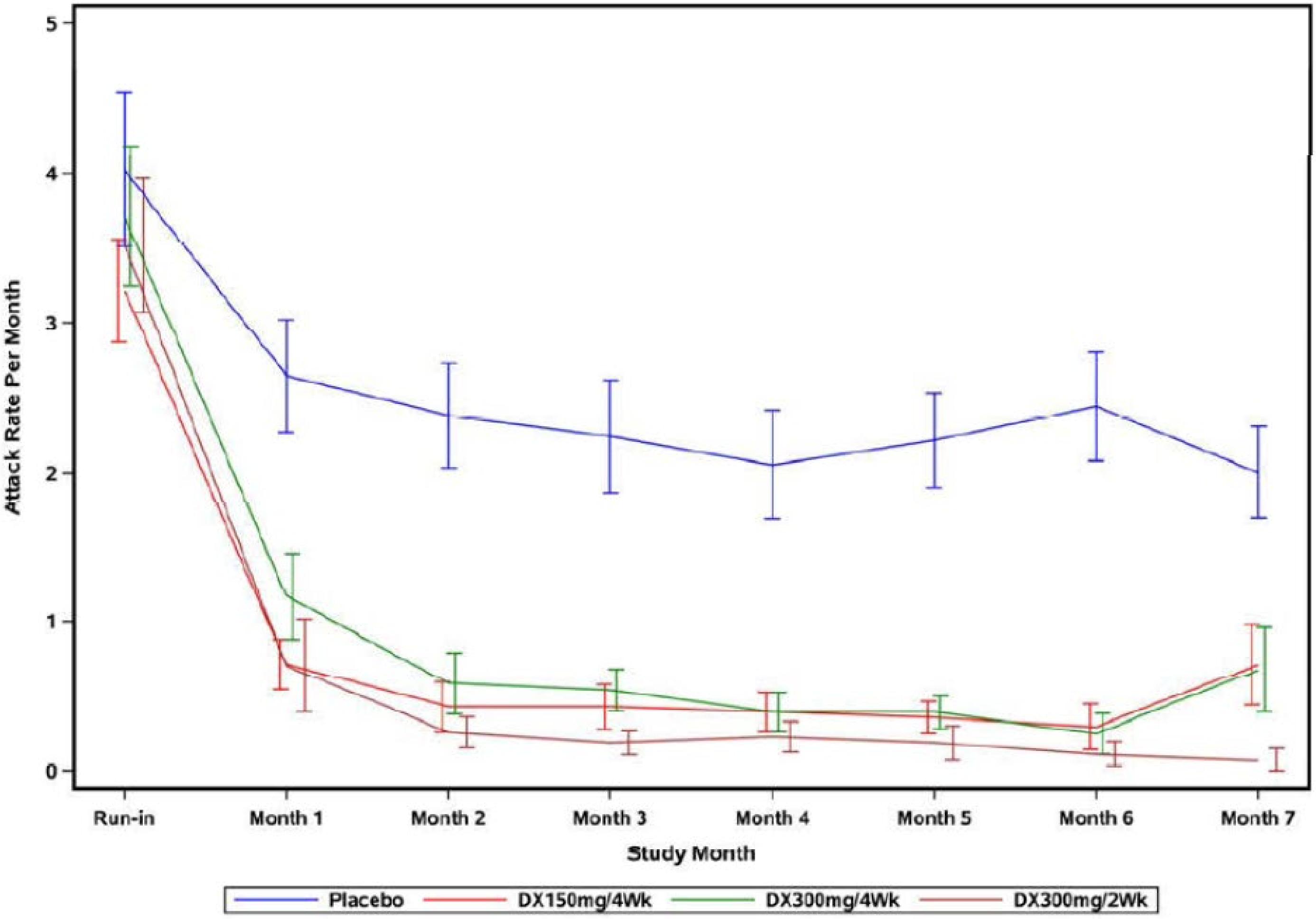
Figure 8: Investigator-Confirmed Hereditary Angioedema Attacks in HELP-03 (Individual Patients)



HAE = hereditary angioedema; LANA = lanadelumab; q.2.w. = every two weeks; q.4.w. = every four weeks.

Source: Clinical Study Report for HELP-03.[5]

Figure 9: Mean (Standard Error) Investigator-Confirmed Hereditary Angioedema Attack Rate per Month in HELP-03



DX = lanadelumab; Wk = week.

Source: Clinical Study Report for HELP-03.[5]

Appendix 3: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures used in the HELP-03 study and review their measurement properties (validity, reliability, responsiveness to change, and minimal clinically important difference [MCID]):

- Angioedema Quality of Life questionnaire (AE-QoL)
- EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L)

Additional outcome measures that were included as tertiary outcomes in HELP-04 extension study are listed below. These measurements are not reviewed, given the limited preliminary data that have been collected in the study and provided by the sponsor at the time of this review.

- Short Form (12) Health Survey, version 2 (SF-12v2)
- Hospital Anxiety and Depression Scale (HADS)
- Work Productivity and Activity Impairment: General Health questionnaire (WPAI-GH)
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Global Impression of Treatment Response
- Angioedema Control Test (AECT)

Findings

Table 54: Summary of Outcome Measures and Their Measurement Properties

Outcome Measure	Type	Conclusions About Measurement Properties	MCID
AE-QoL	The AE-QoL questionnaire is an angioedema-specific, patient-reported, health-related quality of life measure that consists of 17 questions in four domains: functioning, fatigue/mood, fears/shame, and food.[32] Each item has a total of five answers, 1 = never to 5 = very often, with each scored 0 to a maximum of 4 points, respectively. A total score and individual domain scores are generated and converted on to a linear scale of 0 to 100, with higher scores representing higher impairment.	**Validity:** Content, construct, and convergent validity were assessed in one study.[32] Content validity was assessed through a data-acquisition, item-generation, and item-reduction phase. Construct validity was assessed using a known-groups approach and demonstrated a linear relationship between self-rated disease and quality-of-life burden with the total AE-QoL score. Strong correlations were observed between the AE-QoL and DLQI total scores, and between the domain scores, supporting convergent validity of AE-QoL in recurrent angioedema. **Reliability:** Reliability of the AE-QoL instrument was demonstrated through internal consistency and test-retest assessments in one	The MCID was estimated to be 6.0 points for the total AE-QoL score, based on an anchored-based approach in a sample population of 278 patients with recurrent angioedema.[61] No MCID has been determined for domain-specific scores.

Outcome Measure	Type	Conclusions About Measurement Properties	MCID
		study.[32] The AE-QoL was found to have excellent internal consistency for the whole instrument as well as across each domain (Cronbach's alpha > 0.80). The AE-QoL was shown to have acceptable test-retest reliability for the total score and individual domains (Pearson coefficient $r > 0.70$). **Responsiveness:** One study investigated responsiveness of the AE-QoL measure to change in a sample of 278 patients with recurrent angioedema by correlating changes in its scores over time with changes in the applied anchors (self-rated angioedema disease and quality-of-life burden and SF-12).[61] The AE-QoL total score changes over time correlated moderately with changes in the self-rated angioedema activity and strongly with angioedema-specific quality-of-life impairment. The functional domain was observed to be the most sensitive to change. AE-QoL total score changes correlated weakly with changes in the SF-12 PCS and MCS scores.	
EQ-5D-5L	The EQ-5D-5L questionnaire is a generic, preference-based, health-related quality of life measure consisting of descriptive questions and a VAS.[62] The descriptive questions cover 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into 5 levels of perceived problems ranging from "no problems" to "extreme problems." The VAS records the subject's self-rated health on a 20 cm scale with end points 0 to 100 labelled "the worst health you can imagine" and "the best health you can imagine," respectively.	The EQ-5D-5L questionnaire was not validated in the patient population/indication.	The MCID was not determined in the patient population/indication.

AE-QoL = Angioedema Quality of Life questionnaire; DLQI = Dermatology Life Quality Index; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; MCID = minimal clinically important difference; MCS = mental component summary; PCS = physical component summary; SF-12 = Short Form (12) Health Survey; VAS = visual analogue scale.

Angioedema Quality of Life Questionnaire

The AE-QoL questionnaire is an angioedema-specific, patient-reported, health-related quality of life (HRQoL) measure.[32] It was developed and validated as the first instrument to measure HRQoL impairment in patients with any type of recurrent angioedema. It is a short, self-administered questionnaire that consists of 17 questions with five possible answers each (1 = never to 5 = very often). A recall period of four weeks was chosen, based on the heterogeneity in frequency of attacks in patients with recurrent angioedema. Each item answered by the respondent is scored between 0 and 4 points, depending on the answer chosen (i.e., never = 0 points, very often = 4 points). The questions address four domains: functioning (impairment of work, physical activity, and spare time activities); fatigue/mood (difficulties falling asleep, waking up during the night, feeling tired during the day, difficulties concentrating, feeling downhearted); fears/shame (feeling burdened from swellings, fear and embarrassment of new swellings, ashamed to visit public places, fear of long-term negative drug effects); and food (limitations in eating and in the selection of foods and beverages).[32] A total score and individual domain scores can be generated, based on the sum of all completed items divided by the maximum sum of all possible items. The raw scores are converted onto a linear scale ranging from 0 to 100, with higher scores representing higher HRQoL impairment.

Validity

The development and content validity of the AE-QoL instrument consisted of data-acquisition, item-generation, and item-reduction phases, and final instrument validation in a sample of 120 adult patients with recurring angioedema (n = 10, item generation; n = 110, instrument validation).[32] The validation population included 73 (66.4%) girls and women, adults aged 18 years and older, and three diagnosis categories: 1) type I/II hereditary angioedema (HAE), 2) chronic spontaneous urticaria (patients with wheals and angioedema), or 3) other (recurrent angioedema without C1-INH deficiency and without wheals or recurrent angioedema with no clear allocation to either category).

Validation of the AE-QoL consisted of construct and convergent validity assessments.[32] Construct validity was assessed using a known-groups approach: patients received a self-administered questionnaire that included sociodemographic questions, as well as self-rating of angioedema-specific questions based on a five-point scale for disease activity (response options: “none,” “one to two,” “three to four,” “more than four attacks,” and “attacks almost every day”) and quality-of-life impairment (response options: “none,” “mild,” “moderate,” “severe,” and “very severe”). A linear correlation was demonstrated between increasing AE-QoL total scores and increasing levels of self-rated angioedema activity ($P < 0.001$) and quality-of-life impairment ($P < 0.001$).[32] Of note, no correlation coefficients were provided in the study results. Convergent validity was assessed by testing the strength of correlation of the AE-QoL with other instruments that measured similar constructs: the Dermatology Life Quality Index (DLQI) and the generic 36-item Short Form Health Survey (SF-36). A strong correlation (Pearson coefficient $r > 0.50$) was observed between the AE-QoL and DLQI total scores, supporting convergent validity of AE-QoL in recurrent angioedema. The individual domain scores correlated more weakly with the DLQI scores ($r = 0.44$ for functioning, 0.38 for fatigue/mood, 0.40 for fears/shame, and 0.31 for food). The correlation of the AE-QoL total score and the SF-36 mental component summary (MCS) score was strong ($r = -0.68$), while the correlation with the SF-36 physical component summary (PCS) was weak ($r = -0.24$).[32] With respect to the individual domains, only the functioning domain correlated with the PCS score ($r = -0.47$), while the fatigue/mood and fears/shame domains correlated strongly with the MCS score ($r = -0.59$ and -0.525, respectively).

Reliability

Reliability of the AE-QoL instrument was demonstrated through internal consistency and test-retest assessments.[32] The AE-QoL was found to have excellent internal consistency for the whole instrument (Cronbach's alpha 0.89) as well as across each domain (Cronbach's alpha between 0.83 to 0.90). To assess test-retest reliability, a subsample of 46 patients (including 15 patients with HAE) were asked to complete the AE-QoL twice in three-week intervals. The AE-QoL was shown to have acceptable test-retest reliability (Pearson's coefficient for the total score was 0.83, and ranged from 0.68 to 0.90 for individual domains) based on the generally accepted threshold for patient-reported outcome measures.[32,63] The domain with the lowest reproducibility was the fatigue/mood domain.

Responsiveness to Change

A subsequent study by Weller and colleagues sought to assess both responsiveness to change and the MCID for the AE-QoL instrument.[61] Responsiveness of the AE-QoL measure to change was assessed in a sample of 278 patients with recurrent angioedema by correlating changes in its scores over time with changes in the applied anchors. The chosen anchors were self-rated angioedema-specific disease activity and quality-of-life impairment, as described in the initial validation study, as well as the 12-item Short Form Health Survey (SF-12).[32,61] AE-QoL total score changes over time correlated moderately with changes in the self-rated angioedema activity (Spearman's rho $r = 0.39$) and strongly with changes in the self-rated angioedema-specific quality-of-life impairment ($r = 0.5$). Furthermore, a strong correlation was observed with changes in the AE-QoL functioning domain ($r = 0.59$), and moderate correlations were observed in the other three domains, indicating that the functioning domain is the most sensitive to change. AE-QoL total score changes correlated weakly with changes in the SF-12 PCS ($r = −0.26$) and MCS ($r = −0.29$), and correlations were consistently weak across each AE-QoL domain.

Minimal Clinically Important Difference

The MCID of the AE-QoL was evaluated by anchor-based and distributional criterion approaches.[61] For the anchor-based approach, the magnitude (mean ± standard deviation [SD]) of the total AE-QoL score changes during improved (n = 26), unchanged (n = 60), or worsening (n = 18) self-rated angioedema-related quality-of-life impairment were –12.5 ± 16.5 (median –12.5), –0.3 ± 12.6 (median 0), and 6.3 ± 12.4 (median 6.5) points, respectively. A change was defined as a one-step change (e.g., from moderate to severe, or moderate to mild). In a second approach, a receiver operating characteristic (ROC) curve analysis of the self-rated quality-of-life impairment ratings identified the best cut-off point for clinically meaningful changes in the AE-QoL total score to be –5.5 points for QoL improvement and 5.5 points for QoL worsening, based on a desired balance of sensitivity and specificity.[61] The distributional criterion approach (one-half of the SD of the baseline AE-QoL total score values) estimated an MCID of 10.5 points. Given that the anchor-based approach is a more direct and patient-centred method over the distributional criterion approach, the results of the anchor-based approach were favoured by the authors, and an MCID of six points was chosen as a meaningful change in quality of life to the patient.[61] The MCID value for each AE-QoL domain scores was not evaluated in this study. Based on the statistical analysis plan (SAP) protocol for the HELP-03 study, the method of using one-half of the SD in baseline domain scores was used to determine the MCID and responder definition (RD) for the individual domain scores.[5]

Limitations

To date, only one group has evaluated the validity, reliability, and responsiveness of the AE-QoL instrument in recurrent angioedema.[32,61] The validated patient population includes type I and type II HAE, patients with chronic spontaneous urticaria (patients with wheals and angioedema), as well as other patients with undefined recurrent angioedema. As a result, the validation data are limited by the small (n = 110) and heterogenous patient sample. Additionally, the AE-QoL tool was validated only in adults > 18 years and therefore use in adolescents is not currently supported. Furthermore, the validation of the instrument was performed in two specialized centres in Germany, limiting generalizability to additional cultures as well as levels of care (i.e., primary, secondary).[61] The initial validation study included only 21 (19.1%) of patients with type I or type II HAE; based on the clinical experts' opinion, patients with HAE experience additional mucosal and abdominal symptoms that may not be adequately and accurately captured in the AE-QoL instrument. While the second study assessing responsiveness to change and the MCID was performed in a larger sample size (n = 278), the subgroup sample sizes for the number of patients who improved or worsened were not large enough to stratify the MCID analysis for different baseline levels of angioedema-related quality-of-life impairment. Last, a patient-centred MCID for each of the four domains was not evaluated.[61]

Conclusion

The AE-QoL questionnaire is the first validated angioedema-specific, patient-reported, HRQoL measure.[32] The AE-QoL was assessed for validity, reliability, responsiveness to change, and for the MCID by one research group in two subsequent studies.[32,61] Construct validity was demonstrated by a linear correlation between increasing AE-QoL scores and increasing levels of self-rated angioedema activity and quality-of-life impairment. Strong correlations were observed between the AE-QoL and DLQI total scores, and between the domain scores, supporting convergent validity of AE-QoL in recurrent angioedema. Conversely, while the correlation of the AE-QoL total score and the SF-36 MCS score was strong, the correlation with the SF-36 PCS was weak. The AE-QoL was found to have excellent internal consistency for the whole instrument as well as across each domain. The AE-QoL was also shown to have good reproducibility for the total score and individual domains, the least reproducible being the fatigue/mood domain. Responsiveness to change assessments demonstrated that changes in the AE-QoL total score correlated with changes in the patients' self-rated disease activity and quality-of-life impairment, as well as in the functioning domain. However, changes in the AE-QoL total score were not shown to be strongly correlated with changes in the comparator instruments or in the remaining three AE-QoL domains.[61] The MCID for the total AE-QoL score was estimated to be six points. Overall, the validation of the AE-QoL in the patient population is limited by a small sample size, which includes only small subset of patients with type I or type II HAE.

EuroQol 5-Dimensions 5-Levels Questionnaire

The EQ-5D-5L questionnaire is a generic, preference-based, HRQoL measure consisting of descriptive questions and a visual analogue scale (VAS).[62] The descriptive questions cover five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into five levels (1, 2, 3, 4, 5) representing “no problems,” “slight problems,” “moderate problems,” “severe problems,” and “extreme problems,” respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. The five questions are scored and together contribute to the EQ-5D index (utility) score between 0 and 1, where 0 represents death and 1 represents perfect health. Different utility functions are available that reflect the preferences of specific populations (e.g., US, UK). In the SAP protocol for the HELP-03 study, it is indicated that the index utility score was calculated using the developers’ algorithm based on the country-specific reference score set (Germany, UK, and US).[5] The second part of the tool records the subject’s self-rated health on a 20 cm scale with end points 0 and 100, with respective anchors of “the worst health you can imagine” and “the best health you can imagine,” respectively.

The EQ-5D-5L measure has not been validated in patients with recurrent angioedema or type I/type II HAE, specifically. Therefore, its validity, reliability, and responsiveness to change has not been evaluated in the patient population/indication of interest. In the absence of an MCID or RD for the EQ-5D index and VAS score in HAE, a range of estimates was used in the HELP-03 study, which includes the range 0.05 to 0.08 estimated in other conditions, as well as the one-half SD of the baseline scores method (as described in the HELP-03 SAP protocol). Of note, the MCID estimate for the EQ-5D-5L index score determined in a Canadian population is slightly more narrow (summarized mean of 0.056 ± 0.011, interquartile range 0.049 to 0.063).[64] Given that this is neither a patient- nor disease-centred approach, the estimated MCIDs as reported in the SAP protocol may not be clinically relevant. Overall, the EQ-5D-5L is not considered a validated outcome in the study population.

Appendix 4: Summary of World Allergy Organization and the European Academy of Allergy and Clinical Immunology (WAO/EAACI) Recommendations for the Management of Hereditary Angioedema

Category	Recommendation	Grade	Strength
Diagnosis	• Recommend that all patients suspected to have type I or II HAE are assessed for blood levels of C1-INH function, C1-INH protein, and C4. If any of the levels are abnormally low, the tests should be repeated to confirm the diagnosis of type I or II HAE	D	Strong
On-demand treatment	• Recommend that all HAE attacks are considered for on-demand treatment and that any HAE attack affecting or potentially affecting the upper airway is treated	D	Strong
	• Recommend that HAE attacks are treated as early as possible	B	Strong
	• Recommend that HAE attacks are treated with either C1-INH, ecallantide, or icatibant	A	Strong
	• Recommend that intubation or surgical airway intervention is considered early in progressive upper airway edema	C	Strong
	• Recommend that all patients have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times	D	Strong
STP	• Recommend short-term prophylaxis before procedures that can induce an attack	C	Strong
LTP	• Recommend LTP treatment be considered for patients who face events in life that are associated with increased disease activity	D	Strong
	• Recommend that patients are evaluated for LTP treatment at every visit. Disease burden and patient preference should be taken into consideration.	D	Strong
	• Recommend use of C1-inhibitor for first-line LTP treatment	A	Strong
	• Suggest the use of androgens as second-line LTP treatment	C	Weak
	• Suggest adaptation of LTP in terms of dosage and/or treatment interval as needed to minimize burden of disease	D	Weak
Management in children	• Recommend that testing children from HAE-affected families be carried out as soon as possible and that all offspring of an affected parent be tested	D	Strong
	• Recommended that C1-INH be used for treatment of HAE attacks in children under the age of 12	C	Strong
Management in pregnancy / lactation	• Recommend C1-INH as the preferred therapy for HAE attacks during pregnancy and lactation	D	Strong
Other	• Recommend that all patients have an action plan	D	Strong
	• Suggest that HAE-specific comprehensive, integrated care be available for all patients	D	Weak
	• Recommend that all patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer	C	Strong
	• Recommend that all patients with HAE should be educated about possible triggers that may induce HAE attacks	C	Strong

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; LTP = long-term prophylactic; STP = short-term prophylactic.

Source: Mauer et al., 2018.[16]

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