South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary

TITLE: Emicizumab for prophylaxis in the management of patients with Haemophilia A with Factor VIII inhibitors
Date: March 2023 (updated November 2023 and March 2024)

NOTE: Efficacy and safety evidence was presented to the National Essential Medicines List Committee (NEMLC) in March 2023. It was proposed by the Tertiary and Quaternary Hospital Level Expert Review Committee (and agreed to by the NEMLC) that a cost-effectiveness analysis be conducted. Scoping document for cost-effectiveness analysis developed and approved by the NEMLC in July 2023.

Update November 2023: The cost-effectiveness analysis was presented at the NEMLC meeting held on the 30th of November 2023 – see accompanying costing report document "'Evaluating the cost and intermediary cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A with inhibitors in South Africa.' NEMLC requested a cost-neutral price to be determined on the scenario deemed most likely to reflect current setting based on procurement data which favoured bypassing agents.

Update March 2024: NEMLC final recommendation was made by NEMLC on 14 March 2024

Key findings

- A review was conducted of the available clinical evidence pertaining to the use of emicizumab when used as prophylaxis in the management of haemophilia A patients with Factor VIII inhibitors.
- One small open-labelled, randomized controlled trial evaluating annualised bleeding rate and health-related quality of life was identified for inclusion in this review. Emicizumab prophylaxis was administered at a dose of 3.0 mg per kilogram of body weight weekly for 4 weeks, followed by 1.5 mg per kilogram weekly thereafter.
- The annualized bleeding rate was 2.9 events (95% CI = 1.7-5.0) in patients receiving emicizumab prophylaxis (group A, 35 participants) vs 23.3 events (95% CI = 12.3-43.9) among those assigned to no prophylaxis (group B, 18 participants). The observed difference of 87% in favour of emicizumab prophylaxis was significant ($p<0.001$) - moderate certainty of evidence.
- There was statistically significant mean difference of 13.2 points in favour of emicizumab prophylaxis; 95% CI [20.34 to 6.06 lower); $p = 0.0019$) in health-related quality of life across the "Total" domain scores – low certainty of evidence.
- Injection-site reactions was the most frequently reported adverse event (15%) associated with emicizumab use. Thrombotic microangiopathy (n=2) and thrombosis (n=2) were also reported in the primary analysis.
- A single placebo-controlled study in a small cohort of patients investigating the use of emicizumab as prophylaxis in the management of patients with haemophilia A and factor VIII inhibitors has demonstrated statistically significant reduction in annualized bleeding rate. The cost of this agent is such that a formal cost-effectiveness analysis is warranted before finalizing a decision on whether it can be included on the Tertiary/Quaternary Essential Medicines List.
- *Update November 2023: Costing analysis conducted – See accompanying report document.*
- *Update March 2024: Final recommendation.*

NATIONAL ESSENTIAL MEDICINES LIST COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

NEMLC recommended that emicizumab prophylaxis not be included on the Essential Medicines List (EML) for in the management of patients with Haemophilia A with Factor VIII inhibitors.

Rationale:
NEMLC acknowledged the potential benefits associated with the use of emicizumab however with the lack of long-term data, head-to-head comparisons with bypassing agents used prophylactically, small patient numbers involved in clinical trials; together with the price and affordability concerns, it would not be feasible at this stage.

March 2023: Evidence for efficacy and safety presented by TQ ERC. Cost-effectiveness analysis proposed by the Tertiary and Quaternary Hospital Level Expert Review Committee and agreed to by the NEMLC.

UPDATE July 2023: Scoping document for commissioning of cost-effectiveness analysis developed and approved by the NEMLC.

UPDATE November 2023: The cost-effectiveness analysis presented – see accompanying costing report document 'Evaluating the cost and intermediary cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A with inhibitors in South Africa.' Current price deemed unaffordable, request for cost-neutral price to be calculated for procurement-based scenario.

UPDATE March 2024: NEMLC final recommendation was made by NEMLC on 14 March 2024.

Level of Evidence: I (Randomized Controlled Trials)
Review indicator:

- Price (desired reference price set)
- Affordability
- Availability of higher quality evidence with larger effect size

(Refer to appendix 1 for the evidence to decision framework)

Summary of findings table

Emicizumab compared to no prophylaxis for hemophilia A with inhibitors

Patient or population: Patients with hemophilia A with inhibitors
Intervention: Emicizumab
Comparison: no prophylaxis

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no prophylaxis	**Risk with Emicizumab**				
Annualised Bleeding rate assessed with: Rate of treated bleeding events follow-up: 25 weeks	The mean annualised Bleeding rate was **23.3** events	MD **20.4 events fewer** (30.68 fewer to 10.12 fewer)	N/A	53 (1 RCT)	⨁⨁⨁◯ Moderate[a]	Emicizumab likely reduces annualised Bleeding rate.
Total QoL assessed with: Change from baseline scores based on Haemophilia Quality of Life Questionnaire for Adults (Haemo-A-QoL) Scale from: 0 to 100 follow-up: 25 weeks	The mean total QoL was **44.6** points	MD **13.2 points lower** (20.34 lower to 6.06 lower)	N/A	39 (1 RCT)	⨁⨁◯◯ Low[a,b]	Emicizumab may improve Total Quality of life

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded by 1 level due to imprecision: very small sample size and wide confidence intervals
b. Downgraded by 1 level due to risk of bias: the study was at high overall risk of bias due to high risk of attrition bias and in the measurement of the outcome

BACKGROUND

Haemophilia A is a rare hereditary bleeding disorder caused by a deficiency of coagulation factor VIII due to an X-linked recessive mutation. Haemophilia has a prevalence of 17.1 cases per 100 000 males for all severities of Haemophilia A and 6.0 cases per 100 000 males for severe Haemophilia A. In South Africa, there were reported to be 2 419 haemophilia patients in 2021 of which 2 021 patients were diagnosed with Haemophilia A[1].

Haemophilia A is diagnosed by confirming factor VIII deficiency and the clinical manifestation depends on the severity of the disease (severe, moderate or mild) based on the factor VIII level. The presence of factor VIII antibodies (inhibitors) is a major complication of haemophilia A and unfortunately render factor VIII replacement ineffective in approximately 30% of patients with haemophilia.[2]

The current standard of care in South Africa for severe haemophilia A patients with inhibitors is to treat bleeds as they occur with bypassing agents, such as activated factor VIIa (Novo7®) or Activated Prothrombin Complex Concentrate (FEIBA®). These agents are expensive and patients not receiving prophylaxis are at potential increased risk of morbidity associated with bleeds if not treated timeously, thus international guidelines recommend prophylaxis therapy to reduce the frequency of bleeds in patients with severe haemophilia A with and without inhibitors[2].

Emicizumab has been approved globally as a non-replacement therapy for people with Haemophilia A with and without inhibitors. It is a subcutaneously administered monoclonal bispecific factor IXa- and factor X-directed antibody that allows it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade. It is administered subcutaneously and can be dosed weekly, bi-weekly, or monthly. In South Africa, emicizumab is registered for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. There are no data on infants aged ≤1 year, and limited data in children aged 1-2 years. The recommended dose is 3mg/kg once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly thereafter (administered as a subcutaneous injection).[3]

This review aimed to assess the safety and efficacy of emicizumab compared to standard of care in the management of patients with severe haemophilia A with inhibitors.

RESEARCH QUESTION:

Should emicizumab prophylaxis be used in the management of haemophilia A in patient with inhibitors?

METHODS

Eligibility criteria for review

Population: Adults, adolescents and children with Haemophilia A with inhibitors

Intervention: Subcutaneous emicizumab prophylaxis

Comparators: Treatment of bleeds with on-demand bypassing agents

Outcomes: Annualised bleeding rate, target joint damage, adverse events, health related quality of life

Study designs: Randomized controlled trials and systematic reviews.

Search strategy:
The search strategy is represented in Appendix 2 and was approved by the Tertiary/Quaternary Expert Review Committee. We searched PubMed and the Cochrane Library on 24 October 2022 (updated February 2023).

Study selection
Screening of titles and abstracts was conducted manually by 1 reviewer. From the identified potentially eligible full-texts, one author screened the full-texts of identified documents for eligibility. Eligible studies were presented to the Tertiary and Quaternary Expert Review Committee for final selection.

Data extraction
Data extraction was undertaken by 1 author and peer reviewed by two other reviewers.

Risk of bias assessment
Risk of bias of the included study was assessed independently by two reviewers using Cochrane ROB 2.0 tool[4], which assesses the risk of bias across five domains.

Assessing certainty of the evidence
Two reviewers assessed the overall certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[5]. The certainty of the evidence started at high for the included RCT, and five factors were considered for downgrading the certainty (risk of bias, inconsistency, indirectness, imprecision, publication bias). For each factor, we provided a judgement with a rationale included as a footnote in the Summary of Findings (SoF) table. We prepared SoF tables for two key outcomes: annualized bleeding rate and Total quality of life for adults.

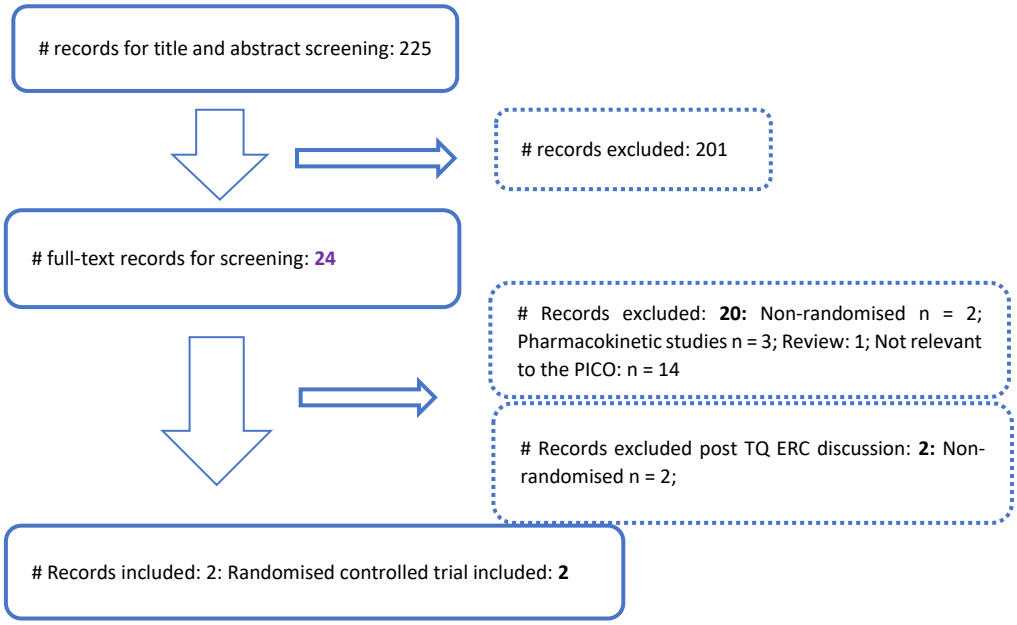
RESULTS

Two hundred and twenty-five documents were found during the search of which 201 documents excluded during screening. Twenty-four documents underwent full text review, and 20 documents were excluded. Four eligible documents (1 randomised controlled trial and two non-randomised trials were presented to the Tertiary/Quaternary Expert Review Committee for agreement on final inclusion. Two further documents were excluded at this stage as they reported on data from non-randomised trials (see Table 1). Thus two documents (emanating from one randomised controlled trial) were selected for final inclusion and underwent data extraction (See Appendix 3 - Table for Characteristics of included studies). The PRISMA diagram below provides a flow chart for study selection.

Table 1: Studies excluded during Tertiary/Quaternary Expert Review Committee Discussion (See Appendix 3 - Table 2 for more details)

Young et al[6]	A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors (HAVEN 2)	Blood 2019;134(24):2127-2138
Callagahan et al.[7]	Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies	Blood. 2021 Apr 22;137(16):2231-2242. doi: 10.1182/blood.2020009217.

Figure 1. PRISMA flow chart of study selection



One randomised-controlled trial (reported in two documents) was included.

Table 2: Description of included documents:

Author	Trial	Title	Journal ref
Oldenburg et al[8]	HAVEN 1	Emicizumab Prophylaxis in Hemophilia A with Inhibitors (HAVEN 1)	N Engl J Med 2017;377:809-18
Oldenburg et al[9]		The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study	Haemophilia. 2019 *25* (1), 33–44. DOI: 10.1111/hae.13618

Oldenburg and colleagues[9] conducted a randomised, open-label, phase III study to evaluate the safety and efficacy of prophylactic emicizumab in patients with haemophilia A of any severity and a history of Factor VIII inhibitors. 109 male patients were randomly assigned to emicizumab (group A = 35) or no prophylaxis (group B = 18); emicizumab through a non-interventional study (group C = 49) and emicizumab prophylaxis for those registered after study enrolment closure (group D = 7). The primary end point was the difference in the rate of treated bleeding events (bleeding rate) over a period ≥24 weeks in group A vs group B after 24 weeks of treatment.

Patients were assigned in a 2:1 ratio to receive subcutaneous emicizumab prophylaxis at a dose of 3.0 mg per kilogram of body weight weekly for 4 weeks, followed by 1.5 mg per kilogram weekly thereafter (group A), or to the control group (no emicizumab prophylaxis and, because the trial was open-label, no subcutaneous control injections; group B). Health related quality of life was collected during the trial and reported in a separate article[9].

Risk of bias of included studies

Risk of bias was assessed for two outcomes from one randomised controlled trial (See Figure 2 below). The outcome of annualised bleeds was evaluated to have some concerns and the quality-of-life outcome as high risk. See Appendix 4 for details of the assessment.

Figure 2. Summary of ROB assessment for two outcomes reported in the included study.

Effects of Intervention

COMPARISON: EMICIZUMAB VS NO PROPHYLAXIS

OUTCOME: BLEEDING EVENTS/RATE

Emicizumab likely reduces bleeding rate (MD -20.4, 95% CI -30.68 to -10.12, 1 trial, 53 participants, moderate certainty of evidence, Summary of Findings Table). The annualized bleeding rate (ABR) was 2.9 events (95% CI = 1.7-5.0) in patients receiving emicizumab prophylaxis (group A, 35 participants) vs 23.3 events (95% CI = 12.3-43.9) among those assigned to no prophylaxis (group B, 18 participants). The observed difference of 87% in favour of emicizumab prophylaxis was significant (p<0.001).

63% (22/35) of patients in group A experienced no bleeding events versus 6% (1/18) in group B.

OUTCOME: HEALTH RELATED QUALITY OF LIFE

Haemophilia Quality of Life Questionnaire for Adults (Haemo-A-QoL)

Emicizumab may improve total quality of life (MD -13.2, 95% CI -20.34 to -6.06, 1 trial, 39 participants, low certainty of evidence, Summary of Findings Table). Among participants previously treated with episodic BPAs, the difference in adjusted mean scores between the emicizumab prophylaxis group (Arm A) and the no prophylaxis group (Arm B) at week 25 was statistically significant in favour of emicizumab for both “Total” (Δ = 14.01; 95% CI: 5.56, 22.45; P = 0.0019) and “Physical Health” domain (Δ = 21.55; 95% CI: 7.89, 35.22; P = 0.0029) scores (Figure 3 and 4).

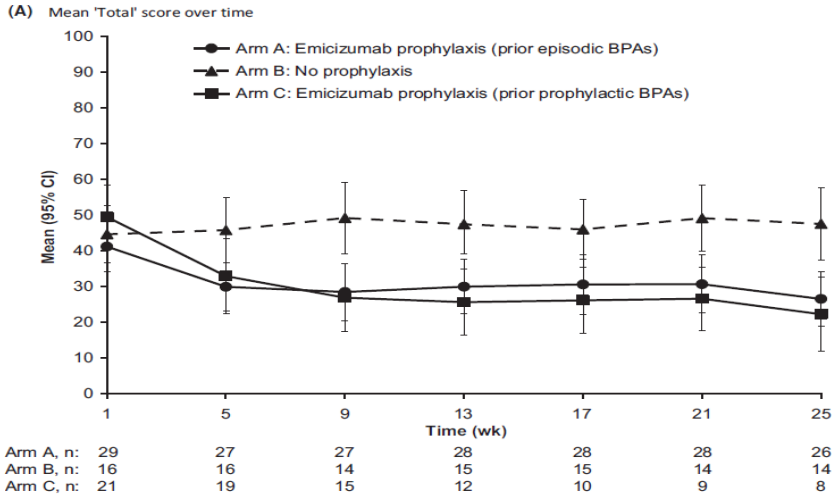


Figure 3: Mean 'Total' score for Quality of Life - Adults

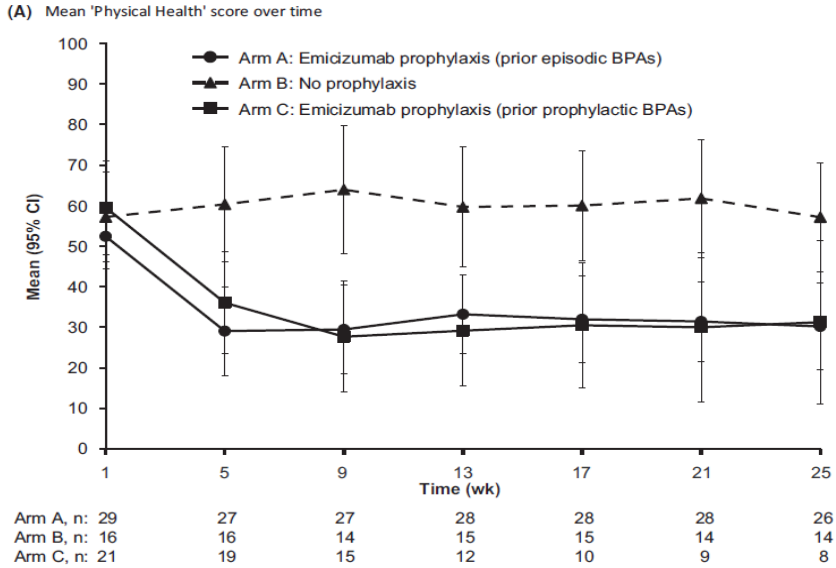


Figure 4: Mean 'Physical Health' score for Quality of Life - Adults

Haemophilia-specific Quality of Life assessment for children and adolescents Short Form (Haemo-QoL SF)
The results for Haemo-QoL SF are only presented for participants previously treated with prophylactic BPAs (Arm C) because too few adolescents completed this questionnaire in Arms A (n = 3) and B (n = 2) for meaningful analysis.

At baseline, mean (95% CI) Haemo-QoL SF "Total" score was 30.7 (24.3, 37.2). At week 25, Total Score had improved by 11.4 points (95% CI -16.6, -6.3).

The mean number of days hospitalized was 1.9 (95% CI 0.0, 5.1) with emicizumab prophylaxis (Arm A), 4.2 (95% CI 0.0, 8.9) with no prophylaxis (Arm B) and 0.7 (95% CI 0.0, 1.5) with emicizumab prophylaxis in participants previously treated with prophylactic BPAs (Arm C).

<u>OUTCOME: Adverse events</u>

In HAVEN 1[8], a total of 198 adverse events (AE) were reported in participants receiving emicizumab prophylaxis; the most frequent events being injection-site reactions (in 15% of participants). Additionally,

thrombotic microangiopathy (n=2) and thrombosis (n=2) were reported in the primary analysis, in patients who had received multiple infusions of activated prothrombin complex concentrate for breakthrough bleeding. No antidrug antibodies were detected.

Certainty of the evidence

The evidence for annualised bleeds was downgraded by 1 (moderate certainty of evidence) and the evidence for quality of life was downgraded by 2 (See Summary of Findings Table).

COST (Update – November 2023)

The cost of emicizumab was considered a significant barrier to access in South Africa thus the TQ ERC recommended a cost-effectiveness analysis be conducted. A comprehensive cost-effectiveness analysis was thus undertaken, refer to full report: *'Evaluating the cost and intermediary cost-effectiveness of emicizumab prophylaxis in patients with haemophilia A with inhibitors in South Africa.'*

The costing model evaluated different scenarios to help address some of the uncertainty around current management of patients. Each scenario had a different threshold for ABRs where emicizumab may be cost-saving. Three out of the four scenarios showed the emicizumab arm to be cost saving, with one favouring the standard of care arm. The scenario favouring the standard of care attempted to replicate the current cost of procurement of bypassing agents in the comparator arm – derived from procurement data.

In order for the scenario to be cost-neutral it was estimated that the price of emicizumab would need to decrease by 17% compared to the state sector price offer, under our assumptions made in this scenario.

Table 3: Cost-neutral price estimate for emicizumab

Emicizumab price per vial	State sector price offer	Cost-neutral price estimate
Emicizumab 30mg/1MI	R8,920	R7,423
Emicizumab 60mg/0.4MI	R17,840	R14,847
Emicizumab 105mg/0.7MI	R31,220	R25,982
Emicizumab 150mg/1MI	R44,601	R37,117

In a sensitivity analysis the emicizumab arm became cost-saving in scenario 4 (replication of procurement data) with an ABR of 16. However, across all scenarios the average per patient cost of those in the emicizumab arm had a relatively narrow range of R1.6-R2.5 million per year.

Refer to full document for details.

CONCLUSION

Notwithstanding the lack of long-term data, head-to-head comparisons with bypassing agents used prophylactically and the small patient numbers involved in clinical trials, emicizumab prophylaxis in patients with haemophilia A and factor VIII inhibitors offers an advantage over on-demand bypassing agents. Emicizumab reduced the annualized bleeding rate by 87% (emicizumab = 2.9 events, 95% CI 1.7 to 5.0) when compared with no prophylaxis (23.3 events (95% CI, 12.3 to 43.9; $p<0.001$).[8] Moreover, emicizumab positively influences health related quality of life when compared with placebo. It is subcutaneously administered and is considered more convenient than treatment with bypassing agents. Cost-effectiveness analysis proposed.

Update November 2023

Although the cost effectiveness analysis showed that in the majority of scenarios emicizumab was cost-effective, the scenario modelling current procurement of bypassing was shown to favour bypassing agents. Thus the cost-neutral price calculated based on procurement data should be used as a reference price guide.

NEMLC Recommendation March 2024:
With limitations around information of management of haemophilia A with inhibitors around the country, and current fiscal state of the country, NEMLC recommended that emicizumab prophylaxis not be considered for inclusion on the essential medicines list for this indication. This can be reconsidered as these factors change.

Reviewers:

Roger Wiseman (Liberty Health (Pty) Ltd); Estelle Verburgh (Division of Haematology Department of Medicine, Groote Schuur Hospital, University of Cape Town); Kim MacQuilkan (RTC); Solange Durao (SAMRC, Cochrane*); Jane Riddin (Essential Drugs Programme, National Department of Health).

Declaration of interests:

- RW is employed by Liberty Health (Pty) Ltd, a private health insurer operating in South Africa and across the broader African continent, and has nothing to declare with respect to emicizumab.
- EV is a clinical haematologist, running a haemophilia clinic at GSH, with no specific interests with respect to emicizumab to declare.
- KM, SD and JR have no interests to declare.

** SD Affiliation: South African Medical Research Council, Cochrane-South Africa. Funding: Partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.*

Appendix 1: Evidence to decision framework

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE OF BENEFIT</td><td>What is the certainty/quality of evidence?
High [ ] Moderate [ ] Low [X] Very low [ ]
High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td>There is some concern around the risk of bias for both the outcomes included in this review. The bleeding rate outcome s regarded as having "some concerns" while the quality of life outcome was regarded as having a "high risk" of bias. The bleeding rate outcome was downgraded by 1 for imprecision (moderate certainty of evidence) and the quality of life outcome was downgraded by 2 for risk of bias and imprecision (low certainty of evidence).</td></tr>
<tr><td>EVIDENCE OF BENEFIT</td><td>What is the size of the effect for beneficial outcomes?
Large [X] Moderate [ ] Small [ ] None [ ]</td><td>The annualized bleeding rate was 2.9 events (95% CI = 1.7-5.0) in patients receiving emicizumab prophylaxis (group A, 35 participants) vs 23.3 events (95% CI = 12.3-43.9) among those assigned to no prophylaxis (group B, 18 participants). The observed difference of 87% in favour of emicizumab prophylaxis was significantly significant (p<0.001).</td></tr>
<tr><td>QUALITY OF EVIDENCE OF HARM</td><td>What is the certainty/quality of evidence?
High [ ] Moderate [x] Low [ ] Very low [ ]
High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td></td></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?
Large [ ] Moderate [ ] Small [X] None [ ]</td><td>Injection-site reactions as the most frequently reported adverse event associated with emicizumab (in 15% of participants). Thrombotic microangiopathy (n=2) and thrombosis (n=2) were also reported in the primary analysis.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [X] Favours control [ ] Intervention = Control or Uncertain [ ]</td><td>ABR is reduced by 87% in patients receiving emicizumab prophylaxis, while the most reported adverse event albeit in a small number of patients, was injection site reactions.</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [ ] No [ ] Uncertain [X]</td><td>Emicizumab is expensive. A global perspective of haemophilia management and the costs thereof with needs to be considered to establish the affordability of this medicine.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Cost of medicines:
<table><tr><th>Medicine</th><th>Cost (SEP)</th><th>State Price</th></tr><tr><td>Hemlibra 105MG/0.7ML</td><td>R 57 173.69</td><td>R 31 220.27</td></tr><tr><td>Hemlibra 150MG/1ML</td><td>R 81 675.99</td><td>R 44 600.50</td></tr></table></td></tr>
</table>

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Hemlibra 60MG/0.4ML</td><td>R 32 670.68</td><td>R 17 840.04</td></tr>
<tr><td>Hemlibra 30MG/1ML</td><td>R 16 335.34</td><td>R 8 919.62</td></tr>
</table>
Dosage:
3.0 mg/kg of body weight weekly for 4 weeks, followed thereafter by maintenance dose of one of:
1.5mg/kg weekly,
3mg/kg every two weeks, or
6mg/kg every 4 weeks

Annual cost (for first year of treatment, based on State prices)

70 kg adult:
R 1 748 355.12*

*Costs are the same for all maintenance dose regimens

50kg patient
1.5mg weekly: R 1 462 965.68
3mg/kg two weekly: R 1 248 814.00
6mg/kg four weekly: R 1 248 814.00

20kg child
R 499 501.92*

*Costs are the same for all maintenance dose regimens

Update: See accompanying document for cost-effectiveness analysis report</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?

Minor [X] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td>Emicizumab is likely to be well accepted - cost has been the limiting factor to its wider acceptance.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [ ] Uncertain [X]</td><td>This intervention has the possibility to positively and negatively impact health inequity. There is an opportunity to improved access due to relative ease of administration, but the associated cost may have a negative impact in this regard.</td></tr>
</table>

Appendix 2: Search strategy

Database: Pubmed

Date of search: 01 February 2023

Search	Query	Results
#7	**Search:** (#4) NOT (#5) **Filters:** Clinical Trial, Meta-Analysis, Review, Systematic Review	24
#6	**Search:** (#4) NOT (#5)	225
#5	**Search:** review[pt]	3,106,475
#4	**Search:** ((#1) AND (#2)) AND (#3)	312
#3	**Search:** ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))	4,928,359
#2	**Search:** emicizumab	478
#1	**Search:** (hemophilia) AND (haemophilia)	33,131

Database: Cochrane Library

Date of search: 01 February 2023

Search strategy

Search	Query	Results
#1	(emicizumab) (Word variations have been searched)	**82**
#2	Haemophilia	**1875**
#3	#1 AND #2	**77**

None included: 1 Cochrane protocol, 1 review not related to the PICO, 75 trials

Appendix 3: Characteristics of studies

Table 1. Characteristics of included documents

Trial	Citation	Study design	Population (n)	Treatment	Main findings
HAVEN 1	Oldenburg et.al. 2017 HAVEN 1[8]	Phase 3, open-label, multicenter, randomized trial	n = 109 Male participants, 12 years and older with haemophilia A with inhibitors	Emicizumab prophylaxis versus no prophylaxis for 24 weeks.	The primary endpoint: difference in bleeding rates between those on emicizumab prophylaxis and those on no prophylaxis. • The annualized bleeding rate was 2.9 events (95% confidence interval [CI], 1.7 to 5.0) among participants who were randomly assigned to emicizumab prophylaxis (35 participants) versus 23.3 events (95% CI, 12.3 to 43.9) among those assigned to no prophylaxis (18 participants), representing a significant difference of 87% in favor of emicizumab prophylaxis (P<0.001). • 22 participants in emicizumab group (63%) had zero bleeding events, as compared with 1 participant (6%) in no prophylaxis group.
	Oldenburg et al. 2019 [9]	Multicentre, open-label, randomized, Phase 3 trial	n = 109 Male participants, 12 years and older with haemophilia A with inhibitors	Prior episodic treatment: Arm A = emicizumab prophylaxis (n = 35) Arm B = no prophylaxis; episodic bypassing agents only (n = 18) Prior Prophylactic treatment: Arm C = emicizumab prophylaxis (n = 49) Emicizumab prophylaxis administered at 3mg/kg weekly for 4 weeks then 1.5mg/kg weekly thereafter.	**Haemophilia Quality of Life Questionnaire for Adults (Haemo-A-QoL)** Among participants previously treated with episodic BPAs, the difference in adjusted mean scores between the emicizumab prophylaxis group (Arm A) and the no prophylaxis group (Arm B) at week 25 was statistically significant in favour of emicizumab for both "Total" (Δ = 14.01; 95% CI: 5.56, 22.45; P = 0.0019) and "Physical Health" domain (Δ = 21.55; 95% CI: 7.89, 35.22; P = 0.0029) scores. **Haemophilia-specific Quality of Life assessment for children and adolescents Short Form (Haemo-QoL SF)** The results for Haemo-QoL SF is only presented for participants previously treated with prophylactic BPAs (Arm C) because too few adolescents completed this questionnaire in Arms A (n = 3) and B (n = 2) for meaningful analysis. At baseline, mean (95% CI) Haemo-QoL SF "Total" score was 30.7 (24.3, 37.2). At week 25, Total Score had improved by 11.4 points (95% CI -16.6, -6.3) The mean number of days hospitalized was 1.9 (95% CI 0.0, 5.1) with emicizumab prophylaxis (Arm A), 4.2 (95% CI 0.0, 8.9) with no prophylaxis (Arm B) and 0.7 (95% CI 0.0, 1.5) with emicizumab prophylaxis in participants previously treated with prophylactic BPAs (Arm C).

Table 2: Details of documents excluded after TQ ERC discussion

Young et.al. 2019 HAVEN 2 [6]	Ongoing phase 3, multicenter, nonrandomized, open label trial	n = 85 participants < 12 years, with haemphilia A and FVIII inhibitors (receiving episodic/prophylactic bypassing agents)	Emicizumab 1.5mg/kg weekly Versus Emicizumab 3 mg/kg every 2 weeks. Versus Emicizumab 6 mg/kg every 4 weeks	Annualized rate of treated bleeding: • Emicizumab 1.5mg/kg (n = 65), 0.3 (95% confidence interval [CI], 0.17 to 0.50), and 77% had no treated bleeding events. Intraindividual comparison of 15 participants who previously took bypassing agent prophylaxis showed that emicizumab prophylaxis reduced the ABR by 99% (95% CI, 97.4 to 99.4). • Emicizumab 3mg/kg (n = 10), 0.2 (95% CI, 0.03 to 1.72). • Emicizumab 6mg/kg (n = 10), 2.2 (95% CI, 0.69 to 6.81).
Pipe et.al. 2019 HAVEN 4[10]	Phase 3, multicenter, open-label, two-stage study	n = 7 (initial run-in) n = 41 (expansion cohort) Participants 12 years or older with severe congenital haemophilia A or haemophilia A with FVIII inhibitors undergoing treatment with either FVIII concentrates or bypassing agents.	Initial run-in: emicizumab 6mg/kg every 4 weeks for 24 weeks Expansion cohort: Four loading doses of 3mg/kg once weekly	Expansion cohort: • Annualised rate of treated bleeds was 2.4 (95% CI 1·4–4.3). 23 (56.1%; 95% CI 39.7–71.5) of 41 reported no treated bleeds and 37 (90%; 76.9–97.3) reported zero to three treated bleeds. The annualised bleed rate was 4.5 (95% CI 3.1–6.6) for all bleeds, 0.6 (0.3–1.5), for treated spontaneous bleeds, 1.7 (0.8–3.7) for treated joint bleeds, and 1.0 (0.3–3.3) for treated target joint bleeds.

Table 3: Other excluded studies

Authors	Title	Citation	Reason for exclusion
Callaghan et. al.[7]	Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies.	Blood. 2021 Apr 22;137(16):2231-2242. doi: 10.1182/blood.2020009217	Not relevant to the PICO
Mahlangu et. al.[11]	Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors.	N Engl J Med. 2018 Aug 30;379(9):811-822. doi: 10.1056/NEJMoa1803550.	Not relevant to the PICO
Schmitt et. al. [12]	Pharmacokinetics and Pharmacodynamics of emicizumab in persons with Hemophilia A with Factor VIII Inhibitors: HAVEN 1 Study.	Thromb Haemost. 2021 Mar;121(3):351-360. doi: 10.1055/s-0040-1717114.	Pharmacokinetic study
Donners et. al [13]	Pharmacokinetics and Associated Efficacy of Emicizumab in Humans: A Systematic Review.	Clin Pharmacokinet. 2021 Nov;60(11):1395-1406. doi: 10.1007/s40262-021-01042-w.	Pharmacokinetic study
Shanmukhaiah et. al [14]	Efficacy of emicizumab in von Willebrand disease (VWD) patients with and without alloantibodies to von Willebrand factor (VWF): Report of two cases and review of literature.	Haemophilia. 2022 Mar;28(2):286-291. doi: 10.1111/hae.14491.	Not relevant to the PICO
Barg et. al [15]	Emicizumab prophylaxis among infants and toddlers with severe hemophilia A and inhibitors-a single-center cohort.	Pediatr Blood Cancer. 2019 Nov;66(11):e27886. doi: 10.1002/pbc.27886.	Non-randomised
Franchini et. al. [16]	Emicizumab for the treatment of haemophilia A: a narrative review.	Blood Transfus. 2019 May;17(3):223-228. doi: 10.2450/2019.0026-19.	Review

Ogiwara et. al. [17]	Assessment of global coagulation function under treatment with emicizumab concomitantly with bypassing agents in haemophilia A with inhibitor (UNEBI Study): multicentre open-label non-randomised clinical trial.	BMJ Open. 2022 Feb 17;12(2):e056922. doi: 10.1136/bmjopen-2021-056922.	Non-randomised
Kotani et. al. [18]	Relative and Absolute Bioavailability Study of Emicizumab to Bridge Drug Products and Subcutaneous Injection Sites in Healthy Volunteers.	Clin Pharmacol Drug Dev. 2019 Aug;8(6):702-712. doi: 10.1002/cpdd.617.	Pharmacokinetics study
Matsushita et. al.[19]	AKATSUKI study: a prospective, multicentre, phase IV study evaluating the safety of emicizumab under and immediately after immune tolerance induction therapy in persons with congenital haemophilia A with factor VIII inhibitors.	BMJ Open. 2022 Mar 14;12(3):e057018. doi: 10.1136/bmjopen-2021-057018.	Not relevant to the PICO
Shima et. al. [20]	Long-term safety and efficacy of emicizumab for up to 5.8 years and patients' perceptions of symptoms and daily life: A phase 1/2 study in patients with severe haemophilia A.	Haemophilia. 2021 Jan;27(1):81-89. doi: 10.1111/hae.14205.	Not relevant to the PICO
Wagle et. al. [21]	Intraindividual Comparisons to Determine Comparative Effectiveness: Their Relevance for G-BA's Health Technology Assessments.	Value Health. 2021 May;24(5):744-752. doi: 10.1016/j.jval.2020.11.016.	Not relevant to the PICO
Chapman et. al. [22]	Does Cost-Effectiveness Analysis Overvalue Potential Cures? Exploring Alternative Methods for Applying a "Shared Savings" Approach to Cost Offsets.	Value Health. 2021 Jun;24(6):839-845. doi: 10.1016/j.jval.2021.02.008.	Not relevant to the PICO
Reyes et. al. [23]	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 Dec;35(12):2079-2087. doi: 10.1080/03007995.2019.1649378.	Not relevant to the PICO
Shima et. al. [24]	A multicentre, open-label study of emicizumab given every 2 or 4 weeks in children with severe haemophilia A without inhibitors.	Haemophilia. 2019 Nov;25(6):979-987. doi: 10.1111/hae.13848.	Not relevant to the PICO
Uchida et. al. [25]	A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects.	Blood. 2016 Mar 31;127(13):1633-41. doi: 10.1182/blood-2015-06-650226.	Not relevant to the PICO
Shima et. al. [26]	Factor VIII-Mimetic Function of Humanized Bispecific Antibody in Hemophilia A.	N Engl J Med. 2016 May 26;374(21):2044-53. doi: 10.1056/NEJMoa1511769.	Not relevant to the PICO
Yoneyama et. al.[27]	A Pharmacometric Approach to Substitute for a Conventional Dose-Finding Study in Rare Diseases: Example of Phase III Dose Selection for Emicizumab in Hemophilia A.	Clin Pharmacokinet. 2018 Sep;57(9):1123-1134. doi: 10.1007/s40262-017-0616-3.	Not relevant to the PICO
von Mackensen et. al [28]	Determining meaningful health-related quality-of-life improvement in persons with haemophilia A using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)	Haemophilia. 2020 Nov;26(6):1019-1030. doi: 10.1111/hae.14184.	Not relevant to the PICO
Schmitt et. al. [29]	Emicizumab dose up-titration in case of suboptimal bleeding control in people with haemophilia A.	Haemophilia. 2023 Jan;29(1):90-99. doi: 10.1111/hae.14679.	Not relevant to the PICO

Appendix 4: Risk of Bias 2 Assessment

Outcome: Bleeding Rate

Unique ID	Oldenburg 2017_bleed rate	**Study ID**	Oldenburg 2017	**Assessor**	SD
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Imicizumab	**Comparator**	No prophylaxis	**Source**	Journal article(s); Trial protocol
Outcome	Bleeding rate	**Results**	RR 0.13 P<0.001	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	A central randomization procedure will be used for all patients that fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the number of bleeds in the last 24 weeks (< 9 or ≥ 9).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	There is some minor imbalance at baseline, compatible with chance.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	The trial was open-label
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	In protocol "Analyses will follow the principle of intention-to-treat (i.e., based on randomized population)."
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Events were objective so less likely to be influenced by lack of blinding
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Yes, data
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Outcome: Quality of Life

Unique ID	Oldenburg 2017_QoL	**Study ID**	Oldenburg 2017	**Assessor**	SD
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Imicizumab	**Comparator**	No prophylaxis	**Source**	Journal article(s); Trial protocol
Outcome	Total quality of life	**Results**	MD 14.0 points (95% CI 5.6 to 22.4)	**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Central randomisation procedure will be used for all patients that fulfill the entry criteria at screening
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Minor imbalance at baseline, compatible with chance
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Open label trial
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis done
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Only participants with data at baseline and 25 weeks were analysed. 29/35 (83%) in Imicizumab group and 14/18 (77.8%) in no
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	No analyses done to demonstrate this
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	Missingness could be related to the outcome, no reasons for LTFU reported
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PY	Open label trial and outcome was self-reported
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

REFERENCES

1. World Federation of Hemophilia. Report on the Annual Global Survey 2021 Montreal, Quebec: World Federation of Hemophilia; 2022 [1 - 98]. Available from: https://wfh.org/research-and-data-collection/annual-global-survey/.

2. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26:1 - 158.

3. Hemlibra® (emicizumab) [package insert]. 2014. Gauteng, Republic of South Africa: Roche Products (Pty) Ltd.

4. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj. 2019;366.

5. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011.

6. Young G, Liesner R, Chang T, Sidonio R, Oldenburg J, Jiménez-Yuste V, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019;134(24):2127-38.

7. Callaghan MU, Negrier C, Paz-Priel I, Chang T, Chebon S, Lehle M, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 2021;137(16):2231-42.

8. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. 2017;377(9):809-18.

9. Oldenburg J, Mahlangu JN, Bujan W, Trask P, Callaghan MU, Young G, et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study. Haemophilia. 2019;25(1):33-44.

10. Pipe SW, Shima M, Lehle M, Shapiro A, Chebon S, Fukutake K, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. 2019;6(6):e295-e305.

11. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. 2018;379(9):811-22.

12. Schmitt C, Adamkewicz JI, Xu J, Petry C, Catalani O, Young G, et al. Pharmacokinetics and Pharmacodynamics of Emicizumab in Persons with Hemophilia A with Factor VIII Inhibitors: HAVEN 1 Study. Thromb Haemost. 2021;121(3):351-60.

13. Donners A, Rademaker CMA, Bevers LAH, Huitema ADR, Schutgens REG, Egberts TCG, et al. Pharmacokinetics and Associated Efficacy of Emicizumab in Humans: A Systematic Review. Clin Pharmacokinet. 2021;60(11):1395-406.

14. Shanmukhaiah C, Jijina F, Kannan S, Pai NG, Kulkarni B, Khuba SV, et al. Efficacy of emicizumab in von Willebrand disease (VWD) patients with and without alloantibodies to von Willebrand factor (VWF): Report of two cases and review of literature. Haemophilia. 2022;28(2):286-91.

15. Barg AA, Avishai E, Budnik I, Levy-Mendelovich S, Barazani TB, Kenet G, et al. Emicizumab prophylaxis among infants and toddlers with severe hemophilia A and inhibitors-a single-center cohort. Pediatr Blood Cancer. 2019;66(11):e27886.

16. Franchini M, Marano G, Pati I, Candura F, Profili S, Veropalumbo E, et al. Emicizumab for the treatment of haemophilia A: a narrative review. Blood Transfus. 2019;17(3):223-8.

17. Ogiwara K, Taki M, Suzuki T, Takedani H, Matsushita T, Amano K, et al. Assessment of global coagulation function under treatment with emicizumab concomitantly with bypassing agents in haemophilia A with inhibitor (UNEBI Study): multicentre open-label non-randomised clinical trial. BMJ Open. 2022;12(2):e056922.

18. Kotani N, Yoneyama K, Kawakami N, Shimuta T, Fukase H, Kawanishi T. Relative and Absolute Bioavailability Study of Emicizumab to Bridge Drug Products and Subcutaneous Injection Sites in Healthy Volunteers. Clin Pharmacol Drug Dev. 2019;8(6):702-12.

19. Matsushita T, Suzuki N, Nagao A, Nagae C, Yamaguchi-Suita H, Kyogoku Y, et al. AKATSUKI study: a prospective, multicentre, phase IV study evaluating the safety of emicizumab under and immediately after immune tolerance induction therapy in persons with congenital haemophilia A with factor VIII inhibitors. BMJ Open. 2022;12(3):e057018.

20. Shima M, Nagao A, Taki M, Matsushita T, Oshida K, Amano K, et al. Long-term safety and efficacy of emicizumab for up to 5.8 years and patients' perceptions of symptoms and daily life: A phase 1/2 study in patients with severe haemophilia A. Haemophilia. 2021;27(1):81-9.

21. Wagle JA, Flacke JP, Knoerzer D, Ruof J, Merkesdal S. Intraindividual Comparisons to Determine Comparative Effectiveness: Their Relevance for G-BA's Health Technology Assessments. Value Health. 2021;24(5):744-52.

22. Chapman RH, Kumar VM, Whittington MD, Pearson SD. Does Cost-Effectiveness Analysis Overvalue Potential Cures? Exploring Alternative Methods for Applying a "Shared Savings" Approach to Cost Offsets. Value Health. 2021;24(6):839-45.

23. Reyes A, Révil C, Niggli M, Chebon S, Schlagmüller S, Flacke J-P, 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. Current Medical Research and Opinion. 2019;35(12):2079-87.

24. Shima M, Nogami K, Nagami S, Yoshida S, Yoneyama K, Ishiguro A, 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):979-87.

25. Uchida N, Sambe T, Yoneyama K, Fukazawa N, Kawanishi T, Kobayashi S, et al. A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. Blood. 2016;127(13):1633-41.

26. Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, et al. Factor VIII-Mimetic Function of Humanized Bispecific Antibody in Hemophilia A. N Engl J Med. 2016;374(21):2044-53.

27. Yoneyama K, Schmitt C, Kotani N, Levy GG, Kasai R, Iida S, et al. A Pharmacometric Approach to Substitute for a Conventional Dose-Finding Study in Rare Diseases: Example of Phase III Dose Selection for Emicizumab in Hemophilia A. Clin Pharmacokinet. 2018;57(9):1123-34.

28. von Mackensen S, Catalani O, Asikanius E, Paz-Priel I, Lehle M, Trask P. Determining meaningful health-related quality-of-life improvement in persons with haemophilia A using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL). Haemophilia. 2020;26(6):1019-30.

29. Schmitt C, Mancuso ME, Chang T, Podolak-Dawidziak M, Petry C, Sidonio R, Jr., et al. Emicizumab dose up-titration in case of suboptimal bleeding control in people with haemophilia A. Haemophilia. 2023;29(1):90-9.