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CADTH DRUG REIMBURSEMENT REVIEW

Clinical Review Report

Emicizumab (HEMLIBRA)

Hoffmann-La Roche Ltd.

Indication: Bleeding prevention, hemophilia A

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Abbreviations

ABR	annualized bleeding rate
AE	adverse event
AHCDC	Association of Hemophilia Clinic of Directors of Canada
ANOVA	analysis of variance
BU	Bethesda unit
CBU	chromogenic Bethesda unit
CI	confidence interval
CHS	Canadian Hemophilia Society
CrI	credible interval
DIC	deviance information criterion
EmiPref	Emicizumab Preference (Survey)
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
EQ VAS	EuroQol Visual Analogue Scale
FVIII	factor VIII
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
Haemo-QoL-SF	Haemophilia-Specific Quality of Life Questionnaire for Children Short Form
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ISTH	International Society on Thrombosis and Haemostasis
ITC	indirect treatment comparison
ITT	Intention to treat
MID	minimal important difference
NIS	non-interventional study
NMA	network meta-analysis
PROBE	Patient-Reported Outcomes, Burdens, and Experiences
RCT	randomized controlled trial
RD	responder definition
RE	random-effects
rFVIII	recombinant factor VIII
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SLR	systematic literature review
SQ-ISHI	Satisfaction Questionnaire – Intravenous Subcutaneous Hemophilia Injection
VAS	visual analogue scale

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Emicizumab (Hemlibra) 30.0 mg/mL, 60.0 mg/0.4 mL (150.0 mg/mL), 105.0 mg/0.7 mL (150.0 mg/mL), 150.0 mg/mL solution for subcutaneous injection
Indication under review	For patients with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes. There is limited clinical experience of emicizumab use in patients with mild or moderate hemophilia A.
Reimbursement request	For patients with severe hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors as per HAVEN 3 trial patient eligibility and including: • Patients who are at significant risk of increased bleeding rates due to factors that lead to poor adherence or persistence despite being candidates for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes with factor VIII • Patients who have limited ability to receive regular IV therapy due to other underlying factors, such as venous access challenges or geographical treatment access restrictions, despite being candidates for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes with factor VIII
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	June 14 2019
Sponsor	Hoffmann-La Roche Ltd.

NOC = Notice of Compliance.

Note: Full indication is for patients with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes. The focus of this review relates to patients with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors.

Introduction

Hemophilia A is a rare, congenital bleeding disorder caused by mutations in the gene that produces factor VIII (FVIII). The disorder causes excessive bleeding due to the inability to form blood clots.[1-4] Hemophilia A is an X-linked disorder, meaning that it affects more male patients than female patients. The severity of hemophilia A is based on factor levels, where severe hemophilia A is defined by factor levels less than 1%.[2,3,5] According to a report from 2019 from the Canadian Blood Disorders Registry, there were 3,091 Canadians living with hemophilia A, of whom 1,040 had severe hemophilia A.[6]

Patients with hemophilia A can experience internal or external bleeding episodes, including bleeding into joints, bleeding into soft tissues and muscles, bleeding in the mouth, blood in the urine, and surface bleeding. Bleeding associated with hemophilia A can result in complications such as joint damage from repetitive bleeding, deep internal bleeding, and neurological problems or death associated with bleeding in the brain. According to the patient input received for this review, hemophilia A negatively affects the lives of patients physically, psychologically, and financially.

In Canada, the standard of care for the treatment of patients with severe hemophilia A is with IV FVIII prophylaxis. Of note, some patients with mild or moderate hemophilia A may require FVIII prophylaxis,[7] while some patients with severe hemophilia may have a preference for episodic FVIII treatment. There are several different recombinant FVIII (rFVIII) products currently available for prophylactic use in Canada. Current treatments with FVIII (prophylactic or episodic) requires IV infusions administered by patients or caregivers in the home setting.

Emicizumab is indicated for patients with hemophilia A (congenital FVIII deficiency) with or without FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.[8] The focus in the current review is patients without FVIII inhibitors. Emicizumab has not been previously reviewed by CADTH, but has been available for use in Canada since August 2018 for patients with hemophilia A (congenital FVIII deficiency) with FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.[9]

The recommended dosage of emicizumab consists of a loading dose of 3.0 mg/kg emicizumab once weekly for the first 4 weeks as a subcutaneous (SC) injection. This is followed by a maintenance dose administered 1 week after the last loading dose. The maintenance dose should be selected based on physician and patient or caregiver preference to support adherence, taking into account the age and weight of the patient:[8]

- Use in adolescents and adults greater than or equal to 40 kg: The recommended maintenance dose for adolescents (12 years to 17 years of age) and adults (greater than or equal to 18 years of age) who weigh greater than or equal to 40 kg, with or without inhibitors to FVIII, is 1.5 mg/kg once weekly, 3.0 mg/kg every 2 weeks, or 6.0 mg/kg every 4 weeks administered as an SC injection. No dosage adjustments are recommended.
- Use in pediatric patients and other patients weighing less than 40 kg: The recommended maintenance dose for pediatric patients (less than 12 years of age) of any weight, or patients of any age who weigh less than 40 kg, with or without inhibitors to FVIII, is 1.5 mg/kg once weekly or 3.0 mg/kg every 2 weeks administered as an SC injection. No dose adjustments are recommended in pediatric patients.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of emicizumab injection for the treatment of hemophilia A (congenital FVIII deficiency) in patients without FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

Stakeholder Engagement

The information in this section is a summary of the input provided by the patient groups who responded to CADTH's call for patient input and the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One patient group submitted patient input. The Canadian Hemophilia Society (CHS) is a national voluntary health charity with a mandate to improve the health and quality of life of Canadians with inherited bleeding disorders and, ultimately, to find cures. CHS solicited patient perspectives through personal meetings or conferences and conducted an online survey between May 31, 2019 and June 15, 2019 to collect perspectives from patients with hemophilia A and their caregivers. A total of 52 responses were collected from patients

affected by hemophilia A without inhibitors. All respondents were affected by hemophilia A without inhibitors: 45 with severe hemophilia, 4 with moderate hemophilia, 2 with mild hemophilia, and 1 with unknown severity.

In preparing their patient input submission, CHS received external help from physicians of the Association of Hemophilia Clinic of Directors of Canada (AHCDC) and other health care professionals. AHCDC conducted a survey in June 2020 through which health care professionals provided treatment outcome data and patient-reported outcome comments from 14 of the 15 patients with hemophilia A without inhibitors who were receiving emicizumab through compassionate access.

Patient input highlighted that hemophilia A has a negative impact on patients' lives on physical, psychological, and financial levels. The key concerns raised by patients are breakthrough bleeds despite FVIII prophylaxis, damage to joints, venous access challenges, time lost from school and work, and adherence difficulties due to the complex treatment regimen. According to the CHS patient input, a vast majority of patients and caregivers expressed a clear desire for longer-lasting treatment, more reliable efficacy, and an easier mode of delivery, such as SC injections instead of IV infusions.

Almost all respondents reported being on FVIII prophylaxis through IV infusion, and most reported being "somewhat satisfied" to "quite satisfied" with currently available factor therapies. However, many patients reported that they still experience breakthrough bleeds. Although access to emicizumab is restricted to patients with hemophilia A with inhibitors in Canada, approximately 15 patients with hemophilia A without inhibitors received emicizumab through compassionate access starting in autumn 2019. In the AHCDC survey, health care providers indicated that these patients experienced an improvement in their quality of life while receiving emicizumab treatment, with fewer bleeds, less joint pain and discomfort, fewer hospital visits, and more independence.

CHS has suggested that patients with severe hemophilia and those with mild and moderate disease who have a severe phenotype would benefit most from treatment with emicizumab. As well, the society believes that the new treatment would greatly benefit babies and children for whom venous access is most difficult, patients who suffer from frequent breakthrough bleeds and joint disease despite FVIII prophylaxis, and patients who have difficulties adhering to the current treatment regimen, which requires frequent IV infusions.

Clinician Input

The clinical experts consulted by CADTH for this review identified access to a user-friendly treatment as the main unmet need for patients with hemophilia A.

The experts identified the following groups of patients with the greatest unmet need as most likely to benefit from treatment with emicizumab:

- children, for whom such treatment could help prevent complications in infancy and early childhood, prevent the need to insert a central line to facilitate easier venous access, and allow for earlier treatment prior to first bleed
- patients with significant venous access issues (e.g., children, anyone with dexterity issues due to age, disease, or injury, and anyone with severe needle phobia)
- patients with adherence issues (e.g., social factors)

- patients at high risk for inhibitor development (e.g., patients with a family history of inhibitor development, intron 22 inversion, or large deletions, or who were previously untreated)
- patients who had prior inhibitors eradicated but who need prophylaxis at a dose and/or frequency beyond the usual schedule
- patients with severe or moderate hemophilia A who continue to have spontaneous bleeding despite appropriate prophylaxis.

Emicizumab is expected to be used as another prophylaxis treatment option for patients, but is not expected to change the overall treatment paradigm. Clinical experts consulted by CADTH identified bleed frequency and absence of bleeds as important outcomes in assessing a patient's response to treatment. A meaningful response to treatment relates to a patient achieving their life goals (e.g., avoiding bleeds or reducing the number, attending school or work, socializing, practising sports, preserving normal joint function, or stopping or minimizing the progression of joint disease). Patient goals vary among patients.

The clinicians stated that the benefits of prophylactic treatment in patients with hemophilia can persist over the patient's entire lifespan, and that it is unlikely that a Canadian clinician would propose discontinuing prophylaxis. Patients may switch to a different treatment based on the degree of bleeding control achieved, patient preference, adverse events (AEs) (e.g., injection-site reactions), or the availability of a new product.

A clinician experienced in hemophilia treatment is required to oversee the treatment of patients who might receive emicizumab. Typically, this would be a hematologist or pediatric hematologist within a multidisciplinary team, such as a team including a nurse, physiotherapist, and social worker.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two phase III trials (HAVEN 3, N = 152, and HAVEN 4, N = 41) submitted by the sponsor were included in the systematic review.

HAVEN 3 was a 24-week, open-label, multi-centre, randomized controlled trial (RCT) that aimed to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with severe hemophilia A (i.e., intrinsic FVIII levels of less than 1%) without FVIII inhibitors who had received prior treatment with episodic or prophylactic FVIII. Patients who received episodic treatment with FVIII prior to study entry were randomized in a 2:2:1 ratio to the following treatment arms: emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly; emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 3.0 mg/kg every 2 weeks; no prophylaxis (control arm). Patients who received FVIII prophylaxis prior to study entry (derived from the non-interventional study [NIS]) were enrolled in a separate, non-randomized, single arm where they received treatment with emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly. Patients in this arm continued their regular FVIII prophylaxis treatment until the second emicizumab loading dose. In HAVEN 3, the primary outcome was related to the annualized bleeding rate (ABR) ratio for treated bleeds, where treated bleeds were defined as any bleed if coagulation factors were administered for the treatment signs or symptoms of bleeding (e.g., pain, swelling) irrespective of the time between the treatment and the

preceding bleed. The ABR was calculated as (number of bleeds divided by the total number of days during the 24-week period) multiplied by 365.25. Secondary outcomes pre-specified in the statistical testing hierarchy included additional bleeding outcomes (ABR ratio for all bleeds, treated joint bleeds, treated spontaneous bleeds, treated target joint bleeds) and health-related quality of life (HRQoL) (i.e., as measured by the Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL] physical health score).

HAVEN 4 was a 24-week, open-label, multi-centre, non-randomized, single-arm trial that aimed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab prophylaxis in patients with severe congenital hemophilia A without inhibitors or patients with congenital hemophilia A with FVIII inhibitors. All patients in HAVEN 4 received treatment with emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 6.0 mg/kg every 4 weeks.

Efficacy Results

In HAVEN 3, the primary outcome related to the ABR ratio for treated bleeds demonstrated a statistically significant reduction in bleeding for both emicizumab 1.5 mg/kg weekly and emicizumab 3.0 mg/kg every 2 weeks compared to no prophylaxis (i.e., episodic FVIII) for patients previously treated with episodic FVIII. In HAVEN 3, 55.6% of patients treated with 1.5 mg/kg weekly emicizumab experienced 0 treated bleeds during the efficacy period (Table 2). The ABR ratio between 1.5 mg/kg weekly emicizumab (ABR = 1.5) and no prophylaxis (ABR = 38.2) was 0.04 (95% confidence interval [CI], 0.020 to 0.075; P < 0.0001) in favour of 1.5 mg/kg weekly emicizumab. Sixty percent of patients treated with 3.0 mg/kg emicizumab every 2 weeks experienced 0 treated bleeds during the efficacy period. The ABR ratio between 3.0 mg/kg emicizumab every 2 weeks (ABR = 1.3) and no prophylaxis (ABR = 38.2) was 0.03 (95% CI, 0.017 to 0.066; P < 0.0001) in favour of 3.0 mg/kg emicizumab every 2 weeks. None of the patients in the no-prophylaxis group experienced 0 treated bleeds. The ABR ratios were clinically relevant, according to clinical experts consulted for this review.

In HAVEN 3, secondary outcomes related to the ABR ratio for all bleeds, treated joint bleeds, and treated spontaneous bleeds demonstrated a statistically significant reduction in bleeding for both 1.5 mg/kg emicizumab weekly and 3.0 mg/kg emicizumab every 2 weeks compared to no prophylaxis (i.e., episodic FVIII) for patients previously treated with episodic FVIII. The results of the sensitivity analyses for all bleeding outcomes in HAVEN 3 were consistent with the primary results.

For treated bleeds, an ABR ratio of 0.32 (95% CI, 0.195 to 0.514; P < 0.0001) in favour of 1.5 mg/kg weekly emicizumab was reported for the intra-patient comparison of patients treated with FVIII prophylaxis in the NIS (ABR = 4.8) compared to treatment with 1.5 mg/kg weekly emicizumab in HAVEN 3 (ABR = 1.5). The reduction in bleeding was clinically relevant, according to clinical experts consulted for this review. Similar efficacy findings were reported for the ABR ratio for all bleeds (Table 2).

In HAVEN 4, 56.1% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced 0 treated bleeds; the ABR was 2.4 (95% CI, 1.38 to 4.28). Similar ABRs were reported for the other bleeding outcomes (i.e., ABR for all bleeds, treated joint bleeds, treated spontaneous bleeds, treated target joint bleeds) (Table 2). Although no statistical hypothesis testing was performed, the clinical experts consulted for this review indicated that the ABR results were clinically relevant.

Haem-A-QoL physical health was a secondary outcome in HAVEN 3 (Table 2). The difference in the adjusted mean Haem-A-QoL physical health subscore at week 25 between patients receiving 1.5 mg/kg weekly emicizumab and those receiving no prophylaxis was 12.51 (95% CI, –1.96 to 26.98; P = 0.891). Given that statistical significance was not achieved, statistical testing according to the pre-specified hierarchy was stopped prior to the assessment of 3.0 mg/kg emicizumab every 2 weeks. Therefore, the potential effect on improved quality of life remains inconclusive.

Harms Results

In HAVEN 3, AEs occurred in 94.4% of patients receiving 1.5 mg/kg emicizumab weekly, 85.7% in those receiving 3.0 mg/kg emicizumab every 2 weeks, 50.0% in the no-prophylaxis arm, and 87.3% in the previous-FVIII-prophylaxis arm (1.5 mg/kg weekly emicizumab) (Table 2). In HAVEN 4, 73.2% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an AE. In both studies, the most common AEs were injection-site reactions. Notable harms identified in the protocol for this review included the following: thrombotic events, injection-site reactions, hypersensitivity reactions, inhibitor development, and blood-borne infections. The only notable harms reported in HAVEN 3 and HAVEN 4 were injection-site reactions, which occurred in 25.0% of patients on 1.5 mg/kg emicizumab weekly, 20.0% on 3.0 mg/kg every 2 weeks, 12.5% in the no-prophylaxis arm, and 31.7% in the previous-FVIII-prophylaxis arm (1.5 mg/kg weekly emicizumab). In HAVEN 4, 22.0% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an injection-site reaction.

Throughout HAVEN 3 and HAVEN 4, no instances of de novo inhibitor development were detected among patients who tested negative for inhibitors (titre less than 0.6 chromogenic Bethesda unit (CBU)/mL) at baseline.

In HAVEN 3, serious adverse events (SAEs) occurred in 2.8% of patients on 1.5 mg/kg emicizumab weekly, 8.6% of patients on 3.0 mg/kg every 2 weeks, 0% of patients in the no-prophylaxis arm, and 12.7% of patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). In HAVEN 4, 2.4% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an SAE. No SAE occurred in more than 1 patient per arm. No patients died in the studies.

The 24-week assessment period of HAVEN 3 and HAVEN 4 was determined to be of sufficient duration to identify harms, according to input provided by the clinical experts consulted in this review. Overall, the safety profiles were likely comparable between the 2 emicizumab treatment regimens (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks); however, due to the small sample size, further study is warranted.

Table 2: Summary of Key Results From Pivotal and Protocol Selected Studies

	HAVEN 3					HAVEN 4
				Intra-patient comparison (data from NIS and HAVEN 3)		
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	FVIII prophylaxis (NIS) N = 48	Previous FVIII prophylaxis (1.5 mg/kg QW emicizumab) N = 48	6.0 mg/kg Q4W emicizumab N = 41
Treated bleeds						
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	48 (100)	48 (100)	41 (100)
Patients experiencing 0 bleeds, n (%)	20 (55.6)	21 (60.0)	0	19 (39.6)	26 (54.2)	23 (56.1)
Annualized bleeding rate (95% CI)	1.5 (0.89 to 2.47)	1.3 (0.75 to 2.25)	38.2 (22.86 to 63.76)	4.8 (3.22 to 7.09)	1.5 (0.98 to 2.33)	2.4 (1.38 to 4.28)[c]
Annualized bleeding rate ratio (95% CI)	0.04 (0.020 to 0.075)[a]	0.03 (0.017 to 0.066)[a]	Reference group	0.32 (0.195 to 0.514)[b]		NA
P value	< 0.0001[a]	< 0.0001[a]		< 0.0001[b]		NA
All bleeds						
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	48 (100)	48 (100)	41 (100)
Patients experiencing 0 bleeds, n (%)	18 (50.0)	14 (40.0)	0	15 (31.3)	20 (41.7)	12 (29.3)
Annualized bleeding rate (95% CI)	2.5 (1.63 to 3.90)	2.6 (1.63 to 4.29)	47.6 (28.45 to 79.59)	8.9 (5.72 to 13.87)	3.3 (2.17 to 5.06)	4.5 (3.10 to 6.60)[c]
Annualized bleeding rate ratio (95% CI)	0.05 (0.028 to 0.099)[a]	0.06 (0.030 to 0.103)[a]	Reference group	0.37 (0.220 to 0.626)[b]		NA
P value	< 0.0001[a]	< 0.0001[a]		< 0.0001[b]		NA
Treated joint bleeds						
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	NR	NR	41 (100)
Patients experiencing 0 bleeds, n (%)	21 (58.3)	26 (74.3)	0	NR	NR	29 (70.7)
Annualized bleeding rate (95% CI)	1.1 (0.59 to 1.89)	0.9 (0.44 to 1.67)	26.5 (14.67 to 47.79)	NR	NR	1.7 (0.82 to 3.68)[c]
Annualized bleeding rate ratio (95% CI)	0.04 (0.019 to 0.085)[a]	0.03 (0.015 to 0.070)[a]	Reference group	NR	NR	NA
P value	< 0.0001[a]	< 0.0001[a]		NR	NR	NA

	HAVEN 3					HAVEN 4
				Intra-patient comparison (data from NIS and HAVEN 3)		
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	FVIII prophylaxis (NIS) N = 48	Previous FVIII prophylaxis (1.5 mg/kg QW emicizumab) N = 48	6.0 mg/kg Q4W emicizumab N = 41
Treated spontaneous bleeds						
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	NR	NR	41 (100)
Patients experiencing 0 bleeds, n (%)	24 (66.7)	31 (88.6)	4 (22.2)	NR	NR	34 (82.9)
Annualized bleeding rate (95% CI)	1.0 (0.48 to 1.91)	0.3 (0.11 to 0.75)	15.6 (7.60 to 31.91)	NR	NR	0.6 (0.27 to 1.53)[c]
Annualized bleeding rate ratio (95% CI)	0.06 (0.025 to 0.151)[a]	0.02 (0.006 to 0.056)[a]	Reference group	NR	NR	NA
P value	< 0.0001[a]	< 0.0001[a]		NR	NR	NA
Treated target joint bleeds						
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	NR	NR	41 (100)
Patients experiencing 0 bleeds, n (%)	25 (69.4)	27 (77.1)	5 (27.8)	NR	NR	35 (85.4)
Annualized bleeding rate (95% CI)	0.6 (0.28 to 1.42)	0.7 (0.27 to 1.64)	13.0 (5.22 to 32.33)	NR	NR	1.0 (0.31 to 3.26)[c]
Annualized bleeding rate ratio (95% CI)	0.05 (0.016 to 0.143)[a,d,e]	0.05 (0.018 to 0.147)[a,d,e]	Reference group	NR	NR	NA
P value	< 0.0001[a,d,e]	< 0.0001[a,d,e]		NR	NR	NA
Haem-A-QoL physical health subscore						
Number of patients contributing to the analysis (%)	34 (94.4)	29 (82.9)	13 (76.5)	NR	NR	38 (92.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25, mean (SD)	31.81[a] (NR)	28.35[a] (NR)	44.32[a] (NR)	NR	NR	32.43 (25.43)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in adjusted mean at week 25 (95% CI)	12.51 (–1.96 to 26.98)[b]	15.97 (1.16 to 30.78)[b]	Reference Group	NR	NR	NA
P value	0.0891[b]	0.0349[b]		NR	NR	NA

	HAVEN 3					HAVEN 4
				Intra-patient comparison (data from NIS and HAVEN 3)		
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	FVIII prophylaxis (NIS) N = 48	Previous FVIII prophylaxis (1.5 mg/kg QW emicizumab) N = 48	6.0 mg/kg Q4W emicizumab N = 41
Harms, n (%)						
Adverse events	34 (94.4)	30 (85.7)	8 (50.0)	NR	55 (87.3)	30 (73.2)
Serious adverse events	1 (2.8)	3 (8.6)	0	NR	8 (12.7)	1 (2.4)
Patients who stopped treatment due to adverse events	0	1 (2.9)	0	NR	0	0
Deaths	0	0	0	NR	0	0
Notable harms, n (%)						
Injection-site reaction	9 (25.0)	7 (20.0)	2 (12.5)	NR	21 (33.3)	9 (22.0)

CI = confidence interval; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; ITT = intention to treat; NA = not applicable; NIS = non-interventional study; NISP = non-interventional study prophylactic FVIII; NR = not reported; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly; SD = standard deviation.

[a] ITT population; negative binomial regression model; P value using stratified Wald test through global model with 3-level categorical effect for treatment.

[b] NISP population; negative binomial regression model; P value using non-stratified Wald test.

[c] All-treated-patients population, negative binomial regression model.

[d] P value has not been adjusted for multiple testing.

[e] Treated target joint bleeds occur in a target joint, defined as a joint in which ≥ 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. Bleeds due to surgery or procedures are excluded.

[f] No instance of de novo inhibitor development was detected in patients who tested negative for inhibitors (titre < 0.6 CBU/mL) at baseline.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Critical Appraisal

The key limitations of the body of evidence relate to the open-label study design, the absence of randomized, direct comparative data between emicizumab and FVIII prophylaxis, and generalizability to the Canadian clinical population.

HAVEN 3 and HAVEN 4 were open-label studies. The open-label design may have biased the subjective outcome results in favour of emicizumab. HAVEN 4, a single-arm study, was limited by its non-controlled study design. In HAVEN 4, analyses of all outcomes were descriptive, and no formal hypothesis testing was performed.

There is no direct comparative evidence to support the efficacy of emicizumab compared to FVIII prophylaxis in patients with severe hemophilia A. There is limited evidence from an intra-patient analysis (group D in HAVEN 3) that supports the efficacy of emicizumab in patients previously treated with FVIII prophylaxis.

The majority of patients with severe hemophilia A enrolled in HAVEN 3 (groups A, B, and C) were previously treated with episodic FVIII. This is not reflective of Canadian clinical practice, in which the standard of care for patients with severe hemophilia A is treatment with FVIII prophylaxis. Furthermore, patients in HAVEN 3 and HAVEN 4 who had previously received treatment with episodic FVIII were required to have 5 or more bleeds in the 24 weeks prior to study entry. This is inconsistent with Canadian clinical practice, as it is unlikely for Canadian patients with 5 or more bleeds over a period of 24 weeks to be treated with episodic FVIII.

Results of HAVEN 3 and HAVEN 4 may have limited generalizability to the Canadian patient population. In both studies of patients without inhibitors, the study population was restricted to patients with severe hemophilia A. According to clinical experts consulted for this review, there is a subset of patients with mild or moderate hemophilia who require prophylaxis. The designs of HAVEN 3 and HAVEN 4 did not include these patients; thus, the magnitude of the treatment effect in patients with mild and moderate hemophilia A is unclear.

Indirect Comparisons

Description of Studies

One network meta-analysis (NMA) provided by the sponsor was reviewed. The sponsor-submitted NMA compared emicizumab prophylaxis with FVIII prophylaxis for patients with hemophilia A without inhibitors.[12,13] The selection of trials for the NMA was based on a systematic literature review (SLR). The SLR was performed in December 2016 and updated for the non-inhibitor population in May 2018.

Efficacy Results

The NMA submitted by the sponsor showed that both emicizumab prophylaxis regimens (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks) were associated with a reduction in total treated bleeds (reductions of 64% and 69%, respectively) compared with FVIII prophylaxis in patients with severe hemophilia A without inhibitors.

Harms Results

Harms were not assessed in the NMA submitted by the sponsor.

Critical Appraisal

Limitations associated with the NMA submitted by the sponsor included the small number of trials with small sample size included in the NMA; the high degree of clinical and statistical heterogeneity across the included studies in terms of disease severity; the use of different comparator FVIII products in different trials; inconsistent or unclear definitions of the bleed outcomes; variable outcome estimation time points across trials; and differences in study design.

These results were aligned with those observed in patients previously treated with FVIII prophylaxis (arm D) in the HAVEN 3 trial. However, due to various methodological limitations, the findings of the sponsor-submitted NMA should be interpreted with caution. In addition, no NMA was performed for safety outcomes, and no evidence for children younger than 7 years old was included in the NMA. No robust conclusions on the comparative clinical efficacy and safety profile of emicizumab prophylaxis regimens versus rFVIII prophylaxis in patients with hemophilia without inhibitors can be drawn.

Other Relevant Evidence

Description of Studies

One other relevant study submitted by the sponsor was reviewed. The HOHOEMI study provides evidence of the efficacy and safety of SC emicizumab prophylaxis in a pediatric population with hemophilia A without FVIII inhibitors. The HOHOEMI study is a phase III, multi-centre, open-label, non-randomized clinical trial evaluating 2 dosing regimens for emicizumab after the administration of 4 loading doses of 3.0 mg/kg emicizumab per week. Patients received 3.0 mg/kg every 2 weeks or 6.0 mg/kg every 4 weeks for at least 24 weeks. For the purpose of this review, only data from the 3.0 mg/kg cohort are presented. The 6.0 mg/kg dose is not relevant to the Canadian pediatric population because it is beyond the dosing recommended by Health Canada for this patient population. The primary efficacy outcome was bleeding frequency, expressed as an ABR. ABR was estimated using negative binomial regression, with the treatment period as an offset to account for varying follow-up periods. Pre-treatment ABRs were calculated using documented bleed information and standardized for the different age groups over different durations: 12 weeks ([redacted]) for patients less than 2 years of age and 24 weeks ([redacted]) for patients 2 years and older. Calculated ABRs were computed by dividing the number of bleeding events by the evaluation period in days and multiplying this rate by 365.25. Patient preference was also identified in the CADTH review protocol as an outcome of relevance. It was also measured in the HOHOEMI study.

To be eligible for the HOHOEMI study, patients had to be less than 12 years of age, weigh more than 3 kg, and have severe (i.e., less than 1% endogenous FVIII) congenital hemophilia A without FVIII inhibitors (i.e., test negative, with less than 0.6 Bethesda unit (BU)/mL inhibitors within 8 weeks prior to enrolment). A total of 6 Japanese male patients were enrolled in the 3.0 mg/kg emicizumab cohort. All were previously on FVIII prophylaxis treatment.

Efficacy Results

Findings from the HOHOEMI study showed that all patients who received 3.0 mg/kg emicizumab experienced bleeding events. Of these patients[redacted]

[redacted]

[redacted]

All caregivers preferred emicizumab prophylaxis over previous hemophilia treatments. The main reasons were lower treatment frequency (38% of caregivers) and fewer effects on daily activities and social interactions (23.1% of caregivers).

Harms Results

[redacted]

Critical Appraisal

Limitations of the HOHOEMI study include the small sample size, the lack of randomization and blinding, and the lack of a control group. No conclusion can be made regarding the efficacy of emicizumab, given that no statistical testing was conducted against a control group. In addition, the study was conducted in Japanese children at 4 study sites in Japan, and may not be generalizable to Canadian patients. Therefore, the evidence from the HOHOEMI study on the efficacy and safety of emicizumab in pediatric patients is limited by concerns regarding internal validity and generalizability to the Canadian population.

Conclusions

Two phase III, open-label clinical trials, HAVEN 3 and HAVEN 4, were included in this review to provide evidence of the efficacy and safety of emicizumab in patients with severe hemophilia A without inhibitors. In HAVEN 3, both doses of emicizumab (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks) showed a reduction in bleeding outcomes compared to no prophylaxis (i.e., episodic FVIII treatment). In HAVEN 4, based on descriptive analysis, patients treated with 6.0 mg/kg emicizumab every 4 weeks had ABRs that were generally aligned with those of patients treated with both doses of emicizumab in HAVEN 3. Despite being assessed in both studies, the effect of emicizumab on HRQoL remains unknown. The most common AE in both studies was injection-site reaction. No major safety signals were identified in the studies, and no patients died.

The body of evidence was limited by the open-label study design, the absence of randomized, direct comparative data between emicizumab (1.5 mg/kg every 2 weeks, 3.0

mg/kg every 2 weeks, and 6.0 mg/kg every 4 weeks mg/kg) and FVIII prophylaxis (the current standard of care), and issues with generalizability to the Canadian clinical population.

Methodological limitations with the sponsor's NMA prevented robust conclusions pertaining to the comparative clinical efficacy and safety profile of emicizumab prophylaxis regimens versus rFVIII prophylaxis in patients with hemophilia without inhibitors.

Introduction

Disease Background

Hemophilia is a bleeding disorder caused by changes in coagulation factors involved in the blood-clotting process.[4] Hemophilia A is the most common form. It is a rare, congenital bleeding disorder caused by mutations in the gene that produces FVIII; this leads to excessive bleeding due to the inability to form blood clots.[1-4] Hemophilia A is an X-linked disorder, meaning that it affects more male patients than female patients. The severity of hemophilia A is categorized as mild, moderate, or severe, and is based on factor levels. Mild hemophilia A is defined by factor levels of 5% to less than 40%. Moderate hemophilia A is defined by factor levels of 1% to 5%.[5] Severe hemophilia A is defined by factor levels of less than 1%; it primarily affects males.[2,5] According to a report from 2019 from the Canadian Blood Disorders Registry, there were 3,091 Canadians living with hemophilia A, of whom 1,040 had severe hemophilia A.[6]

Common symptoms of hemophilia include bleeding into joints, bleeding into soft tissues and muscles, bleeding in the mouth, blood in the urine, surface bleeding, and easy bruising.[1] Patients with hemophilia A can experience bleeding episodes that occur internally or externally. In some cases, there is a known cause, such as an injury; alternatively, the cause may be unknown and is referred to as a spontaneous bleed. Spontaneous bleeding events are more common in patients with severe hemophilia A than in patients with mild or moderate hemophilia A.

Bleeding associated with hemophilia A can result in complications such as joint damage from repetitive bleeding, deep internal bleeding, and neurological problems or death associated with bleeding in the brain. According to the patient input received for this review, hemophilia A has a negative impact on patients' lives on physical, psychological, and financial levels. The key concerns raised by patients are breakthrough bleeds, venous access challenges, and adherence difficulties due to the complex treatment regimen.

Diagnosis of hemophilia A is based on factor assays (through blood tests) for FVIII.[5] Patients with a family history of hemophilia A are typically diagnosed at birth. Patients without a family history are typically diagnosed after presentation of large bruising or bleeding; this often occurs prior to their first birthday. Diagnosis can also occur through laboratory abnormalities (e.g., clotting factor) detected at screening (usually pre-surgical). The clinical experts consulted for this review indicated that diagnostic factor assays are readily available in Canada and misdiagnosis of hemophilia A is unlikely.

In Canada, patients with hemophilia A are typically treated in a hemophilia treatment centre by a multidisciplinary team that includes a physician with specific skills in treating bleeding disorders, a nurse, a physiotherapist, and a social worker.[2] In some cases, access to an orthopedic surgeon, internal medicine specialists, and infectious disease specialists may be incorporated for patients with comorbidities.

Standards of Therapy

Currently, there is no cure for hemophilia A. Desmopressin can be used to treat patients with mild or moderate hemophilia A. Alternatively, episodic FVIII can be used to treat bleeding episodes in these patients.[5,14] Although it is less common, some patients with mild or moderate hemophilia A may require FVIII prophylaxis to control bleeding.[7]

In Canada, the standard of care for treatment of severe hemophilia A is FVIII prophylaxis.[5,15] Nonetheless, some patients may be treated with an episodic FVIII regimen. However, this is not recommended as a long-term treatment option.[5]

In the past, FVIII was replaced through blood product, plasma, cryoprecipitate, and plasma-derived FVIII. Currently, virus-inactivated, plasma-derived FVIII and rFVIII are used.[5] Recombinant FVIII is manufactured from a cell line and is blood product-free; this eliminates the risk of transmission of blood-borne infections (e.g., HIV). There are several different rFVIII products currently available for prophylactic use in Canada (e.g., Eloctate, Adynovate, Jivi, Kovaltry, Nuwiq, Xyntha). Alternatively, plasma-derived FVIII products can be used (e.g., Humate-P, Wilate). FVIII replacements can be administered through fixed dosing regimens or tailored regimens that are individualized to patients' needs.[5]

Current treatments with FVIII (prophylactic or episodic) require IV infusions administered by patients or caregivers in the home setting. Patients treated prophylactically are typically treated 3 times a week. IV infusions are usually performed through venous puncture; however, a venous access port may be used in patients with challenging venous access (e.g., pediatric or geriatric patients) or in those who require more frequent infusions (e.g., patients who develop inhibitors).

According to the clinical experts consulted for this review, treatment of hemophilia A typically begins in children as soon as they are active and mobile (12 months to 15 months of age), or as soon as feasible after diagnosis (before the first bleed or after 1 or 2 bleeds). Most pediatric patients in Canada are treated with FVIII prophylaxis. Despite prophylactic FVIII being the standard of care for the treatment of severe hemophilia A, a greater proportion of adult patients (compared to pediatric patients) are treated with episodic FVIII; this may be attributed to patient preference. There are some adult patients who are more familiar with episodic FVIII treatment (e.g., it may have been the only available treatment during their childhood) and choose to remain on it instead of switching to prophylactic FVIII treatment despite the expected advantages associated with prophylaxis.

The transition from pediatric patient care (where treatment is administered by parents or caregivers) to adolescent or adult care (when patients may begin to self-administer treatment) presents a challenge, largely due to adherence.[5] During this time, patients are transitioning to greater independence in their everyday lives, may be involved in more extracurricular activities, and may be more focused on their social lives.

Patients who provided input to CADTH reported experiencing breakthrough bleeds, damage to joints, pain, reduced mobility, and iatrogenic complications due to frequent IV infusions, despite prophylaxis therapy. Patients and caregivers expressed a clear desire for a longer-lasting treatment, less frequent administration, and an easier mode of treatment delivery (i.e., not IV). Clinicians indicate that a simpler mode of delivery would be especially beneficial to babies and children, for whom venous access is the most challenging.

Drug

Emicizumab (Hemlibra) is an engineered, humanized, monoclonal modified immunoglobulin G4 bispecific antibody.[8] It bridges activated factor IX and factor X to restore the natural function of activated FVIII that is missing in patients with hemophilia A and needed for effective hemostasis.[8]

Emicizumab is indicated for patients with hemophilia A (congenital FVIII deficiency) with or without FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes. There is limited clinical experience of emicizumab use in patients with mild or moderate hemophilia A.[8] Emicizumab has been available for use in Canada since August 2018 for patients with hemophilia A (congenital FVIII deficiency) with FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.[9] The National Advisory Committee on Blood and Blood Products has already reviewed the efficacy and safety of emicizumab in patients with FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

The focus of this review is on patients with hemophilia A (congenital FVIII deficiency) without FVIII inhibitors using routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes. Emicizumab has undergone expedited (priority) review by Health Canada to add patients without inhibitors to the indication.

The sponsor's reimbursement request differs from the Health Canada indication and is as follows:

- For patients with severe hemophilia A (congenital FVIII deficiency) without FVIII inhibitors as per HAVEN 3 trial patient eligibility and including:[16]
  - patients at significant risk of increased bleeding rates due to factors that lead to poor adherence or persistence despite being candidates for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes with FVIII
  - patients who have limited ability to receive regular IV therapy due to other underlying factors, such as venous access challenges or geographical treatment access restrictions, despite being candidates for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes with FVIII.

The recommended dosage regimen of emicizumab consists of a loading dose of 3.0 mg/kg emicizumab once weekly for the first 4 weeks as an SC injection. This is followed by a maintenance dose administered 1 week after the last loading dose. The maintenance dose should be selected based on physician and patient or caregiver dosing regimen preference to support adherence, and should take into account the age and weight of the patient:[8]

- Use in adolescents and adults greater than or equal to 40 kg: The recommended maintenance dose for adolescents (12 years to 17 years of age) and adults (greater than or equal to 18 years of age) who weigh greater than or equal to 40 kg, with or without inhibitors to FVIII, is 1.5 mg/kg once weekly, 3.0 mg/kg every 2 weeks, or 6.0 mg/kg every 4 weeks, administered as an SC injection. No dosage adjustments are recommended.
- Use in pediatric patients and patients less than 40 kg: The recommended maintenance dose for pediatric patients less than 12 years of age of any weight or patients of any age who weigh less than 40 kg, with or without inhibitors to FVIII, is 1.5 mg/kg once weekly or 3.0 mg/kg every 2 weeks, administered as an SC injection. No dose adjustments are recommended in pediatric patients.

Table 3: Key Characteristics of FVIII Replacements Available in Canada

	Hemlibra (emicizumab)	Eloctate (Antihemophilic Factor [Recombinant] BDD Fusion Protein)	Adynovate (Antihemophilic Factor [Recombinant], PEGylated)	Jivi (Antihemophilic Factor [Recombinant] BDD, PEGylated)	Kovaltry (Antihemophilic Factor [Recombinant])	Nuwiq (Antihemophilic Factor [Recombinant] BDD)	Xyntha (Antihemophilic Factor [Recombinant], BDD)	Humate-P (Coagulation Factor)	Wilate (Human Coagulation FVIII)
		Extended half-life, recombinant			Standard half-life, recombinant			Plasma-derived	
Mechanism of action	Bridges activated factor IX and factor X to restore the natural function of activated factor VIII	FVIII replacement[a]							
Indication[b]	Patients with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes	Adults and children with hemophilia A for: • routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes • control and prevention of bleeding episodes • perioperative management.				Treatment and prophylaxis of bleeding in patients of all ages with hemophilia A (congenital factor VIII deficiency)	Control and prevention of hemorrhagic episodes and for routine and surgical prophylaxis in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia)	Adult patients with hemophilia A for treatment and prevention of bleeding	Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital or acquired FVIII deficiency) and prevention and treatment of bleeding in minor surgical procedures
Route of administration	SC	IV							
Recommended dose	• 3.0 mg/kg/week for 4 weeks followed by 1.5 mg/kg QW • 3.0 mg/kg/week for 4 weeks followed by 3.0 mg/kg Q2W • 3.0 mg/kg/week for 4 weeks	Prophylaxis: 50 IU/kg every 3 to 5 days The dose may be adjusted based on patient response in the range of 25 IU/kg to 65 IU/kg. More frequent or	Prophylaxis: Adolescents and adults (12 years and older): 40 IU/kg to 50 IU/kg of Adynovate administered	Prophylaxis: The recommended initial regimen is 30 IU/kg to 40 IU/kg twice weekly. Based on the bleeding episodes, the	Prophylaxis: Adults and Adolescents (> 12 years of age): 20 IU to 40 IU per kg of body weight 2 or 3	Prophylaxis: 30 IU to 40 IU of FVIII/kg every other day Children: 30 IU to 40 IU of FVIII/kg every other day or 3	Prophylaxis: Xyntha has been administered prophylactically in a pivotal clinical trial in adolescent and adult previously treated patients at a dose	As a general rule, 1 IU of factor VIII activity per kg body weight will increase the circulating factor VIII level by approximately	Prophylaxis: doses of approximately 20 IU/kg body weight should be given at intervals of 2 days to 3 days. In some cases, especially in younger patients, shorter dosage

	Hemlibra (emicizumab)	Eloctate (Antihemophilic Factor [Recombinant] BDD Fusion Protein)	Adynovate (Antihemophilic Factor [Recombinant], PEGylated)	Jivi (Antihemophilic Factor [Recombinant] BDD, PEGylated)	Kovaltry (Antihemophilic Factor [Recombinant])	Nuwiq (Antihemophilic Factor [Recombinant] BDD)	Xyntha (Antihemophilic Factor [Recombinant], BDD)	Humate-P (Coagulation Factor)	Wilate (Human Coagulation FVIII)
		Extended half-life, recombinant			Standard half-life, recombinant			Plasma-derived	
	followed by 6.0 mg/kg Q4W (adults)	higher doses up to 80 IU/kg may be required in pediatric patients < 12 years of age.	2 times per week Children (less than 12 years): 40 IU/kg to 60 IU/kg administered 2 times per week.	regimen may be adjusted to 45 IU/kg to 60 IU/kg every 5 days. A regimen may be further individually adjusted to more or less frequent dosing.	times per week Children ≤ 12 years old: 20 IU to 50 IU per kg body weight twice weekly, 3 times weekly, or every other day according to individual requirements.	times per week	of 30 + 5 IU/kg 3 times weekly.	2 IU/dL. Adequacy of treatment must be judged by the clinical effects; thus, the dosage may vary with individual cases.	intervals or higher doses may be necessary.
Serious adverse effects or safety issues	• Thrombotic microangiopathy • Thromboembolism	Development of inhibitors to FVIII						• Serious thromboembolic events • Development of inhibitors to FVIII	• This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases. • Development of inhibitors to FVIII.

BDD = B-domain deleted; SC = subcutaneous; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly.

[a] For detailed mechanism of action please refer to each drug's corresponding product monograph.

[b] Health Canada–approved indication.

Source: Product monographs for: Hemlibra,[8] Eloctate,[17] Adynovate,[18] Jivi,[19] Kovaltry,[20] Nuwiq,[21] Xyntha,[22] Humate-P,[23] Wilate.[24]

Stakeholder Engagement

Patient Group Input

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

About the Patient Group and Information Gathered

One patient group responded to CADTH's call for patient input for emicizumab. The CHS is a national voluntary health charity with a mandate to improve the health and quality of life of all people in Canada with inherited bleeding disorders, and ultimately to find cures. The CHS has 10 provincial chapters and is affiliated with the World Federation of Hemophilia along with more than 125 national member organizations around the world. It has approximately 300 active volunteers, family members, individuals affected by bleeding disorders, and health care providers who work in bleeding disorder treatment centres. As well, the CHS collaborates with health care providers from Canada's 26 inherited bleeding disorder comprehensive care centres, whose physicians make up the Association of Hemophilia Clinic Directors of Canada, Canada Blood Services and Héma-Québec, the Network of Rare Blood Disorder Organizations, the Canadian Organization for Rare Diseases, the hepatitis C community, the AIDS community, and others who share common interests.

A disclosure of any conflicts of interest for the CHS is available on the CADTH website.

In preparing their patient input submission, the CHS received external help from AHCDC physicians and other health care professionals. They provided treatment outcome data and patient-reported outcome comments from 14 of the 15 patients with hemophilia A without inhibitors who were receiving emicizumab through compassionate access. The CHS is a collaborator in the Patient-Reported Outcomes, Burdens, and Experiences (PROBE) study.

The CHS solicited information on patient experiences and perspectives in multiple ways. Because it is in regular contact with its members, it hears about the experiences of patients, caregivers, and physicians through personal meetings or conferences. The CHS also conducted an online survey between May 31, 2019 and June 15, 2019 to collect perspectives from patients with hemophilia A and their caregivers. The objective of was to gain insight into burdens of disease and treatment, satisfaction with current treatments, and improvements that patients and caregivers would like to see in new treatments. The survey was publicized through different CHS and chapter communication tools, such as email, the CHS website, Facebook, Twitter, and Instagram. A total of 52 responses were obtained from 6 provinces. All respondents were affected by hemophilia A without inhibitors: 45 with severe hemophilia, 4 with moderate hemophilia, 2 with mild hemophilia, and 1 with unknown severity.

Disease Experience

According to the patient input received for this review, hemophilia A negatively affects patients' lives on physical, psychological, and financial levels. The key concerns raised by patients are breakthrough bleeds, venous access challenges, and treatment adherence difficulties due to the complex regimen. Despite prophylaxis therapy, patients reported that they still experience breakthrough bleeds, damage to joints, pain, reduced mobility, and iatrogenic complications due to frequent IV infusions. Chronic joint damage is an insidious consequence of hemophilia. In the survey, 8 out of 52 patients reported damage to joints when asked about key difficulties in an open-ended question. One patient noted that

hemophilia A imposes limits on patients' and families' daily lives because they worry constantly about bleeds and whether hospital care will be accessible. One family noted that *"globally…the majority of decisions about family activities and permissions granted to the children are dictated by hemophilia."* Many families live with anxiety, stress, and depression, which severely affects their quality of life. One parent indicated that their child's inability to live a normal childhood is the *"most difficult aspect of the illness,"* while others noted that their children live with anxiety and low self-esteem. Two older patients with severe hemophilia A compared the difficulties they have experienced throughout their lives to having *"swords of Damocles hanging over [them],"* especially being victims of the HIV and hepatitis C contaminated blood supplies in the 1980s. Both lived with chronic pain and now have severely damaged joints. One of them *"[ended] up in a coma for an entire summer"* from a fall. Like many others, they were also concerned about passing on the genetic disorder to their children and grandchildren.

Treatment for hemophilia A is *"mentally taxing not only on [the patient] but [also] on the person who helps [them]."* Given the high frequency of infusions with FVIII, vein access is difficult and time-consuming for many. Parents and patients alike worry about *"destroying"* veins from frequent IV access. As well, many respondents mentioned difficulties in adhering to prophylactic regimens. Venous access through a port or catheter can be extremely painful and traumatizing. One parent stated that *"one of the biggest impacts…is the constant needles…if he has a breakthrough bleed, the frustration and exhaustion is compounded by even more needles*." Parents are often the caregivers. As a result, many have been unable to maintain full-time employment or have had to reduce their work hours to provide care. This puts a significant financial burden on some families, adding to their existing exhaustions.

The PROBE study collected patient perspectives and experiences from 181 Canadian boys and men aged 11 and older with hemophilia A. Almost all respondents (89%) were receiving regular FVIII prophylaxis, and some (5%) were receiving on-demand treatment. Results of the PROBE study show the considerable burden of disease and impact of living of severe hemophilia A across all age groups, despite widespread access to and use of modern prophylactic treatment with FVIII. In the PROBE study, 142 out of 181 respondents reported having a reduced range of motion in at least 1 joint, suggesting that chronic joint damage is very common in older children and adults.

Experience With Treatment

The CHS survey reported that the majority of patients with severe hemophilia A (and almost all respondents) were on FVIII prophylactic treatment, with IV infusions administered 2 to 7 times per week. Most respondents reported being "somewhat satisfied" to "quite satisfied" with currently available factor therapies. Although most respondents found that treatment is quite effective in stopping and preventing bleeds, many reported that it provides insufficient protection, given that breakthrough bleeds still occur. One parent stated that they are *"so glad that there is some type of treatment available so that [their] son can have some normality in his life… but [they are] frustrated with so many needles…Frustrated with the breakthrough bleeds. Very frustrated."* Additionally, FVIII prophylaxis does not fully protect against joint damage. In the survey, 5 out of 52 patients reported experiencing breakthrough joint bleeding — and some respondents mentioned developing long-term joint damage — despite FVIII prophylaxis. This can lead to a reduction in the range of motion in certain joints, which may affect mobility

The short half-life of FVIII therapy creates many challenges. The frequent treatment administration is not only time-consuming, but physically and emotionally exhausting. The most common challenge reported in the survey is venous access, which is particularly difficult in babies or children. One parent indicated that their son's veins *"were extremely difficult to find and it was taking 4-6 pokes each time to find a vein."* Parents feel as though they are "destroying" their child's veins and worry about venous scarring. Additionally, the surgeries for the insertion and removal of venous access ports or catheters are *"traumatic"* and patients have difficulty adjusting. One parent noted that because the port gripper is left in place for a week, their son *"cannot have a bath, or go swimming"* during this time. Another common challenge is long distances to treatment centres for check-ups, treatments, or to pick up factor supplies for home use. This can make it difficult for patients to adhere to the treatment regimen. One parent expressed that *"it is great that we have treatment available to us that allows him some involvement in physical activity"* but that the complex schedule, due to frequent administrations, *"was the main contributor to our decision to have one parent home to care for him. The costs of travel were significant."* The time-sensitive and short-lasting treatment regimen meant that parents had to coordinate their child's activities with treatments meticulously *"by calculating the approximate level of FVIII in his blood, which is very laborious."* Time lost from school and work resulting from the complicated treatment regimen is another challenge faced by many. One parent indicated that when they are unable to infuse due to venous access issues, her son *"misses school"* and both parents miss *"a full day of work"* to go to the hospital, where they also have to worry about parking fees.

Based on input from the patient group, in Canada, access to emicizumab is currently restricted to people with hemophilia A with inhibitors. Approximately 15 people with hemophilia A without inhibitors were granted compassionate access starting in autumn 2019. The Association of Hemophilia Clinic Directors of Canada conducted a survey in June 2020, which was sent to health care providers in 12 bleeding disorder centres caring for 14 patients; 13 surveys were returned. The median age of patients at the time of application to the program was 11 years (range: 13 months to 65 years). Prior to switching to emicizumab, patients were on standard or extended half-life FVIII therapy, with multiple infusions per week or on-demand infusions. With emicizumab, health care providers described the improvement in health outcomes and quality of life as dramatic, especially because the frequency of administration is reduced. The SC mode of administration allowed for greater adherence to treatment regimens, leading to better bleed protection and improved quality of life. Nine out of 13 patients had 0 bleeds on emicizumab. Other improvements included less joint pain and discomfort, fewer hospital visits, better mental health, and more independence. No side effects were reported. The family of a patient with severe hemophilia A, autism spectrum disorder, and severe global developmental delay indicated that while receiving recombinant FVIII treatment, their son *had "roughly 100 ER visits in the first 4 years of life, despite being on home treatments"* and *"showed signs of severe anxiety."* After receiving emicizumab, his bleeds were reduced, but *"the most substantial improvements we observed have been to his mental health and development…[He] has become active, learning to run, jump, and climb like other 4-year-olds. He has become extremely social…In the past 6 months, he was able to catch up on almost every developmental milestone and is now exceeding his age level in several areas… We now spend our days just as any other family does."* With emicizumab, *"Parents feel less vulnerable, more empowered and in control"* and patients say they have less anxiety, more independence, better self-esteem, and an overall better quality of life. For

many patients on emicizumab, *"family dynamics are better*" and hemophilia is no longer *"the focus of the day."*

Improved Outcomes

Patient input from the CHS indicated that the vast majority of patients and caregivers want a longer-lasting treatment that requires less frequent administration and an easier mode of delivery (i.e., not IV). A simpler mode of delivery would be especially beneficial to babies and children, for whom venous access is the most challenging. As well, patients noted that being able to self-administer the treatment would greatly improve independence. One patient stated that *"treating once a week under the skin is [their] ultimate wish."* A less frequent dosing interval would likely greatly benefit patients who have difficulty adhering to frequent administrations. Additionally, patients hope for more reliable efficacy to achieve better protection from bleeding because many still experience breakthrough bleeds with the current FVIII replacement therapy. These outcomes are expected to improve the quality of life of patients and caregivers by reducing worry and stress; by allowing patients to be more active, more involved in society, and less dependent on health services; and by decreasing absenteeism from school and work. With a more constant factor level, 1 parent noted that they would not have to be *"on call 24 hours a day…[and] could decide to go back to work or even commit to activities with greater certainty they would happen."* Another family said that a longer-lasting treatment would result in a *"better overall family atmosphere*." Two older patients with severe hemophilia A — grandfathers to grandsons who inherited the disorder — have seen significant improvements in their own health with emicizumab, and wish that everyone with hemophilia A could have access to it so they could *"lead more normal lives"* and minimize long-term joint morbidity.

The CHS has suggested that patients with severe hemophilia — and those with mild and moderate disease who have a severe phenotype — would benefit most from treatment with emicizumab. As well, the CHS believes that the new treatment would greatly benefit babies and children (for whom venous access is most difficult), patients who suffer from frequent breakthrough bleeds and joint disease despite FVIII prophylaxis, and patients who have difficulties adhering to the current treatment regimen, which requires frequent IV infusions.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise in diagnosing and managing 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 emicizumab review, a panel of 5 clinical experts from across Canada was convened to characterize unmet therapeutic needs, identify and communicate situations where gaps in the evidence could be addressed by collecting additional data, promote the early identification of potential implementation challenges, gain further insights into the clinical management of patients living with the condition, and explore the drug's potential place in therapy (e.g., potential reimbursement conditions). A summary of this panel discussion is presented in the following section.

Unmet Needs

The experts consulted by CADTH for this review indicated that the main unmet need is for a user-friendly treatment. The currently available treatment is a burden on patients. The IV

route of administration for FVIII concentrates is a challenge. This is reflected in patient adherence: few patients are 100% adherent. Due to the short half-life of available FVIII products, missing even 1 dose can put the individual at risk of a bleeding event. The clinical experts indicated that IV infusions are more complex, take longer, and are less convenient than other routes of administration. The alternative mode of delivery (SC) associated with emicizumab is anticipated to increase adherence, especially when venous access is difficult or inconvenient (e.g., pediatric patients, geriatric patients). To illustrate this further, a person with severe hemophilia A on prophylaxis with good adherence would receive 150 IV infusions in a 12-month period, plus additional treatments if breakthrough bleeding occurs, whereas a patient receiving emicizumab could achieve similar protection with 12 to 52 SC injections per year.

According to the panelists, not all patients respond to available treatments. Some patients' individual pharmacokinetics make it unlikely for them to achieve a protective level of FVIII with a reasonable or acceptable infusion frequency (e.g., they may require too high a dose or too many infusions).

Exposure to exogenous FVIII increases patients' risk of developing a factor inhibitor. Development of an inhibitor increases bleeding risk and requires much more intensive treatment. A less immunogenic treatment would be especially useful for newly diagnosed patients at high risk of inhibitor development.

According to the panelists, the patients with the greatest unmet need are:

- children, in whom emicizumab could help prevent complications (e.g., due to spontaneous intracranial hemorrhage), prevent the need to insert a central line for easier venous access, and allow for earlier treatment (e.g., prior to first bleed) with factor prophylaxis for reasons related to inhibitors and vascular access issues
- patients with significant venous access issues (e.g., children, anyone with dexterity issues due to age, disease, or injury, and anyone with severe needle phobia)
- patients with adherence issues (e.g., social factors)
- patients at high risk for inhibitor development (e.g., those with family history of inhibitor development, intron 22 inversion or large deletions, and previously untreated patients)
- patients who had prior inhibitor eradicated, but need prophylaxis at a dose and/or frequency beyond the usual schedule
- patients with severe or moderate hemophilia A who are continuing to have spontaneous bleeding despite appropriate prophylaxis.

Place in Therapy

For patients without FVIII inhibitors, the clinical experts consulted for this review anticipated that the use of emicizumab would likely be on case-by-case basis. They also suggested that emicizumab could be used as an alternate treatment for patients not adequately controlled on their current FVIII regimen. For those successfully protected by prophylaxis, emicizumab may represent a way of diminishing the burden of care or achieving protection from bleeding with a lower injection frequency. Patient preference is anticipated to play an important role.

Emicizumab is expected to be used as another prophylaxis treatment option for patients. However, it is not expected to change the overall treatment paradigm.

The experts were of the view that emicizumab can be used in patients naïve to FVIII — who would bear a high risk of developing inhibitors to FVIII — without inducing anti-FVIII antibody. However, it is unknown whether exposure to FVIII later in life (if needed for surgery or because of emicizumab failure or insufficiency) would carry the same risk, or a lower or higher risk, of developing inhibitors.

There is debate among the hemophilia community with respect to whether or not it is appropriate for patients to try other treatments before emicizumab. Some clinicians suggest that in the absence of evidence, there is no clear clinical indication to start with another treatment before emicizumab. Some clinicians suggest that emicizumab could be used prior to FVIII for patients who have a strong family history of developing inhibitors or who are at high risk of developing inhibitors, trouble with venous access, bleeds, or other complications despite being on prophylaxis.

Patient Population

Patients would be identified by specialists involved in their hemophilia care. After a laboratory diagnosis of hemophilia, they would be identified based on the historical factors. Use of emicizumab early in infancy (e.g., prior to 12 months of age) could potentially allow the ability to introduce factor as a low, regular dose to induce tolerance rather than more frequent but necessary factor exposure at prophylaxis or bleed treatment doses, which increases the risk of inhibitor development. Pre-symptomatic infants could be treated with factor prophylaxis earlier than what is done now (e.g., prior to first bleed) for the reasons stated earlier, related to inhibitors and vascular access issues.

The clinical experts did not identify many situations where treatments with emicizumab would not be appropriate. However, there are situations where clinical evidence is limited or absent, such as:

- patients expected to undergo major surgery
- patients travelling frequently to settings where emicizumab will be unfamiliar
- very physically active patients, who might not be sufficiently protected
- patients living in settings where there might not be access to specialized laboratory measurements (some tests for clotting and FVIII do not work in the presence of emicizumab).

Assessing Response to Treatment

The experts consulted by CADTH for this review indicated that a meaningful response to treatment would involve the patient achieving their life goals — e.g., avoiding or reducing the number of bleeds, increasing their ability to attend school or work, being able to socialize and practise sports, and preserving normal joint function and/or stopping or minimizing the progression of joint disease. Patient goals vary. Clinicians identified bleed frequency and the absence of bleeds as important outcomes in assessing a patient's response to treatment. They highlighted the importance of assessing both joint and non-joint (soft tissue) bleeds, given that both effect HRQoL. It is expected that some patients may feel better and then become more active, leading to more traumatic bleeds. Clinicians receive automated notifications from the national Canadian Bleeding Disorders Registry for every bleed. They also receive these if a patient reports 4 or more treatments for the same bleed or if the bleed is in a critical location (e.g., the head). HRQoL, while not typically formally assessed in routine clinical practice using a scale, is important for clinicians to

discuss with patients. Treatment response based on bleeding outcomes and patient goals is assessed in an ongoing manner, at least annually in adults and semi-annually in pediatrics (consistent with guidelines followed in Canada).

Discontinuing Treatment

The panellists stated that the benefits of prophylactic treatment in patients with hemophilia can persist over a patient's lifespan. There is little to no evidence about discontinuing prophylaxis at any age, and it is unlikely that a Canadian clinician would propose this. Patients may switch to a different treatment based on preference, the degree of bleeding control achieved, AEs (e.g., injection-site reaction), or the availability of a new product. The decision to change treatment depends on a patient's goals (highly variable); some may want to become more active (and thus may accept a treatment with more frequent administration), while others may prioritize fewer injections. Clinicians agreed that 1 bleed every 1 or 2 months is problematic and indicates that treatment is not working optimally, and that it is important to determine if bleeding events are attributed to the development of an inhibitor, or if bleeding is not well-controlled despite good treatment.

Prescribing Conditions

A current treatment goal for patients with hemophilia receiving prophylactic treatment with factor replacement is to learn how to access their own veins so they can self-treat at home on a regular basis for both bleeding and prophylaxis, without needing to go to a hospital or clinic. This would be patient- or parent-directed therapy, and would apply to severe and moderate patients receiving prophylaxis. The setting is not expected to change for a patient receiving emicizumab, but administration is anticipated to be easier because SC administration is simpler.

There are selected occasions where drugs used to treat hemophilia would need to be given in a hospital inpatient or outpatient setting. These include: the beginning of the treatment, when the patient or parent is learning how to give the drug; during surgery; and in trauma situations. All patients (even those who live in remote areas) have access to treatment centres, either in person or through video. Nevertheless, it is easier to teach a patient how to self-administer an SC injection than an IV infusion or a central line. Most sponsors have programs in place to assist with local nursing support for in-home teaching.

A clinician experienced in hemophilia treatment is required to oversee the treatment of patients who might receive emicizumab. Typically, this would be a hematologist or pediatric hematologist within a multidisciplinary team including a nurse, physiotherapist, and social worker. Other clinicians may be involved depending on comorbidities, such as orthopedic surgeons, internal medicine specialists, infectious disease specialists (for patients with HIV or hepatitis C virus), or cardiologists. Primary care physicians do not lead treatment of hemophilia. If a hematologist is not providing care for the patient, a clinician who has experience in treating hemophilia and is supported by a multidisciplinary team could be used. In emergency situations, an emergency doctor may be responsible for treating the patient, but they would typically be in contact with the hematologist or a hemophilia treatment centre.

Additional Considerations

The SC route of administration of emicizumab is a key feature that is expected to increase adherence in patients transitioning from pediatric to adolescent or adult care.

The availability of a treatment with weekly or less frequent SC administration may be welcomed in the Canadian setting because of its ability to simplify treatment administration and its potential for higher adherence.

It is important to consider the needs of patients with moderate hemophilia A, given that some of them may require prophylaxis consistent with the treatment of severe patients.

Clinical Evidence

The clinical evidence included in the review of emicizumab is presented in 3 sections. The first section, Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada. The second section includes indirect evidence from the sponsor. The third section includes 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)

Objective

To perform a systematic review of the beneficial and harmful effects of emicizumab injection for the treatment of hemophilia A (congenital FVIII deficiency) in patients without FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

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 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Patients with hemophilia A without FVIII inhibitors Subgroups: • Age (pediatric, adolescent, adult, geriatric) • Severity of disease • Severity of bleeding (e.g., major, minor) • Type of bleeding (e.g., spontaneous bleed, joint bleed) • Previous FVIII prophylaxis (e.g., situational, primary)
Intervention	Emicizumab, subcutaneous injection, 3.0 mg/kg/week for 4 weeks followed by 1.5 mg/kg once weekly, 3.0 mg/kg every 2 weeks, or 6.0 mg/kg every 4 weeks
Comparators	Recombinant FVIII concentrates Plasma-derived FVIII concentrates Desmopressin
Outcomes	**Efficacy outcomes:** • Bleeding events[a] (e.g., number of bleeds) • Productivity[a] (e.g., absenteeism from school or work) • HRQoL[a] (e.g., Haem-A-QoL) • Use of rescue therapy • Hospitalization[a] • Pain[a] • Patient satisfaction[a] **Harms outcomes:** AEs, SAEs, WDAEs, mortality Notable harms: • Thrombotic events (e.g., thrombotic microangiopathy, thromboembolism) • Injection-site reactions • Hypersensitivity reactions • Inhibitor development • Blood-borne infections

Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; FVIII = factor VIII; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; HRQoL= health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[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).[25]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through 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 concept was Hemlibra (emicizumab). Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov, the World Health Organization's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

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 July 29, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on November 18, 2020.

Grey literature (literature that is not commercially published) was identified by searching 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):[26] Health Technology Assessment (HTA) 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. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the drug sponsor was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to include in the review, and differences were resolved through discussion.

Findings From the Literature

A total of 2 studies were identified for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

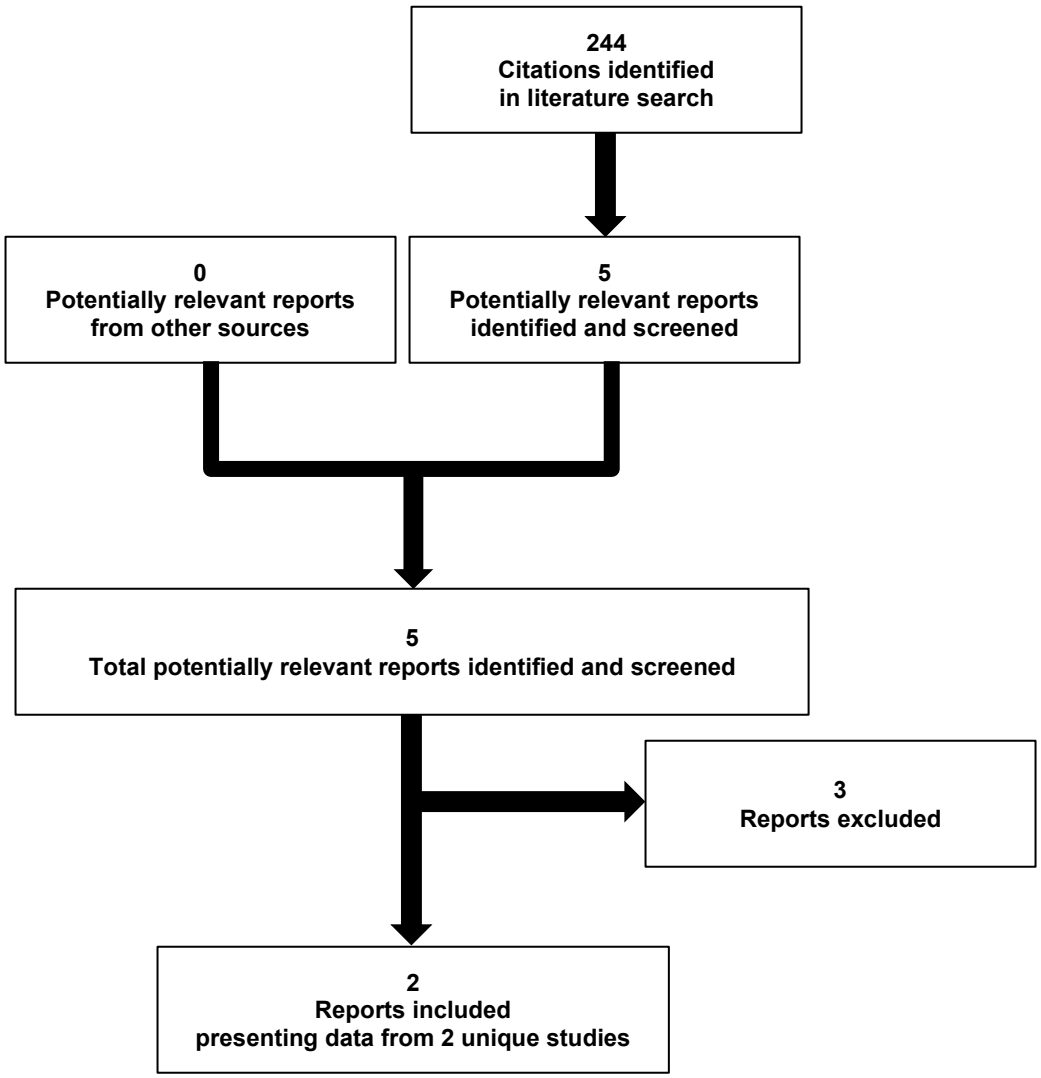


Table 5: Details of Included Studies

		HAVEN 3	HAVEN 4
Designs & Populations	Study design	OL RCT	OL non-randomized
	Locations	Australia, Costa Rica, France, Germany, Ireland	Italy, Japan, Poland, South Africa, South Korea, Spain, Taiwan, UK, US
	Randomized (N)	152	41 patients enrolled in expansion cohort
	Inclusion criteria	• ≥ 12 years of age • ≥ 40 kg at screening • Severe congenital hemophilia A (intrinsic FVIII level < 1%) • A negative test for inhibitor (i.e., < 0.6 BU) within 8 weeks of enrolment • No documented inhibitor (i.e., < 0.6 BU), FVIII half-life < 6 hours, or FVIII recovery < 66% in the last 5 years • For patients on no prophylaxis (episodic treatment) pre-study, ≥ 5 bleeds in the last 24 weeks prior to study entry • Patients who were on FVIII prophylaxis for at least the last 24 weeks could be enrolled regardless of the number of bleeds during this period • Adequate hematologic, hepatic, renal function	• ≥ 12 years of age • ≥ 40 kg at screening • Severe congenital hemophilia A or hemophilia A with inhibitors • For patients on an episodic regimen, ≥ 5 bleeds in the prior 24 weeks, regardless of inhibitor status • Patients without FVIII inhibitors (< 0.6 BU/mL; < 1.0 BU/mL for laboratories with a historical sensitivity cut-off for inhibitor detection of 1.0 BU/mL) who completed successful ITI therapy must have done so ≥ 5 years before screening and must have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor > 0.6 BU/mL since ITI • Adequate hematologic, hepatic, renal function
	Exclusion criteria	• Inherited or acquired bleeding disorder other than hemophilia A • Previous (in the past 12 months) or current treatment for thromboembolic disease or signs of thromboembolic disease • At high risk for microangiopathy • Previous (in the past 12 months) or current treatment for thromboembolic disease • Other conditions (e.g., certain autoimmune diseases) that may increase risk of bleeding or thrombosis • Concurrent disease, treatment, or abnormality in clinical laboratory tests that could have interfered with the conduct of the study, posed additional risk, or would have, in the opinion of the investigator, precluded the patient's safe participation in and completion of the study • Known HIV infection with CD4 count < 200 cells/µL within 24 weeks prior to screening	• Inherited or acquired bleeding disorder other than hemophilia A • Ongoing or planned ITI therapy • At high risk for microangiopathy • Previous (in the past 12 months) or current treatment for thromboembolic disease or signs of thromboembolic disease • Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis • Concomitant disease, condition, significant abnormality on screening evaluations or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator or co-investigator, pose an additional unacceptable risk in administering study drug to the patient • Known HIV infection with CD4 count < 200 cells/µL
Drugs	Intervention	Emicizumab prophylaxis at 3.0 mg/kg QW SC for 4 weeks, followed by 1.5 mg/kg QW SC for 20 weeks Emicizumab prophylaxis at 3.0 mg/kg QW SC for 4 weeks, followed by 3.0 mg/kg Q2W SC for 20 weeks	Emicizumab prophylaxis at 3.0 mg/kg QW SC for 4 weeks, followed by 6.0 mg/kg Q4W SC for 20 weeks

		HAVEN 3	HAVEN 4
		Emicizumab prophylaxis at 3.0 mg/kg QW SC for 4 weeks, followed by 1.5 mg/kg QW SC (FVIII prophylaxis prior to study entry) for 20 weeks	
	Comparator(s)	No prophylaxis	None
Duration	Phase		
	Run-in	None	None
	Efficacy period	24 weeks	24 weeks
	Follow-up	NR	NR
Outcomes	Primary end point	Bleed rate (defined as the number of treated bleeds over the efficacy period)	No formal hypothesis testing planned
	Secondary and exploratory end points	Secondary: • All bleeds • Treated joint bleeds • Treated spontaneous bleeds • Treated bleeds compared with the patient's historical bleed rate • All bleeds compared with the patient's historical bleed rate • Haem-A-QoL physical health domain Other: • Treated target joint bleeds • Haem-A-QoL total score • EQ-5D-5L VAS and index utility score • All bleeds compared with the patient's historical bleed rate • Adequate control of bleeding Exploratory: • Descriptive analyses for: • All bleeds • EQ-5D-5L, Haem-A-QoL, Haemo-QoL-SF • Number of days away from school/work, days hospitalized • Patient preference	• Treated bleeds • All bleeds • Treated spontaneous bleeds • Treated joint bleeds • Treated target joint bleeds • Haem-A-QoL • Haemo-QoL-SF • EQ-5D-5L index utility score and EQ-5D-5L VAS • Number of days away from school/work, days hospitalized • Patient preference
Notes	Publications	Mahlangu 2018[27]	Pipe 2019[28]

BU = Bethesda unit; CD4 = cluster of differentiation 4; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; FVIII = factor VIII; Haem-A-QoL = Hemophilia Quality of Life Questionnaire for Adults; Haemo-QoL-SF = Haemophilia-specific Quality of Life for Children Short Form; ITI = immune tolerance induction; RCT = randomized controlled trial; SC = subcutaneous; NR = not reported; OL = open-label; Q2W = every 2 weeks; Q4W = every 4 weeks; QW = weekly.

Note: Two additional reports were included (CADTH submission[16] and Health Canada's Reviewers Report[29]).

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Description of Studies

Two sponsor-submitted trials, HAVEN 3 (N = 152) and HAVEN 4 (N = 41), were included in the systematic review. Details of the included studies are provided in Table 5.

HAVEN 3 was a 24-week, open-label, multi-centre RCT that aimed to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in adult (greater than or equal to 18 years of age) and adolescent (greater than or equal to 12 and less than 18 years of age) patients with hemophilia A without FVIII inhibitors. HAVEN 3 was performed between September 27, 2016 and September 15, 2017 in 39 investigational sites across 14 countries. None of the study sites were located in Canada.

Patients were eligible for enrolment in HAVEN 3 if they had previously received treatment with episodic FVIII or FVIII prophylaxis. Patients who received episodic treatment with FVIII prior to study entry were centrally randomized through an interactive voice or web response system with block-based randomization in a 2:2:1 ratio to the following treatment arms:

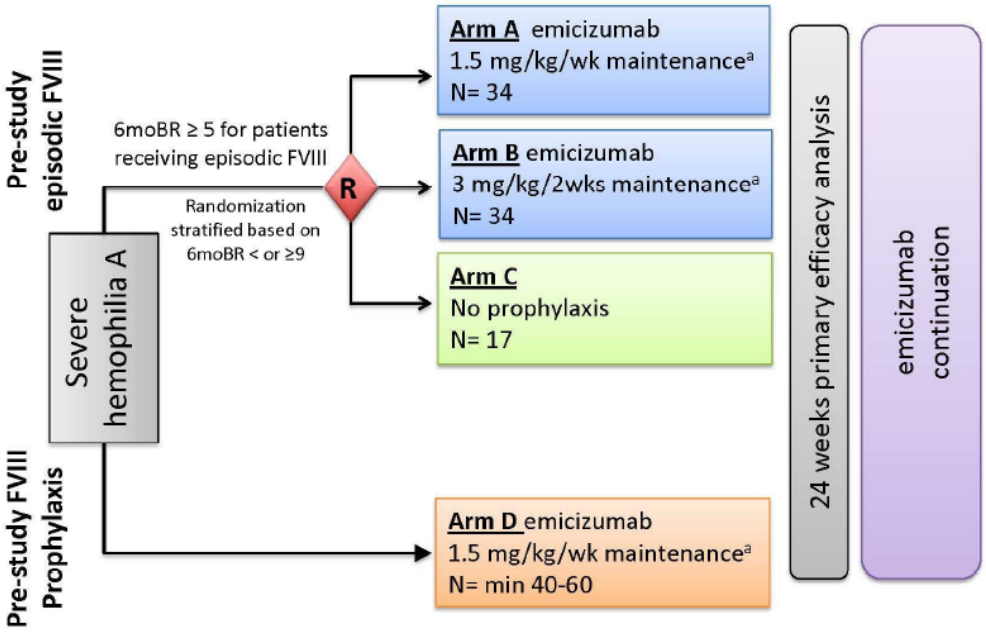
- Emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly
- Emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 3.0 mg/kg every 2 weeks
- No prophylaxis (control arm)

Randomization was stratified by the number of bleeds experienced during the 24 weeks prior to study entry (less than 9 bleeds or greater than or equal to 9 bleeds [equivalent to ABR = 18]). Patients randomized to the no-prophylaxis (control) arm could switch to emicizumab prophylaxis 3.0 mg/kg weekly for 4 weeks, followed by 3.0 mg/kg every 2 weeks, after completing 24 weeks in the study.

Patients who received FVIII prophylaxis prior to study entry were enrolled in a separate, non-randomized arm where they received treatment with emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly. Patients in this arm continued their regular FVIII prophylaxis treatment until the second emicizumab loading dose. Patients in this arm were derived from the NIS, a study preceding HAVEN 3.

The NIS (BH29768) was a prospective study that documented the number and types of bleeds, treatments, HRQoL, and safety in patients treated with episodic or prophylactic FVIII drugs. One cohort in the NIS consisted of adult and adolescent patients without FVIII inhibitors. Patients who participated in this cohort with the NIS and who met the eligibility criteria for HAVEN 3 could enroll in HAVEN 3; these patients were included in the non-randomized FVIII prophylaxis arm. The subset of patients that entered HAVEN 3 after the NIS allowed for a 1-way crossover design and intra-patient analysis.

Figure 2: HAVEN 3 Study Design



2wks = 2 weeks; 6moBR = 6 months' bleed rate; FVIII = factor VIII; R = randomization; wk = week.

[a] For all patients, emicizumab was administered at a loading dose of 3.0 mg/kg weekly for the first 4 weeks of treatment prior to starting maintenance.

Source: Clinical Study Report for HAVEN 3.[10]

HAVEN 4 was a 24-week, open-label, multi-centre, non-randomized, single-arm trial that aimed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab prophylaxis in patients 12 years of age and older with hemophilia A with or without FVIII inhibitors. Patients in HAVEN 4 received treatment with emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 6.0 mg/kg every 4 weeks.

Patients enrolled in HAVEN 4 included a cohort of patients for the purpose of pharmacokinetic and pharmacodynamic characterization ("pharmacokinetic run-in cohort;" n = 7) and a cohort for the evaluation of efficacy and safety ("expansion cohort;" n = 41). The primary objective of the pharmacokinetic run-in cohort was to investigate the pharmacokinetics of emicizumab after single and multiple SC administration of 6.0 mg/kg every 4 weeks without a loading dose. The expansion cohort is of relevance to the CADTH review and will be the focus of this report. The expansion cohort period of HAVEN 4 was assessed between May 24, 2017 and December 15, 2017 in 17 investigational sites across 6 countries. None of the study sites were located in Canada. No formal hypothesis testing was performed; however, several outcomes of interest were assessed (e.g., bleeding outcomes, HRQoL, productivity).

Populations

Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria for HAVEN 3 and HAVEN 4 are presented in Table 5. Both trials included patients 12 years of age and older who weighed 40 kg or more at screening and had adequate hematologic function (platelet count greater than or equal to

100,000/µL and hemoglobin greater than or equal to 8 g/dL). In both trials, patients on episodic regimens were required to have 5 or more bleeds in the 24 weeks prior to study entry. HAVEN 3 included patients with severe congenital hemophilia A (intrinsic FVIII level less than 1%). Patients in HAVEN 3 were required to have a negative test for inhibitor (i.e., less than 0.6 BU/mL) within 8 weeks of enrolment. Conversely, HAVEN 4 included patients with severe congenital hemophilia A (intrinsic FVIII level not specified) without FVIII inhibitors or congenital hemophilia A with FVIII inhibitors.

Baseline Characteristics

The baseline characteristics were generally balanced between the 3 randomized treatment arms in HAVEN 3 (Table 6). All patients in HAVEN 3 and HAVEN 4 were male. In HAVEN 3, patients were 36.4 (standard deviation [SD] = 14.4) years to 40.4 (SD = 11.4) years of age, with no patients under the age of 18 in the arms receiving 1.5 mg/kg emicizumab weekly or 3.0 mg/kg emicizumab every 2 weeks. The mean age in HAVEN 4 was 38.7 (SD = 15.7); 7.3% of patients were under the age of 18. In both studies, White patients represented the largest racial group (HAVEN 3: 57.1% to 66.7%; HAVEN 4: 75.6%). In HAVEN 3, there were fewer Asian patients in the 1.5 mg/kg weekly arm, and fewer Black or African American patients in the arm receiving 3.0 mg/kg every 2 weeks. In HAVEN 4, 12.2% (n = 5) had FVIII inhibitors at study entry. The number of bleeds in the 24 weeks prior to study entry ranged from 15.1 (SD = 6.5) to 21.6 (SD = 16.4) in the randomized arms of HAVEN 3; there were 6.4 (SD = 17.7) in the patients that had previously between treated with FVIII prophylaxis. In HAVEN 4, the number of bleeds in the 24 weeks prior to study was 9.0 (SD = 15.2). The number of patients with more than 1 target joint prior to study entry ranged from 58.8% to 93.3% in the randomized arms of HAVEN 3; it was 69.2% in the patients previously treated with FVIII prophylaxis. In HAVEN 4, 68.0% of patients had more than 1 target joint prior to study entry.

Table 6: Summary of Baseline Characteristics

Characteristics	HAVEN 3				HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	Previous FVIII prophylaxis;[a] 1.5 mg/kg QW emicizumab N = 63	6.0 mg/kg Q4W emicizumab N = 41
Sex, male, n (%)	36 (100)	35 (100)	18 (100)	63 (100)	41 (100)
Age, years, mean (SD)	39.8 (14.0)	40.4 (11.4)	37.8 (12.9)	36.4 (14.4)	38.7 (15.7)
Min to max	19 to 77	20 to 65	16 to 57	13 to 78	14 to 68
< 18 years, n (%)	0	0	1 (5.6)	7 (11.1)	3 (7.3)
Race, n (%)					
Asian	6 (16.7)	10 (28.6)	4 (22.2)	12 (19.0)	8 (19.5)
Black or African American	3 (8.3)	1 (2.9)	3 (16.7)	1 (1.6)	1 (2.4)
Native Hawaiian or other Pacific Islander	1 (2.8)	0	0	0	NR
White	24 (66.7)	20 (57.1)	11 (61.1)	47 (74.6)	31 (75.6)
Unknown	2 (5.6)	4 (11.4)	0	3 (4.8)	1 (2.4)

Characteristics	HAVEN 3				HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	Previous FVIII prophylaxis;[a] 1.5 mg/kg QW emicizumab N = 63	6.0 mg/kg Q4W emicizumab N = 41
Weight, kg, mean (SD)	80.87 (13.58)	81.83 (18.93)	70.61 (17.27)	79.0 (15.42)	72.82 (13.32)
Min to max	53.1 to 107.3	56.3 to 121.4	43.0 to 114.6	52.8 to 139.0	45.9 to 101.8
Hemophilia severity at baseline, n (%)					
Mild	0	0	0	0	1 (2.4)
Moderate	0	0	0	0	0
Severe	36 (100)	35 (100)	18 (100)	63 (100)	40 (97.6)
Patient inhibitor status at study entry, n (%)					
Inhibitor	NR	NR	NR	NR	5 (12.2)
Non-inhibitor	NR	NR	NR	NR	36 (87.8)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
Number of target joints prior to study entry, mean (SD)	2.1 (1.4)	2.2 (1.7)	2.2 (1.4)	1.0 (1.6)	1.4 (1.5)
[redacted]					
[redacted]					

max = maximum; min = minimum; NIS = non-intervention study; Q2W = every 2 weeks; Q4W = every 4 weeks; QW = weekly; SC = subcutaneous; SD = standard deviation.

Note: All patients.

[a] "Previous FVIII prophylaxis; 1.5 mg/kg emicizumab" includes patients treated with FVIII prophylaxis in the NIS, then SC emicizumab prophylaxis at 3.0 mg/kg once weekly for 4 weeks, followed by SC emicizumab 1.5 mg/kg once weekly for 20 weeks in HAVEN 3.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Interventions

In HAVEN 3, after screening, eligible study participants previously treated with episodic FVIII were randomly assigned in a 2:2:1 ratio to the following arms:

- Emicizumab prophylaxis at 3.0 mg/kg SC weekly for 4 weeks, followed by 1.5 mg/kg SC weekly for 20 weeks (arm A)
- Emicizumab prophylaxis at 3.0 mg/kg SC weekly for 4 weeks, followed by 3.0 mg/kg SC every 2 weeks for 20 weeks (arm B)
- No prophylaxis for 24 weeks (control arm; arm C). Following 24 weeks of treatment, patients could switch to emicizumab prophylaxis at 3.0 mg/kg SC weekly for 4 weeks, followed by 3.0 mg/kg SC every 2 weeks.

Patients in HAVEN 3 previously treated with prophylactic FVIII were assigned to the following treatment:

- Emicizumab prophylaxis at 3.0 mg/kg SC weekly for 4 weeks, followed by 1.5 mg/kg SC weekly for 20 weeks (arm D).

In HAVEN 3, breakthrough bleeds, surgeries, and procedures were treated using episodic treatment with FVIII at the lowest expected dose to achieve hemostasis, where a specific dose was not required.

In HAVEN 4, after screening, eligible study participants were assigned to the following treatment:

- Emicizumab prophylaxis at 3.0 mg/kg SC weekly for 4 weeks, followed by 6.0 mg/kg SC every 4 weeks for 20 weeks.

Permitted therapy in HAVEN 4 included drugs intended to control bleeds (including FVIII concentrates) at the lowest dose expected to achieve hemostasis, where a specific dose was not required.

Patients in the randomized arms of HAVEN 3 and all patients in HAVEN 4 were able to up-titrate their emicizumab dose to 3.0 mg/kg weekly after 24 weeks emicizumab prophylaxis if they met the protocol-defined criteria of suboptimal response (2 or more qualifying bleeds within 24 weeks on emicizumab treatment). Patients in HAVEN 3 previously treated with prophylactic FVIII could up-titrate their emicizumab dose to 3.0 mg/kg weekly at any time after experiencing 2 qualifying bleeds. Up-titrated patients in HAVEN 4 could subsequently down-titrate to 6.0 mg/kg every 4 weeks, 3.0 mg/kg every 2 weeks, or 1.5 mg/kg weekly.

In both studies, patients previously treated with FVIII prophylaxis were permitted to continue their regular FVIII prophylaxis until the second emicizumab loading dose in order to avoid bleeds before an adequate emicizumab level was reached.

In both HAVEN 3 and HAVEN 4, health care providers were trained on how to administer emicizumab. Patients (and caregivers, if applicable) were trained by health care providers during a period of in-clinic administration on how to self-administer emicizumab. The first 5 administrations were monitored in a clinical setting; patients required the health care provider's approval to start home administration.

The use of drugs intended to treat bleeds on an episodic basis, including FVIII, was permitted in both studies. While the specific dosages of FVIII were not mandated, breakthrough bleeds were to be treated with the lowest FVIII dose expected to achieve hemostasis.

In both studies, prohibited therapies included: drugs that would affect hemostasis (except those intended to control bleeding episodes or used in the context of minor surgery or injuries to prevent deterioration); systemic immunomodulators other than antiretrovirals; elective surgery; and other investigational drugs. HAVEN 4 prohibited the use of activated prothrombin complex concentrate for short-term prophylaxis and anti-fibrinolytics in conjunction with activated prothrombin complex concentrate or Byclot.

Outcomes

The efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review are provided in Table 7 and discussed in the text that

follows. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4. No outcomes in HAVEN 4 were designated as primary or secondary outcomes.

Table 7: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	HAVEN 3	HAVEN 4
Treated bleeds	Primary	Unspecified
All bleeds	Secondary	Unspecified
Treated joint bleeds	Secondary	Unspecified
Treated spontaneous bleeds	Secondary	Unspecified
Treated target joint bleeds	Other	Unspecified
All bleeds compared with the patient's historical bleed rate (intra-patient comparison)	Secondary	NA
Treated bleeds compared with the patient's historical bleed rate (intra-patient comparison)	Secondary	NA
Number of days away from school/work	Exploratory	Unspecified
Haem-A-QoL physical health score	Secondary	Unspecified
Haem-A-QoL	Other	Unspecified
Haemo-QoL-SF	Other	Unspecified
EQ-5D-5L index utility score and EQ-5D-5L VAS	Other	Unspecified
Number of days hospitalized	Exploratory	Unspecified
Patient preference	Exploratory	Unspecified

EQ-5D-5L= EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; Haemo-QoL-SF= Haemophilia-specific Quality of Life Questionnaire for Children Short Form; NA = not applicable.

Note: The Haem-A-QoL is completed by patients aged 18 years and older.

Bleeding

The efficacy of emicizumab was assessed using various outcomes related to the frequency of bleeding episodes. The following bleeding outcomes were assessed in both HAVEN 3 and HAVEN 4: treated bleeds, all bleeds, treated joint bleeds, treated spontaneous bleeds, and treated target bleeds. Definitions for bleeds were based on standardized, adapted from criteria defined by the factor VIII, Factor IX and Rare Coagulation Disorders Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH). Definitions for bleeds were consistent in HAVEN 3 and HAVEN 4. Two bleeds of the same type and anatomical location were considered as 1 bleed if the second occurred within 72 hours of the last treatment for the first bleed. The ABR for each outcome was calculated using the following formula: ABR = (number of bleeds divided by total number of days during the efficacy period) multiplied by 365.25.

The primary efficacy outcome in HAVEN 3 was based on the number of treated bleeds over time. An event was considered a treated bleed if coagulation factors were administered for the treatment signs or symptoms of bleeding (e.g., pain, swelling), irrespective of the time between the treatment and the preceding bleed. A primary efficacy outcome was not identified for HAVEN 4.

All bleeds included both treated and non-treated bleeds. Bleeds due to surgery or procedures were excluded.

Treated joint bleeds were defined as bleeds occurring in a joint with at least 1 of the following symptoms: increasing swelling or warmth of the skin over the joint and/or

increasing pain, decreased range of motion, or difficulty in using the joint compared with baseline.

Treated spontaneous bleeds were defined as a treated bleed with no known contributing factor, such as trauma, surgery, or procedure.

Treated target joint bleeds were defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of greater than or equal to 3 bleeds into the same joint over the last 24 weeks prior to study entry).

Data on bleeds (including start date and time, cause, type, location, and associated symptoms of each bleed) were collected through an electronic bleed and medication questionnaire that was developed and validated by the sponsor as part of the emicizumab clinical development program.

Productivity

Days away from school or work were recorded at baseline and week 25 based on the 4-week period preceding each data entry.

Health-Related Quality of Life

HRQoL was assessed using the Haem-A-QoL, Haemophilia-specific Quality of Life Questionnaire for Children Short Form (Haemo-QoL-SF), and the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) index utility score and the EuroQol Visual Analogue Scale (EQ VAS).

The Haem-A-QoL is a disease-specific, self-reported questionnaire used to measure HRQoL in adult patients (18 years or older) with hemophilia.[30,31] It measures the following 10 domains: Physical Health, Feelings, View of Self, Sports and Leisure, Work and School, Dealing With Hemophilia, Treatment, Future, Family Planning, and Partnership and Sexuality. In total, the questionnaire has 46 items, with a 5-point Likert frequency scale (never, rarely, sometimes, often, all the time). Scores are transformed to a value ranging from 0 to 100, with higher scores indicating poorer HRQoL. The validity, reliability, and responsiveness of the Haem-A-QoL have been established.[31] Construct validity was adequate for 8 out of 10 domains and the total score.[30] Convergent validity and internal consistency were determined to be acceptable in patients with hemophilia.[30] The Haem-A-QoL was sensitive to detect change over time in patients with hemophilia. A minimal important difference (MID) was not identified in the literature for patients with hemophilia A for the Haem-A-QoL; however a 7-point reduction in total score was found to indicate a threshold for responders which showed a benefit in the HRQoL of individual patients with hemophilia.[32] Another study of patients with hemophilia used half an SD of the mean as the MID.[33]

The Haemo-QoL-SF is a 35-item, disease-specific, age-related questionnaire for children and adolescents aged 8 years to 16 years with hemophilia.[34] It includes the following 9 dimensions: Physical Health, Feelings, View of Self, Family, Friends, Other Persons, Sports and School, Dealing With Hemophilia, and Treatment.[35] Responses for the 35 items are scored on a 5-point Likert scale (never, seldom, sometimes, often, and always). The overall score ranges from 0 to 100, with higher scores indicating poorer HRQoL. The Haemo-QoL-SF was modified from the Haemo-QoL long form, which has been validated and shown to be reliable.[34] Convergent validity, internal consistency, inter-rater reliability, and test-retest reliability of the Haemo-QoL-SF were determined to be acceptable in patients with

hemophilia.[35] No literature assessing the responsiveness of the Haemo-QoL-SF in patients with hemophilia was identified. No MID was identified in the literature for the Haemo-QoL-SF.

The EQ-5D-5L is a generic, preference-based HRQoL instrument consisting of a Visual Analogue Scale (VAS) and a composite index score of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[36] Each dimension has 5 levels of function: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS is a vertical VAS from 0 to 100 (20 cm), with anchors of the worst imaginable and best imaginable health states, respectively.[37] Validity and reliability of the EQ-5D-5L has been demonstrated in patients with hemophilia.[37,38] Item-total correlation and internal consistency of the index score was satisfactory in patients with hemophilia.[38] No literature assessing the responsiveness of the EQ-5D-5L utility index in patients with hemophilia was identified. Convergent validity was low to moderate in patients with hemophilia for the EQ VAS.[39] No literature assessing reliability and responsiveness of the EQ VAS in patients with hemophilia was identified. No MID was identified for the EQ-5D-5L index or the EQ VAS in populations with hemophilia. The MID was estimated to range from 0.037 to 0.056 in the general population.[40]

Hospitalization

Days hospitalized were recorded at baseline and week 25 based on the 4-week period preceding each data entry.

Pain

Pain was assessed as a domain within the EQ-5D-5L. The 5 levels within the pain domain ranged from “I have no pain or discomfort” to “I have extreme pain or discomfort.”[36] Item-total correlation was satisfactory for all domains in the EQ-5D-5L and highest for the “pain/discomfort” domain in patients with hemophilia.[37] Construct validity was acceptable for the “pain/discomfort” domain in patients with hemophilia.[38] A MID was not identified in the literature for patients with hemophilia A for the pain domain of the EQ-5D-5L.

Patient Satisfaction

Patient preference and satisfaction with treatment were assessed through the Emicizumab Preference (EmiPref) Survey and the Satisfaction Questionnaire – Intravenous Subcutaneous Hemophilia Injection (SQ-ISHI).

The sponsor-developed EmiPref Survey asked patients to report which treatment they would prefer to continue to receive after having been treated with FVIII (episodic or prophylaxis) and emicizumab. No literature was identified that tested the EmiPref Survey for reliability, validity, or responsiveness in patients with hemophilia A. A MID was not identified in the literature for patients with hemophilia A.

Patients who previously received treatment with FVIII prophylaxis completed the SQ-ISHI. This 13-item measure was designed to assess satisfaction with emicizumab or with FVIII prophylaxis by probing the general concepts of discomfort, worry, and difficulty with injections; confidence with treatment; duration and frequency of treatment; ease of treatment; impact on daily activities; adherence; and overall satisfaction. No literature was identified that tested the SQ-ISHI for reliability, validity, or responsiveness in patients with hemophilia A. A MID was not identified in the literature for patients with hemophilia A.

Statistical Analysis

HAVEN 3

In HAVEN 3, an estimated 75 patients were required to achieve at least 90% power at the 2-sided 0.05 level of significance. The sample size was based on randomization of 2:2:1 (i.e., 30 patients in each emicizumab arm, 15 patients in the control arm). It was assumed that patients from each treatment group would be followed for up to 24 weeks. Simulations of varying follow-up times anticipated that power would be greater than 90% at the 2-sided 0.05 level of significance.

In HAVEN 3, the number of bleeds (e.g., treated bleeds, all bleeds) were analyzed using a negative binomial regression model with efficacy period as an offset to account for the difference in follow-up times. The number of bleeds (less than 9 or greater than or equal to 9) in the last 24 weeks prior to study entry were used as a stratification factor. The ABR ratio was estimated from the model and presented with a 95% CI.

The secondary efficacy outcome for the physical health subscore of the Haem-A-QoL at 24 weeks was analyzed using analysis of variance (ANOVA). The model included the treatment group, baseline score, and treatment by baseline interaction as covariates. The primary analysis consisted of a global approach, with a 3-level categorical effect for treatment (1.5 mg/kg weekly, 3.0 mg/kg every 2 weeks, or no prophylaxis) for the comparisons of arm A versus arm C and arm B versus arm C.

Haem-A-QoL total score, the EQ-5D-5L index utility score, and EQ VAS at 24 weeks were analyzed using the same analysis methodology as for the Haem-A-QoL physical health subscore (i.e., through ANOVA).

In HAVEN 3, hierarchical testing was used to account for multiple testing. The first test evaluated the emicizumab 1.5 mg/kg weekly maintenance dose (group A) versus control. This was followed by the second test, which evaluated the maintenance dose of emicizumab 3.0 mg/kg every 2 weeks (group B) versus control. A global approach incorporating a model statement with a 3-level categorical effect for treatment and an appropriate contrast statement was used to allow both tests to be performed.

Secondary efficacy outcomes in HAVEN 3 were tested according to the following hierarchy:

- A versus C randomized comparison: all bleeds
- B versus C randomized comparison: all bleeds
- A versus C randomized comparison: treated joint bleeds
- B versus C randomized comparison: treated joint bleeds
- A versus C randomized comparison: treated spontaneous bleeds
- B versus C randomized comparison: treated spontaneous bleeds
- D intra-patient: all bleeds
- D intra-patient: treated bleeds
- A versus C randomized comparison: Haem-A-QoL physical health at 24 weeks
- B versus C randomized comparison: Haem-A-QoL physical health at 24 weeks

Other outcomes and exploratory outcomes in HAVEN 3 were analyzed using descriptive statistics.

Preplanned subgroup analysis for treated bleeds relevant to the review included the following:

- Age: less than 18, greater than or equal to 18
- Age: less than 65, greater than or equal to 65
- Number of bleeds during 24 weeks prior to study entry: less than or equal to 9, greater than 9
- Number of target joints: no target joint, any target joint

For patients in arm A, B, or D, the end of the efficacy period was defined as the clinical cut-off date or the date of withdrawal from the initial study period (i.e., treatment phase), whichever was earlier. For patients randomized to arm C (no prophylaxis), the end of the efficacy period was defined as the day before the first emicizumab dose was administered (for patients who switched to receive emicizumab after 24 weeks), the date of withdrawal from the initial study period, or the clinical cut-off date. For patients whose dose was up-titrated, the efficacy period on the initial dose ended the day prior to the first day on the higher dose.

Sensitivity analysis in HAVEN 3 was performed using various methods to define bleeds (e.g., analysis without the 72-hour bleed rule) and different statistical models (e.g., alternative negative binomial modelling approach, ANOVA).

Safety data in HAVEN 3 were reviewed by an independent data-monitoring committee consisting of hemostasis/thrombosis experts and a statistician.

A formal method of imputing missing data was not used in HAVEN 3. Responses to questionnaires were reported through a personal electronic handheld device and onsite tablet designed to prevent respondents from leaving questions unanswered or submitting partial (incomplete) data. Therefore, the data for the primary and secondary bleed related end points and the HRQoL questionnaires are considered complete, according to the sponsor.

HAVEN 4

The sample size planned for the expansion cohort in HAVEN 4 was 40 patients. Although no formal sample-size calculation was reported, the sponsor stated that a sample size of 40 was expected to provide robust point estimates with meaningfully narrow CIs in ABR calculations. There was no formal hypothesis testing planned for HAVEN 4. All analyses were descriptive. A primary efficacy outcome was not specified. Bleeding outcomes were analyzed as described for HAVEN 3.

The efficacy period for each patient started on the day of the first emicizumab dose and ended when the last enrolled patient reached 24 weeks of treatment.

In HAVEN 4, preplanned subgroup analysis for treated bleeds and all bleeds relevant to the review were consistent with those previously described for HAVEN 3, with the addition of the following:

- FVIII inhibitor status (with FVIII inhibitor, without FVIII inhibitors)
- Previous treatment regimen (prior episodic, prior prophylactic)

Sensitivity analysis was not performed in HAVEN 4. The study did not use an independent data-monitoring committee or a formal method of imputing missing data. Data were

collected using a personal electronic handheld device and onsite tablet, as described for HAVEN 3.

Analysis Populations

HAVEN 3

- The randomized, intention-to-treat (ITT) population consisted of all randomized patients. The ITT population was the primary analysis population for efficacy. This population included patients in arms A, B, and C.
- The all-patient population consisted of all patients in their originally assigned treatment arms, including patients in arm D.
- Two safety analysis populations consisted of the following patients:
  - Safety population 1 included all patients in arms A, B, and D who received at least 1 dose of emicizumab and patients in arm C who started the study period, defined as having a week 1 visit.
  - Safety population 2 was the same as safety population 1 for patients in arms A, B, and D. For patients in arm C, safety population 2 included all patients who switched to emicizumab and received at least 1 dose.
- The NIS population consisted of all patients who participated in the NIS prior to enrolment in HAVEN 3.
  - The NISE population consisted of the NIS population previously treated with episodic FVIII.
  - The NISP population consisted of the NIS population previously treated with prophylactic FVIII.

HAVEN 4

- The treated patient population consisted of all patients who received at least 1 dose of emicizumab (primary analysis population).
- The all-patient population consisted of all patients enrolled in the study.

Results

Patient Disposition

In HAVEN 3, 161 patients were screened. Among them, 36 were randomized to maintenance treatment with 1.5 mg/kg emicizumab weekly, 35 were randomized to 3.0 mg/kg every 2 weeks, and 18 were randomized to the no-prophylaxis arm. A total of 63 patients were enrolled in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). Three patients discontinued HAVEN 3.

In HAVEN 4, 44 patients were screened, and 41 were enrolled in the expansion cohort for the purpose of efficacy and safety analysis. No patients discontinued from HAVEN 4. Details of patient disposition for HAVEN 3 and HAVEN 4 are presented in Table 8.

Table 8: Patient Disposition

	HAVEN 3				HAVEN 4
	1.5 mg/kg QW emicizumab	3.0 mg/kg Q2W emicizumab	No prophylaxis	Previous FVIII prophylaxis; 1.5 mg/kg QW emicizumab	6.0 mg/kg Q4W emicizumab
Screened, N	161				44
Randomized/enrolled, N (%)	36	35	18	63	41
Discontinued from study, N (%)	1 (2.8)	1 (2.9)	1 (5.6)	0	0
Reason for discontinuation, N (%)					
Adverse events	0	1 (2.9)	0	0	0
Lost to follow-up	1 (2.8)	0	1 (5.6)	0	0
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Note: [redacted]

NIS = non-interventional study; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly.

Note: NIS patients include patients who also participated in HAVEN 3.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Exposure to Study Treatments

In HAVEN 3, exposure to treatment was similar in the randomized emicizumab arms. The mean (SD) duration of exposure to emicizumab was [redacted] for those taking 1.5 mg/kg emicizumab weekly and [redacted] for those taking 3.0 mg/kg every 2 weeks. Patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly maintenance) had a mean (SD) duration of exposure to emicizumab of [redacted]. Five patients had their emicizumab dose up-titrated during the study (1 patient in the 1.5 mg/kg emicizumab weekly arm and 4 in the previous-FVIII-prophylaxis arm [1.5 mg/kg emicizumab weekly maintenance]). The mean durations of the efficacy periods for the randomized patients ranged from [redacted] to [redacted] it is presented in Table 9.

In HAVEN 3 and HAVEN 4, a patient was considered to be adherent if they completed the electronic bleed and medication questionnaire at least every 8 days. In HAVEN 3, adherence was similar between arms in the ITT population (99.4%, 92.5%, and 96.4% adherent days in arms receiving 1.5 mg/kg emicizumab weekly, 3.0 mg/kg emicizumab every 2 weeks, and no prophylaxis, respectively). A total of 98.2% adherent days were reported for the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab maintenance).

Use of non-emicizumab hemophilia medication (e.g., FVIII) was similar for patients randomized to 1.5 mg/kg emicizumab weekly (47.2%) and to 3.0 mg/kg every 2 weeks (48.65%), while all patients in the no-prophylaxis arm (100%) required use of non-emicizumab hemophilia medication (Table 10). Use of non-emicizumab preventive hemophilia medication before activity was higher (44.4%) in the no-prophylaxis group compared to the emicizumab groups (2.8% to 5.7%)

In HAVEN 4, the mean duration of exposure to 6.0 mg/kg emicizumab every 4 weeks was 24.68 weeks (SD = 1.44 weeks). A total of 94.7% of adherent days were reported. The duration of the efficacy period was 25.98 weeks (Table 10). Twenty-five patients (61.0%) received a non-emicizumab hemophilia medication. No patients had their emicizumab dose up-titrated during the study (Table 10).

Table 9: Efficacy Period Duration

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	6.0 mg/kg Q4W emicizumab N = 41
Efficacy period, weeks[a,b]				
n (%)	36 (100)	35 (100)	18 (100)	41 (100)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy period ≥ 24 weeks, n (%)	35 (97.2)	34 (97.1)	16 (88.9)	41 (100)

ITT = intention to treat; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly.

[a] HAVEN 3: ITT population.

[b] HAVEN 4: All-treated-patients population, expansion cohort.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Table 10: Summary of Non-Emicizumab Hemophilia Medication

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	6.0 mg/kg Q4W emicizumab N = 41
Total number of patients with at least 1 treatment, n (%)[a,b]	17 (47.2)	17 (48.6)	18 (100)	25 (61.0)
Purpose of the medication, n (%)				
Preventive dose before activity	1 (2.8)	2 (5.7)	8 (44.4)	16 (39.0)
Preventive dose for procedure or surgery	1 (2.8)	2 (5.7)	1 (5.6)	1 (2.4)
Treatment for bleed	17 (47.2)	16 (45.7)	18 (100)	18 (43.9)

ITT = intention to treat; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly.

[a] HAVEN 3: ITT population.

[b] HAVEN 4: All-treated-patients population, expansion cohort

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported. See Appendix 3 3 for detailed efficacy data.

Bleeding

Treated Bleeds

In HAVEN 3, 55.6% of patients treated with 1.5 mg/kg emicizumab weekly experienced 0 treated bleeds over the efficacy period (Table 11). The ABR was 1.5 versus 38.2 per year for groups receiving 1.5 mg/kg emicizumab weekly versus no prophylaxis, respectively (ABR ratio = 0.04; 95% CI, 0.020 to 0.075; P < 0.0001) in favour of 1.5 mg/kg emicizumab weekly. Sixty percent of patients treated with 3.0 mg/kg emicizumab every 2 weeks experienced 0 treated bleeds over the efficacy period. Similarly, the ABR was 1.3 versus 38.2 per year for groups taking 3.0 mg/kg emicizumab every 2 weeks and no prophylaxis, respectively (ABR ratio = 0.03; 95% CI, 0.017 to 0.066; P < 0.0001), in favour of 3.0 mg/kg emicizumab every 2 weeks. None of the patients in the no- prophylaxis group experienced 0 treated bleeds over the efficacy period. Results of the sensitivity analyses were aligned with the primary analysis.

Compared with the no-prophylaxis group, both of the emicizumab groups (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks) experienced consistent reductions in treated bleed rates in the subgroup analyses for bleed rate in during the 24 weeks prior to enrolment (less than 9 bleeds, greater than or equal to 9 bleeds) (Appendix 3, Table 39).

An intra-patient analysis was conducted in the patients on prior prophylaxis with FVIII (non-randomized arm D) who entered HAVEN 3 from a previous NIS. In the NIS, an estimated 39.6% of patients treated with FVIII prophylaxis experienced 0 treated bleeds. In HAVEN 3, an estimated 54.2% of patients in the intra-patient analysis (i.e., patients who subsequently received treatment with 1.5 mg/kg emicizumab weekly) experienced 0 treated bleeds over the efficacy period. An ABR of 4.8 versus 1.5 per year was reported for the patients treated with FVIII prophylaxis versus their treatment with 1.5 mg/kg emicizumab weekly, respectively. An ABR ratio of 0.32 (95% CI, 0.195 to 0.514; P < 0.0001) in favour of 1.5 mg/kg emicizumab weekly was reported for the intra-patient comparison of patients treated with FVIII prophylaxis in the NIS compared to their treatment with 1.5 mg/kg emicizumab weekly in HAVEN 3. The results favoured treatment with 1.5 mg/kg emicizumab weekly (Table 12).

In HAVEN 4, 56.1% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced 0 treated bleeds; the ABR was 2.4 (95% CI, 1.38 to 4.28) (Table 11). ABRs were reported for the following subgroups: bleed rate during the 24 weeks prior to enrolment (less than 9 bleeds, greater than or equal to 9 bleeds), presence or absence of target joints, previous treatment regimen (episodic, prophylactic), and FVIII inhibitor status (Appendix 3, Table 39).

All Bleeds

In HAVEN 3, 50.0% of patients treated with 1.5 mg/kg emicizumab weekly experienced 0 bleeds over the efficacy period (Table 11). The ABR was 2.5 versus 47.6 for the groups receiving 1.5 mg/kg emicizumab weekly and no prophylaxis, respectively (ABR ratio = 0.05; 95% CI, 0.028 to 0.099; P < 0.0001) in favour of 1.5 mg/kg emicizumab weekly. Forty percent of patients treated with 3.0 mg/kg emicizumab every 2 weeks experienced 0 bleeds over the efficacy period. The ABR was 2.6 versus 47.6 between the groups receiving

3.0 mg/kg emicizumab every 2 weeks and no prophylaxis, respectively (ABR ratio = 0.06; 95% CI, 0.030 to 0.103; P < 0.0001) in favour of 3.0 mg/kg emicizumab every 2 weeks. None of the patients in the no-prophylaxis group experienced 0 bleeds. Results of the sensitivity analyses were aligned with the primary analysis.

In the NIS, an estimated 31.3% of patients previously treated with FVIII prophylaxis experienced 0 bleeds. In HAVEN 3, an estimated 41.7% of patients in the intra-patient analysis (i.e., patients who subsequently received treatment with 1.5 mg/kg emicizumab weekly) experienced 0 bleeds over the efficacy period. An ABR of 3.3 versus 8.9 (ABR ratio = 0.37; 95% CI, 0.220 to 0.626; P < 0.0001) was reported for the intra-patient comparison of patients treated with FVIII prophylaxis in the NIS compared with treatment with 1.5 mg/kg emicizumab weekly in HAVEN 3, respectively (Table 12).

In HAVEN 4, 29.3% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced 0 bleeds; the ABR was 4.5 (95% CI, 3.10 to 6.60) over the efficacy period (Table 11). ABRs were reported for the following subgroups: bleed rate during the 24 weeks prior to enrolment (less than 9 bleeds, greater than or equal to 9 bleeds), presence or absence of target joints, previous treatment regimen (episodic, prophylactic), and FVIII inhibitor status (Appendix 3, Table 39).

Treated Joint Bleeds

In HAVEN 3, 58.3% of patients treated with 1.5 mg/kg emicizumab weekly experienced 0 treated joint bleeds over the efficacy period (Table 11). The ABR ratio between the groups taking 1.5 mg/kg emicizumab weekly (ABR = 1.1) and no prophylaxis (ABR = 26.5) was 0.04 (95% CI, 0.019 to 0.085; P < 0.0001) in favour of 1.5 mg/kg emicizumab weekly. A total of 74.3% of patients treated with 3.0 mg/kg emicizumab every 2 weeks experienced 0 treated joint bleeds over the efficacy period. The ABR ratio between 3.0 mg/kg every 2 weeks (ABR = 0.9) and no prophylaxis (ABR = 26.5) was 0.03 (95% CI, 0.015 to 0.070; P < 0.0001) in favour of 3.0 mg/kg emicizumab every 2 weeks. None of the patients in the no-prophylaxis group experienced 0 treated joint bleeds. Results of the sensitivity analyses were aligned with the primary analysis.

In HAVEN 4, 70.7% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced 0 treated joint bleeds; the ABR was 1.7 (95% CI, 0.82 to 3.68) over the efficacy period (Table 11).

Treated Spontaneous Bleeds

In HAVEN 3, 66.7% of patients treated with 1.5 mg/kg emicizumab weekly experienced 0 treated spontaneous bleeds over the efficacy period (Table 11). The ABR ratio between 1.5 mg/kg emicizumab weekly (ABR = 1.0) and no prophylaxis (ABR = 15.6) was 0.06 (95% CI, 0.025 to 0.151; P < 0.0001) in favour of 1.5 mg/kg emicizumab weekly. A total of 88.6% of patients treated with 3.0 mg/kg emicizumab every 2 weeks experienced 0 treated spontaneous bleeds over the efficacy period. The ABR ratio between 3.0 mg/kg every 2 weeks (ABR = 0.3) and no prophylaxis (ABR = 15.6) was 0.02 (95% CI, 0.006 to 0.056; P < 0.0001) in favour of 3.0 mg/kg emicizumab every 2 weeks. A total of 22.2% of the patients in the no-prophylaxis group experienced 0 treated spontaneous bleeds. Results of the sensitivity analyses were aligned with the primary analysis.

In HAVEN 4, 82.9% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced 0 treated spontaneous bleeds; the ABR was 0.6 (95% CI, 0.27 to 1.53) over the efficacy period (Table 11).

Treated Target Joint Bleeds

In HAVEN 3, 69.4% of patients treated with 1.5 mg/kg emicizumab weekly experienced 0 treated target joint bleeds over the efficacy period (Table 11). The ABR ratio between 1.5 mg/kg emicizumab weekly (ABR = 0.6) and no prophylaxis (ABR = 13.0) was 0.05 (95% CI, 0.016 to 0.143; P < 0.0001) in favour of 1.5 mg/kg emicizumab weekly. A total of 77.1% of patients treated with 3.0 mg/kg emicizumab every 2 weeks experienced 0 treated target joint bleeds over the efficacy period. The ABR ratio between 3.0 mg/kg emicizumab every 2 weeks (ABR = 0.7) and no prophylaxis (ABR = 13.0) was 0.05 (95% CI, 0.018 to 0.147; P < 0.0001) in favour of 3.0 mg/kg emicizumab every 2 weeks. A total of 27.8% of the patients in the no-prophylaxis group experienced treated target joint bleeds. Results of the sensitivity analyses were aligned with the primary analysis.

In HAVEN 4, 85.4% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced 0 treated target joint bleeds; the ABR was 1.0 (95% CI, 0.31 to 3.26) over the efficacy period (Table 11).

Table 11: Bleeding Outcomes

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	6.0 mg/kg Q4W emicizumab N = 41
Treated bleeds				
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	41 (100)
Patients experiencing 0 bleeds, n (%)	20 (55.6)	21 (60.0)	0	23 (56.1)
Annualized bleeding rate (95% CI)	1.5 (0.89 to 2.47)	1.3 (0.75 to 2.25)	38.2 (22.86 to 63.76)	2.4 (1.38 to 4.28)[b]
Annualized bleeding rate ratio (95% CI)	0.04 (0.020 to 0.075)[a]	0.03 (0.017 to 0.066)[a]	Reference group	NA
P value	< 0.0001[a]	< 0.0001[a]		NA
All bleeds				
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	41 (100)
Patients experiencing 0 bleeds, n (%)	18 (50.0)	14 (40.0)	0	12 (29.3)
Annualized bleeding rate (95% CI)	2.5 (1.63 to 3.90)	2.6 (1.63 to 4.29)	47.6 (28.45 to 79.59)	4.5 (3.10 to 6.60)[b]
Annualized bleeding rate ratio (95% CI)	0.05 (0.028 to 0.099)[a]	0.06 (0.030 to 0.103)[a]	Reference group	NA
P value	< 0.0001[a]	< 0.0001[a]		NA
Treated joint bleeds				
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	41 (100)
Patients experiencing 0 bleeds, n (%)	21 (58.3)	26 (74.3)	0	29 (70.7)
Annualized bleeding rate (95% CI)	1.1 (0.59 to 1.89)	0.9 (0.44 to 1.67)	26.5 (14.67 to 47.79)	1.7 (0.82 to 3.68)[b]
Annualized bleeding rate ratio (95% CI)	0.04 (0.019 to 0.085)[a]	0.03 (0.015 to 0.070)[a]	Reference group	NA
P value	< 0.0001[a]	< 0.0001[a]		NA

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	6.0 mg/kg Q4W emicizumab N = 41
Treated spontaneous bleeds				
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	41 (100)
Patients experiencing 0 bleeds, n (%)	24 (66.7)	31 (88.6)	4 (22.2)	34 (82.9)
Annualized bleeding rate (95% CI)	1.0 (0.48 to 1.91)	0.3 (0.11 to 0.75)	15.6 (7.60 to 31.91)	0.6 (0.27 to 1.53)[b]
Annualized bleeding rate ratio (95% CI)	0.06 (0.025 to 0.151)[a]	0.02 (0.006 to 0.056)[a]	Reference group	NA
P value	< 0.0001[a]	< 0.0001[a]		NA
Treated target joint bleeds				
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	41 (100)
Patients experiencing 0 bleeds, n (%)	25 (69.4)	27 (77.1)	5 (27.8)	35 (85.4)
Annualized bleeding rate (95% CI)	0.6 (0.28 to 1.42)	0.7 (0.27 to 1.64)	13.0 (5.22 to 32.33)	1.0 (0.31 to 3.26)[b]
Annualized bleeding rate ratio (95% CI)	0.05 (0.016 to 0.143)[a,c,d]	0.05 (0.018 to 0.147)[a,c,d]	Reference group	NA
P value	< 0.0001[a,c,d]	< 0.000 [a,c,d]		NA

CI = confidence interval; ITT = intention to treat; NA = not applicable; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly.

[a] ITT population; negative binomial regression model; P value using stratified Wald test through global model with 3-level categorical effect for treatment.

[b] All treated-patients-population; negative binomial regression model.

[c] P value has not been adjusted for multiple testing.

[d] Treated target joint bleeds occur in a target joint, defined as a joint in which ≥ 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. Bleeds due to surgeries or procedures are excluded.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Productivity

Days Away From School

In HAVEN 3, students were away from school in the 4 weeks prior to baseline for an average of [redacted]

During the 4 weeks prior to week 25, patients were away from school [redacted] (Table 13).

In HAVEN 4, students were away from school in the 4 weeks prior to baseline for an average of [redacted] During the 4 weeks prior to week 25, patients were away from school [redacted] (Table 13).

Days Away From Work

In HAVEN 3, patients were away from work in the 4 weeks prior to baseline for an average of [redacted] During the 4 weeks prior to week 25, patients were away from work for [redacted]

[redacted] (Table 13).

In HAVEN 4, patients were away from work in the 4 weeks prior to baseline for an average of [redacted] During the 4 weeks prior to week 25, patients were away from work for [redacted] (Table 13).

Table 12: Bleeding Outcomes for Intra-Patient Comparison (Data From NIS and HAVEN 3)

	HAVEN 3	
	FVIII prophylaxis (NIS) N = 48	Previous FVIII prophylaxis (1.5 mg/kg QW emicizumab) N = 48
Treated bleeds		
Number of patients contributing to the analysis (%)	48 (100)	48 (100)
Patients experiencing 0 bleeds, n (%)	19 (39.6)	26 (54.2)
Annualized bleeding rate (95% CI)	4.8 (3.22 to 7.09)	1.5 (0.98 to 2.33)
Annualized bleeding rate ratio (95% CI)	0.32 (0.195 to 0.514)[a]	
P value	< 0.0001[a]	
All bleeds		
Number of patients contributing to the analysis (%)	48 (100)	48 (100)
Patients experiencing 0 bleeds, n (%)	15 (31.3)	20 (41.7)
Annualized bleeding rate (95% CI)	8.9 (5.72 to 13.87)	3.3 (2.17 to 5.06)
Annualized bleeding rate ratio (95% CI)	0.37 (0.220 to 0.626)[a]	
P value	< 0.0001[a]	

CI = confidence interval; FVIII = factor VIII; NIS = non-interventional study; QW = once weekly.

Note: Only patients who participated in the NIS and HAVEN 3 are included. For patients initially on episodic treatment in HAVEN 3, only data on or after the prophylaxis prescription date from the case report form are included.

[a] NIS prophylactic FVIII population; negative binomial regression model; P value using non-stratified Wald test.

Source: Clinical Study Report for HAVEN 3.[10]

Table 13: Productivity

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 17	6.0 mg/kg Q4W emicizumab N = 41
Days away from school[a]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Days away from work[a]				
[redacted]				

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 17	6.0 mg/kg Q4W emicizumab N = 41
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; ITT = intention to treat; NR = not reported; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly; SD = standard deviation; SE = standard error.

[a] No-prophylaxis arm based on N = 18.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Health-Related Quality of Life

Haemophilia Quality of Life Questionnaire for Adults

In HAVEN 3, the difference in adjusted mean Haem-A-QoL physical health subscore at week 25 between 1.5 mg/kg emicizumab weekly and no prophylaxis was 12.51 (95% CI, –1.96 to 26.98; P = 0.891) (Table 14). The difference in adjusted mean Haem-A-QoL physical health subscore at week 25 between 3.0 mg/kg emicizumab every 2 weeks and no prophylaxis was 15.97 (95% CI, –1.16 to 30.78; P = 0.0349).

In HAVEN 4, the unadjusted mean change from baseline for the Haem-A-QoL physical health subscore at week 25 was −15.14 (95% CI, −22.44 to −7.83) in the 6.0 mg/kg emicizumab every 4 weeks group (Table 14).

In HAVEN 3, the difference in adjusted mean Haem-A-QoL total score at week 25 between 1.5 mg/kg emicizumab weekly and no prophylaxis was 5.91 (95% CI, –1.72 to 13.55; P = 0.1269) (Table 14). The difference in adjusted mean Haem-A-QoL total score at week 25 between 3.0 mg/kg emicizumab every 2 weeks and no prophylaxis was 8.56 (95% CI, 0.77 to 16.35; P = 0.0317).

In HAVEN 4, the unadjusted mean change from baseline for the Haem-A-QoL total score at week 25 was −13.62 (95% CI, −18.36 to −8.88) in the group receiving 6.0 mg/kg emicizumab every 4 weeks (Table 14).

Haemophilia-Specific Quality of Life Questionnaire for Children Short Form

Collated results for patients under the age of 18 for the Haemo-QoL-SF were not reported in HAVEN 3.

In HAVEN 4, the mean change from baseline for the Haemo-QoL-SF at week 25 was −8.10 (SD = 6.48) based on data from 3 patients under the age of 18 in the group receiving 6.0 mg/kg every 4 weeks.

EuroQol 5-Dimensions 5-Levels Questionnaire

In HAVEN 3, the difference in adjusted mean EQ-5D-5L index utility score at week 25 between 1.5 mg/kg emicizumab weekly and no prophylaxis was –0.13 (95% CI, –0.22 to –0.04; P = 0.0060) (Table 14). The difference in adjusted mean EQ-5D-5L index utility score

at week 25 between 3.0 mg/kg emicizumab every 2 weeks and no prophylaxis was –0.13 (95% CI, –0.23 to –0.04; P = 0.0059).

In HAVEN 4, the unadjusted mean change from baseline for the EQ-5D-5L index utility score at week 25 was 0.06 (95% CI, 0.03 to 0.10) in the group receiving 6.0 mg/kg emicizumab every 4 weeks (Table 14).

In HAVEN 3, the difference in adjusted mean EQ VAS at week 25 between 1.5 mg/kg emicizumab weekly and no prophylaxis was –4.04 (95% CI, –12.43 to 4.35; P = 0.3402) (Table 14). The difference in adjusted mean EQ VAS at week 25 between 3.0 mg/kg emicizumab every 2 weeks and no prophylaxis was –9.15 (95% CI, –17.74 to –0.55; P = 0.0373).

In HAVEN 4, the unadjusted mean change from baseline for the EQ VAS at week 25 was 5.53 (95% CI, 1.15 to 9.90) in the group receiving 6.0 mg/kg every 4 weeks (Table 14).

Table 14: Health-Related Quality of Life

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 17	6.0 mg/kg Q4W emicizumab N = 41
Haem-A-QoL physical health subscore				
Number of patients contributing to the analysis (%)	34 (94.4)	29 (82.9)	13 (76.5)	38 (92.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25, mean (SD)	31.81[a] (NR)	28.35[a] (NR)	44.32[a] (NR)	32.43 (25.43)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in adjusted mean at week 25 (95% CI)	12.51 (–1.96 to 26.98)[b]	15.97 (1.16 to 30.78)[b]	Reference group	NA
P value	0.0891[b]	0.0349[b]		NA
Haem-A-QoL total score				
Number of patients contributing to the analysis (%)	34 (94.4)	29 (82.9)	13 (76.5)	38 (92.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25, mean (SD)	24.04[a] (NR)	21.39[a] (NR)	29.95[a] (NR)	26.32 (16.62)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in adjusted mean at week 25 (95% CI)	5.91 (–1.72 to 13.55)[b]	8.56 (0.77 to 16.35)[b]	Reference group	NA
P value	0.1269[b]	0.0317[b]		NA
EQ-5D-5L index utility score				
Number of patients contributing to the analysis (%)	34 (94.4)	29 (82.9)	14 (82.4)	40 (97.6)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25, mean (SD)	0.76 [a]	0.76[a]	0.63[a]	0.75 (0.22)

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 17	6.0 mg/kg Q4W emicizumab N = 41
Change from baseline, unadjusted mean (95% CI)	[redacted]	[redacted]	[redacted]	0.06 (0.03 to 0.10)
Difference in adjusted mean at week 25 (95% CI)	–0.13 (–0.22 to –0.04)[b,]	–0.13 (–0.23 to –0.04)[b]	Reference group	NA
P value	0.0060[b]	0.0059[b]		NA
EQ VAS				
Number of patients contributing to the analysis (%)	34 (94.4)	29 (82.9)	14 (82.4)	40 (97.6)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 25, mean (SD)	76.61 (NR)[a]	81.72 (NR)[a]	72.57 (NR)[a]	79.53 (15.27)
Change from baseline, unadjusted mean (95% CI)	[redacted]	[redacted]	[redacted]	5.53 (1.15 to 9.90)
Difference in adjusted mean at week 25 (95% CI)	–4.04 (–12.43 to 4.35)[b]	–9.15 (–17.74 to –0.55)[b]	Reference group	NA
P value	0.3402[b]	0.0373[b]		NA

ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; FAS = full analysis set; LS = least squares; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; ITT = intention to treat; NA = not applicable; NR = not reported; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly; SD = standard deviation; SE = standard error.

Note: The Haem-A-QoL is completed by patients aged 18 years and older.

[a] Means adjusted for covariates: baseline score, treatment group, and treatment by baseline interaction term.

[b] ANCOVA; ITT population; means adjusted for covariates: baseline score, treatment group, and treatment by baseline interaction term.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Hospitalization

In HAVEN 3, the mean number of days hospitalized within the 24-week period was 0.17 (SD = 1.0) in the arm receiving 1.5 mg/kg emicizumab weekly, 0.43 (SD = 1.77) in the arm receiving 3.0 mg/kg emicizumab every 2 weeks, and 0.11 (SD = 0.47) in the no-prophylaxis arm (Table 15).

In HAVEN 4, the mean number of days hospitalized within the 24-week period was 0 in the arm receiving 6.0 mg/kg emicizumab every 4 weeks (Table 15).

Table 15: Hospitalization

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	6.0 mg/kg Q4W emicizumab N = 41
Days hospitalized				
Number of patients contributing to the analysis (%)	36 (100)	35 (100)	18 (100)	41 (100)
Number of days hospitalized within 24-week period, mean (SD)	0.17 (1.0)	0.43 (1.77)	0.11 (0.47)	0

Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly; SD = standard deviation.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Pain

In HAVEN 3 and HAVEN 4, the proportion of patients who experienced pain or discomfort at baseline and week 25 according to the EQ-5D-5L is summarized in Table 16.

Table 16: Pain or Discomfort Based on EQ-5D-5L

	HAVEN 3			HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	6.0 mg/kg Q4W emicizumab N = 41
Pain or discomfort [a]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

EQ-5D-5L = EuroQol 5-Dimension 5-Levels questionnaire; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly.

[a] Distribution of pain/discomfort response from EQ-5D-5L.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Patient Satisfaction

In HAVEN 3, based on results of the EmiPref, 96.4%, 81.0%, and 97.8% of patients in the arms taking 1.5 mg/kg emicizumab weekly, 3.0 mg/kg emicizumab every 2 weeks, and previous FVIII prophylaxis (1.5 mg/kg emicizumab weekly), respectively, preferred treatment with emicizumab compared to their previous hemophilia treatment (Table 17).

In HAVEN 4, all patients (100%) treated with 6mg/kg emicizumab every 4 weeks preferred treatment with emicizumab compared to their previous hemophilia treatment, based on findings from the EmiPref (Table 17).

In HAVEN 3, 73.1% of patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly) were "much more satisfied" with their current hemophilia treatment (1.5 mg/kg emicizumab weekly) compared to their pre-study prophylactic treatment (FVIII prophylaxis), as assessed by item 16 of the SQ-ISHI (Table 17).

Table 17: Patient Satisfaction Outcomes

	HAVEN 3				HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 18	Previous FVIII prophylaxis; 1.5 mg/kg QW emicizumab N = 63	6.0 mg/kg Q4W emicizumab N = 41
EmiPref Survey[a]					
Number of patients contributing to the analysis (%)	28 (77.8)	21 (60.0)	NA	46 (73.0)	41 (100.0)
Prefer the new study drug treatment (%)	27 (96.4)	17 (81.0)	NA	45 (97.8)	41 (100.0)
Prefer my old (IV) hemophilia treatment (%)	0	2 (9.5)	NA	0	0
Have no preference (%)	1 (3.6)	2 (9.5)	NA	1 (2.2)	0
SQ-ISHI item 16 – overall satisfaction[a]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EmiPref = Emicizumab Preference; NR = not reported; SQ-ISHI = Satisfaction Questionnaire – Intravenous Subcutaneous Hemophilia Injection.

[a] All-patient population.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Harms

Only those harms identified in the review protocol are reported in this section. See Table 18 for detailed harms data.

Adverse Events

In HAVEN 3, AEs occurred in 94.4% of patients in the arm receiving 1.5 mg/kg emicizumab weekly, 85.7% of patients in the arm receiving 3.0 mg/kg emicizumab every 2 weeks, 50.0% of patients in the no-prophylaxis arm, and 87.3% of patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). In HAVEN 4, 73.2% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an AE. In HAVEN 3 and HAVEN 4, the most common AE was injection-site reactions, as described in the *Notable Harms* section.

Serious Adverse Events

In HAVEN 3, SAEs occurred in 2.8% of patients receiving 1.5 mg/kg emicizumab weekly, 8.6% of those receiving 3.0 mg/kg emicizumab every 2 weeks, 0% of those on no prophylaxis, and 12.7% of those in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). In HAVEN 4, 2.4% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an SAE.

Withdrawals Due to Adverse Events

One patient (2.9%) treated with 3.0 mg/kg emicizumab every 2 weeks in HAVEN 3 stopped treatment due to AEs.

Mortality

No deaths were reported during HAVEN 3 or HAVEN 4.

Notable Harms

Notable harms identified in the protocol for this review included the following: thrombotic events, injection-site reactions, hypersensitivity reactions, inhibitor development, and blood-borne infections.

The only notable harms reported in HAVEN 3 and HAVEN 4 were injection-site reactions. Injection-site reactions were local AEs that occurred within 24 hours after the study drug was administered and were judged to be related to the study drug injection, based on assessment by the investigator. In HAVEN 3, injection-site reactions occurred in 25.0% of patients receiving 1.5 mg/kg emicizumab weekly, 20.0% of patients receiving 3.0 mg/kg emicizumab every 2 weeks, 12.5% of patients in the no-prophylaxis arm, and 31.7% of patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). In HAVEN 4, 22.0% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an injection-site reaction.

Throughout HAVEN 3 and HAVEN 4, no instances of de novo inhibitor development were detected in patients who tested negative for inhibitors (titre less than 0.6 CBU/mL) at baseline.

Table 18: Summary of Harms

	HAVEN 3				HAVEN 4
	1.5 mg/kg QW emicizumab N = 36	3.0 mg/kg Q2W emicizumab N = 35	No prophylaxis N = 16	Previous FVIII prophylaxis; 1.5 mg/kg QW emicizumab N = 63	6.0 mg/kg Q4W emicizumab N = 41
Patients with ≥ 1 adverse event					
n (%)	34 (94.4)	30 (85.7)	8 (50.0)	55 (87.3)	30 (73.2)
Most common events,[a] n (%)					
Injection-site reaction	9 (25.0)	7 (20.0)	2 (12.5)	20 (31.7)	9 (22.0)
Nasopharyngitis	2 (5.6)	6 (17.1)	0	10 (15.9)	11 (26.8)
Upper respiratory tract infection	4 (11.1)	4 (11.4)	0	8 (12.7)	3 (7.3)
Influenza	1 (2.8)	3 (8.6)	0	5 (7.9)	0
Arthralgia	7 (19.4)	6 (17.1)	1 (6.3)	14 (22.2)	8 (19.5)
Headache	3 (8.3)	4 (11.4)	1 (6.3)	8 (12.7)	5 (12.2)
Patients with ≥ 1 serious adverse event					
n (%)	1 (2.8)	3 (8.6)	0	8 (12.7)	1 (2.4)
Most common events[b]					
Epistaxis	0	1 (2.9)	0	1 (1.6)	
Patients who stopped treatment due to adverse events					
n (%)	0	1 (2.9)	0	0	0
Deaths					
n (%)	0	0	0	0	0
Notable harms					
Thromboembolic event, n (%)	0	0	0	0	0
Thrombotic microangiopathy, n (%)	0	0	0	0	0
Systemic hypersensitivity/ anaphylactic/anaphylactoid reaction, n (%)	0	0	0	0	0
Injection-site reaction	9 (25.0)	7 (20.0)	2 (12.5)	21 (33.3)	9 (22.0)
Inhibitor development	0	0	0	0	0[c]
Blood-borne infections	NR	NR	NR	NR	NR

NR = not reported; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QW = once weekly; SAE = serious adverse event.

Note: No SAE occurred in more than 1 patient per arm.

Note: HAVEN 3 safety population 2; HAVEN 4 safety population.

[a] Frequency ≥ 5%.

[b] SAEs occurring in more than 1 patient per study.

[c] No instance of de novo inhibitor development was detected in patients who tested negative for inhibitors (titre < 0.6 CBU/mL) at baseline

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Critical Appraisal

Internal Validity

Aspects of the study design in HAVEN 3 and HAVEN 4 may have affected the internal validity of the studies. Both studies were open-label; HAVEN 4 was a single-arm study. The open-label design may have biased the subjective outcome results in favour of emicizumab.

Both studies were 24 weeks in duration, an acceptable length of time to determine bleeding-related efficacy and safety, according to clinical experts.

HAVEN 4, a single-arm study, was limited by its non-controlled design. HAVEN 4 included patients with inhibitors (N = 5, 12.2%), which could have introduced heterogeneity in the patient population, although the impact of this on efficacy and harms outcomes is unknown. While some subgroup analysis was available for these patients, it is unclear how their inclusion may have influenced the results.

The baseline characteristics were generally balanced between the 3 randomized treatment arms in HAVEN 3, indicating adequate randomization. Minor imbalances were observed for the number of bleeds in the 24 weeks prior to study entry. Of note, patients in the no-prophylaxis (control) arm had a mean number of bleeds of [redacted] conversely, patients in the emicizumab arms had means of [redacted] and [redacted] for 1.5 mg/kg emicizumab weekly and 3.0 mg/kg emicizumab every 2 weeks, respectively. A greater number of bleeds in the arm with no prophylaxis at baseline may have introduced bias in the efficacy results in favour of emicizumab.

Definitions for bleeding outcomes were based on standardized definitions, adapted from criteria defined by the FVIII, Factor IX and Rare Coagulation Disorders Subcommittee of the ISTH. The definitions were used consistently across studies (HAVEN 3, HAVEN 4, HOHOEMI). The clinical experts consulted by CADTH for this review indicated that the bleeding outcomes assessed in HAVEN 3 and HAVEN 4 were consistent with those used in clinical practice. Although bleeding outcomes are not associated with formal MIDs, the consulted clinicians were able to assess the clinical relevance of the bleeding outcomes. Several relevant sensitivity analyses performed for the assessment of bleeding outcomes were aligned with the primary analysis, thereby indicating robust findings.

All bleeding outcomes in HAVEN 3 were analyzed using appropriate statistical methods. Hierarchical testing was used to account for multiplicity. While it is important to note that treated target bleeds (an outcome identified as “of interest” to clinicians) were not included in the testing hierarchy, the large magnitude of difference in efficacy between the 2 doses of emicizumab and the control arm were observed consistently for the other bleeding outcomes. Therefore, it is unlikely that the effect on this outcome was due to chance.

One outcome related to HRQoL, the Haem-A-QoL physical health subscore, was analyzed based on a statistical hierarchical approach. Therefore, multiplicity of testing with potential inflated type I error likely does not explain the observed difference. Yet, the statistically significant difference was observed only in the arm receiving 3.0 mg/kg every 2 weeks but not in the arm receiving
1.5 mg/kg weekly, even though the magnitude of reduction in terms of ABR for different types of bleeding was similar between the 2 different treatment regimens. Thus, the effect on improved quality of life remains inconclusive. Of note, the EQ-5D-5L index utility score — a general, non-disease–specific measure — showed a statistically significant difference

(P = 0.006) in both treatment regimens in comparison to no-prophylaxis control. However, this outcome measure was out of the statistical testing hierarchy.

In HAVEN 4, analyses of all outcomes were descriptive, and no formal hypothesis testing was performed. HAVEN 4 was the only pivotal study that assessed the maintenance dose of 6.0 mg/kg emicizumab every 4 weeks in patients with and without inhibitors, and its descriptive nature affects the interpretation of results. Input from the Health Canada Reviewers Report indicates sufficient pharmacokinetic and clinical data to support the efficacy of this maintenance dose in adult and adolescent patients.[29]

Relevant subgroup analyses performed in HAVEN 3 and/or HAVEN 4 included age, number of bleeds, number of target joints, FVIII inhibitor status, and previous treatment regimen. However, subgroup analysis was limited by the small number of patients in each subgroup, which in turn limited the interpretation of the results.

Outcomes related to productivity, hospitalization, pain, and patient preference were reported descriptively in both studies without performing formal statistical testing; this prevents the interpretation of the results for these outcomes.

Missing data were not accounted for statistically in either study. However, the impact of missing data is expected to be minimal in both, given that the amount of missing data were minimal. Discontinuations in HAVEN 3 and HAVEN 4 were low and balanced between treatment arms (0 or 1 patient per treatment arm) and were not expected to affect the validity of the results.

External Validity

The majority of patients with severe hemophilia A enrolled in HAVEN 3 (groups A, B, and C) were previously treated with episodic FVIII. This does not reflect Canadian clinical practice, in which the standard of care for patients with severe hemophilia A is treatment with FVIII prophylaxis. Furthermore, patients in HAVEN 3 and HAVEN 4 who previously received treatment with episodic FVIII were required to have 5 or more bleeds in the 24 weeks prior to study entry. This is also inconsistent with Canadian clinical practice, as it is unlikely for Canadian patients with 5 or more bleeds over a period of 24 weeks to be treated with episodic FVIII.

The impact of including a study population that has greater uncontrolled bleeding may exaggerate the efficacy of emicizumab compared to what would be seen in the Canadian clinical setting. Thus, the magnitude of the treatment effect in patients with better control (consistent with the Canadian clinical population) compared with those included in the trials is unknown.

There is no direct comparative evidence to support the efficacy of emicizumab compared to FVIII prophylaxis in patients with severe hemophilia A. There is limited evidence from an intra-patient analysis (group D in HAVEN 3) that supports the efficacy of emicizumab in patients previously treated with FVIII prophylaxis.

All patients included in HAVEN 3 and HAVEN 4 were male. While most patients in Canada with severe hemophilia A are male, there are a few female patients, and they were not represented in the studies.

The results of HAVEN 3 and HAVEN 4 may have limited generalizability to the Canadian patient population, given that the study population was restricted to patients (without inhibitors) with severe hemophilia A. According to the clinical experts consulted for this

review, there is a subset of patients with mild or moderate hemophilia who require prophylaxis. The design of HAVEN 3 and HAVEN 4 did not include them; thus, the magnitude of the treatment effect in patients with mild and moderate hemophilia A is unclear.

Eligibility criteria in both trials excluded patients with thromboembolic disease, at high risk for microangiopathy, and with certain autoimmune diseases, thereby decreasing the trials' generalizability to the Canadian clinical population. An assessment of baseline characteristics (e.g., gender, age) with the exception of previous bleeds showed reasonable consistency with the Canadian clinical population.

Patients in the randomized arms of HAVEN 3 and all patients in HAVEN 4 were able to up-titrate their emicizumab dose to 3.0 mg/kg if they met the protocol-defined criteria of suboptimal response. In HAVEN 3, 5 patients had their emicizumab dose up-titrated (one in the 1.5 mg/kg emicizumab weekly arm and 4 in the previous-FVIII-prophylaxis arm [1.5 mg/kg emicizumab weekly maintenance]). These patients were sufficiently accounted for in the efficacy period on the initial dose ended the day before the first day on the higher dose. The criterion allowing patients to up-titrate their emicizumab dose after suboptimal response was consistent with methods used in clinical practice.

HAVEN 3 and HAVEN 4 excluded patients under the age of 12; however, given the mechanism of action and body of evidence of emicizumab in children with inhibitors and the absence of direct data on children without inhibitors, the exclusion would not be expected to affect efficacy or safety, according to clinical experts consulted for this review.

Bleeding outcomes assessed in the studies (e.g., treated bleeds, all bleeds) were consistent with those assessed in Canadian clinics. The patient-reported outcomes assessed in the studies (e.g., school and work attendance, pain, HRQoL) are also assessed in clinic during follow-up visits; however, this is done without the use of scales or questionnaires, which differs from the methods used in the studies. Long-term outcomes of clinical interest, such as resolution of target joints, were not assessed in HAVEN 3 or HAVEN 4. However, the sponsor provided additional information pertaining to long-term treatment with emicizumab in its submission from a post hoc pooled analysis across all 4 HAVEN trials (HAVEN 1, HAVEN 2,[a] HAVEN 3, HAVEN 4). These data suggest that long-term treatment with emicizumab consistently resolved more than 99% of target joints. However, this conclusion is speculative due to the paucity of methodological detail available to assess the validity of these results.

Adherence to treatment was high in both studies. It was likely inflated compared to what would be seen in the real world, given that the patients were part of a clinical trial. Given the lack of comparative data between FVIII prophylaxis and SC emicizumab, the impact of the SC formulation on adherence in the real-world setting remains unknown.

Surgeries, procedures, and breakthrough bleeds (i.e., bleeding episodes) were treated using episodic treatment with FVIII at the lowest dose expected to achieve hemostasis while continuing the assigned treatment. The use of episodic FVIII to treat breakthrough bleeds is consistent with Canadian clinical practice.

[a] The HAVEN 1 and HAVEN 2 trials evaluated the efficacy and safety of emicizumab in patients with hemophilia A with FVIII inhibitors. This group is beyond the patient population in this review.

In HAVEN 3 and HAVEN 4, patients received in-clinic training on administering SC emicizumab prior to self-administering in the home setting. This form of training is consistent with training provided in the clinical setting.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

Due to the lack of direct evidence comparing emicizumab to FVIII for the prophylactic treatment of patients with hemophilia A without FVIII inhibitors, the sponsor conducted an NMA comparing these treatments.[12,13] The objective of this section is to summarize and critically appraise the available indirect evidence comparing emicizumab with relevant treatment regimens of interest (i.e., FVIII, as specified in the CADTH review protocol) for the prophylactic treatment of patients with hemophilia A without FVIII inhibitors.

CADTH conducted an independent literature search for published indirect treatment comparisons (ITCs) that compared emicizumab with other relevant comparators for the treatment of patients with hemophilia A without inhibitors. MEDLINE, Embase, and PubMed were searched.

The only evidence identified by CADTH was a draft evidence report published by the Institute for Clinical and Economic Review (ICER) on therapies for hemophilia A in patients without FVIII inhibitors.[41] However, the ITC conducted by ICER did not provide any additional information. Therefore, this ITC is neither summarized in detail nor critically appraised in this section. Only the sponsor-submitted NMA[12] was reviewed, summarized, and critically appraised in this section.

Description of Indirect Comparison

The sponsor submitted an NMA that compared the efficacy of emicizumab (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks) with Antihemophilic Factor Recombinant BDD, Fc Fusion Protein (Elocta/Eloctate), Antihemophilic Factor Recombinant (Kovaltry), Antihemophilic Factor (Recombinant) – formulated with sucrose (Kogenate), and Antihemophilic Factor (Recombinant), (Advate) for the prophylactic treatment of patients with hemophilia A without inhibitors.[12] The selection of trials for the NMA was based on an SLR.

Systematic Literature Review

A search strategy was developed based on the Population, Intervention, Comparator, Outcome, Study type framework presented in Table 19 to identify relevant published data investigating the efficacy and safety of pharmacological interventions for hemophilia A. The SLR was performed in December 2016 and updated for the non-inhibitor population in May 2018.

Table 19: Original Study Selection Criteria and Methods for the Sponsor-Submitted ITC (2016)

	Sponsor-submitted ITC
Population	Patients of all ages with mild,[a] moderate, or severe hemophilia A with and without inhibitors
Intervention	Only pharmacological interventions
Comparator	Only pharmacological interventions
Outcomes[b]	• ABR, AJBR, 0 bleeds, re-bleeding rate, all bleeds, joint bleeds, target joint bleeds, spontaneous bleeds, treated (joint, spontaneous, target joint) bleeds, target joint ≥ 2 bleeds, reduction in bleeds, pain severity and use of pain medication, joint scores, joint mobility, global evaluation, MRI or radiographic assessments, factor consumption, employment status and work productivity, hospitalization events • HRQoL: HRQoL questionnaires (generic or disease-specific), utilities, preference, physical activity, adherence, and compliance • Safety: AE, SAE, severe AE (grade 3 or 4), development of inhibitors, injection-site reactions, thromboembolic events, systemic hypersensitivity reactions, disseminated intravascular coagulation, thrombotic microangiopathy
Study design	Any phase II and beyond trial
Publication characteristics	No restriction for language, country, or time frame
Exclusion criteria	The 2 most common exclusion criteria were non-randomized and single-arm; and inclusion of children (patients typically younger than 12 years). Other exclusion criteria were acquired hemophilia, short-term efficacy (e.g., hemostatic effect of treatment after 2, 12, 24, 36, and 48 hours).
Databases searched	The following databases were searched without time restrictions: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the HTA Database. Study registries, including Clinicaltrials.gov and EU Clinical Trials Register, were searched for studies with results. A supplementary search was done for abstracts from conferences, including the World Federation of Hemophilia, ISTH, the International Conference on Thrombosis, Bleeding Disorders and Hemostasis, the American Society of Hematology, the National Hemophilia Foundation, the European Hemophilia Consortium, the European Association of Hemophilia and Allied Disorders, and the Hemophilia Foundation Australia for the years 2015 and 2016. The SLR was updated in 2018.
Selection process	2 reviewers independently screened the titles/abstract and assessed the full-text articles.
Data extraction process	2 reviewers independently performed the data extraction.
Quality assessment	2 reviewers independently performed the critical appraisal. RCTs were assessed using the NICE critical appraisal checklist.[42] A single-arm study with within-trial comparison (Valentino et al. [2012])[43] was assessed according to the NIH Quality Assessment Tool for Case Series Studies.

ABR = annualized bleeding rate; AE = adverse event; AJBR = annualized joint bleeding rate; HRQoL = health-related quality of life; HTA = Health Technology Assessment; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NIH = National Institutes of Health; NMA = network meta-analysis; RCT = randomized controlled trial; SAE = serious adverse event; SLR = systematic literature review.

[a] The decision to include hemophilia A of mild severity was made after the search had been conducted. This did not affect the completeness of results because the search terms for hemophilia were not restricted to severity.

[b] The original list of outcomes was smaller and had been extended during the review. This was possible because the search was not limited to specific outcomes.

Source: Sponsor-submitted NMA report.[12]

The original search (in 2016) identified 175 relevant publications. An additional 545 records were identified in the updated search conducted in 2018. Trials with mixed populations (i.e., inhibitor and non-inhibitor patients) were eligible for inclusion in the updated SLR, provided they reported stratified results; however, none of the studies identified in mixed populations reported stratified results. Following screening, a total of 94 studies in patients with hemophilia A without FVIII inhibitors were identified for further feasibility assessment.

NMA Feasibility Assessment

Following the feasibility assessment, single-arm studies, non-randomized studies, observational studies, and post-marketing surveillance studies were excluded. Studies in pediatric populations were excluded to ensure the target population of the trials included in the NMA would match the population in the HAVEN 3 trial as closely as possible. Trials of FVIII products not currently approved were excluded. Only licensed doses of these treatments were of interest in the NMA. Finally, 5 studies on patients with hemophilia A without inhibitors were included in the NMA. The 5 studies included HAVEN3,[27] A-LONG, LEOPOLD2,[44] SPINART,[45] and Valentino et al. (2012).[43] Valentino et al. 2012 was included only for 1 sensitivity analysis.[7]

The sponsor-submitted NMA was only interested in comparisons of prophylaxis versus on-demand treatment/no prophylaxis. Therefore, arm D from HAVEN 3 did not qualify for inclusion and was not included in the NMA.[12]

Methods of the Sponsor-Submitted ITC

The NMA methods are summarized in Table 20, Table 21, and Table 22. Briefly, the NMA was conducted using a Bayesian framework. Random-effects (RE) models were chosen as the base case for the total treated bleed outcomes because of various heterogeneities across the 5 included trials. The between-study variance could not be accurately estimated due to the small number of studies available; therefore, informative priors were used. Total treated bleeds were modelled as a bleed rate and fitted using a generalized linear model with a log link Poisson likelihood. Model inputs included total treatment exposure in person-years and number of bleeding events. Exposure was based on exposure time reported in the trial or calculated using mean or median duration of controlled period and number of patients. The actual number of treated bleeds was used in the model, given that this outcome was reported in all studies that were identified for the NMA.

Four different FVIII products investigated in the included studies (Advate, Elocta, Kovaltry, and Kogenate) were combined as 1 FVIII treatment group in the NMA based on the assumption of comparable efficacy for all FVIII products included in the NMA. Additional assumptions were that when different dosages or treatment regimens were published in the same pivotal trial, the licensed one was used in the comparison.

A multi-arm adjustment was made for HAVEN 3 only: the correlation between multiple arms in HAVEN 3 was accounted for in the modelling through the methods detailed in the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 2.[42]

Vague priors were used for study-specific baselines and treatment-effect parameters; i.e., N(0, 1,000) for log-rate ratios. The prior for tau was selected according to the relative plausibility of what different values of tau signify,[12,46] such as implausible values not given probability mass. The base case was an informative prior for tau ~ uniform (0, 0.5).

Base-case model: A Bayesian RE model was used for the base-case analysis for total treated bleeds due to the heterogeneity in the measurement of this outcome. The base-case analyses included only RCT data (SPINART, HAVEN 3, LEOPOLD2, and A-LONG).

Four sensitivity analyses were performed (see Table 20):

- Sensitivity analysis 1 explored a fixed-effects model instead of the RE model for base-case studies.
- Sensitivity analysis 2 separated FVIII products into short- or long-acting FVIII drugs.
- Sensitivity analysis 3 was based on an expanded dataset — including the single-arm study Valentino et al. (2012) — in addition to the 4 RCTs included in the base case.
- [redacted]

Table 20: NMA Sensitivity Analysis Overview

Analysis	Model		Network structure		Trials included in NMA				
	RE	FE	1 FVIII node	2 FVIII nodes (short-acting and long-acting)	HAVEN3	LEOPOLD 2	SPINART	A-LONG	VALENTINO et al. (single-arm study)
Base case	+		+		+	+	+	+	
SA 1		+	+		+	+	+	+	
SA 2	+			+	+	+	+	+	
SA 3	+		+		+	+	+	+	+
[redacted]									

FE = fixed-effects; NMA = network meta-analysis; RE = random-effects; SA = sensitivity analysis.

[redacted]

Source: NMA report.[12]

- The sponsor-submitted NMA indicated that there was no clear evidence of potential effect modifiers other than severity of hemophilia. Given that trials included in the NMA were mostly in severe patients and activity level was not reported, no sensitivity analyses were done to explore the impact of any effect modifiers.
- The deviance information criterion (DIC) was used to compare the relative fit of competing models. Models with a lower DIC value were preferred. Differences in DIC of less than 5 points were not considered meaningful (Table 21).[12]

Table 21: Model Fit Comparison for NMA Models on Total Treated Bleeds

Analysis	Model	DIC
Base case	RE (tau~Uniform 0.5)	85.20
SA 1	FE	156.89
SA 2	RE (tau~Uniform 0.5)	84.97
SA 3	RE (tau~Uniform 0.5)	104.88
[redacted]	[redacted]	[redacted]

DIC = deviance information criterion; FE = fixed-effects; NMA = network meta-analysis; RE = random-effects; SA = sensitivity analysis.

Source: NMA report.[12]

For each network, heterogeneity assessments informed by at least 2 studies were conducted for each pairwise comparison. Forest plots were used to illustrate the heterogeneity between the studies. Heterogeneity was quantified using the I^2 statistic. I^2 values were interpreted roughly as follows: less than or equal to 25%: low heterogeneity; 25% to 50%: low to moderate heterogeneity; 50% to 75%: moderate to high heterogeneity; greater than 75%: high heterogeneity.[12,47]

There were no closed loops in the evidence network. Therefore, a consistency assessment was not applicable.

The analysis was implemented on the Roche BEE environment using R version 3.4.2 and JAGS version 4.6.0 (called form R).

An appropriate burn-in and number of iterations for the Markov chain Monte Carlo were selected to converge. At least 2 parallel chains in all model fits were run. Convergence was assessed by inspecting trace plots and the Brooks-Gelman-Rubin statistics (Rhat). Sufficient numbers of iterations were used to achieve effective sample sizes (n.eff) allowing for posterior inference (typically n.eff greater than 1,000 if credible intervals are sought). In some cases, model convergence was not achieved despite best efforts. In such cases, simpler models were preferred.

The NMA reported outcome was rate ratio as “emicizumab versus comparator.” The summaries reported were posterior medians and credible intervals.

Table 22: NMA Analysis Methods

	Sponsor-submitted NMA[12]
ITC methods	NMA
Priors	Vague priors were used for study-specific baselines and treatment-effect parameters; i.e., N(0, 1,000) for log-rate ratios.
Assessment of model fit	The model selected was chosen based on DIC and residual deviance (The inferential framework used is Bayesian, given that it captures and propagates uncertainty. RE models were chosen as the principal (base-case) analyses for the total treated bleed end point, given that absence of heterogeneity is implausible. The between-study variance cannot be estimated accurately due to the small number of studies available; informative priors were used instead.)
Assessment of consistency	Based on the updated SLR, there were no closed loops in the NMA that would enable the conduct of a consistency assessment.
Assessment of convergence	Convergence was assessed by inspecting trace plots and the Brooks-Gelman-Rubin statistics (Rhat).
Follow-up time points	Up to 3 years
Sensitivity analyses	[redacted]sensitivity analyses were conducted
Subgroup analysis	No subgroup analysis

DIC = deviance information criterion; ITC = indirect treatment comparison; NMA = network meta-analysis; RE = random-effects; SLR = systematic literature review.

Source: Sponsor-submitted ITC.[12]

Results of the Sponsor-Submitted ITC

Summary of Included Studies

Five studies were included in the NMA.

One trial was included for emicizumab: HAVEN 3[27] enrolled adults and adolescents (aged greater than or equal to 12 years) with severe hemophilia A without FVIII inhibitors. The 4 included trials on rFVIII comparators were A-LONG (Antihemophilic Factor Recombinant BDD, Fc Fusion Protein, Elocta/Eloctate),[48] LEOPOLD2 (Antihemophilic Factor Recombinant ,Kovaltry),[44] SPINART (Antihemophilic Factor [Recombinant] – formulated with sucrose, Kogenate),[45] and Valentino et al. (2012) (Antihemophilic Factor [Recombinant], Advate).[43]

The characteristics of the 5 included studies are presented in Table 23. The sample size varied in the included studies (n = 89,
n = 165, n = 80, n = 84, and n = 135 for HAVEN 3, A-LONG, LEOPOLD 2, SPINART, and Valentino et al. [2012], respectively). Median age was similar in the A-LONG, LEOPOLD 2, SPINART and Valentino et al. (2012) studies (30, 28.5, 29, and 26 years, respectively), but higher in the HAVEN 3 study, in which the median age ranged from 36.5 years to 41.0 years across the 3 included arms. In all studies, the majority of patients were diagnosed as having severe hemophilia A: 100% of patients in HAVEN 3, A-LONG, and LEOPOLD; 86% in the Valentino et al. (2012) study; and 93% and 100% in SPINART (Table 23). The characteristics of 4 FVIII products included in the NMA are presented in Table 24. The efficacy outcomes assessed were total treated bleeds for emicizumab prophylactic and FVIII episodic treatment (i.e., no FVIII prophylaxis), respectively. The definitions of bleed outcomes in each trial are presented in Table 25.

Table 23: Characteristics for the Trials Included in the NMA

Study/countries	Design and trial duration	Treatment	Sample size	Age (years)	Patients with severe hemophilia A
HAVEN 3 **Costa Rica, France, Italy, Japan, Germany, South Africa, Spain, USA**	Randomized, multi-centre, open-label, phase III 25 weeks	• P1 (arm A): emicizumab SC 3.0 mg/kg QW for 4 weeks; 1.5 mg/kg QW • P2 (arm B): emicizumab SC 3.0 mg/kg QW for 4 weeks; 3.0 mg/kg Q2W • E: (arm C): control, no prophylaxis	Total randomized: 89[a] P1: 36; P2: 35; E: 18 (Note: 63 patients were assigned to arm D)	Median (range) P1 36.5 (19 to 77) P2: 41.0 (20 to 65) E: 40.0 (15 to 57)	100% (defined as per intrinsic FVIII level of < 1%)
A-LONG **Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hong Kong, India, Israel, Italy,**	Partially randomized Median: 28 weeks	P1: Antihemophilic Factor Recombinant BDD, Fc Fusion Protein,Elocta/Eloctate, individualized); P2: Antihemophilic Factor Recombinant BDD, Fc Fusion	Total: 165 P1: 118; P2: 24; E: 23	Median (range) 30 (12 to 65)	100%

Study/countries	Design and trial duration	Treatment	Sample size	Age (years)	Patients with severe hemophilia A
Japan, New Zealand, South Africa, Spain, Sweden, Switzerland, UK, US		Protein,rFVIIIFc (Elocta /Eloctate (weekly); E: Antihemophilic Factor Recombinant BDD, Fc Fusion Protein,rFVIIIFc (Elocta /Eloctate			
LEOPOLD 2 Argentina, China, Colombia, Czech Republic, India, Indonesia, Japan, Mexico, Romania, Russian Federation, Serbia, Slovakia, South Africa, Taiwan, Thailand, Turkey, Ukraine, US	Randomized controlled, crossover 12 months (crossover after 6 months)	P1: Antihemophilic Factor Recombinant (Kovaltry) 2 times per week; P2: Antihemophilic Factor Recombinant (Kovaltry) 2 times per week; E: Antihemophilic Factor Recombinant (Kovaltry)	Total: 80 P1: 28; P2: 31; E: 21	Median (range) 28.5 (14 to 59) Mean: 29.6;	100%
SPINART Argentina, Bulgaria, Romania, US	Randomized controlled; primary end point: 1 year; total duration: 3 years	P: Antihemophilic Factor (Recombinant) – formulated with sucrose (Kogenate); E: Antihemophilic Factor (Recombinant) – formulated with sucrose (Kogenate)	Total: 84 P: 42; E: 42	Median (range) 29 (15 to 50)	P: 93%[b] E: 100%
Valentino et al. (2012) Austria, Czech Republic, Greece, Hungary, Italy, Poland, Russian Federation, Slovenia, UK, US	Part 1: non-randomized; part 2: randomized, parallel assignment; part 1: 6 months; part 2: 12 months	Part 1: E: Antihemophilic Factor (Recombinant) (Advate); Part 2: P1: Antihemophilic Factor (Recombinant), (Advate) standard; P2: Antihemophilic Factor (Recombinant) (Advate) P-tailored	Part 1: 69; Part 2: 66; P1: 32; P2: 34	Median: 26 Range: 7 to 59	86%[c]

E = episodic; Fc = Fc fusion protein; FS = formulated with sucrose; ITC = indirect treatment comparison; NMA = network meta-analysis; P = prophylactic; Q2W = every 2 weeks; QW = weekly; rFVIII = recombinant factor VIII; SC = subcutaneous.

[a] There were 152 patients in HAVEN 3. Among them, 89 were randomize and 63 were assigned to arm D.

[b] Seven percent of patients had an FVIII level of 1.1% to 1.3%.

[c] Fourteen percent of patients had moderately severe Hemophilia A, with FVIII levels < 2%.

Source: Sponsor-submitted ITC.[12]

Table 24: Characteristics of Factor VIII Products Included in the NMA

FVII product (study name)	Half-life	Long-acting/ short-acting grouping
Elocta/Eloctate (A-LONG)[48]	19 hours / 12.3 to 16 hours (one stage); 20.9 hours / 14.3 to 17.5 hours (chromogenic) (Elocta SmPC)	Long-acting FVIII (extended)
Kogenate (SPINART)[45]	15 hours 13.74 to 14.6 hours / 10.7 hours (children)	Short-acting FVIII
Kovaltry (LEOPOLD2)[44]	13.3 to 14.8 hours (chromogenic)	Short-acting FVIII
Advate (Valentino et al. [2012])[43]	9 to 12.9 hours (1-stage assay) (Advate SmPC)	Short-acting FVIII

FVIII = factor VII; NMA = network meta-analysis.

Source: NMA report [12]

Table 25: Definitions of Bleeds Outcomes in Each Study

Trials	Bleeds outcomes reported	Definitions of bleed types (clear or unclear)
A-LONG[48]	Bleeding episodes	Unclear
HAVEN 3[27]	Treated bleeds, all bleeds	Clear
LEOPOLD 2[44]	Bleeds	Unclear
SPINART [45]	Bleeding episode, joint bleeds	Clear
Valentino et al. (2012)[43]	Bleeding episodes	Unclear

Source: Network meta-analysis report.[12]

Assessment of Risk of Bias of Included Trials

The risk of bias in the 4 included RCTs (i.e., LEOPOLD 2, A-LONG, SPINART, and HAVEN 3) was assessed according to the NICE critical appraisal checklist (Table 26). Valentino et al. (2012) was a single-arm study with within-trial comparison; therefore, it was assessed according to the National Institutes of Health Quality Assessment Tool for Case Series Studies (Table 27 and Table 24).

It was reported that overall, according to the NICE criteria, all RCTs carried at least some risk of bias, most notably the risk introduced by lack of blinding. HAVEN 3, LEOPOLD 2, and SPINART showed low risk of bias for most of the categories assessed. The National Institutes of Health Quality Assessment Tool rated the quality of the Valentino et al. (2012) study as fair to good.[12]

Table 26: Results of Risk of Bias Assessment of RCTs

	Study, author, and year			
	HAVEN 3 Mahlangu 2018 (published after the SLR update)[27]	LEOPOLD 2 Kavakli (2015)[44]	A-LONG Mahlangu (2014)[48]	SPINART Manco-Johnson (2013)[45]
1. Was randomization carried out appropriately?	**Low risk**	**Low risk**	**Not clear**	**Low risk**
2. Was the concealment of treatment allocation adequate?	**Low risk**	**Low risk**	**Not clear**	**Low risk**
3. Were the groups similar at the outset of the study in terms of prognostic factors?	**Low risk**	**Low risk**	**High risk**	**Low risk**
4. Were the care providers, participants, and outcome assessors blind to treatment allocation?	**Not clear**	**High risk**	**Not clear**	**High risk**
5. Were there any unexpected imbalances in drop-outs between groups?	**Low risk**	**Low risk**	**Low risk**	**Low risk**
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	**Low risk**	**Not clear**	**Low risk**	**Not clear**
7. Did the analysis include an ITT analysis? If so, was this appropriate, and were appropriate methods used to account for missing data?	**Low risk**	**Low risk**	**High risk**	**Low risk**

ITT = intention to treat; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; RCT = randomized controlled trial; SLR = systematic literature review.

Note: The risk of bias of RCTs was assessed using the NICE critical appraisal checklist (June 2012).[49]

Source: NMA report.[12]

Table 27: Results of Risk of Bias Assessment in the Single-Arm Study (Valentino et al. [2012], Part 1)

Study, author, and year	1. Was the study question or objective clearly stated?		2. Was the study population clearly and fully described, including a case definition?		3. Were the cases consecutive?		4. Were the patients comparable?		5. Was the intervention clearly described?	
	Yes, no, other (CD, NA, NR)	Justification	Yes, no, other (CD, NA, NR)	Justification	Yes, no, other (CD, NA, NR)	Justification	Yes, no, other (CD, NA, NR)	Justification	Yes, no, other (CD, NA, NR)	Justification
Valentino et al. (2012)[43]	Yes	Objective is clearly stated	Yes	Inclusion criteria and patients' characteristics clearly explained	CD	NR	Yes	NR	Yes	Dose and dose adjustments explained

CD = cannot determine; NA = not applicable; NR = not reported.

Source: Network meta-analysis report.[12]

Table 28: Results of Risk of Bias Assessment in the Single-Arm Study (Valentino et al. [2012], Part 2)

Author and year	6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		7. Was the length of follow-up adequate?		8. Were the statistical methods well-described?		9. Were the results well-described?		Quality rating
	Yes, no, other (CD, NA, NR)	Justification	Yes, no, other (CD, NA, NR)	Justification	Yes, no, other (CD, NA, NR)	Justification	Yes, no, other (CD, NA, NR)	Justification	Good, fair, poor. If poor, please state why.
Valentino et al. (2012)[43]	Yes	Mean annualized bleeding rates, median annualized bleeding rates	Yes	On demand: 6 months Prophylactic: 12 months	Yes	Median differences in ABRs and percentage reductions in ABRs between treatment regimens were evaluated using the	Yes	Mean annualized bleeding rates, median annualized bleeding rates, hemostatic	Good

Author and year	6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		7. Was the length of follow-up adequate?		8. Were the statistical methods well-described?		9. Were the results well-described?		Quality rating
						non-parametric Wilcoxon signed-rank test, with each test performed at a 5% alpha level and adjusted for multiple testing (0.05, number of tests), with no P value > 0.01 considered statistically significant. The comparisons between on-demand treatment and prophylaxis were paired, given that each patient was treated on demand first and then on prophylaxis.		efficacy/ratings well explained	

ABR = annualized bleeding rate; CD = cannot determine; NA = not applicable; NMA = network meta-analysis; NR = not reported.

Note: The risk of bias was assessed with Quality Assessment Tool for Case Series Studies developed by Agency for Healthcare Research and Quality.[50]

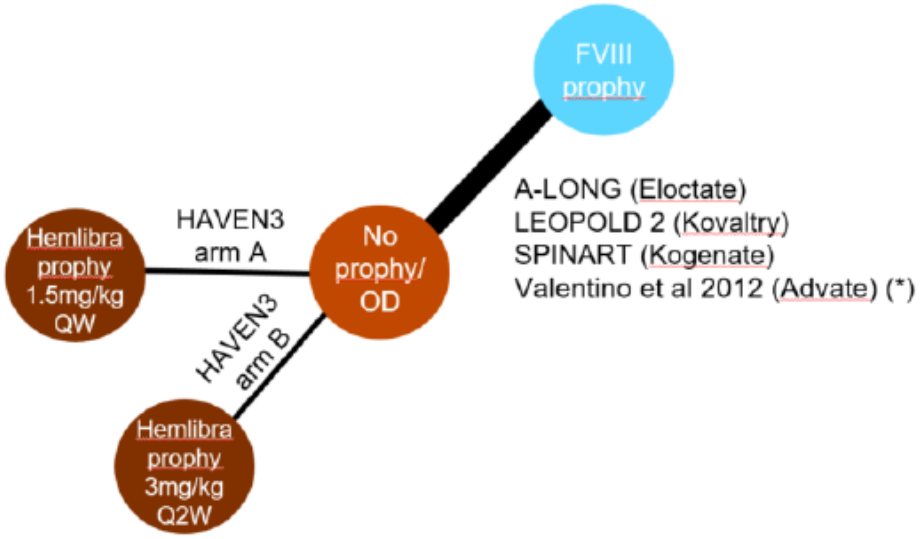
Source: NMA report.[12]

Results

The evidence networks of studies included for base-case analysis and sensitivity analysis are presented in Figure 3 and Figure 4, respectively.

In addition to arm A (1.5 mg/kg weekly) and arm B (3.0 mg/kg every 2 weeks) of the HAVEN 3 trial, 4 studies (A-LONG for Antihemophilic Factor Recombinant BDD, Fc Fusion Protein [Elocta/Eloctate], LEOPOLD 2 for Antihemophilic Factor Recombinant [Kovaltry], SPINART for Antihemophilic Factor (Recombinant) – formulated with sucrose [Kogenate], and Valentino et al. (2012) for Antihemophilic Factor (Recombinant) [Advate]) comparing FVIII prophylaxis versus on-demand treatment (i.e., no prophylaxis) informed this network. All 4 FVIII products were combined as 1 group (i.e., 1 FVIII node in the networks). Of these, 3 trials [43-45] compared short-acting FVIII treatments versus on-demand treatment (i.e., no prophylaxis). The A-LONG study[48] compared long-acting FVIII treatment to on-demand treatment (i.e., no prophylaxis). (See Table 24). The single-arm study (Valentino et al. [2012]) was only included in sensitivity analysis 3.

Figure 3: Base-Case Analysis Network of Studies Included



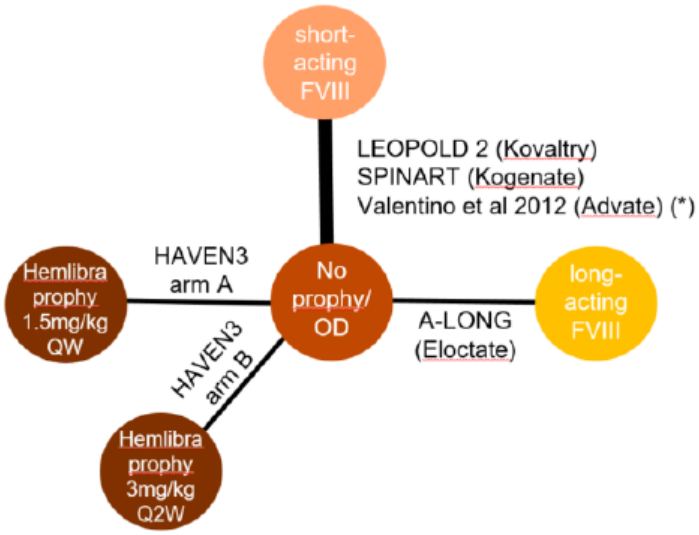
ITC = indirect treatment comparison; OD = on demand; prophy = prophylaxis; Q2W = every 2 weeks; QW = per week.

Note: Edge width is proportional to the number of inputs for each comparison.
* Valentino et al. (2012) was only included in sensitivity analysis 3.

Source: Sponsor-submitted ITC.[12]

The number of bleeds and the total exposure (patient-year) in each treatment arm reported in the 5 included studies are presented in Table 29.

Figure 4: Network of Studies Included in Sensitivity Analyses 2 and 3



ITC = indirect treatment comparison; OD = on demand; prophy = prophylaxis; Q2W = every 2 weeks; QW = per week.

Note: Sensitivity analysis where long- and short-acting FVIII treatments were separated into 2 nodes (sensitivity analysis 2). Edge width is proportional to the number of inputs for each comparison.

* Valentino et al. (2012) was only included in sensitivity analysis 3.

Source: Sponsor-submitted ITC.[12]

Table 29: Number of Bleeds and Total Exposure Reported in Included Studies

Trial	Treatment arms	Total exposure (patient-years)	Number of bleeds	Included in base case	Included in SA 3	[redacted]
A-LONG[48]	FVIII prophy (long-acting)	12.38	92.00	Yes	Yes	[redacted]
	On demand	12.78	456.00	Yes	Yes	[redacted]
HAVEN3[27]	Emicizumab prophy (1.5 mg/kg QW)	22.10	37.00 (56.0 used in SA 4)[a]	Yes	Yes	[redacted]
	Emicizumab prophy (3.0 mg/kg Q2W)	22.30	32.00 (58.00 used in SA 4)[a]	Yes	Yes	[redacted]
	On demand	8.18	369.0 (410.00 used in SA 4)[a]	Yes	Yes	[redacted]
LEOPOLD2[44]	FVIII prophy (short-acting)	59.00	293.00	Yes	Yes	[redacted]
	On demand	21.00	1,204.00	Yes	Yes	[redacted]
SPINART[45]	FVIII prophy (short-acting)	127.44	264.00	Yes	Yes	[redacted]
	On demand	126.58	4,338.00	Yes	Yes	[redacted]
Valentino et al. (2012)[43]	FVIII prophy (short-acting)	31.68	104.00	No	Yes	[redacted]
	On demand	33.51	1,640.00	No	Yes	[redacted]

ITC = indirect treatment comparison; prophy = prophylactic; Q2W = once every 2 weeks; QW = once a week; SA = sensitivity analysis.

Note: SA 1 included the same studies as in the base-case analysis, but used a fixed-effects model; SA 2 included the same studies as in the base-case analysis, but split long-acting and short-acting study into 2 nodes.

[a] For SA 4 in HAVEN3, the number of all bleeds (instead of total treated bleeds) was used.

Source: Sponsor-submitted ITC.[12]

Efficacy Outcomes NMA Results

Base-case NMA results

The NMA base-case analysis results are presented in Table 30. In terms of total treated bleeds, emicizumab prophylaxis (1.5 mg/kg weekly) showed a reduction compared with FVIII prophylaxis (rate ratio = 0.36; 95% credible interval [CrI], 0.13 to 0.95). Emicizumab prophylaxis (3.0 mg/kg every 2 weeks) also showed a reduction compared with FVIII prophylaxis (rate ratio = 0.31; 95% CrI, 0.11 to 0.84). These findings were in line with those reported in HAVEN 3.

Table 30: Base-Case NMA Results for Total Treated Bleeds

	Rate ratio (95% CrI), emicizumab versus comparators			
	FVIII prophylaxis	On demand/no prophylaxis	Emicizumab prophylaxis (1.5 mg/kg QW)	Emicizumab prophylaxis (3.0 mg/kg QW)
Emicizumab prophylaxis (1.5 mg/kg QW)	0.36 (0.13 to 0.95)	0.04 (0.01 to 0.08)	–	1.13 (0.46 to 2.84)
Emicizumab prophylaxis (3.0 mg/kg Q2W)	0.31 (0.11 to 0.84)	0.03 (0.01 to 0.08)	0.88 (0.35 to 2.18)	–

CrI = credible interval; ITC = indirect treatment comparison; Q2W = every 2 weeks; QW = per week.

Source: Sponsor-submitted ITC.[12]

Sensitivity analyses NMA results

The results of the sensitivity analyses are presented in Table 31.

In sensitivity analysis 1, as expected, the CrIs for the fixed-effects model were narrower than for the base-case RE model. The results were similar to those of the base-case analysis for both emicizumab prophylaxis (1.5 mg/kg weekly) versus FVIII prophylaxis (rate ratio = 0.46; 95% CrI, 0.32 to 0.63) and emicizumab prophylaxis (3.0 mg/kg every 2 weeks) versus FVIII prophylaxis (rate ratio = 0.39; 95% CrI, 0.27 to 0.56) (Table 31).

Sensitivity analysis 2, which separated FVIII treatments into short- or long-acting FVIII, suggested that emicizumab prophylaxis (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks) was associated with a reduction in total treated bleeds compared with long-acting FVIII prophylaxis, but not compared with short-acting FVIII prophylaxis (Table 31).

Sensitivity analysis 3 also included the single-arm study (Valentino et al. [2012] on rFVIII [Advate]) in addition to the base-case studies. The results suggested that emicizumab prophylaxis (3.0 mg/kg every 2 weeks) was associated with a reduction in treated bleeds compared with FVIII prophylaxis (rate ratio = 0.35; 95%CrI, 0.13 to 0.96). Whether there was a difference in the reduction of treated bleeds between emicizumab prophylaxis (1.5 mg/kg weekly) and FVIII prophylaxis remains uncertain (rate ratio = 0.40; 95% CrI, 0.15 to 1.10) (Table 31).

The results from sensitivity analysis 4 suggested [redacted] (Table 31).

Table 31: Sensitivity Analysis NMA Results for Total Treated Bleeds

	Rate ratio (95% CrI) (emicizumab versus comparators)					
	On demand/no prophylaxis	FVIII prophylaxis	Long-acting FVIII prophylaxis	Short-acting FVIII prophylaxis	Emicizumab prophylaxis (1.5 mg/kg QW)	Emicizumab prophylaxis (3.0 mg/kg Q2W)
SA 1						
Emicizumab prophylaxis (1.5 mg/kg QW)	0.04 (0.03 to 0.05)	0.46 (0.32 to 0.63)	NA	NA	–	1.17 (0.73 to 1.84)
Emicizumab prophylaxis (3.0 mg/kg Q2W)	0.03 (0.02 to 0.04)	0.39 (0.27 to 0.56)	NA	NA	0.86 (0.54 to 1.37)	–
SA 2						
Emicizumab prophylaxis (1.5 mg/kg QW)	0.04 (0.02 to 0.08)	NA	[redacted]	[redacted]	[redacted]	[redacted]
Emicizumab prophylaxis (3.0 mg/kg Q2W)	0.03 (0.01 to 0.07)	NA	[redacted]	[redacted]	[redacted]	[redacted]
SA 3						
Emicizumab prophylaxis (1.5 mg/kg QW)	0.04 (0.01 to 0.09)	0.40 (0.15 to 1.10)	NA	NA	–	1.12 (0.47 to 3.07)
Emicizumab prophylaxis (3.0 mg/kg Q2W)	0.03 (0.01 to 0.08)	0.35 (0.13 to 0.96)	NA	NA	0.89 (0.33 to 2.15)	–
SA 4						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CrI = credible interval; ITC = indirect comparison; NA = not applicable; Q2W = every 2 weeks; QW = per week; SA = sensitivity analysis.

Source: Sponsor-submitted ITC.[12]

Critical Appraisal of the Sponsor-Submitted ITC

One limitation of the NMA submitted by the sponsor was the small number of trials included in the analysis (N = 4 for the base-case analysis). In addition, each trial enrolled a small number of patients in the emicizumab prophylaxis (1.5 mg/kg weekly or 3.0 mg/kg every 2 weeks) and FVIII prophylaxis groups; the results of the analysis were associated with uncertainty due to the small evidence base. The small number of studies also made the sensitivity analysis impossible by removing the studies with high risk of bias.

There was a high degree of heterogeneity across the included studies, including the variable severity of hemophilia A. That is, 7% of patients had an FVIII level of 1.1% to 1.3% in SPINART and 14% had moderate hemophilia (i.e., FVIII of less than 2%) in Valentino et al. (2012); different comparator FVIII products (e.g., long- versus short-acting FVIII) were used in the different trials; there were also inconsistent or unclear definitions of the bleed outcomes (i.e., the treated bleed), variable outcome estimation time points across trials, and differences in study designs (i.e., randomization versus partial randomization, blind versus open-label, and parallel versus crossover). Various sensitivity analyses were conducted; however, the results from these analyses were not always aligned with the findings reported in the base-case analysis. This may be due, in part, to the fact that fewer trials were included in the sensitivity analysis. Therefore, the concern about the robustness of the NMA findings remains.

Considering that the main objective of the sponsor's NMA was to compare the efficacy of emicizumab prophylaxis with that of FVIII prophylaxis,[13] an important limitation was that NMA sensitivity analysis 2 did not include the results from study arm D in HAVEN 3 (i.e., the intra-patient comparison of emicizumab prophylaxis with FVIII prophylaxis), but did include results of the single-arm trial by Valentino et al. (2012). The NMA findings were aligned with those reported in arm D of HAVEN 3.

Given that there were no head-to-head trials comparing emicizumab prophylaxis with FVIII prophylaxis (i.e., there were no closed loops in the NMA), a consistency assessment was not feasible. However, it is noted that the results of the NMA in terms of treated bleeds aligned with those reported in arm D of HAVEN 3.

The NMA submitted by the sponsor did not address a number of evidence gaps. One is that HRQoL is an important outcome for patients with hemophilia, yet there was no NMA of comparative efficacy of HRQoL between emicizumab prophylaxis and FVIII prophylaxis. In addition, the NMA provided only the clinical efficacy outcome (i.e., total treated bleeds). No NMAs were conducted for safety outcomes. Therefore, the comparative safety profile of emicizumab prophylaxis with FVIII prophylaxis remains unknown. Furthermore, no trial included in the NMA enrolled pediatric patients younger than 7 years old. Therefore, it is not clear whether the NMA finding is generalizable to children younger than 7 years old.

Summary

In the absence of direct evidence comparing emicizumab prophylaxis versus rFVIII prophylaxis, the sponsor conducted an NMA in patients with severe hemophilia A without inhibitors. The only outcome analyzed was total treated bleeds.

In terms of total treated bleeds, the NMA showed that both emicizumab prophylaxis regimens (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks) were associated with reductions (64% and 69% reduction respectively) compared with rFVIII prophylaxis in patients with severe hemophilia A without inhibitors. However, due to the methodological limitations

discussed earlier, these findings should be interpreted with caution. In addition, no NMA was performed for safety outcomes, and no evidence for children younger than 7 years old was included.

CADTH noted that the ITC conducted by ICER was also based on a systematic review. The ICER ITC included 2 studies (HAVEN 3[27] and SPINART[45]) that were also included in the sponsor's NMA. ICER concluded that in terms of treated bleeds, it remains uncertain whether there was a difference in the reduction of treated bleeds between emicizumab prophylaxis (combination of
1.5 mg/kg weekly and 3.0 mg/kg weekly) and FVIII prophylaxis (rate ratio = 0.57; 95% CrI, 0.22 to 1.47). Further, the ICER ITC did not address any evidence gaps of the NMA submitted by the sponsor (i.e., HRQoL and safety profile).

In conclusion, the sponsored-submitted NMA suggested that emicizumab prophylaxis was associated with a reduction in bleed rates compared with FVIII prophylaxis in the treatment of patients with severe hemophilia A without inhibitors. These results were aligned with those observed in patients previously treated with FVIII prophylaxis (arm D) in the HAVEN 3 trial. However, due to various methodological limitations, no robust conclusions can be drawn about the comparative clinical efficacy and safety profile of emicizumab prophylaxis regimens versus rFVIII prophylaxis in patients with hemophilia without inhibitors.

Other Relevant Evidence

This section includes 1 study included in the sponsor's submission to CADTH that was considered to address important gaps in the evidence included in the systematic review. The HOHOEMI study is the only phase III clinical trial that provides evidence regarding the efficacy and safety of emicizumab in pediatric patients with hemophilia A without FVIII inhibitors.

Pediatric Study: HOHOEMI

Methods

The HOHOEMI study was a phase III, multi-centre, open-label, non-randomized clinical trial to evaluate the efficacy, safety, and pharmacokinetics of emicizumab in Japanese pediatric patients aged less than 12 years with hemophilia A without FVIII inhibitors. The study was conducted at 4 sites in Japan from September 2017 to July 2019. All patients received emicizumab administered SC at a dose of 3.0 mg/kg every 2 weeks or 6.0 mg/kg every 4 weeks following 4 loading doses of 3.0 mg/kg per week. Patients received emicizumab for at least 24 weeks or until study withdrawal. Patients were enrolled sequentially in each cohort and were not randomized to the treatment arms. For the purpose of this review, only data from the 3.0 mg/kg arm will be presented. The 6.0 mg/kg dose is not relevant to the Canadian population, given that it is beyond the dosing recommended by Health Canada for the pediatric population.

Populations

To be eligible for the HOHOEMI study, patients needed to be less than 12 years of age, weigh more than 3 kg, and have severe congenital hemophilia A without FVIII inhibitors (i.e., an endogenous FVIII level of less than 1%). Patients had to test negative for inhibitors (less than 0.6 BU/mL) within 8 weeks prior to enrolment. The main exclusion criteria were having a bleeding disorder other than hemophilia A, previous or current thromboembolic

disease, or other conditions that may increase risk of bleeding or thrombosis, and being at high risk of thrombotic microangiopathy.

A summary of the baseline characteristics of patients in the cohort receiving emicizumab every 2 weeks is shown in Table 32. With regard to baseline demographics, all patients were Japanese male children. The median age was 6.6 years (range = 1.5 years to 10.7 years), the median weight was 19.50 (range = 10.9 kg to 35.6 kg), and the median height was [redacted]As for the medical history of hemophilia A, all patients received at least 1 treatment for hemophilia A, and all patients but 1 were previously on FVIII prophylaxis treatment; the patient who had never received prophylaxis was aged 4 months in the 6.0 mg/kg cohort. The prior FVIII prophylaxis was administered approximately 2 to 3 times per week in most patients. Four patients also received short-acting FVIII episodic treatment, and 2 received long-acting FVIII. One patient had target joints at baseline. One patient had been previously treated with immune tolerance induction therapy.

Table 32: Summary of Baseline Characteristics

	Emicizumab 3.0 mg/kg Q2W N = 6
Demographics	
n (%)	6 (100)
Age, years, mean (SD)	6.6 (4.0)
Median (min to max)	6.6 (1.5 to 10.7)
0 years to 2 years, n (%)	1 (16.7)
2 years to 6 years, n (%)	2 (33.3)
6 years to 12 years, n (%)	3 (50.0)
Sex, male, n (%)	6 (100)
Asian, n (%)	6 (100)
Weight, kg, mean (SD)	[redacted]
Median (min to max)	19.50 (10.9 to 35.6)
[redacted]	[redacted]
[redacted]	[redacted]
Medical history of hemophilia A	
Target joint at baseline	
n (%)	6 (100)
Yes, n (%)	1 (16.7)
Previously treated patient with factor VIII	
n (%)	6 (100)
Yes, n (%)	6 (100)
Treatment regimen	
n (%)	6 (100)
Prophylactic, n (%)	6 (100)
Prior episodic treatment[a]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

	Emicizumab 3.0 mg/kg Q2W N = 6
Prior prophylactic treatment[a]	
n (%)	6 (100)
Factor VIII (short-acting), n (%)	5 (71.4)
Factor VIII (long-acting), n (%)	(2 (28.6)
History of ITI therapy	
n (%)	6 (100)
Yes, n (%)	1 (16.7)
[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]

ITI = immune tolerance induction; NE = not estimable; Q2W = every 2 weeks; SD = standard deviation.

[a] Multiple answers were possible.

Source: Clinical Study Report for HOHOEMI.[51]

Interventions

Patients in the cohort receiving emicizumab every 2 weeks were administered the drug SC, with loading doses of 3.0 mg/kg every week for the first 4 weeks followed by maintenance doses of 3.0 mg/kg every 2 weeks. The minimum follow-up period was 24 weeks. Patients with insufficient bleeding control after 12 weeks were eligible to receive up-titration of the maintenance dose to 3.0 mg/kg weekly. Patients were initially treated at the study site, and patients aged 7 years or older (or their caregivers) were able to administer treatment at home if the investigator deemed it feasible. Patients showing sustained clinical benefits with emicizumab during the first 24 weeks were eligible to continue receiving emicizumab prophylaxis. Concomitant medications were permitted, but authors did not list which medications were permitted. Breakthrough bleeds were managed with episodic FVIII treatment.

Outcomes

The primary efficacy outcome was bleeding frequency, expressed as an ABR. The efficacy end points included various definitions of bleeds — namely, treated bleeds, treated spontaneous bleeds, treated joint bleeds, treated target joint bleeds, and all bleeds consistent with the definitions of the FVIII, Factor IX and Rare Coagulation Disorders Subcommittee of the ISTH used in the HAVEN 3 and HAVEN 4 studies. Another evaluated efficacy outcome was patient preference. Safety outcomes were reported in the form of AEs.

Statistical Analysis

The efficacy analysis was performed using the efficacy analysis set, which included all enrolled patients who received at least 1 dose of emicizumab. The efficacy analysis evaluated bleeding rates and was conducted once all patients had reached week 24 or withdrawn from the study. ABRs were estimated using negative binomial regression with the treatment period as an offset to account for varying follow-up periods. Pre-treatment ABRs were calculated using documented bleed information and standardized for the different age groups over different durations: 12 weeks [redacted] for patients less than 2 years of age and 24 weeks [redacted] for patients 2 years of age and older. ABRs in the post-treatment period were calculated using duration in days. A model with different data elements was used to calculate the ABR ratio between pre- and post-treatment ABRs. Calculated ABRs were computed by dividing the number of bleeding events by the evaluation period in days and multiplying this rate by 365.25.

Patient-reported outcomes were estimated at week 17 using the patient-reported outcomes analysis set, which included all patients who received at least 1 dose of emicizumab and completed the EmiPref Survey. Summary statistics were computed for the patient-reported outcomes.

The safety analysis was performed using the safety analysis set, which included all patients who received emicizumab at least once. Safety was assessed by summarizing the number of AEs and patients with AEs by system organ class, preferred term, and severity.

Patient Disposition

Patient disposition in the HOHOEMI study is summarized in Table 33. In this study, 6 pediatric patients with hemophilia A without FVIII inhibitors were enrolled sequentially in the cohort receiving emicizumab every 2 weeks. All patients were treated with emicizumab and completed the study. Patients continued to receive emicizumab until it was available for commercial use. No patients required up-titration. No patients were excluded from the analysis.

Table 33: Patient Disposition

	Emicizumab 3.0 mg/kg Q2W N = 6	Emicizumab 6.0 mg/kg Q4W N = 7
Screened	NR	NR
Completed study	6 (100)	7 (100)
Discontinued study	0	0
Efficacy set, N	6 (100)	7 (100)
Patient-reported outcome set, N	6 (100)	7 (100)
Safety set, N	6 (100)	7 (100)
Up-titrated set, N	0	0

NR = not reported; Q2W = every 2 weeks; Q4W = every 4 weeks.

Source: Clinical Study Report for HOHOEMI.[51]

Exposure to Study Treatments

Exposure to the study treatment is summarized in Table 34. All patients in the cohort receiving emicizumab every 2 weeks received 3.0 mg/kg emicizumab every 2 weeks and continued their allocated dosing regimen. [redacted] No patients had a dose up-titration during the study period. After study termination, all patients continued to receive emicizumab prophylaxis until it was available for commercial use. The median treatment duration for the cohort receiving emicizumab every 2 weeks was [redacted]

Table 34: Exposure to Study Treatment

	Emicizumab 3.0 mg/kg Q2W N = 6
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

min = minimum; max = maximum; Q2W = every 2 weeks; SD = standard deviation.

Source: Clinical Study Report for HOHOEMI.[51]

Efficacy

[redacted] (Table 35). [redacted]

[redacted]

Table 35: Bleeding Outcomes

	Emicizumab 3.0 mg/kg Q2W N = 6
[redacted]	
[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; NE = not estimable; Q2W = every 2 weeks; SD = standard deviation.

[redacted]

Source: Clinical Study Report for HOHOEMI.[51]

Pre- and post-treatment intra-patient bleeding outcomes are summarized in Table 36. [redacted]

Table 36: Bleeding Outcomes (Pre- and Post-Treatment)

	Emicizumab 3.0 mg/kg Q2W N = 6	
	Pre-treatment	Post-treatment
[redacted]		

CI = confidence interval; NE = not estimable; Q2W = every 2 weeks; SD = standard deviation.

[redacted]

Source: Clinical Study Report for HOHOEMI.[51]

At week 17, all caregivers (n = 13) completed the EmiPref. All caregivers preferred emicizumab prophylaxis over previous hemophilia treatments. The main reasons for this preference were a lower treatment frequency (38%) and fewer effects on other activities, such as work, school, and social interactions (23.1%) (data not shown).

Harms

The AEs are summarized in Table 37. All patients in the cohort receiving emicizumab every 2 weeks experienced at least one AE. A total of 112 AEs were reported. Of these, 1 was listed as having grade 3 severity, while the others were grade 1 or 2. The most common AEs reported were contusion (100%), ligament sprain (50%), scratch (50%), and arthralgia (50%). One patient experienced local injection-site reaction, which resolved without treatment. One patient experienced an SAE (post-traumatic pain). No AEs led to treatment discontinuation, and no deaths were reported.

Table 37: Summary of Harms

	Emicizumab 3.0 mg/kg Q2W N = 6
Patients with ≥ 1 adverse event	
n (%)	6 (100)
Most common events,[a] n (%)	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Patients with ≥ 1 SAE	
n (%)	1 (16.7)
Patients who stopped treatment due to adverse events	
n (%)	0
Deaths	
n (%)	0
Notable harms	
Local injection-site reaction, n (%)	1 (16.7)

Q2W = every 2 weeks; SAE = serious adverse event.

[a] Frequency of affected patients is ≥ 2 patients.

Source: Clinical Study Report for HOHOEMI.[51]

Critical Appraisal

Internal Validity

The HOHOEMI study was the first clinical trial of emicizumab in pediatric patients with severe hemophilia A without inhibitors. A notable limitation of the study design was the lack of an appropriate control group with blinding in the assessment of outcomes. This may have introduced observer or reporting bias for subjective measures such as the responses on the EmiPref and AEs. Another limitation was the small sample size (total N = 13). There was no loss to follow-up, and all patients remained on the treatment regimen they were assigned to receive. In terms of outcomes, the primary efficacy outcome of ABR is the same one used in the pivotal hemophilia trials, HAVEN 3 and HAVEN 4. Except for all bleeds — which showed no difference between pre- and post-treatment comparison — all other bleeding outcomes showed large reductions, as demonstrated in the ABR ratios, with 95% CI, excluding the null. The HOHOEMI study showed results that were consistent with the HAVEN 3 and HAVEN 4 trials regarding the efficacy of emicizumab.

External Validity

In the HOHOEMI study, all patients had severe congenital hemophilia A without inhibitors (i.e., endogenous FVIII levels of less than 1%) and were less than 12 years of age (range = 1.5 years to 10.7 years). It is worth noting that the population of this study may not reflect the Canadian population, given that all participants were Japanese children from Japan with severe hemophilia.

The efficacy outcome of annualized bleeding rates and the safety outcome of AEs were relevant; these are outcomes that Canadian patients deem important, and they are also used by physicians in clinical practice. Bleeds were defined using standardized definitions from the FVIII, Factor IX and Rare Coagulation Disorders Subcommittee of the ISTH. The study did not measure the impact on productivity (i.e., days of school missed), which was deemed important based on the patient group input received for this review. According to the experts consulted by CADTH, the impact of emicizumab treatment on the frequency of treated bleeds was of greater interest than its impact on productivity.

The HOHOEMI study evaluated 2 emicizumab treatment regimens: 3.0 mg/kg every 2 weeks and 6.0 mg/kg every 4 weeks. The latter regimen is not relevant to the Canadian population, given that Health Canada currently recommends a treatment regimen of 1.5 mg/kg every week or 3.0 mg/kg every 2 weeks for emicizumab prophylaxis in children under the age of 12 years. A treatment regimen consisting of 1.5 mg/kg emicizumab every week would have been more applicable to the Canadian context.

All patients enrolled in the study except for 1 had been treated with FVIII prophylaxis before switching over to emicizumab prophylaxis. This reflects the current situation in Canada, given that the majority of children with severe hemophilia A are receiving FVIII prophylaxis. In the event that emicizumab did not provide sufficient bleeding control, patients could receive episodic FVIII treatment; this also reflects clinical practice in Canada. Treatment in the HOHOEMI study was administered in patients' homes by their caregivers when this was deemed acceptable by the investigator. This also likely reflects the anticipated treatment setting for emicizumab in Canada. Lastly, patients and caregivers who were unable to administer the treatment successfully could continue to receive injections at the study site, which may not be typical in real-world settings.

Discussion

Summary of Available Evidence

Two phase III trials (HAVEN 3, N = 152; HAVEN 4, N = 41) submitted by the sponsor were included in the systematic review. HAVEN 3 included patients with severe congenital hemophilia A (i.e., with intrinsic FVIII levels of less than 1%) without FVIII inhibitors. HAVEN 4 included patients with severe congenital hemophilia A or hemophilia A with FVIII inhibitors.

HAVEN 3 was a 24-week, open-label, multi-centre RCT that aimed to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with severe hemophilia A without FVIII inhibitors. Patients who received episodic treatment with FVIII prior to study entry were randomized in a 2:2:1 ratio to the following treatment arms: emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly; emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks followed by 3.0 mg/kg every 2 weeks; or no prophylaxis (control arm). Patients who received FVIII prophylaxis prior to study entry (derived from the NIS) were enrolled in a separate, non-randomized arm where they received treatment with emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly. Patients in this arm continued their regular FVIII prophylaxis treatment until the second emicizumab loading dose. In HAVEN 3, the primary outcome was related to the ABR ratio for treated bleeds. Secondary outcomes pre-specified in the statistical testing hierarchy included additional bleeding outcomes (ABR ratio for all bleeds, treated joint bleeds, treated spontaneous bleeds, treated target joint bleeds) and HRQoL (based on the Haem-A-QoL physical health subscore).

HAVEN 4 was a 24-week, open-label, multi-centre, non-randomized, single-arm trial that aimed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab prophylaxis in patients receiving emicizumab every 4 weeks. Patients in HAVEN 4 received treatment with emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks followed by 6.0 mg/kg every 4 weeks. No formal hypothesis testing was performed, and no primary efficacy end point was identified. Analyses for all outcomes (e.g., bleeding outcomes, productivity, and HRQoL) were descriptive.

The key limitations of the body of evidence related to the open-label study design, absence of randomized, direct comparative data between emicizumab and FVIII prophylaxis, and generalizability to the Canadian clinical population.

One sponsor-submitted NMA compared emicizumab prophylaxis with FVIII prophylaxis for patients with hemophilia A without inhibitors.[12,13]

The HOHOEMI study (n = 6) was a phase III, multi-centre, open-label, non-randomized clinical trial that evaluated the efficacy and safety of SC emicizumab prophylaxis in a pediatric population with hemophilia A without FVIII inhibitors who were previously treated with FVII prophylaxis.

Interpretation of Results

Efficacy

In HAVEN 3, the primary outcome related to the ABR ratio for treated bleeds demonstrated a statistically significant reduction in bleeding for both 1.5 mg/kg emicizumab weekly and

3.0 mg/kg emicizumab every 2 weeks compared to no prophylaxis (i.e., episodic FVIII) for patients previously treated with episodic FVIII. This reduction was also considered to be clinically meaningful, according to the clinical experts consulted by CADTH for this review. Similar efficacy findings were reported for secondary bleeding outcomes (i.e., ABR ratio for all bleeds, treated joint bleeds, treated spontaneous bleeds). The data for all bleeding outcomes in HAVEN 3 were robust, given the consistency of the primary results with various sensitivity analyses. HAVEN 3 assessed treated target joint bleeds as an "other" outcome outside the statistical testing hierarchy. Treated target joint bleeds showed consistent results with the primary and secondary bleeding outcomes. This reduction was also considered to be clinically meaningful, according to the clinical experts consulted by CADTH for this review.

The only data available for patients previously treated with FVIII prophylaxis are from a small sample (n = 48) in the HAVEN 3 study. In an intra-patient assessment, patients treated with FVIII prophylaxis in the NIS entered HAVEN 3, where they received maintenance treatment with 1.5 mg/kg emicizumab weekly. The ABR ratio was statistically significant and considered clinically meaningful by the clinical experts for the bleeding outcomes assessed (i.e., all bleeds, treated bleeds).

In the single-arm HAVEN 4 study, ABRs for patients treated with 6.0 mg/kg emicizumab every 4 weeks were generally aligned with the reductions in bleeding reported in HAVEN 3 (i.e., ABR for treated bleeds, all bleeds, treated joint bleeds, treated spontaneous bleeds, treated target joint bleeds). HAVEN 4 is the only study included in this review that evaluated the efficacy and safety of 6.0 mg/kg emicizumab every 4 weeks, which is one of the doses approved for use in adolescents and adults greater than or equal to 40 kg. Although all analyses were descriptive, and no formal hypothesis testing was performed, Health Canada concluded that "…the model based ABR (in HAVEN 4) was consistent with HAVEN 3, although slightly higher but limited by cross-study comparisons. The HAVEN 4 results are consistent with the results of HAVEN 3 and HAVEN 1, indicating the 6.0 mg/kg Q4W [every 4 weeks] dose is an acceptable maintenance dose in this patient population (greater than or equal to 12 years of age and greater than 40 kg)."[29]

HAVEN 3 and HAVEN 4 included several pre-specified subgroup analyses that were identified as relevant in the CADTH review protocol (bleed rate in the 24 weeks prior to enrolment [less than 9, greater than or equal to 9], age category at baseline, presence or absence of target joints, previous treatment regimen [episodic, prophylactic], and FVIII inhibitor status). For the subgroups with sufficient data, there were no clear differences observed in ABR. However, due to small sample sizes, most these subgroups could not be appropriately analyzed. This was acknowledged by the sponsor, who wrote: "…due to the small sample size, all subgroup analyses are highly sensitive to variability caused by individual patients and should be interpreted with caution."[10]

The current standard of care in Canada for patients with severe hemophilia A is treatment with FVIII prophylaxis. Although some Canadian patients are treated with episodic FVIII (generally related to patient preference in adults), the use of episodic FVIII only, as required by HAVEN 3 in arms A, B, and C, is not generally reflective of Canadian clinical practice. Additionally, patients previously treated with episodic FVIII were required to have 5 or more bleeds in the 24 weeks prior to study entry. This inclusion criteria creates a study population with more uncontrolled bleeding than would be observed in the Canadian clinical population. It is possible that the efficacy results observed in the trials may be exaggerated compared to what would be seen in clinical practice in Canada. This highlights a gap in

evidence, given that the true magnitude of the treatment effect in patients with better control than those included in the trials (i.e., consistent with the Canadian clinical population) is unknown. In the clinical setting, it is also important to consider that patients with moderate hemophilia A may require prophylaxis; however, data from HAVEN 3 and HAVEN 4 were based primarily on severe patients, illustrating another gap in evidence.

The magnitude of the effect of emicizumab in patients previously treated with episodic FVIII in HAVEN 3 may be overestimated based on these limitations to external validity. However, differences in the magnitude of the efficacy results are not expected to invalidate the clinical significance of the bleeding outcomes in HAVEN 3, which are expected to address a gap in therapy experienced by patients currently treated with FVIII.

Based on the patient group input received for this review, HRQoL was an outcome of importance. The Haem-A-QoL physical health subscore was a secondary outcome (within the statistical testing hierarchy) in HAVEN 3 that did not show a statistically significant improvement for the arm receiving 1.5 mg/kg emicizumab weekly, which stopped statistical testing based on the pre-specified statistical testing hierarchy. Results from the Haem-A-QoL total score, EQ-5D-5L, and EQ VAS were outside the statistical testing hierarchy specified in HAVEN 3, and the results associated with each dosing regimen were inconsistent, although the 24-week evaluation period may not have been of sufficient duration to observe an effect. Additionally, the open-label study design rendered the interpretation of these results questionable. Despite the similar magnitude of ABRs for the different bleeding types in both emicizumab treatment regimens, the inconsistent HRQoL results prevent conclusions from being drawn regarding the impact of emicizumab on HRQoL. Additionally, minimal data assessing the effect of emicizumab on HRQoL in patients aged less than 18 years of age were available at the time of this review.

Input from the patient group and clinical experts consulted for this review highlights the importance for patients of being able to attend school and work. Based on descriptive analysis, patients in HAVEN 3 who were treated with emicizumab (1.5 mg/kg weekly, 3.0 mg/kg every 2 weeks) did not report missing any days of school, while those in the no-prophylaxis arm reported being away for an average of 10 days. In HAVEN 4, patients treated with 6.0 mg/kg emicizumab every 4 weeks were away from school for an average of less than 1 day. Based on descriptive analyses, patients were away from work for an average of less than 1 day. Data on days away from school and work were assessed based on a period of 4 weeks prior to baseline and prior to week 25. The effect of treatment for the remaining duration is unclear.

HAVEN 3 and HAVEN 4 provided descriptive results of patient preference assessed through the EmiPref and SQ-ISHI. The results showed a consistent patient preference for treatment with emicizumab compared to their previous treatment (FVIII). While this finding is consistent with the expectations of the patients and clinicians consulted for this review, it should be noted that EmiPref was a sponsor-developed scale; as well, neither scale was validated and neither had a recognized MID. Based on patient group input, the main unmet need for patients with severe hemophilia A is a user-friendly treatment, given that the IV route of administration for FVIII concentrates is challenging, complex, time-consuming, and less convenient than other routes of administration. Patients and clinicians anticipate that the SC route of administration associated with emicizumab could increase adherence in patients transitioning from pediatric to adolescent or adult care as well as in patients for whom venous access is difficult or inconvenient (e.g., geriatric patients). Patients and clinicians expect that the availability of a weekly or less frequent SC treatment (compared to

frequent IV treatment with FVIII prophylaxis) will simplify treatment administration and may promote greater adherence. While adherence was assessed in both trials, the level of adherence in the real-world clinical population remains unknown.

Data from the NMA submitted by the sponsor suggested that emicizumab prophylaxis was associated with a reduction of bleed rates compared with FVIII product prophylaxis in the treatment of patients with severe hemophilia A without inhibitors. Limitations included: the small number of trials with small sample size included in the NMA; the high degree of heterogeneity across the included studies in disease severity; the use of different comparator FVIII products in different trials; inconsistent or unclear definitions of bleed outcomes; variable outcome estimation time points across trials; and differences in study design. The ICER ITC findings indicated uncertainty in terms of whether there was a difference in the reduction of treated bleeds between patients receiving emicizumab prophylaxis (combination of 1.5 mg/kg weekly and 3.0 mg/kg every 2 week) and those receiving FVIII prophylaxis. Overall, no robust conclusions can be drawn regarding the comparative clinical efficacy and safety profile of emicizumab prophylaxis versus rFVIII prophylaxis in patients with hemophilia without inhibitors.

Patients under 12 years of age were not included in HAVEN 3 or HAVEN 4. However, this is unlikely to affect the study results' generalizability to patients under 12 years of age, given the mechanism of action of emicizumab, which functions independently of inhibitor status or age.[8] The clinical efficacy of emicizumab in children with inhibitors was assessed in a previous submission by the National Advisory Committee on Blood and Blood Products (not reviewed in this report). The only data available in pediatric patients with hemophilia A for this review were from the HOHOEMI study. Results showed that emicizumab prophylaxis was associated with a reduction in bleeding events when comparing pre- and post-treatment ABRs. The model-based ABR for treated bleeds was 8.9 bleeds per year (95% CI, 4.43 to 17.80) for the pre-treatment period (FVIII prophylaxis) and 1.1 bleeds per year (95% CI, 0.65 to 1.97) for the treatment period (3.0 mg/kg every 2 weeks emicizumab). Generally, these data are consistent with the intra-patient analysis in HAVEN 3. Data from the HOHOEMI study showed that all caregivers of pediatric patients preferred emicizumab prophylaxis over previous hemophilia treatments (FVIII prophylaxis). The main reasons provided were lower treatment frequency (38%) and fewer effects on daily activities and social interactions (23.1%). However, only 6 patients were included in the treatment group of interest to this review, and no efficacy conclusions can be drawn regarding the efficacy of emicizumab, given that no statistical testing was conducted. Overall, the evidence from the HOHOEMI study on the efficacy and safety of emicizumab in pediatric patients is limited by concerns regarding internal validity and generalizability to the Canadian population. Despite the lack of high-quality evidence available for pediatric patients, the clinical experts consulted for this review did not express any concerns with using emicizumab in this population.

Harms

In HAVEN 3, AEs occurred in 94.4% of patients receiving 1.5 mg/kg emicizumab weekly, 85.7% of patients receiving 3.0 mg/kg emicizumab every 2 weeks emicizumab, 50.0% of patents in the no-prophylaxis arm, and 87.3% of patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). In HAVEN 4, 73.2% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an AE. The most common AEs in both studies were injection-site reactions. In HAVEN 3, injection-site reactions occurred in 25.0% of patients receiving 1.5 mg/kg emicizumab weekly, 20.0% of patients receiving 3.0 mg/kg

emicizumab every 2 weeks, 12.5% of patients in the no-prophylaxis arm, and 31.7% of patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). In HAVEN 4, 22.0% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an injection-site reaction.

Throughout HAVEN 3 and HAVEN 4, there were no instances of de novo inhibitor development detected in patients who tested negative for inhibitors (titre less than 0.6 CBU/mL) at baseline.

In HAVEN 3, SAEs occurred in 2.8% of patients receiving 1.5 mg/kg emicizumab weekly, 8.6% of patients receiving 3.0 mg/kg emicizumab every 2 weeks, 0% of patients in the no-prophylaxis arm, and 12.7% of patients in the previous-FVIII-prophylaxis arm (1.5 mg/kg emicizumab weekly). In HAVEN 4, 2.4% of patients treated with 6.0 mg/kg emicizumab every 4 weeks experienced an SAE. No patients died in the studies.

The 24-week assessment period of HAVEN 3 and HAVEN 4 was determined to be of sufficient duration by the clinical experts consulted in this review. Overall, the safety profiles were likely comparable between the 2 emicizumab treatment regimens (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks); however, due to the small sample size, further study is warranted.

The safety profile of emicizumab compared to FVIII prophylaxis remains unknown due to the absence of direct, comparative evidence. An assessment of harms data was not conducted in the NMA submitted by the sponsor.

Other Considerations

Emicizumab has been available for use through Canadian Blood Services throughout Canada (with the exception of Quebec) since August 2018 for patients with hemophilia A with FVIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.[9] HAVEN 1 and HAVEN 2 were trials that assessed the efficacy and safety of emicizumab in this population. HAVEN 1 was a multi-centre, open-label, phase III clinical study that involved male patients with hemophilia A with FVIII inhibitors who were greater than or equal to 12 years of age. HAVEN 2 aimed to investigate the safety and efficacy of emicizumab in pediatric and adolescent patients with hemophilia A with FVIII inhibitors.

Conclusions

Two phase III, open-label clinical trials, HAVEN 3 and HAVEN 4, were included in this review to provide evidence of the efficacy and safety of emicizumab in patients with severe hemophilia A without inhibitors. In HAVEN 3, both doses of emicizumab (1.5 mg/kg weekly and 3.0 mg/kg every 2 weeks) showed a reduction in bleeding outcomes compared to no prophylaxis (episodic FVIII treatment). In HAVEN 4, based on descriptive analysis, patients treated with 6.0 mg/kg emicizumab every 4 weeks had ABRs that were generally aligned with those of patients treated with both doses of emicizumab in HAVEN 3. Despite being assessed in both studies, the effect of emicizumab on HRQoL remains unknown. The most common AE in both studies was injection-site reactions. No major safety signals were identified in the studies, and no patients died.

The body of evidence was limited by the open-label study design, the absence of randomized, direct comparative data between emicizumab dosages (1.5 mg/kg every 2 weeks, 3.0 mg/kg every 2 weeks, and 6.0 mg/kg every 4 weeks mg/kg) and FVIII prophylaxis (the current standard of care), and issues with generalizability to the Canadian clinical population.

Methodological limitations in the sponsor's NMA prevented robust conclusions from being drawn with regard to the comparative clinical efficacy and safety profile of emicizumab prophylaxis regimens versus rFVIII prophylaxis in patients with hemophilia without inhibitors.

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:	July 29, 2020
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
#	Truncation symbol for one character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.ot	Original title
.nm	Name of substance word
.rn	Registry number
.dq	Candidate term word (Embase)
.pt	Publication type
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	(Hemlibra* or emicizumab* or ace-910 or ace910 or rg 6013 or rg6013 or ro 5534262 or ro5534262 or 7NL2E3F6K3).ti,ab,kf,ot,hw,nm,rn.
2	1 use medall
3	*emicizumab/ or (Hemlibra* or emicizumab* or ace-910 or ace910 or rg 6013 or rg6013 or ro 5534262 or ro5534262).ti,ab,kw,dq.

MULTI-DATABASE STRATEGY	
4	3 use oemezd
5	4 not (conference review or conference abstract).pt.
6	2 or 5
7	remove duplicates from 6

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: Hemlibra (emicizumab)
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: Hemlibra (emicizumab)
Health Canada's Clinical Trials Database	Produced by Health Canada. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: Hemlibra (emicizumab)
EU Clinical Trials Register	European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: Hemlibra (emicizumab)

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

Search dates:	July 2020
Keywords:	Hemlibra (emicizumab); hemophilia A
Limits:	Publication years: none
Updated:	Search updated prior to the completion of stakeholder feedback period

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:

- HTA 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: Excluded Studies

Table 38: Excluded Studies

Reference	Reason for exclusion
McCary I, Guelcher C, Kuhn J, et al. Real-world use of emicizumab in patients with haemophilia A: bleeding outcomes and surgical procedures. *Haemophilia.* 2020;20:20.[52]	Study design, not RCT
Reyes A, Revil C, Niggli M, et al. Efficacy of emicizumab prophylaxis versus factor VIII prophylaxis for treatment of hemophilia A without inhibitors: network meta-analysis and sub-group analyses of the intra-patient comparison of the HAVEN 3 trial. *Curr Med Res Opin.* 2019;35(12):2079-2087.[13]	Study design, not RCT
Shima M, Nogami K, Nagami S, et al. A multicentre, open-label study of emicizumab given every 2 or 4 weeks in children with severe haemophilia A without inhibitors. *Haemophilia.* 2019;25(6):979-987.[53]	Study design, not RCT

RCT = randomized controlled trial.

Appendix 3: Detailed Outcome Data

Table 39: Subgroup Analysis for Treated Bleeds (HAVEN 3 and HAVEN 4) and All Bleeds (HAVEN 4)

Subgroup		HAVEN 3			HAVEN 4	HAVEN 4
		1.5 mg/kg emicizumab N = 36	3.0 mg/kg emicizumab N = 35	6.0 mg/kg emicizumab N = 41	6.0 mg/kg emicizumab N = 41	6.0 mg/kg emicizumab N = 41
		Treated bleeds				All bleeds
Treated bleed rate, last 24 weeks prior to enrolment						
< 9	Number of patients contributing to the analysis (%)	9 (25.0)	5 (14.3)	4 (22.2)	28 (68.3)	28 (68.3)
	Annualized bleeding rate (95% CI)	1.1 (0.44 to 2.88)[a]	1.3 (0.40 to 4.18)[a]	26.7 (12.51 to 56.81)[a]	2.6 (1.37 to 4.96)	4.5 (1.37 to 11.01)
	Annualized bleeding rate ratio (95% CI)	0.04 (0.013 to 0.141)[a]	0.05 (0.012 to 0.196)[a]	Reference group	NA	NA
≥ 9	Number of patients contributing to the analysis (%)	27 (0.75)	30 (85.7)	14 (77.8)	13 (31.7)	13 (31.7)
	Annualized bleeding rate (95% CI)	1.9 (1.10 to 3.20)	1.6 (0.93 to 2.69)[a]	49.7 (28.52 to 86.57)[a]	2.0 (0.59 to 7.05)	4.4 (1.31 to 10.86)
	Annualized bleeding rate ratio (95% CI)	0.04 (0.018 to 0.082)[a]	0.03 (0.015 to 0.069)	Reference group	NA	NA
Age group (18)						
< 18	Number of patients contributing to the analysis (%)	0	0	1 (5.6)	NR	NR
	Annualized bleeding rate (95% CI)	NA	NA	NA	NR	NR
	Annualized bleeding rate ratio (95% CI)	NA	NA	NA	NR	NR
≥ 18	Number of patients contributing to the analysis (%)	36 (100)	35 (100)	17 (94.4)	NR	NR
	Annualized bleeding rate (95% CI)	1.7 (1.07 to 2.73)[a]	1.5 (0.95 to 2.52)[a]	45.9 (27.85 to 75.69)[a]	NR	NR
	Annualized bleeding rate ratio (95% CI)	0.04 (0.019 to 0.074)[a]	0.03 (0.017 to 0.068)[a]	Reference group	NR	NR
Age group (65)						
< 65	Number of patients contributing to the analysis (%)	34 (94.4)	34 (97.1)	18 (100)	NR	NR
	Annualized bleeding rate (95% CI)	1.5 (0.94 to 2.44)[a]	1.6 (0.99 to 2.56)[a]	44.6 (28.38 to 70.01)[a]	NR	NR
	Annualized bleeding rate ratio (95% CI)	0.03 (0.018 to 0.066)[a]	0.04 (0.019 to 0.069)[a]	Reference group	NR	NR

Subgroup		HAVEN 3			HAVEN 4	HAVEN 4
		1.5 mg/kg emicizumab N = 36	3.0 mg/kg emicizumab N = 35	6.0 mg/kg emicizumab N = 41	6.0 mg/kg emicizumab N = 41	6.0 mg/kg emicizumab N = 41
		Treated bleeds				All bleeds
≥ 65	Number of patients contributing to the analysis (%)	2 (5.6)	1 (2.9)	0	NR	NR
	Annualized bleeding rate (95% CI)	NA	NA	NA	NR	NR
	Annualized bleeding rate ratio (95% CI)	NA	NA	Reference group	NR	NR
Presence of target joints						
No target joints	Number of patients contributing to the analysis (%)	2 (5.6)	8 (22.9)	3 (16.7)	16 (39.0)	16 (39.0)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any target joints [c]	Number of patients contributing to the analysis (%)	34 (94.4)	27 (77.1)	15 (83.3)	25 (61.0)	25 (61.0)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous treatment regimen						
Episodic	Number of patients contributing to the analysis (%)	NR	NR	NR	11 (26.8)	11 (26.8)
	Annualized bleeding rate (95% CI)	NR	NR	NR	[redacted]	[redacted]
	Annualized bleeding rate ratio (95% CI)	NR	NR	NR	NA	NA
Prophylactic	Number of patients contributing to the analysis (%)	NR	NR	NR	30 (73.2)	30 (73.2)
	Annualized bleeding rate (95% CI)	NR	NR	NR	[redacted]	[redacted]
	Annualized bleeding rate ratio (95% CI)	NR	NR	NR	NA	NA
Inhibitor status						
Inhibitor	Number of patients contributing to the analysis (%)	NR	NR	NR	5 (12.2)	5 (12.2)
	Annualized bleeding rate (95% CI)	NR	NR	NR	[redacted]	[redacted]
	Annualized bleeding rate ratio (95% CI)	NR	NR	NR	NA	NA

Subgroup		HAVEN 3			HAVEN 4	HAVEN 4
		1.5 mg/kg emicizumab N = 36	3.0 mg/kg emicizumab N = 35	6.0 mg/kg emicizumab N = 41	6.0 mg/kg emicizumab N = 41	6.0 mg/kg emicizumab N = 41
		Treated bleeds				All bleeds
Non-inhibitor	Number of patients contributing to the analysis (%)	NR	NR	NR	36 (87.8)	36 (87.8)
	Annualized bleeding rate (95% CI)	NR	NR	NR	[redacted]	[redacted]
	Annualized bleeding rate ratio (95% CI)	NR	NR	NR	NA	NA

CI = confidence interval; ITT = intention to treat; NA = not applicable; NR = not reported.

[a] ITT population; global model with 3-level categorical effect for treatment.

[b] All-treated-patients population.

[c] Treated target joint bleeds occur in a target joint, defined as a joint in which ≥ 3 treated joint bleeds occurred during the last 24 weeks prior to study entry. Bleeds due to surgeries or procedures are excluded.

Source: Clinical Study Reports for HAVEN 3 and HAVEN 4.[10,11]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Haem-A-QoL
- Haemo-QoL-SF
- EQ-5D-5L (utility index and VAS)
- EmiPref Survey
- SQ-ISHI.

Findings

Table 40: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Haem-A-QoL questionnaire	Disease-specific measure of HRQoL in adult patients with hemophilia, consisting of 10 domains: Physical Health, Feelings, View of Yourself, Sports and Leisure, Work and School, Dealing with Hemophilia, Treatment, Future, Family Planning, and Partnership and Sexuality. Scores range from 0 to 100, with higher scores indicating worse health status.	Construct validity was adequate for 8 out of 10 domains and the total score. Convergent validity was determined to be acceptable in patients with hemophilia. Internal consistency was determined to be acceptable in patients with hemophilia. The Haem-A-QoL was sufficiently sensitive to detect change over time in patients with hemophilia.	No generally accepted MID was identified; however, 1 study in patients with hemophilia used half a standard deviation of the mean baseline score as the MID. Responder definitions were estimated to be a 7-point reduction for the total score and a 10-point reduction in the Physical Health and Sports and Leisure domains in patients with hemophilia. 1 study in patients with hemophilia used half a standard deviation of the mean as the MID.
Haemo-QoL-SF (35-item) questionnaire	Disease-specific measure of HRQoL in children and adolescents with hemophilia consisting of 9 dimensions: Physical Health, Feelings, View of Yourself, Family, Friends, Other Persons, Sports and School, Dealing with Hemophilia, and Treatment. Scores range from 0 to 100, with higher scores indicating worse health status.	Convergent validity was determined to be good in patients with hemophilia. Internal consistency was determined to be high. Inter-rater reliability was moderate between children and parents. Test-retest reliability was very high for both children and parents. No literature assessing the responsiveness of the	No generally accepted MID was identified in populations with hemophilia.

Outcome measure	Type	Conclusions about measurement properties	MID
		Haemo-QoL-SF in patients with hemophilia was identified.	
EQ-5D-5L and EQ VAS questionnaires	The EQ-5D-5L is a generic, preference-based measure of HRQoL consisting of 5 domains: Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Scores range from 0 to 1, with higher scores indicating better health status. The EQ VAS is a generic, preference-based measure of HRQoL presented as a visual analogue scale from 0 to 100, with 0 as the worst possible health state and 100 as the best.	*EQ-5D-5L utility index* Item-total correlation was satisfactory for all domains and highest for the pain/discomfort domain in patients with hemophilia. Construct validity was acceptable for the pain/discomfort domain of the EQ-5D-5L in patients with hemophilia. Internal consistency of the index score was determined to be acceptable in patients with hemophilia, and was not evaluated for the separate domains. No literature assessing the responsiveness of the EQ-5D-5L utility index in patients with hemophilia was identified. *EQ VAS* Convergent validity was low to moderate in patients with hemophilia. No literature assessing the reliability or responsiveness of the EQ VAS in patients with hemophilia was identified.	No MID was identified for the EQ-5D-5L or the EQ VAS in populations with hemophilia. The MID was estimated to range from 0.037 to 0.056 in the general Canadian population.
EmiPref Survey	A non-validated, disease-specific, fit-for-purpose questionnaire developed by the sponsor that measures patient preference for emicizumab treatment.	No literature was identified that tested the EmiPref Survey for reliability, validity, or responsiveness in patients with hemophilia.	No MID information was identified in patients with hemophilia.
SQ-ISHI	A non-validated, disease-specific, fit-for-purpose questionnaire that measures patient satisfaction with hemophilia treatments.	No literature was identified that tested the SQ-ISHI for reliability, validity, or responsiveness in patients with hemophilia.	No MID information was identified in patients with hemophilia.

EmiPref = Emicizumab Preference; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; Haem-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; Haemo-QoL-SF = Haemophilia-specific Quality of Life Questionnaire for Children Short Form; HRQoL = health-related quality of life; MID = minimal important difference; SQ-ISHI = Satisfaction Questionnaire – Intravenous Subcutaneous Hemophilia Injection.

Haemophilia Quality of Life Questionnaire for Adults

The Haem-A-QoL is a disease-specific, self-reported questionnaire used to measure HRQoL in adult patients (18 years or older) with hemophilia.[30] Its 10 domains measure Physical Health (5 items), Feelings (4 items), View of Yourself (5 items), Sports and Leisure (5 items), Work and School (4 items), Dealing With Hemophilia (3 items), Treatment (8 items), Future (5 items), Family Planning (4 items), and Partnership and Sexuality (3 items). In total, the questionnaire has 46 items with a 5-point Likert frequency scale (never, rarely, sometimes, often, all the time). Provided that a minimum number of questions (38 out of 46) have been answered for the respective domain, raw scores for each domain are computed by calculating the sum of all item values, and scores are then transformed to a value ranging from 0 to 100, with higher scores indicating poorer HRQoL.

In 1 study by Wyrwich et al., the validity, reliability, and responsiveness of the Haem-A-QoL were evaluated over a period of 6 months in 133 and 73 adult patients (greater than or equal to 17 years) with severe hemophilia A and B from 6 continents who participated in the A-LONG and B-LONG studies, respectively.[31] These clinical trials evaluated longer-lasting factor concentrates: rFVIIIFc in A-LONG and rFIXFc in B-LONG. In the A-LONG study, the mean age was 36.0 years (SD = 12.5 years); in the B-LONG study, it was 33.6 years (SD = 12.8 years). At baseline, the Physical Health and Sports and Leisure domains were identified as those where patients experienced the greatest impairments in both studies.

Internal consistency was evaluated using the Cronbach alpha, and was determined to be acceptable (alpha > 0.70) for 9 out of the 10 domains of the Haem-A-QoL; the Dealing With Hemophilia (A-LONG, alpha = 0.64) and Treatment (B-LONG, alpha = 0.68) domains had lower reliability.[30] Reliability was high for the total score of the Haem-A-QoL in both studies (alpha > 0.90).

Construct validity was evaluated using a 1-way ANOVA for the Haem-A-QoL mean domain and total scores at baseline for each EQ-5D item between responders with no problems (level 1) and between those with problems (level 2 to level 3).[30] Known-group validity was adequate for 8 out of 10 domains and the total score. Comparisons between patients with and without bleeds also showed significant differences in the baseline domain scores and total score.

Convergent validity was assessed using the Pearson correlation coefficient (r) and determined to be acceptable.[30] When compared with the EQ-5D index (US, UK), strong negative correlations ($|r| \geq 0.60$) were reported for the total score, Physical Health, and Feelings domains, while moderately negative correlations (r greater than 0.30 and less than 0.60) were reported for the View of Self, Sports and Leisure, Work and School, Treatment, Future, and Partnership and Sexuality domains of the Haem-A-QoL at baseline. When compared with the modified Hemophilia Joint Health Score, moderate correlations were observed between the Physical Health, Feelings, Sports and Leisure, Work and School, and Future domain scores and the total score of the Haem-A-QoL.

Responsiveness was evaluated by examining the correlation of changes in the total score and domain scores of the Haem-A-QoL with changes in the EQ-5D (US, UK) index, activity measure, and bleeding rates from baseline to the 28-week mark.[30] The change score correlations of the Haem-A-QoL with the EQ-5D were moderate ($|r| > 0.33$) for the total score and the Physical Health and Feelings domain of the Haem-A-QoL, which suggests sensitivity of the instrument to detect change. When comparing respective Haem-A-QoL domain scores with the change in activity measure ($r = 0.38$) and the change in ABR ($r =$

0.38) and traumatic bleed rate (r = 0.33), the instrument was shown to be able to detect change over time. Individualized treatment arms showed more improvements than the on-demand treatment arms, as evidenced by greater mean change in the total Haem-A-QoL score, which was expected.

No literature was identified for the MID of the Haem-A-QoL; however, a study done in patients with hemophilia used half an SD of the mean baseline score as the MID of the Haem-A-QoL, which has been shown to be a good threshold of discrimination in HRQoL changes for chronic diseases in a systematic review. [33,54] In addition, thresholds in the score difference in the Haem-A-QoL indicating a benefit in the HRQoL of individual patients with hemophilia have been estimated using anchor- and distribution-based triangulation methods using data from the A-LONG and B-LONG studies described earlier.[32] These thresholds are referred to as HRQoL responder definitions (RDs). The RD for the total score was estimated to be a 7-point reduction and the RDs for the Physical Health and Sports and Leisure domains were estimated to be a 10-point reduction,. In addition, another study done in patients with hemophilia used half an SD of the mean as the MID.[33]

Haemophilia-Specific Quality of Life Questionnaire for Children Short Form

The Haemo-QoL-SF is a disease-specific, age-related questionnaire for children and adolescents aged 4 years to 16 years with hemophilia.[34] Haemo-QoL has 3 age-specific long versions: age group 1 (4 years to 7 years, 8 domains, 21 items); age group 2 (8 years to 12 years, 10 domains, 64 items); and age group 3 (13 years to 16 years, 12 domains, 77 items). The long version includes 9 to 11 subscales depending on the age group. Two age-specific short-form questionnaires were also designed: Short Form 1 (age group 1, 16 items) and Short Form 2 (age groups 2 and 3, 35 items). In addition, an even shorter 8-item instrument, the Haemo-QoL Index, was constructed using a multivariate approach to represent the long version and to merge the age-specific instruments into an age-generic measure.[55] Each version of the questionnaire has 2 possible modes of administration: self-report by children and proxy report by parents.

In the HAVEN 3 and HAVEN 4 studies, the Short Form 2 (Haemo-QoL-SF) was used to assess HRQoL. The 9 dimensions assessed were Physical Health, Feelings, View of Yourself, Family, Friends, Other Persons, Sports and School, Dealing With Hemophilia, and Treatment.[35] Responses for the 35 items were scored on a 5-point Likert scale (never, seldom, sometimes, often, and always). The overall score ranges from 0 to 100, with higher scores indicating poorer HRQoL. The Haemo-QoL-SF was modified from the Haemo-QoL long form, which has been validated and shown to be reliable.[34] In the long questionnaire, all 3 age groups showed acceptable internal consistency, test-retest reliability, and discriminant and convergent validity.

In 1 study by Bradley et al., the validity and reliability of the Haemo-QoL-SF was evaluated in 52 Canadian (provisional Haemo-QoL-SF) and 90 European male children aged 8 years to 16 years with hemophilia and their parents.[35] In the Canadian sample, 57.7% had severe hemophilia A and 11.5% had severe hemophilia B; 23.1% and 7.7% had moderate hemophilia A and B, respectively. In the European sample, 78.7% had severe hemophilia A and 7.6% had severe hemophilia B; 10.4% and 3.3% had moderate hemophilia A and B, respectively.

Internal consistency of the Haemo-QoL-SF was evaluated using the Cronbach alpha for both child self-report and parent proxy-report versions of the instrument.[35] The internal consistency was determined to be high (alpha > 0.80).

Inter-rater reliability between children and their parents and test-retest reliability between 2 time points for parent proxy-reports were assessed using the interclass and intraclass correlation coefficient (ICC), respectively.[35] Inter-rater reliability was moderate between child and parents (ICC = 0.55). The test-retest reliability was only evaluated using European data and was very high in the Haemo-QoL-SF for both children (ICC = 0.78) and parents (ICC = 0.86), suggesting that it is a reliable instrument for repeated measures.

Convergent validity was assessed by creating Pearson correlation matrices for the child and parent data of the Haemo-QoL-SF with the Canadian Hemophilia Outcomes – Kids' Life Assessment Tool, the Pediatric Quality of Life Inventory, the global VAS of QoL, and the KINDL.[35] Based on the Canadian data, the Haemo-QoL-SF was highly correlated with the Canadian Hemophilia Outcomes – Kids' Life Assessment Tool ($0.55 < |r| < 0.82$), the Pediatric Quality of Life Inventory ($0.39 < |r| < 0.76$) and the VAS scores ($0.35 < |r| < 0.78$), particularly in children ($|r| > 0.70$), suggesting good convergent validity.

The Haemo-QoL-SF has not been evaluated in the context of responsiveness. No MID was identified in the literature for the Haemo-QoL-SF; however, a study done in patients with hemophilia used half an SD of the mean baseline score as the MID of the Haemo-QoL, which has been shown to be a good threshold of discrimination in HRQoL changes for chronic diseases in a systematic review.[33,54]

EQ-5D-5L

The EQ-5D-5L is a generic, preference-based HRQoL measure that is widely used in clinical trials, population studies, and real-world clinical settings for clinical and economic appraisal.[36] There are 2 versions: the EQ-5D-5L index and the EQ VAS. The EQ-5D-5L index is composed of a short, multiple-choice questionnaire, with multiple modes of administration, including self-complete, interview, proxy, and interactive voice response system versions. As the name suggests, the EQ-5D-5L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and each has 5 levels of function: no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses for each dimension are coded as single-digit numbers on an ordinary scale (range = 1 to 5), which indicates the severity level, with 1 corresponding to no problems and 5 corresponding to extreme problems. The digits can be combined into a 5-digit code to describe the respondent's health state (e.g., 21111 meaning slight problems in mobility and no problems in self-care, usual activities, pain/discomfort, and anxiety/depression). However, these digits have no arithmetic properties and cannot be summed into an overall score. Instead, the 5-digit EQ-5D-5L health states can be summarized into an index value ranging from 0 (death) and 1 (full health) to represent the HRQoL, which reflects the severity of a health state according to the preferences of the general population of a country or region. The index value is computed using a formula with weights for each dimension derived from valuation studies in a representative sample of said population. The standardized valuation protocol used to place values on EQ-5D-5L health states is based on a composite time trade-off valuation technique supplemented with a discrete choice experiment. The EQ VAS is a vertical VAS from 0 to 100 (20 cm) with anchors of the worst imaginable and best imaginable health states, respectively.[37] It records the self-rated health state of patients.

The validity and reliability of the EQ-5D-5L index was evaluated in the Pain, Functional Impairment, and Quality of Life study consisting of 375 male adults (aged greater than18 years) with hemophilia with or without inhibitors to coagulation factors VIII or IX with a history of joint pain or bleeding in 15 US sites.[37,38] The EuroQol index value calculator was

used to calculate index summary scores.[37] The item-total correlation for the EQ-5D-5L was assessed using Pearson's correlation coefficient and was shown to be satisfactory for all domains (mobility, $r = 0.70$; self-care, $r = 0.53$; usual activities, $r = 0.71$; pain/discomfort, $r = 0.73$; anxiety/depression, $r = 0.39$). Construct validity of the EQ-5D-5L was assessed against the Brief Pain Inventory version 2 Short Form, the Short Form 36 version 2, and the Hemophilia Activities List using Pearson's correlation coefficient (r) and shown to be acceptable.[38] The pain/discomfort domain score correlated with the bodily pain ($|r| = –0.72$) and physical summary ($|r| = –0.64$) domains on the Short Form 36 version 2, the overall activity ($|r| = –0.63$) on the Hemophilia Activities List, and all pain domains ($|r| > –0.64$) on the Brief Pain Inventory. Internal consistency of the EQ-5D-5L index score was assessed using the Cronbach alpha, which was determined to be equal to 0.81, suggesting acceptable reliability of the instrument in adult patients with hemophilia.[38] The internal consistency of the pain/discomfort domain was not reported.

The validity of the EQ VAS was indirectly assessed in a study evaluating a hemophilia-specific instrument, Haem-A-QoL in 25 patients (mean age = 31.28 years, SD = 12.86) with hemophilia A (88%) with the severe phenotype (80%) receiving on-demand treatment.[39] Convergent validity was assessed using Pearson's correlation coefficient by comparing baseline correlations among total scores of the Haem-A-QoL with the EQ VAS. The EQ VAS has moderate negative correlations with the total score ($r = –0.38$), and the Physical Health, Sports and Leisure, Future, and Family Planning domains of the Haem-A-QoL, suggesting low to moderate validity of this version of the instrument in patients with hemophilia.

No literature was identified that reported on the responsiveness of the EQ-5D-5L index for patients with hemophilia. No MIDs for the EQ-5D-5L and the EQ VAS were identified for patients with hemophilia in the literature. However, a simulation-based approach estimated the MID for the general Canadian population to be 0.037 (SD = 0.001) when excluding maximum-valued transitions for each dimension and 0.056 (SD = 0.011) when including transitions from all dimensions.[40]

Emicizumab Preference Survey

The EmiPref Survey is a non-validated, disease-specific, fit-for-purpose questionnaire developed by the sponsor that measures patient preference for emicizumab treatment.[10] The survey consists of 3 questions. The first question asked patients to indicate whether they would prefer to take the study drug, would prefer to take their former hemophilia treatment, or have no preference. The second question asked patients who expressed a preference to identify reasons for their choice and rank their top 3 reasons. The final question was an open-text field for additional information that patients would like to share about their experience with the study drug. This information is entirely based on the sponsor's submission, given that no literature was identified in CADTH's independent literature search for the EmiPref. No literature was identified that tested the EmiPref for validity, reliability, or responsiveness in patients with hemophilia. No MID information was identified in patients with hemophilia.

Satisfaction Questionnaire – Intravenous Subcutaneous Hemophilia Injection

The SQ-ISHI is a non-validated, disease-specific, fit-for-purpose questionnaire that measures patient satisfaction with hemophilia treatments.[10] The questionnaire is composed of 13 items assessing discomfort, worry, and difficulty with injections; confidence with treatment; duration and frequency of treatment; ease of treatment; impact on daily activities; adherence; and overall satisfaction. Items are measured using a 10-point Likert scale for all items except for the overall satisfaction item, which uses a 7-point Likert scale. This information is entirely based on the sponsor's submission, given that no literature was identified in CADTH's independent literature search for the SQ-ISHI. No literature was identified that tested the SQ-ISHI for validity, reliability, or responsiveness in patients with hemophilia. No MID information was identified in patients with hemophilia.

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