NHS England Evidence Review:

Emicizumab for prophylaxis of bleeding episodes in people with moderate haemophilia A without factor VIII inhibitors

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety, and cost-effectiveness of emicizumab prophylaxis compared with standard care in people with moderate haemophilia A without coagulation factor VIII (FVIII) inhibitors.

People with haemophilia A have a deficiency of FVIII which causes increased bleeding. Emicizumab is a bispecific monoclonal antibody which mimics the action of FVIII by bridging factor X and activated factor IX, enabling the activation of FX by FIXa, restoring the coagulability of blood.

Emicizumab is licensed in all age groups for routine prophylaxis of bleeding episodes in people with haemophilia A with FVIII inhibitors, severe haemophilia A without FVIII inhibitors and moderate haemophilia A without FVIII inhibitors and a severe bleeding phenotype. So, the population included in the review scope is within the licensed indication.

There is no cure for haemophilia A and lifelong prophylaxis treatment is required with the aim of prevention of bleeding episodes or a reduction in frequency. Prophylaxis is indicated in people with severe haemophilia A, or mild-moderate haemophilia A with a severe bleeding phenotype. A severe bleeding phenotype is identified when there are spontaneous joint bleeds, 3 to 4 bleeds per year that require treatment, joint damage due to recurrent joint bleeds, or when people are currently established on prophylaxis for more than 6 months. Standard of care prophylaxis is regular replacement of the missing factor VIII every 2 to 3 days.

NHS England currently has two commissioning policies for emicizumab. It is currently commissioned as prophylaxis in people with congenital haemophilia A with FVIII inhibitors, and in people with severe congenital haemophilia A without FVIII inhibitors. There is no NICE guidance on emicizumab for prophylaxis of bleeding episodes in people with congenital haemophilia A.

The review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with emicizumab more than others.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety, and cost-effectiveness of emicizumab prophylaxis compared with standard care in people with moderate haemophilia A without coagulation factor VIII (FVIII) inhibitors.

The searches for evidence published since January 2013 were conducted on 10 October 2023 and identified 660 references. The titles and abstracts were screened, and 27 full text papers were obtained and assessed for relevance.

One open-label, single-arm study is included in the evidence review (Négrier et al. 2023) including 72 people with moderate (n=51) or mild haemophilia A (n=21) without inhibitors. At baseline 37/72 (51%) people with mild or moderate haemophilia A without inhibitors were receiving FVIII prophylaxis. In the moderate haemophilia A group, it was 25/51 (49%). The median length of follow up on emicizumab treatment in the study was 55.6 weeks (interquartile range (IQR) 52.3 to 61.6 weeks). Négrier et al. 2023, was a multi-centre study conducted at 22 centres in Europe, North America, and South Africa, including 3 centres in the UK which recruited 12 participants. No studies directly compared emicizumab to a control group in people with moderate haemophilia A without inhibitors.

In terms of clinical effectiveness:

Critical to decision making

- **Rate of treated bleeding events.** One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence for the critical outcome of rate of treated bleeding events. This study showed that in 72 people with mild or moderate haemophilia A without inhibitors, the model-based annualised bleed rate (ABR) for treated bleeds was 0.9 (95% confidence interval (CI) 0.55 to 1.52) after a median follow up of 55.6 weeks on emicizumab treatment. In the 51 people with moderate haemophilia A without inhibitors, the model-based ABR for treated bleeds was 0.9 (95% CI 0.50 to 1.78) after a median follow up of 55.6 weeks on emicizumab treatment. Model-based ABR accounts for different follow up times. Baseline ABR for treated bleeds was not provided.
- **Rate of all bleeding events.** One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence for the critical outcome of rate of all bleeding events. This study showed that in 72 people with mild or moderate haemophilia A without inhibitors, the model-based ABR for all bleeds was 2.3 (95% CI 1.67 to 3.12) after a median follow up of 55.6 weeks on emicizumab treatment, compared with 10.1 (95% CI 6.93 to 14.76) over the 24 weeks before study entry. In the 51 people with moderate haemophilia A without inhibitors, the model-based ABR for all bleeds was 2.2 (95% CI 1.57 to 3.20) after a median follow up of 55.6 weeks on emicizumab treatment, compared with 6.0 (95% CI 4.33 to 8.22) over the 24 weeks before study entry.
- **Joint health.** One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence for the critical outcome of joint health. This study showed that in people with mild or moderate haemophilia A without inhibitors, who had target joints at baseline and were in the study for at least 52 weeks, 20/21 (95%) had resolved joints. Resolved joints were defined in the study as a report of fewer than three bleeds over a 52-week period. In people with mild or moderate haemophilia A without inhibitors on emicizumab treatment, the mean total Haemophilia Joint Health Score (HJHS) was 6.48 (standard deviation [SD] 8.96) at week 49 in 56 participants compared with 7.20 (SD 10.37) in 65 participants at baseline. The maximum total score of the HJHS is 124 and

higher scores indicate worse joint health. In 52 study participants there was a mean improvement of −1.25 (SD 3.95) in the total HJHS at week 49 compared with baseline. Data for people with moderate haemophilia A were not provided separately for joint health outcomes.

Important to decision making

- **Health related quality of life.** One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence for the important outcome of health related quality of life. This study reported that in children, young people and adults aged 8 years or older with mild or moderate haemophilia A without inhibitors on emicizumab (n=60), the Comprehensive Assessment Tool of Challenges in Haemophilia (CATCH) mean scores in the treatment burden domain showed a trend to improvement. However, the results were only presented graphically (up-to week 61), and interpretation is difficult. Other domains were reported to be stable, with baseline values maintained until week 49. Specific values for these outcomes were not reported. Data for people with moderate haemophilia A were not provided separately for health related quality of life outcomes.
- **Patient treatment preference.** One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence for the important outcome of patient treatment preference. This study showed that in young people and adults aged 12 years or older with mild or moderate haemophilia A without inhibitors responding to the EmiPref questionnaire at week 17, 50/52 (96%) preferred emicizumab to their previous treatment. In caregivers responding to the EmiPref questionnaire at week 17, 24/28 (86%) preferred emicizumab to their child's previous treatment. Data for people with moderate haemophilia A were not provided separately for patient treatment preference outcomes.
- **Rate of joint bleeding events.** One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence for the important outcome of rate of joint bleeding events. This study showed that in 72 people with mild or moderate haemophilia A without inhibitors, the model-based ABR for treated joint bleeds was 0.2 (95% CI 0.09 to 0.57) after a median follow up of 55.6 weeks on emicizumab treatment. In 24 people with mild or moderate haemophilia A without inhibitors and target joints at baseline, the model-based ABR for treated target joint bleeds was 0.1 (95% CI 0.03 to 0.40) after a median follow up of 55.6 weeks on emicizumab treatment. Baseline ABR for treated joint and treated target joint bleeds was not provided. Data for people with moderate haemophilia A were not provided separately for joint bleeding event outcomes.
- **Activities of daily living.** One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence for the important outcome of activities of daily living. This study showed that in children, young people and adults aged 5 years or older with mild or moderate haemophilia A without inhibitors (n= not reported), duration of time spent in moderate-to-vigorous activity and mean daily step count remained stable compared to baseline, after 49 weeks of emicizumab treatment. Specific values for these outcomes were not reported. The results were presented graphically. Data for people with moderate haemophilia A were not provided separately for activities of daily living outcomes.

In terms of safety:

- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 60/72 (83%) people with mild or moderate haemophilia A without inhibitors had an adverse event on emicizumab treatment over a median follow up of

55.6 weeks. In people with moderate haemophilia A without inhibitors, 42/51 (82%) had an adverse event.

- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 15/72 (21%) people with mild or moderate haemophilia A without inhibitors had an adverse event considered related to emicizumab treatment over a median follow up of 55.6 weeks. Most treatment-related adverse events were local injection-site reactions.
- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 8/72 (11%) people with mild or moderate haemophilia A without inhibitors had a serious adverse event on emicizumab treatment over a median follow up of 55.6 weeks. None were considered to be emicizumab-related. In people with moderate haemophilia A without inhibitors, 6/51 (12%) had a serious adverse event.
- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 4/72 (6%) people with mild or moderate haemophilia A without inhibitors had a grade 3 or above adverse event on emicizumab treatment over a median follow up of 55.6 weeks.
- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 0/72 people with mild or moderate haemophilia A without inhibitors on emicizumab treatment had an adverse event which led to treatment withdrawal, modification, or interruption over a median follow up of 55.6 weeks.
- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 0/72 people with mild or moderate haemophilia A without inhibitors on emicizumab treatment had a thrombotic microangiopathy event over a median follow up of 55.6 weeks.
- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 1/72 (1%) people with mild or moderate haemophilia A without inhibitors had a thrombotic event (grade 1 thrombosed haemorrhoids) on emicizumab treatment over a median follow up of 55.6 weeks (not considered to be emicizumab-related).
- One open-label single-arm study (Négrier et al. 2023) provided very low certainty evidence that 2/72 (3%) people with mild or moderate haemophilia A without inhibitors developed treatment-induced anti-drug antibodies on emicizumab treatment over a median follow up of 55.6 weeks.

In terms of cost-effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- One open-label, single-arm study (Négrier et al. 2023) provided non-comparative evidence for several subgroups for the model-based ABR for treated bleeds and all bleeds over a median follow up of 55.6 weeks. Subgroup results were reported based on whether there had been prophylactic or episodic treatment at baseline, whether there were target joints at baseline, maintenance dose regimen, sex, and age. Baseline model-based ABRs were not reported for any of the subgroups for treated bleeds and most of the subgroups for all bleeds. The subgroups were also small and statistical analyses for comparisons between subgroups were not reported. Conclusions cannot be drawn on whether there are any subgroups of patients that may benefit from emicizumab prophylaxis more than the wider population of interest based on this evidence.

In terms of regimen and duration of emicizumab used in the study:

- One open-label, single-arm study (Négrier et al. 2023) used an initial loading dose of emicizumab subcutaneous injection 3 mg/kg once a week for 4 weeks. This was followed by a maintenance dose of either 1.5 mg/kg once a week, 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. Median follow-up on treatment was 55.6 weeks (IQR 52.3 to 61.6 weeks).

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

This evidence review includes one open-label single-arm study (Négrier et al. 2023). The study has significant limitations, and all outcomes were considered to have very low certainty using modified GRADE. It is non-randomised and open-label with no blinding of investigators or participants. There is also no control or comparator group. Négrier et al. 2023 included a mixed population of people with mild or moderate haemophilia A without inhibitors but most (71%) of the population had moderate haemophilia A. Data were mostly reported for the mixed population, with few outcomes in people with moderate haemophilia A reported separately. It should be noted that emicizumab is not licensed in the UK for treating people with mild haemophilia A without inhibitors (summary of product characteristics, SPC).

The results from this study should not be considered representative of all people with moderate or mild haemophilia A without inhibitors as study participants were selected based on investigator assessment that prophylaxis treatment was warranted. The reasons given for warranting prophylaxis included a history of frequent bleeding, frequent joint bleeding and severe bleeding. How this correlates to prophylaxis initiation in UK practice is unclear. At baseline 51% of the study population were on prophylactic FVIII treatment. In the moderate haemophilia A population, 49% were on prophylactic FVIII treatment at baseline. Efficacy and safety results were not presented separately for people with moderate haemophilia A who were having prophylactic treatment at baseline.

Négrier et al. 2023 was a multi-centre study conducted in Europe, North America and South Africa, it only included 12/72 participants recruited from the UK. The majority of the people in the study were male, however this reflects the increased prevalence of the condition in males.

The study provided evidence for all the critical and important outcomes. However, for several of the outcomes such as treated bleeds or joint bleeds, the baseline bleeding rates were not reported. So, it is difficult to assess the effect of emicizumab treatment on these outcomes. In addition, where baseline values were reported such as for the outcome of all bleeds, statistical methods did not examine changes from before to after emicizumab treatment and p values for the pre-to-post changes were not provided. Also, bleed data for the 24 weeks before the study were collected retrospectively. This is a possible source of inaccuracy as participants may have under or overreported their bleeds. Therefore, comparisons of bleed rates on emicizumab prophylaxis to baseline bleed rates may be subject to bias due to the data collection method.

Evidence on safety outcomes was reported in the study. However, the study may not have been large enough or long enough to detect uncommon or rare safety concerns.

Conclusion

One study provided evidence on the clinical effectiveness and safety of emicizumab prophylaxis in people with moderate haemophilia A without inhibitors. The study (Négrier et al. 2023) was an open-label single-arm study and it provided very low certainty evidence on the critical outcomes of rate of treated bleeding events, rate of all bleeding events and joint health; and the important outcomes of health related quality of life, patient treatment preference, rate of joint bleeding events, activities of daily living and safety. Most of the outcomes were reported for a mixed population of mild or moderate haemophilia A (29% and 71% of the population respectively). For the clinical effectiveness outcomes, only rate of treated bleeds and all bleeds were provided separately for the moderate haemophilia A population.

In Négrier et al. 2023, model-based ABRs for treated bleeds, treated joint bleeds and treated target joint bleeds were reported after a median follow-up of 55.6 weeks on emicizumab treatment in people with mild or moderate haemophilia A without inhibitors (n=72). Model-based ABR for treated bleeds was also reported separately for those with moderate haemophilia A (n=51). However, it's difficult to assess the effect of emicizumab treatment on these outcomes as no baseline values were reported.

The model-based ABR of all bleeding events reduced from 10.1 to 2.3 in people with mild or moderate haemophilia A without inhibitors after a median follow-up of 55.6 weeks on emicizumab treatment. In people with moderate haemophilia A, it reduced from 6.0 to 2.2. However, no statistical analyses were provided for before and after treatment comparisons and pre-study data collection methods for bleeds may have introduced bias.

Joint health was assessed using target joint resolution and HJHS. In participants who had target joints at baseline and were in the study for at least 52 weeks, 20/21 (95%) had resolved joints. There was also a mean improvement in total HJHS at week 49. The effect size of this improvement in joint health is very small and the clinical significance is unclear. However, adult participants may have established irreversible joint damage which may limit any improvements in HJHS. Additionally, the study may not have been long enough to allow for significant changes in HJHS to be seen.

Emicizumab showed a trend to improvement from baseline in the treatment burden domain of the CATCH health related quality of life questionnaire; all other domains remained stable. Duration of time spent on moderate or vigorous activity or mean daily step count were also reported to be stable from baseline to week 49.

The majority of young people and adults aged 12 years or older in the study preferred emicizumab to their previous treatment when questioned on this at week 17. It was also preferred by the majority of caregivers compared with their child's previous treatment.

The most common adverse events reported in 15% to 17% of participants were headache, injection-site reaction, and arthralgia, which reflects the adverse effects profile in the SPC. Adverse events considered to be related to emicizumab treatment were reported in 21% of participants, most of which were local injection-site reactions. There were no adverse events which led to treatment withdrawal, modification, or treatment interruption. Treatment-induced anti-drug antibodies were detected in 2 participants, with no clinical consequence of bleeds, injection-site reactions, hypersensitivity or anaphylactic reactions. There were no thrombotic microangiopathy events and 1 participant had a thrombotic event (grade 1 thrombosed haemorrhoids, considered unrelated to treatment). Very little safety data was provided separately for people with moderate haemophilia A.

The initial loading and maintenance dosages of emicizumab used in Négrier et al. 2023 were in-line with those in the SPC. People in the study were able to choose their maintenance dosage regimen, 25/72 (35%) chose 1.5 mg/kg once a week, 39/72 (54%) chose 3 mg/kg every 2 weeks and 8/72 (11%) chose 6 mg/kg every 4 weeks.

No evidence was identified on the cost-effectiveness of emicizumab prophylaxis.

The findings of this review are important because they suggest that emicizumab prophylaxis may reduce the annualised bleed rate for all bleeding events, resolve target joints, prevent further deterioration of joint health and be preferred by people compared with their previous treatments. However, interpretation of the data is limited by the lack of a control group, bias in the study due to its open-label design and data collection methods, the lack of statistical analysis from before to after emicizumab treatment, and the fact that baseline data was not provided for all outcomes.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people with moderate haemophilia A without inhibitors, what is the clinical effectiveness of emicizumab prophylaxis compared with current standard care?
2. In people with moderate haemophilia A without inhibitors, what is the safety of emicizumab prophylaxis compared with current standard care?
3. In people with moderate haemophilia A without inhibitors, what is the cost-effectiveness of emicizumab prophylaxis compared with current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from emicizumab prophylaxis more than the wider population of interest?
5. From the evidence selected, what doses, frequency, and route of administration of emicizumab prophylaxis were used and what was the duration of treatment?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 10 October 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included study and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included study

One study was identified for inclusion (Négrier et al. 2023), this was a multi-centre open-label, single-arm study with no comparator. Table 1 provides a summary of the included study and full details are given in Appendix E.

Table 1: Summary of included study

Study	Population	Intervention and comparison	Outcomes reported
Négrier et al. (2023) Multi-centre open-label, single-arm study. 22 centres in Europe, North America and South Africa (including 3 centres in the UK which recruited 12/72 participants).	People of all ages who weigh at least 3 kg with a diagnosis of moderate or mild haemophilia A without FVIII inhibitors, who warranted prophylaxis based on the treating physician's assessment. • N=72. • Moderate haemophilia A, 51/72 (71%) and mild haemophilia A, 21/72 (29%). • Age range 2 to 71 years, median age 23.5 years (IQR 12.0 to 36.0 years). • Male, 69/72 (96%); White, 61/72 (85%). • Target joints in 24/72 (33%) participants. Mean number of target joints 0.6 (SD 1.2). • Taking prophylactic treatment at baseline, 37/72 (51%) and 35/72 (49%) taking episodic treatment. 25/37 (68%) of those taking prophylactic treatment at baseline had moderate haemophilia and 12/37 (32%) had mild haemophilia. • People with moderate haemophilia A taking prophylactic treatment at baseline, 25/51 (49%). • Model-based ABR for all bleeds over the 24 weeks before study entry, 10.1 (95% CI 6.93 to 14.76).	**Interventions** Emicizumab subcutaneous injection. Loading dose of 3 mg/kg once a week for 4 weeks. Followed by a maintenance dose of either 1.5 mg/kg once a week (25/72, 35%), 3 mg/kg every 2 weeks (39/72, 54%) or 6 mg/kg every 4 weeks (8/72, 11%). The maintenance dosage regimen was chosen by the study participant. All participants with suboptimal control of bleeding had the option to increase the emicizumab maintenance dosage to 3 mg/kg once a week (off-label dosage). The primary efficacy and safety analyses were planned to be based only on data collected before a potential up-titration to evaluate the intended maintenance dose. Median follow-up on treatment was 55.6 weeks (IQR 52.3 to 61.6 weeks). **Comparators** No comparator.	**Critical outcome** • Model-based ABR for treated bleeds after a median follow-up of 55.6 weeks. • Model-based ABR for all bleeds after a median follow-up of 55.6 weeks. • Percentage of participants with target joints at baseline and in study for at least 52 weeks with resolved target joints. • Mean total HJHS at week 49 and change from baseline. **Important Outcomes** • Mean CATCH scores at week 49 and change from baseline. • Participants and carers preference for emicizumab compared with previous treatment assessed using EmiPref questionnaire at week 17. • Model-based ABR for treated joint bleeds and for treated target joint bleeds after a median follow-up of 55.6 weeks. • Duration of time spent in moderate-to-vigorous activity and mean daily step counts from baseline to week 49. • Safety after a median follow-up of 55.6 weeks.

Abbreviations

ABR, annualised bleed rate; CATCH, the Comprehensive Assessment Tool of Challenges in Haemophilia; CI, confidence interval; HJHS, Haemophilia Joint Health Score; IQR, interquartile range; SD, standard deviation

5. Results

In people with moderate haemophilia A without inhibitors, what is the clinical effectiveness and safety of emicizumab prophylaxis compared with current standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Rate of treated bleeding events **Certainty of evidence:** Very low	Rate of treated bleeding events is important to patients because bleeding events can cause serious complications including disability and death. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to rate of treated bleeding events (Négrier et al. 2023, n=72) in people with moderate (n=51) or mild haemophilia A (n=21) without FVIII inhibitors, who warranted prophylaxis based on the treating physician's assessment. After a median of 55.6 weeks (interquartile range (IQR) 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors (n=72) the model-based annualised bleed rate (ABR) for treated bleeds was 0.9 (95% confidence interval (CI) 0.55 to 1.52). Model-based ABR accounts for different follow-up times. Baseline ABR for treated bleeds was not provided. **(VERY LOW)** • Négrier et al. 2023 showed that in people with moderate haemophilia A without inhibitors (n=51) the model-based ABR for treated bleeds was 0.9 (95% CI 0.50 to 1.78). Model-based ABR accounts for different follow-up times. Baseline ABR for treated bleeds was not provided. **(VERY LOW)** Treated bleeds were defined as bleeds in which coagulation factors were given to treat signs or symptoms of bleeding. Two bleeds of the same type and at the same anatomical location were considered to be 1 bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed. **This study provides very low certainty evidence for the rate of treated bleeding events in people after a median of 55.6 weeks of emicizumab treatment. In 72 people with mild or moderate haemophilia A without inhibitors, the model-based ABR for treated bleeds was 0.9. In 51 people with moderate haemophilia A without inhibitors, the model-based ABR was also 0.9. However, baseline ABRs for treated bleeds were not provided, so no conclusions can be drawn about the effect of emicizumab on the rate of treated bleeds.**
Rate of all bleeding events **Certainty of evidence:** Very low	Rate of all bleeding events is important to patients because bleeding events can cause serious complications including disability and death. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to rate of all bleeding events (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors (n=72) the model-based ABR for all bleeds was 2.3 (95% CI 1.67 to 3.12) compared with 10.1 (95% CI 6.93 to 14.76) over the

	24 weeks before study entry. Model-based ABR accounts for different follow-up times. No statistical analysis reported. **(VERY LOW)** • Négrier et al. 2023 showed that in people with moderate haemophilia A without inhibitors (n=51) the model-based ABR for all bleeds was 2.2 (95% CI 1.57 to 3.20) compared with 6.0 (95% CI 4.33 to 8.22) over the 24 weeks before study entry. Model-based ABR accounts for different follow-up times. No statistical analysis reported. **(VERY LOW)** **This study provides very low certainty evidence that a median of 55.6 weeks of emicizumab treatment reduced the model-based ABR for all bleeds from 10.1 to 2.3 in 72 people with mild or moderate haemophilia A without inhibitors, and from 6.0 to 2.2 in 51 people with moderate haemophilia A without inhibitors. However, no statistical analyses were reported.**
Joint health **Certainty of evidence:** Very low	Joint health is important to patients because joint arthropathy and target joints (when there is recurrent bleeding into a certain joint) occur due to joint bleeding in haemophilia A. This complication is irreversible and causes pain, disability, and difficulty with activities of daily living. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to joint health over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks) (Négrier et al. 2023, n=72). After 52 weeks on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, who had target joints at baseline and were in the study for at least 52 weeks, 20/21 (95%) had resolved joints. Resolved joints were defined in the study as a report of fewer than three bleeds over a 52-week period. **(VERY LOW)** Target joints were defined as joints with 3 or more bleeds occurring in the same joint during the last 24 weeks or unresolved target joints, defined as a target joint that does not fulfil the criterion of 2 or less bleeds into this joint within a consecutive 12-month period. At week 49 on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, mean total Haemophilia Joint Health Score (HJHS) was 6.48 (standard deviation (SD) 8.96) in 56 participants. This compared with 7.20 (SD 10.37) in 65 participants at baseline, with a mean change from baseline of −1.25 (SD 3.95) in 52 participants. **(VERY LOW)** The HJHS measures joint health of the joints most commonly affected by bleeding in haemophilia: the knees, ankles, and elbows. The maximum total score is 124. Higher scores indicate worse joint health. Due to irreversible joint damage expected in adults, large improvements in HJHS score in adults over the timeframe of the study would not be expected. **This study provides very low certainty evidence that emicizumab resolved target joints in 20/21 (95%) people with mild or moderate haemophilia A without inhibitors, who had target joints at baseline and were in the study for at least 52 weeks. Data for people with moderate severity haemophilia A were not reported separately.** **This study provides very low certainty evidence that 49 weeks of emicizumab treatment improved the mean total HJHS in 72 people with mild or moderate haemophilia A without inhibitors compared with baseline. The clinical**

	significance of the improvement is unclear. Data for people with moderate haemophilia A were not reported separately.
Important outcomes	
Health related quality of life (HRQL) **Certainty of evidence:** Very Low	Health related quality of life is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to health related quality of life over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks) (Négrier et al. 2023, n=72). At week 49 and week 61 on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, the CATCH mean scores in the treatment burden domain were reported to show a trend to improvement in children, young people and adults aged 8 years or older (n=60). However, the results were only presented graphically (up-to week 61), and interpretation is difficult. Other domains were reported to be stable, with baseline values maintained until week 49. Specific values for these outcomes were not reported. **(VERY LOW)** The CATCH (the Comprehensive Assessment Tool of Challenges in Haemophilia) is a tool to assess outcomes important to children, young people, and adults with haemophilia. It includes domains related to quality of life, lifestyle restrictions, physical activity, and treatment burden. In adults irreversible joint damage may contribute to quality of life assessment scores and large improvements for this age group over the timeframe of the study would not be expected. **This study provides very low certainty evidence that there is a trend to improvement in treatment burden with up-to 61 weeks of emicizumab treatment, as measured by the CATCH assessment tool in 60 people aged 8 years and over with mild or moderate haemophilia A without inhibitors. All other domains of the CATCH assessment tool remained stable at week 49. The clinical significance of this is unclear. Data for people with moderate haemophilia A were not reported separately.**
Patient treatment preference **Certainty of evidence:** Very low	Patient treatment preference is important to patients as it reflects the burden of treatment and is a surrogate marker for control of symptoms and quality of life, and safety/adverse events. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to patient treatment preference over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks) (Négrier et al. 2023, n=72). At week 17 on emicizumab treatment: • Négrier et al. 2023 showed that in young people and adults aged 12 years or older with mild or moderate haemophilia A without inhibitors responding to the EmiPref questionnaire, 50/52 (96%) preferred emicizumab to their previous treatment. **(VERY LOW)** • Négrier et al. 2023 showed that in caregivers responding to the EmiPref questionnaire, 24/28 (86%) preferred emicizumab to their child's previous treatment. **(VERY LOW)** The EmiPref Questionnaire is a questionnaire to assess treatment preference. Participants or caregivers were asked to report what treatment regimen they

	preferred: emicizumab or their pre-study treatment. The questionnaire was conducted at week 17 in the study. **This study provides very low certainty evidence that the majority of people with mild or moderate haemophilia A without inhibitors aged 12 years and over (96%), and caregivers (86%), preferred emicizumab to their, or their child's, previous treatment, when responding to the EmiPref questionnaire after 17 weeks of treatment. Data for people with moderate haemophilia A were not reported separately.**
Rate of joint bleeding events **Certainty of evidence:** Very low	Rate of joint bleeding events is important to patients because joint arthropathy secondary to haemophilia A is an irreversible complication that causes pain and difficulty with activities of daily living. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to rate of joint bleeding events (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors (n=72) the model-based ABR for treated joint bleeds was 0.2 (95% CI 0.09 to 0.57). Model-based ABR accounts for different follow-up times. Baseline ABR for treated joint bleeds was not provided. **(VERY LOW)** • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors and target joints at baseline (n=24) the model-based ABR for treated target joint bleeds was 0.1 (95% CI 0.03 to 0.40). Model-based ABR accounts for different follow-up times. Baseline ABR for treated target joint bleeds was not provided. **(VERY LOW)** **This study provides very low certainty evidence for the rate of treated joint bleeds in people after a median of 55.6 weeks of emicizumab treatment. In 72 people with mild or moderate haemophilia A without inhibitors, the model-based ABR for treated joint bleeds was 0.2. In 24 people with mild or moderate haemophilia A without inhibitors and target joints at baseline, the model-based ABR for treated target joint bleeds was 0.1. However, baseline ABRs were not provided, so no conclusions can be drawn about the effect of emicizumab on the rate of treated joint bleeds. Data for people with moderate haemophilia A were not reported separately.**
Activities of daily living **Certainty of evidence:** Very low	Activities of daily living is important to patients because it reflects daily functioning and how well people can engage in education, employment, and recreational activities. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to activities of daily living over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks) (Négrier et al. 2023, n=72). At week 49 on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, aged 5 years or older, duration of time spent in moderate-to-vigorous activity and mean daily step count were reported to be stable from baseline to week 49 (n=not reported). Specific values for these outcomes were not reported. The results were presented graphically. **(VERY LOW)** **This study provides very low certainty evidence that duration of time spent in moderate-to-vigorous activity and mean daily step count remained stable in people aged 5 years and over with mild or moderate haemophilia A without**

	inhibitors after 49 weeks of emicizumab treatment compared with baseline. Data for people with moderate haemophilia A were not reported separately.
Safety	
All adverse events **Certainty of evidence:** Very low	Safety is important to patients as it reflects the risks involved in what is likely to be a long-term prophylactic treatment. This allows a risk benefit assessment to be undertaken. One multi-centre, open-label, single-arm study provided non-comparative evidence relating to safety (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, 60/72 (83%) had an adverse event. The most common adverse events were headache (12/72, 17%), injection-site reaction (12/72, 17%) and arthralgia (11/72, 15%). **(VERY LOW)** • Négrier et al. 2023 showed that in people with moderate haemophilia A without inhibitors, 42/51 (82%) had an adverse event. Injection-site reactions were reported by 8/51 (16%). **(VERY LOW)** **This study provides very low certainty evidence that the most commonly reported adverse events with emicizumab were headache, injection-site reactions and arthralgia, reported in 15 to 17% of people with mild to moderate haemophilia A without inhibitors. A similar rate of adverse events were reported in people with mild or moderate and moderate haemophilia A without inhibitors (83% and 82% respectively).**
Treatment-related adverse events **Certainty of evidence:** Very low	One multi-centre, open-label, single-arm study provided non-comparative evidence relating to safety (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, 15/72 (21%) had an adverse event considered related to emicizumab. Most treatment-related adverse events were local injection-site reactions. **(VERY LOW)** **This study provides very low certainty evidence that the majority of emicizumab-related adverse events in people with mild or moderate haemophilia A without inhibitors were local injection-site reactions. Data for people with moderate haemophilia A were not reported separately.**
Serious adverse events **Certainty of evidence:** Very low	One multi-centre, open-label, single-arm study provided non-comparative evidence relating to safety (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, 8/72 (11%) had a serious adverse event. None were considered to be emicizumab-related. There were no deaths, no systemic hypersensitivity, anaphylactic, or anaphylactoid reactions and no clinically significant changes from baseline in vital signs or ECG parameters. **(VERY LOW)** • Négrier et al. 2023 showed that in people with moderate haemophilia A without inhibitors, 6/51 (12%) had a serious adverse event. **(VERY LOW)**

	This study provides very low certainty evidence on serious adverse events with emicizumab in people with mild or moderate, or moderate, haemophilia A without inhibitors. None were considered to be emicizumab-related. There were no deaths or anaphylactic reactions.
Grade ≥3 adverse events **Certainty of evidence:** Very low	One multi-centre, open-label, single-arm study provided non-comparative evidence relating to safety (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, 4/72 (6%) had a grade 3 or above adverse event. **(VERY LOW)** **This study provides very low certainty evidence on the incidence of grade 3 or above adverse events with emicizumab in people with mild or moderate haemophilia A without inhibitors, but information on the nature of these events is not provided. Data for people with moderate haemophilia A were not reported separately.**
Emicizumab treatment withdrawal, modification, or interruption due to adverse event **Certainty of evidence:** Very low	One multi-centre, open-label, single-arm study provided non-comparative evidence relating to safety (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors (n=72), there were no adverse events which led to treatment withdrawal, modification, or treatment interruption. **(VERY LOW)** **This study provides very low certainty evidence that there were no adverse events that led to emicizumab treatment withdrawal, interruption, or modification in people with moderate haemophilia A without inhibitors.**
Thrombotic microangiopathies or thrombotic events **Certainty of evidence:** Very low	One multi-centre, open-label, single-arm study provided non-comparative evidence relating to safety (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment: • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors (n=72), none had a thrombotic microangiopathy event. **(VERY LOW)** • Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, 1/72 (1%) had grade 1 (mild) thrombosed haemorrhoids which were classified as a thrombotic event, not considered to be emicizumab-related. **(VERY LOW)** **This study provides very low certainty evidence that there were no thrombotic microangiopathies in people with moderate haemophilia A without inhibitors on emicizumab. One grade 1 (mild) thrombotic event was reported in people with mild or moderate haemophilia A without inhibitors, which was not considered to be emicizumab-related.**
Treatment-induced anti-drug antibodies **Certainty of evidence:** Very low	One multi-centre, open-label, single-arm study provided non-comparative evidence relating to safety (Négrier et al. 2023, n=72). After a median of 55.6 weeks (IQR 52.3 to 61.6 weeks) follow up on emicizumab treatment:

	• Négrier et al. 2023 showed that in people with mild or moderate haemophilia A without inhibitors, treatment-induced anti-drug antibodies were detected in 2/72 (3%). There were no bleeds, no injection-site reactions, hypersensitivity, or anaphylactic reactions in either of these 2 people. **(VERY LOW)** **This study provides very low certainty evidence that 2/72 (3%) people with mild or moderate haemophilia A without inhibitors developed emicizumab-induced anti-drug antibodies, but with no clinical consequence of bleeds, injection-site reactions, hypersensitivity or anaphylactic reactions. Data for people with moderate haemophilia A were not reported separately.**

Abbreviations

ABR, annualised bleed rate; CI, confidence interval; IQR, interquartile range; SD, standard deviation.

In people with moderate haemophilia A without inhibitors, what is the cost-effectiveness of emicizumab prophylaxis compared with current standard care?

Outcome	Evidence statement
Cost-effectiveness	No evidence was identified for this outcome.

From the evidence selected, are there any subgroups of patients that may benefit from emicizumab prophylaxis more than the wider population of interest?

Outcome	Evidence statement
Rate of treated bleeding events	One multi-centre, open-label, single-arm study (Négrier et al. 2023) (n=72, 51 with moderate haemophilia A and 21 with mild haemophilia A) provided non-comparative evidence for several subgroups for the model-based ABR for treated bleeds over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks). For participants receiving prophylactic FVIII treatment at baseline (n=37; 25 with moderate haemophilia A and 12 with mild haemophilia A), the model-based ABR for treated bleeds over a median follow up of 55.6 weeks was 0.7 (95% CI 0.36 to 1.34) and for participants on episodic treatment at baseline (n=35), it was 1.2 (95% CI 0.54 to 2.48). Baseline model-based ABRs not reported. No statistical analysis reported. For participants having 1.5 mg/kg once a week maintenance dose (n=25), the model-based ABR for treated bleeds over a median follow up of 55.6 weeks was 1.2 (95% CI 0.50 to 2.73); for those having 3 mg/kg every 2 weeks (n=39), it was 0.7 (95% CI 0.37 to 1.37) and for those having 6 mg/kg every 4 weeks (n=8), it was 1.1 (95% CI 0.17 to 7.61). Baseline model-based ABRs not reported. No statistical analysis reported. For participants with no target joints at baseline (n=48), the model-based ABR for treated bleeds over a median follow up of 55.6 weeks was 0.8 (95% CI 0.44 to 1.45); and for participants with any target joints at baseline (n=24), it was 1.1 (95% CI 0.45 to 2.84). Baseline model-based ABRs not reported. No statistical analysis reported. For male participants (n=69), the model-based ABR for treated bleeds over a median follow up of 55.6 weeks was 0.9 (95% CI 0.54 to 1.51); for female participants (n=3), it was 1.4 (95% CI 0.04 to 44.10); for participants <18 years, it was 1.0 (95% CI 0.03 to 5.63) and for participants ≥18 years, it was 0.9 (95% CI 0.01 to 5.36). Baseline model-based ABRs not reported. No statistical analysis reported.

	This study provides evidence for several subgroups on the rate of treated bleeds in people with mild or moderate haemophilia A without inhibitors on emicizumab. However, baseline rates were not reported, the subgroups were small and data for those with moderate haemophilia A were not reported separately. Statistical analyses for comparisons between subgroups were also not reported. Conclusions cannot be drawn on whether there are any subgroups of patients that may benefit from emicizumab prophylaxis more than the wider population of interest.
Rate of all bleeds	One open-label, single-arm study (Négrier et al. 2023) (n=72, 51 with moderate haemophilia A and 21 with mild haemophilia A) provided non-comparative evidence for several subgroups for the model-based ABR for all bleeds over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks). For participants receiving prophylactic FVIII treatment at baseline (n=37; 25 with moderate haemophilia A and 12 with mild haemophilia), the model-based ABR for all bleeds over a median follow up of 55.6 weeks was 2.2 (95% CI 1.49 to 3.12) compared with 12.2 (95% CI 6.15 to 24.05) over the 24 weeks before study entry. For participants on episodic treatment at baseline (n=35), it was 2.4 (95% CI 1.42 to 4.09) compared with 8.0 (95% CI 5.68 to 11.13) before study entry. No statistical analysis reported. For participants having 1.5 mg/kg once a week maintenance dose (n=25), the model-based ABR for all bleeds over a median follow up of 55.6 weeks was 1.9 (95% CI 1.27 to 2.96); for those having 3 mg/kg every 2 weeks (n=39), it was 2.1 (95% CI 1.37 to 3.26) and for those having 6 mg/kg every 4 weeks (n=8), it was 4.3 (95% CI 1.42 to 13.32). Baseline model-based ABRs not reported. No statistical analysis reported. For participants with no target joints at baseline (n=48), the model-based ABR for all bleeds over a median follow up of 55.6 weeks was 2.1 (95% CI 1.39 to 3.03); and for participants with any target joints at baseline (n=24), it was 2.7 (95% CI 1.64 to 4.54). Baseline model-based ABRs not reported. No statistical analysis reported. For male participants (n=69), the model-based ABR for all bleeds over a median follow up of 55.6 weeks was 2.1 (95% CI 1.53 to 2.77); for female participants (n=3), it was 9.1 (95% CI 1.42 to 58.67). Baseline model-based ABRs not reported. No statistical analysis reported. **This study provides evidence for several subgroups on the rate of all bleeds in people with mild or moderate haemophilia A without inhibitors on emicizumab. However, baseline rates were not reported for most of the subgroups, the subgroups were small and data for those with moderate severity were not reported separately. Statistical analyses for comparisons between subgroups or differences from baseline were also not reported. Conclusions cannot be drawn on whether there are any subgroups of patients that may benefit from emicizumab prophylaxis more than the wider population of interest.**

Abbreviations

ABR, annualised bleed rate; CI, confidence interval; IQR, interquartile range

From the evidence selected, what doses, frequency and route of administration of emicizumab prophylaxis were used and what was the duration of treatment?

Study	Regimen and duration of emicizumab prophylaxis
Négrier et al. 2023	Emicizumab subcutaneous injection. Loading dose of 3 mg/kg once a week for 4 weeks.

	Followed by a maintenance dose of either 1.5 mg/kg once a week, 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. The maintenance dosage regimen was chosen by the study participant. 25/72 (35%) choose 1.5 mg/kg once a week, 39/72 (54%) choose 3 mg/kg every 2 weeks and 8/72 (11%) choose 6 mg/kg every 4 weeks. All participants with suboptimal control of bleeding had the option to increase the emicizumab maintenance dosage to 3 mg/kg once a week (off-label dosage). The primary efficacy and safety analyses were planned to be based only on data collected before a potential up-titration to evaluate the intended maintenance dose. Median follow-up on treatment was 55.6 weeks (IQR 52.3 to 61.6 weeks).

Abbreviations

IQR, interquartile range

6. Discussion

This evidence review includes one open-label single-arm study (Négrier et al. 2023). The study has significant limitations which affect the interpretation of the evidence it provides.

Because Négrier et al. 2023 was non-randomised, all outcomes were considered to have low certainty using modified GRADE. The outcomes were downgraded to very low certainty for risk of bias and indirectness. The study was open-label with no blinding of investigators or participants. Due to the lack of randomisation or blinding, bias cannot be avoided. The study also had no control or comparator group and only provides non-comparative evidence for emicizumab.

Négrier et al. 2023 included a mixed population of people with mild or moderate haemophilia A without inhibitors but most (71%) of the population had moderate haemophilia A. Some outcomes were provided for the moderate haemophilia A subgroup, but the majority were reported for the mixed population only. It should be noted that emicizumab is not licensed in the UK for treating people with mild haemophilia A without inhibitors (summary of product characteristics, SPC). The study participants' diagnosis of moderate or mild haemophilia A was provided by the investigators, but without specific information on endogenous FVIII activity. Moderate haemophilia A was defined in the study as FVIII activity ≥1% to ≤5%, and mild as >5% to <40%.

The results from Négrier et al. 2023 should not be considered representative of all people with moderate or mild haemophilia A without inhibitors as study participants were selected based on investigator assessment that prophylaxis treatment was warranted. The reasons given for warranting prophylaxis included a history of frequent bleeding, frequent joint bleeding and severe bleeding. How this correlates to prophylaxis initiation in UK practice is unclear. At baseline 51% of the study population were on prophylactic FVIII treatment. In the moderate haemophilia A population, 49% were on FVIII prophylaxis at baseline. Efficacy and safety results were not presented separately for people with moderate haemophilia A who were having prophylactic treatment at baseline.

Négrier et al. 2023 was a multi-centre study conducted at 22 centres in Europe, North America and South Africa, it only included 12/72 participants recruited from the UK. The majority of the people in the study were male, however this reflects the increased prevalence of the condition in males.

Négrier et al. 2023 provided evidence for all the critical and important outcomes. However, for several of the outcomes such as treated bleeds or joint bleeds, the baseline bleeding rates were not reported. So, it is difficult to assess the effect of emicizumab treatment on these outcomes. In addition, where baseline values were reported such as for the outcome of all bleeds, statistical methods did not examine changes from before to after emicizumab treatment and p values for the pre-to-post changes were not provided. Also, bleed data for the 24 weeks before the study was collected retrospectively. This is a possible source of inaccuracy as participants may have under or overreported their bleeds. Therefore, comparisons of bleed rates on emicizumab prophylaxis to baseline bleed rates may be subject to bias due to the data collection method.

Health related quality of life was captured using the Comprehensive Assessment Tool of Challenges in Haemophilia questionnaire (CATCH). Joint health was assessed using target joint resolution and the Haemophilia Joint Health Score (HJHS). Established irreversible joint damage, which is likely in adults with haemophilia, may limit improvement in CATCH and HJHS

scores. Any improvement in HJHS may occur over longer periods of time and the study may not have been long enough to detect these changes.

Evidence on safety outcomes were reported in Négrier et al. 2023. However, this was a small study, as would be expected for a rare condition, and although it had a median follow up of 55.6 weeks, emicizumab prophylaxis would be a long-term treatment in people with haemophilia A. The study may not have been large enough or long enough to detect uncommon or rare safety concerns.

The initial loading and maintenance dosages of emicizumab used in Négrier et al. 2023 were in-line with those in the SPC. There was the option to increase the maintenance dose to an off-label dosage if there was suboptimal control of bleeding. However, the primary efficacy and safety analyses were based on data collected before a potential up-titration.

Evidence on several different subgroups were reported in Négrier et al. 2023. However, the subgroups were small and baseline bleed rates were not provided for all subgroups. There were also no statistical analyses between subgroups and subgroup data was only provided for the mixed mild or moderate haemophilia A population.

No evidence was identified on the cost-effectiveness of emicizumab prophylaxis.

7. Conclusion

One study provided evidence on the clinical effectiveness and safety of emicizumab prophylaxis in people with moderate haemophilia A without inhibitors. The study (Négrier et al. 2023) was an open-label, single-arm study and it provided very low certainty evidence on the critical outcomes of rate of treated bleeding events, rate of all bleeding events and joint health; and the important outcomes of health related quality of life, patient treatment preference, rate of joint bleeding events, activities of daily living and safety. The study was a mixed population of people with mild or moderate haemophilia A, however the majority (71%) of the population had moderate haemophilia A. Most of the outcomes were reported for the mixed population. For the clinical effectiveness outcomes, only rate of treated bleeds and all bleeds were provided separately for the moderate haemophilia A population.

No studies were found which directly compared emicizumab to a control group in people with moderate haemophilia A without inhibitors. Therefore, the clinical effectiveness and safety of emicizumab prophylaxis compared with current standard care in this population cannot be determined from the evidence provided in this review.

In Négrier et al. 2023, rates of bleeding events were reported after a median follow-up of 55.6 weeks on emicizumab treatment in people with mild or moderate haemophilia A without inhibitors (n=72). The model-based annualised bleed rate (ABR) for treated bleeds was 0.9 (95% confidence interval [CI] 0.55 to 1.52) and for treated joint bleeds was 0.2 (95% CI 0.09 to 0.57). For those who had target joints at baseline (n=24), the model-based ABR for treated target joint bleeds was 0.1 (95% CI 0.03 to 0.40). The model-based ABR for treated bleeds for people with moderate haemophilia A (n=51); was 0.9 (95% CI 0.50 to 1.78). No conclusions can be drawn about the effect of emicizumab treatment on these outcomes as no baseline values were reported.

The model-based ABR of all bleeding events was reduced by 77% in people with mild or moderate haemophilia A without inhibitors from 10.1 (95% CI 6.93 to 14.76) over the 24 weeks before study entry to 2.3 (95% CI 1.67 to 3.12) after a median follow-up of 55.6 weeks on emicizumab treatment. In people with moderate haemophilia A it reduced by 63% from 6.0 (95% CI 4.33 to 8.22) to 2.2 (95% CI 1.57 to 3.20). However, no statistical analyses were provided for before and after treatment comparisons and pre-study data collection methods for bleeds may have introduced bias.

Joint health was assessed using target joint resolution and the Haemophilia Joint Health Score (HJHS). In participants who had target joints at baseline and were in the study for at least 52 weeks, 20/21 (95%) had resolved joints. Resolved joints were defined in the study as a report of fewer than three bleeds over a 52-week period. There was a mean improvement of −1.25 (standard deviation [SD] 3.95) in total HJHS at week 49 compared with baseline, with a change from 7.20 (SD 10.37) to 6.48 (SD 8.96). The effect size of this improvement in joint health is very small and the clinical significance is unclear. However, adult participants may have established irreversible joint damage which may limit any improvement in HJHS. Additionally, the study may not have been long enough to allow for significant improvements in HJHS to be seen.

The study reported health related quality of life using the Comprehensive Assessment Tool of Challenges in Haemophilia (CATCH) in people aged 8 years and over. There was reported to be a trend to improvement in the treatment burden domain with up-to 61 weeks of emicizumab treatment; however, the results were only presented graphically, and interpretation is difficult. All other domains of the CATCH were reported to have remained stable.

Duration of time spent on moderate or vigorous activity or mean daily step count in people aged 5 years and over were also reported to be stable from baseline to week 49.

The majority 50/52 (96%) of young people and adults aged 12 years or older in the study preferred emicizumab to their previous treatment when questioned on this at week 17. It was also preferred by the majority 24/28 (86%) of caregivers compared with their child's previous treatment.

The most common adverse events reported in the study were headache (12/72, 17%), injection-site reactions (12/72, 17%), and arthralgia (11/72, 15%) which reflects the adverse effects profile in the summary of product characteristics (SPC). Adverse events considered to be related to emicizumab treatment were reported in 15/72 (21%) of participants, most of which were local injection-site reactions. Limited safety data was provided separately for people with moderate haemophilia A, but a similar proportion (8/51, 16%) reported injection-site reactions. There were no adverse events which led to treatment withdrawal, modification, or treatment interruption. Treatment-induced anti-drug antibodies were detected in 2/72 (3%) participants, with no clinical consequence of bleeds, injection-site reactions, hypersensitivity or anaphylactic reactions. There were no thrombotic microangiopathy events and 1/72 (1%) participant had a thrombotic event (grade 1 thrombosed haemorrhoids, considered unrelated to treatment). Safety data were reported over a median follow-up of 55.6 weeks. However, the study may not have been large enough or long enough to detect uncommon or rare safety concerns.

Négrier et al. 2023 provided evidence on rates of treated bleeds and all bleeds for subgroups based on whether there had been prophylactic or episodic treatment at baseline, whether there were target joints at baseline, maintenance dose regimen, sex, and age. However, baseline rates were not reported for most of the subgroups, the subgroups were small, and data for those with moderate haemophilia A were not reported separately. Also, statistical analyses for comparisons between subgroups or differences from baseline were not reported. Therefore, conclusions cannot be drawn on whether there are any subgroups of people that may benefit from emicizumab prophylaxis more than the wider population of interest.

The initial loading and maintenance dosages of emicizumab used in Négrier et al. 2023 were in-line with those in the SPC. People in the study were able to choose their maintenance dosage regimen, 25/72 (35%) chose 1.5 mg/kg once a week, 39/72 (54%) chose 3 mg/kg every 2 weeks and 8/72 (11%) chose 6 mg/kg every 4 weeks.

No evidence was identified on the cost-effectiveness of emicizumab prophylaxis.

The findings of this review are important because they suggest that emicizumab prophylaxis may reduce the annualised bleed rate for all bleeding events, resolve target joints, prevent further deterioration of joint health and be preferred by people compared with their previous treatments. However, interpretation of the data is limited by the lack of a control group, bias in the study due to its open-label design and data collection methods, the lack of statistical analysis from before to after emicizumab treatment, and the fact that baseline data was not provided for all outcomes.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with moderate haemophilia A without inhibitors, what is the clinical effectiveness of emicizumab prophylaxis compared with current standard care?
2. In people with moderate haemophilia A without inhibitors, what is the safety of emicizumab prophylaxis compared with current standard care?
3. In people with moderate haemophilia A without inhibitors, what is the cost-effectiveness of emicizumab prophylaxis compared with current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from emicizumab prophylaxis more than the wider population of interest?
5. From the evidence selected, what doses, frequency, and route of administration of emicizumab prophylaxis were used and what was the duration of treatment?

P – Population and Indication	People of all ages with moderate haemophilia A without inhibitors [Haemophilia A may be referred to as HA, and inhibitors may be referred to as factor eight inhibitors, factor VIII inhibitors, FVIII inhibitors. Severity is categorised by plasma FVIII activity: severe (<1% of normal levels), moderate (≥1%–≤5%), and mild (>5%–<40%).]
I – Intervention	Emicizumab for prophylaxis of bleeding episodes [Prophylactic treatment may be referred to as preventative treatment]
C – Comparator(s)	Standard care [Standard care for this patient group is prophylaxis/prevention with any intravenous FVIII]
O – Outcomes	**<u>Clinical Effectiveness</u>** Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown. Outcomes ideally measured at 6, 12, 24 months as well as long-term outcomes. *<u>Critical to decision making</u>* • **Rate of treated bleeding events** *This outcome is important to patients because bleeding events can cause serious complications including disability and death.* [Treated bleeding events may be reported as annualised bleeding rates (ABR) for treated bleeds. Model-based ABR accounts for different follow-up times. ABR should ideally be calculated from baseline to a follow up of at least 24 weeks.] • **Rate of all bleeding events**

	This outcome is important to patients because bleeding events can cause serious complications including disability and death. [Bleeding events may be reported as annualised bleeding rates for all bleeds. Model-based ABR accounts for different follow-up times.] • **Joint health** *This outcome is important to patients because joint arthropathy and target joints (when there is recurrent bleeding into a certain joint) occur due to joint bleeding in haemophilia A. This complication is irreversible and causes pain, disability, and difficulty with activities of daily living.* [Joint health can be assessed by the presence or absence of target joint resolution. Target joints are defined as joints with >= 3 bleeds occurring to the same joint during the last 24 weeks. Other measures of joint health include the total Haemophilia Joint Health Score] *Important to decision making:* • **Health related quality of life (HRQL)** *This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.* [Other terms used to describe or indicate quality of life include but are not limited to; patient-reported quality of life outcomes, health related quality of life. Examples of metrics to assess quality of life include but are not limited to: Short Form (SF-36), EuroQuality of Life Five Dimensions (EQ-5D), Haem-A-QoL physical health subscale, and the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) questionnaire. Other methods of assessing quality of life include but are not limited to subjective/self-reported/carer reported quality of life experiences.] • **Patient treatment preference** *This outcome is important to patients as it reflects the burden of treatment and is a surrogate marker for control of symptoms and quality of life, and safety/adverse events.* [Patient preference can be measured by the Emicizumab Preference (EmiPref) survey] • **Rate of joint bleeding events** *This outcome is important to patients because joint arthropathy secondary to haemophilia A is an*

	irreversible complication that causes pain and difficulty with ADLs. [Rates of joint bleeding events include rates of joint bleeding into target joints (defined as joints with >= 3 bleeds occurring to the same joint during the last 24 weeks). Rates of joint bleeding events may be reported as annualised bleeding rates for joint bleeds or target joint bleeds. Model-based ABR accounts for different follow-up times] • **Activities of daily living** *This outcome is important to patients because it reflects daily functioning and how well people can engage in education, employment and recreational activities.* **<u>Safety</u>** • **Complications of prophylactic therapy** *Safety is important to patients as it reflects the risks involved in what is likely to be a long-term prophylactic treatment. This allows a risk benefit assessment to be undertaken.* [Other terms used to describe or indicate safety include, but are not limited to; adverse events, serious/ major adverse events. Examples may include but are not limited to; thromboembolic events, thrombotic microangiopathies, injection-site reactions, hypersensitivity, anaphylaxis, and anaphylactoid events, adverse events leading to drug discontinuation, incidence and significance of anti-drug antibodies, de-novo development of FVIII inhibitors, and laboratory abnormalities. Anti-drug antibody prevalence can be measured by bridging ELISA and anti-drug antibody neutralisation activity can be measured by chromogenic assay] **<u>Cost-effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013 – 2023

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, preprints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Database search strategies

Database: Medline ALL

Platform: Ovid
Version: 1946 to October 09 2023
Search date: 10/10/2023
Number of results retrieved: 387
Search strategy:

Ovid MEDLINE(R) ALL <1946 to October 09, 2023>

1	Hemophilia A/	22946
2	(hemophil* or haemophil*).tw.	52643
3	((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight) adj4 deficien*).tw.	92
4	or/1-3	56676
5	(emicizumab or hemlibra).tw.	500
6	(ACE910 or ACE-910 or "ACE 910").tw.	27
7	(RG6013 or RG-6013 or "RG 6013").tw.	0
8	or/5-7	514
9	4 and 8	473
10	limit 9 to english language/	454
11	limit 10 to (letter or historical article or comment or editorial or news)	63
12	10 not 11	391
13	animals/ not humans/	5127578
14	12 not 13	389
15	limit 14 to yr="2013 -Current"	387

Database: Embase

Platform: Ovid
Version: 1974 to 2023 October 09
Search date: 10/10/2023
Number of results retrieved: 640; conferences removed
Search strategy:

Embase <1974 to 2023 October 09>

1	hemophilia A/	25707
2	(haemophil* or hemophil*).tw.	71998
3	((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight) adj4 deficien*).tw.	156
4	or/1-3	75426
5	emicizumab/	1712
6	(emicizumab or hemlibra).tw.	1436
7	(ACE910 or ACE-910 or "ACE 910").tw.	116
8	(RG6013 or RG-6013 or "RG 6013").tw.	2
9	or/5-8	1810
10	4 and 9	1640
11	limit 10 to english language/	1608
12	(letter or editorial).pt.	2073522
13	11 not 12	1488
14	nonhuman/ not (human/ and nonhuman/)	5302057
15	13 not 14	1441
16	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5697372
17	15 not 16	640
18	limit 17 to yr="2013 - 2024"	640

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley

Version:

CDSR –Issue 10 of 12, October 2023

CENTRAL – Issue 10 of 12, October 2023

Search date: 10/10/2023

Number of results retrieved: CDSR 0 ; CENTRAL 29

Search Name: Emicizumab

Date Run: 09/10/2023 17:19:04

Comment:

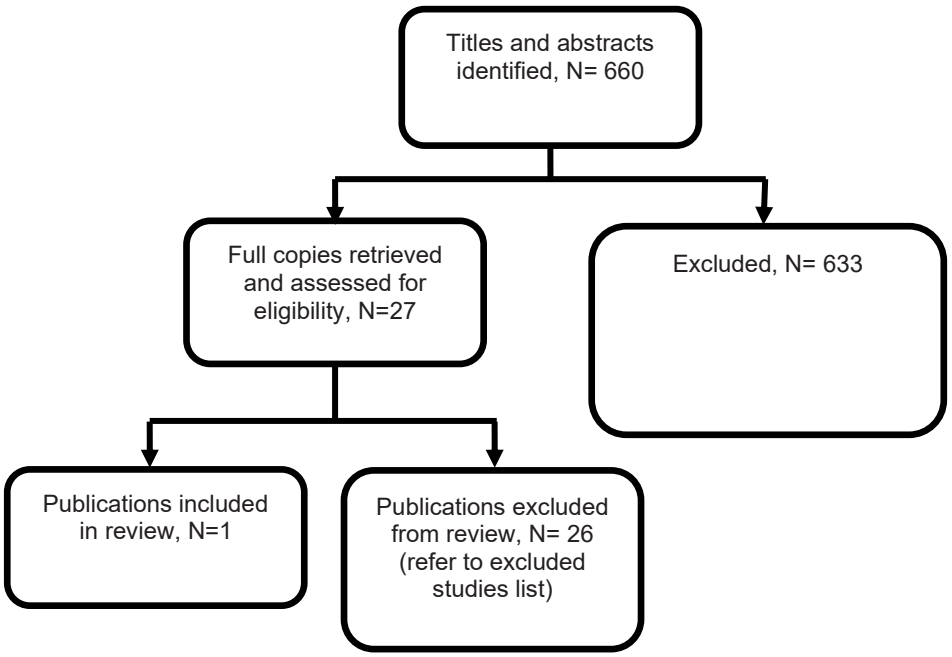
ID	Search	Hits

#1	MeSH descriptor: [Hemophilia A] this term only	673
#2	(haemophil* or hemophil*):ti,ab,kw	4219
#3	((heredit* or inherit* or congen*) near (8 or VIII or eight) near deficienc*):ti,ab,kw	34
#4	#1 or #2 or #3	4224
#5	(emicizumab or hemlibra):ti,ab,kw	81
#6	(ACE910 or ACE-910 or ACE 910):ti,ab,kw	23
#7	(RG6013 or RG-6013 or RG 6013):ti,ab,kw	0
#8	#5 or #6 or #7	89
#9	#4 and #8	78
#10	"conference":pt or (clinicaltrials or trialsearch):so	710021
#11	#9 not #10	29

Appendix C Evidence selection

The literature searches identified 660 references. These were screened using their titles and abstracts and 27 references were obtained in full text and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 26 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Négrier et al. (2023) Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study. Lancet Haematology. 10 (3): e168-e177. doi: 10.1016/S2352-3026 (22)00377-5	Included
Callaghan et al. (2021) Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 137 (16):2231-2242. DOI: 10.1182/blood.2020009217.	Excluded: Population haemophilia A with inhibitors or severe haemophilia A without inhibitors
Wall et al. (2023) Emicizumab prophylaxis in haemophilia A with inhibitors: Three years follow-up from the UK Haemophilia Centre Doctors' Organisation (UKHCDO). Haemophilia. 29 (3):743-752. doi:10.1111/hae.14762-5.	Excluded: Population haemophilia A with inhibitors

Appendix D Excluded studies table

Study reference	Reason for exclusion
Agboola et al. (2021) The effectiveness and value of emicizumab and valoctocogene roxaparvovec for the management of hemophilia A without inhibitors. Journal of managed care & specialty pharmacy 27(5): 667-673	Population severe haemophilia A
Anonymous. (2023) Erratum: Callaghan MU, Negrier C, Paz-Priel I, 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):2231-2242. (Blood (2021) 137(16) (2231-2242), (S0006497121008703), (10.1182/blood.2020009217). Blood 142(15): 1329	Population either haemophilia A with inhibitors or severe haemophilia A without inhibitors - correction to excluded paper
Anonymous. (2021) Corrigendum to: Development and testing of the Satisfaction Questionnaire with Intravenous or Subcutaneous Hemophilia Injection and results from the Phase 3 HAVEN 3 study of emicizumab prophylaxis in persons with haemophilia A without FVIII inhibitors (Haemophilia, (2021), 27, 2, (221-228), 10.1111/hae.14222). Haemophilia 27(5): 887	Population severe haemophilia A - correction to excluded paper
Callaghan et al. (2022) Untreated bleeds in people with hemophilia A in a noninterventional study and intrapatient comparison after initiating emicizumab in HAVEN 1-3. Research and practice in thrombosis and haemostasis 6(6): e12782 DOI: 10.1002/rth2.12782	Population either haemophilia A with inhibitors or severe haemophilia A without inhibitors
Callaghan et al. (2021) Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood 137(16): 2231-2242	Population either haemophilia A with inhibitors or severe haemophilia A without inhibitors
Cohen et al (2021) Emicizumab in pediatric hemophilia: Bleeding and surgical outcomes from a single-center retrospective study. Pediatric blood & cancer 68(11): e29325	Population retrospective chart review most (96%) had severe haemophilia A
Ebbert et al. (2020) Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. Haemophilia: the official journal of the World Federation of Hemophilia 26(1): 41-46	Population most (83%) of without inhibitors group had severe haemophilia A and results presented for group
Escobar et al. (2023) Impact of switching prophylaxis treatment from factor VIII to emicizumab in hemophilia A patients without inhibitors. Journal of medical economics 26(1): 574-580	Population unclear does not include details on severity of haemophilia A
Escobar et al. (2023) A real-world evidence analysis of the impact of switching from factor VIII to emicizumab prophylaxis in patients with hemophilia A without inhibitors. Expert review of hematology 16(6): 467-474	Population unclear does not include details on severity of haemophilia A
Glonnegger et al. (2022) Emicizumab in children: bleeding episodes and outcome before and after transition to Emicizumab. BMC pediatrics 22(1): 487	Population retrospective analysis of 13 children - 12 with severe haemophilia A
Gourzoulidis et al. (2022) Application of Multicriteria Decision Analysis to Determine the Value of Prophylaxis Relative to On-Demand Treatment in Hemophilia A and Emicizumab versus Replacement Therapy in the Greek Healthcare Setting. Clinical drug investigation 42(1): 75-85	Population severe haemophilia A
Jimenez-Yuste et al. (2018) Preference for Emicizumab over Prior Factor Treatments: results from the HAVEN 3 and HAVEN 4 Studies. Blood 132(suppl1): 1187	Publication type conference abstract
Kempton et al. (2021) Development and testing of the Satisfaction Questionnaire with Intravenous or Subcutaneous Hemophilia Injection and results from the	Population severe haemophilia A

Phase 3 HAVEN 3 study of emicizumab prophylaxis in persons with haemophilia A without FVIII inhibitors. Haemophilia: the official journal of the World Federation of Hemophilia 27(2): 221-228	
Kiialainen et al. (2022) Effect of emicizumab prophylaxis on bone and joint health markers in people with haemophilia A without factor VIII inhibitors in the HAVEN 3 study. Haemophilia: the official journal of the World Federation of Hemophilia 28(6): 1033-1043	Population severe haemophilia A
Klamroth et al. (2021) Efficacy of rFVIIIFc versus Emicizumab for the Treatment of Patients with Hemophilia A without Inhibitors: Matching-Adjusted Indirect Comparison of A-LONG and HAVEN Trials. Journal of blood medicine 12: 115-122	Population severe haemophilia A
Kragh et al. (2023) Cost-effectiveness of recombinant factor VIII Fc versus emicizumab for prophylaxis in adults and adolescents with haemophilia A without inhibitors in the UK. European journal of haematology 110(3): 262-270	Population cost-effectiveness model-based on matching-adjusted indirect comparison study which has already been excluded (severe haemophilia A)
Langer et al. (2018) Evaluating the safety of emicizumab in patients with hemophilia A. Expert opinion on drug safety 17(12): 1233-1237	Study design non-systematic review
Levy-Mendelovich et al. (2021) Real-World Data on Bleeding Patterns of Hemophilia A Patients Treated with Emicizumab. Journal of clinical medicine 10(19)	Population severe haemophilia A
Mahlangu et al. (2018) Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. The New England journal of medicine 379(9): 811-822	Population severe haemophilia A
Mancuso et al. (2022) Cost-minimization analysis of recombinant factor VIII Fc versus emicizumab for treating patients with hemophilia A without inhibitors in Europe. Journal of medical economics 25(1): 1068-1075 DOI: 10.1080/13696998.2022.2115777	Population severe haemophilia A
McCary et al. (2020) Real-world use of emicizumab in patients with haemophilia A: Bleeding outcomes and surgical procedures. Haemophilia: the official journal of the World Federation of Hemophilia 26(4): 631-636	Population most (97%) had severe haemophilia A and results presented for group
Ocana et al. (2023) Efficacy and safety of prophylaxis with emicizumab in hemophilia A: A study of 13 patients. Medicina clinica DOI: 10.1016/j.medcli.2023.07.024	Non-English language
Reyes et al. (2019) Efficacy of emicizumab prophylaxis versus factor VIII prophylaxis for treatment of hemophilia A without inhibitors: network meta-analysis and subgroup analyses of the intra-patient comparison of the HAVEN 3 trial. Current medical research and opinion 35(12): 2079-2087	Population severe haemophilia A
Rodriguez-Merchan et al. (2019) Emicizumab: Review of the literature and critical appraisal. Haemophilia: the official journal of the World Federation of Hemophilia 25(1): 11-20	Study design and population non-systematic review on all populations of haemophilia A
Sun et al. (2022) Real-world study of rurioctocog alfa pegol and emicizumab in US clinical practice among patients with hemophilia A. Expert review of hematology 15(10): 943-950 DOI: 10.1080/17474086.2022.2112171	Population most (87%) had severe haemophilia A and results presented for group
Warren et al. (2021) Emicizumab initiation and bleeding outcomes in people with hemophilia A with and without inhibitors: A single-center report. Research and practice in thrombosis and haemostasis 5(5): e12571	Population most (79%) had severe haemophilia A and results presented for group

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Négrier C; Mahlangu J; Lehle M et al. (2023) Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study. Lancet Haematology. 10 (3): e168-e177. doi: 10.1016/S2352-3026(22)00377-5 **Study location** 22 centres in Europe, North America and South Africa (including 3 centres in the UK which recruited 12/72 participants). **Study type** Multi-centre, open-label, single-arm study. **Study aim** The study reports 'the primary analysis results, assessing the safety, efficacy, and pharmacokinetics of emicizumab prophylaxis in people with non-severe haemophilia A without FVIII inhibitors.' **Study dates** Participants recruited to study between 10 February 2020 and 31 August 2021.	**Inclusion criteria** People of all ages who weigh at least 3 kg with a diagnosis of moderate or mild haemophilia A without FVIII inhibitors, who warranted prophylaxis based on the treating physician's assessment. Participants had to have a negative test for FVIII inhibitors (less than 0.6 BU/mL) within 8 weeks before enrolment onto the study, and no documented inhibitor (<0.6 BU/mL), FVIII half-life less than 6 hours, or FVIII recovery of less than 66% in the past 5 years. **Exclusion Criteria** Exclusion criteria included: inherited or acquired bleeding disorder other than moderate or mild congenital haemophilia A; history of illicit drug or alcohol abuse within 48 weeks before screening; previous (within the past 12 months) or current treatment for thromboembolic disease or signs of thromboembolic disease; other conditions that might increase the risk of bleeding or thrombosis; a history of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection; planned surgery during the emicizumab loading dose phase; known HIV infection with CD4+ cell counts	**Interventions** Emicizumab subcutaneous injection. Loading dose of 3 mg/kg once a week for 4 weeks. Followed by a maintenance dose of either 1.5 mg/kg once a week (25/72, 35%), 3 mg/kg every 2 weeks (39/72, 54%) or 6 mg/kg every 4 weeks (8/72, 11%). The maintenance dosage regimen was chosen by the study participant. All participants with suboptimal control of bleeding had the option to increase the emicizumab maintenance dosage to 3 mg/kg once a week (off-label dosage). The primary efficacy and safety analyses were planned to be based only on data collected before a potential up-titration to evaluate the intended maintenance dose. Median follow-up on treatment was 55.6 weeks (IQR 52.3 to 61.6 weeks). **Comparators** No comparator.	**Critical outcomes** **Rate of treated bleeding events** After a median of 55.6 weeks follow-up of all participants taking emicizumab, the model-based ABR for treated bleeds was 0.9 (95% CI 0.55 to 1.52). Model-based ABR accounts for different follow-up times. Baseline ABR for treated bleeds was not provided. In participants with moderate haemophilia A taking emicizumab (n=51) the model-based ABR for treated bleeds was 0.9 (95% CI 0.50 to 1.78). Other subgroup analysis model-based ABR's for treated bleeds with emicizumab treatment: participants receiving prophylaxis at baseline (n=37), 0.7 (95% CI 0.36 to 1.34); on episodic treatment at baseline (n=35), 1.2 (95% CI 0.54 to 2.48). 1.5 mg/kg once a week maintenance dose (n=25), 1.2 (95% CI 0.50 to 2.73); 3 mg/kg every 2 weeks (n=39), 0.7 (95% CI 0.37 to 1.37); 6 mg/kg every 4 weeks (n=8), 1.1 (95% CI 0.17 to 7.61). No target joints (n=48), 0.8 (95% CI 0.44 to 1.45); any target joints (n=24), 1.1 (95% CI 0.45 to 2.84). Male (n=69), 0.9 (95% CI 0.54 to 1.51); female (n=3), 1.4 (95% CI 0.04 to 44.10); <18 years, 1.0 (95% CI 0.03 to 5.63); ≥18 years, 0.9 (95% CI 0.01 to 5.36). **Rate of all bleeding events** After a median of 55.6 weeks follow-up of all participants taking emicizumab, the model-based ABR for all bleeds was 2.3 (95% CI 1.67 to 3.12) compared with 10.1 (95% CI 6.93 to 14.76) over the 24 weeks before study entry.	This study was appraised using the National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) studies with no (concurrent) control group. 1. Yes 2. Yes 3. Cannot determine 4. Cannot determine 5. Cannot determine 6. Yes 7. Yes 8. No 9. Yes 10. No 11. No 12. N/A Quality Rating: Fair Other comments: Mixed population of mild and moderate haemophilia A but most (71%) had moderate haemophilia A. Participants' diagnosis of moderate or mild haemophilia A was provided by the investigators, but without specific information on endogenous FVIII activity. Moderate haemophilia A defined as FVIII activity ≥1% to ≤5%, and mild >5% to <40%. Study participants warranted prophylaxis by investigator assessment; therefore, results should not be considered representative of all

	less than 200 cells per microlitre and any concomitant disease, condition, significant abnormality on screening evaluation or laboratory tests, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator, pose an additional unacceptable risk in administering the study drug to the participant. Individuals who were pregnant or breastfeeding or intending to become pregnant during the study were also excluded. Female participants required a negative serum pregnancy test result within 7 days before initiation of the study drug. **Total sample size** 72 in safety and efficacy analyses. No comparator group. **Baseline characteristics** Median age 23.5 years (IQR 12.0 to 36.0 years). Age range 2.0 to 71.0 years. 69/72 (96%) male. 61/72 (85%) were white. 51/72 (71%) had moderate haemophilia A and 21/72 (29%) had mild haemophilia A. 37/72 (51%) currently taking prophylactic treatment and 35/72 (49%) taking episodic treatment. 25/37 (68%) of those taking prophylactic treatment at baseline had moderate haemophilia and 12/37 (32%) had mild haemophilia. 25/51 (49%) people with moderate haemophilia A		After a median of 55.6 weeks follow up of participants with moderate haemophilia A (n=51) taking emicizumab, the model-based ABR for all bleeds was 2.2 (95% CI 1.57 to 3.20) compared with 6.0 (95% CI 4.33 to 8.22) over the 24 weeks before study entry. In participants receiving prophylaxis at baseline (n=37), the model-based ABR for all bleeds was 2.2 (95% CI 1.49 to 3.12) with emicizumab compared with 12.2 (95% CI 6.15 to 24.05) before study entry; in those on episodic treatment at baseline (n=35), the model-based ABR for all bleeds was 2.4 (95% CI 1.42 to 4.09) compared with 8.0 (95% CI 5.68 to 11.13) before study entry. Other subgroup analysis model-based ABR's for all bleeds with emicizumab treatment. Baseline ABR for all bleeds not provided for these subgroups: 1.5 mg/kg once a week maintenance dose (n=25), 1.9 (95% CI 1.27 to 2.96); 3 mg/kg every 2 weeks (n=39), 2.1 (95% CI 1.37 to 3.26); 6 mg/kg every 4 weeks (n=8), 4.3 (95% CI 1.42 to 13.32). No target joints (n=48), 2.1 (95% CI 1.39 to 3.03); any target joints (n=24), 2.7 (95% CI 1.64 to 4.54). Male (n=69), 2.1 (95% CI 1.53 to 2.77); female (n=3), 9.1 (95% CI 1.42 to 58.67). **Joint health** 21 out of 24 participants with target joints at baseline were in the study for at least 52 weeks. 20/21 (95%) of these reported fewer than three bleeds over a 52-week period (meeting criteria for resolved target joints in the study). At baseline, mean total HJHS was 7.20 (SD 10.37) in 65 participants; at week 49, this was 6.48 (SD 8.96) in 56 participants, with a mean change from baseline of −1.25 (SD 3.95) in 52 participants. Higher scores on the HJHS indicate worse joint health. The maximum total score is 124. **Important outcomes** **Health related quality of life (HRQL)**	individuals with moderate or mild haemophilia A. Haemophilia treatment information and bleed data had to be reported by participants using a Bleed and Medication Questionnaire at least once weekly via a handheld device. Bleed data for the 24 weeks before the study was collected retrospectively. Baseline ABR for treated bleeds or joint bleeds not provided. Subgroups for subgroup analysis on ABRs are small and baseline ABRs not provided for all subgroups so difficult to draw conclusions on these results. p values for comparisons between subgroups were not reported. Only 12/72 participants from the UK. Source of funding: F Hoffmann-La Roche.

	currently taking prophylactic treatment. Model-based ABR for all bleeds 10.1 (95% CI 6.93 to 14.76). 24/72 (33%) had target joints. Mean number of target joints 0.6 (SD 1.2). Investigator-reported reason for warranting prophylaxis (more than 1 reason could be given): history of frequent bleeding 41/72 (57%); history of frequent joint bleeding 32/72 (44%); history of severe bleeding 15/72 (21%); prevention of traumatic bleeds 9/72 (13%); other 5/72 (7%).		The mean CATCH score in the treatment burden domain was reported to show a trend to improvement in children and young people and adults aged 8 years and over, although results only presented graphically (up-to week 61). Other domains were reported to be stable, with baseline values maintained until week 49. Specific values were not reported. **Patient treatment preference** 50/52 (96%) participants aged 12 years or older responding to the EmiPref questionnaire preferred emicizumab to their previous treatment. 24/28 (86%) caregivers responding to the questionnaire preferred emicizumab to their child's previous treatment. EmiPref questionnaire conducted at week 17. **Rate of joint bleeding events** After a median of 55.6 weeks follow-up of all participants taking emicizumab**,** model-based ABR were 0.2 (95% CI 0.09 to 0.57) for treated joint bleeds and 0.1 (95% CI 0.03 to 0.40) for treated target joint bleeds. Baseline ABR for treated joint or target joint bleeds was not provided. **Activities of daily living** For all treated children, young people and adults aged 5 years and over, duration of time spent in moderate-to-vigorous activity and mean daily step counts were reported to be stable from baseline to week 49. Results presented graphically. **Safety** Over a median follow up of 55.6 weeks, 60/72 (83%) participants had an adverse event.15/72 (21%) participants had an adverse event considered related to emicizumab. Most treatment-related adverse events were local injection-site reactions. The most common adverse events were headache (12/72, 17%), injection-site reaction (12/72, 17%), and arthralgia (11/72, 15%).	

			8/72 (11%) had a serious adverse event, none were considered to be emicizumab-related. 4/72 (6%) had a grade 3 or above adverse event. Treatment-induced anti-drug antibodies were detected in 2/72 (3%) of participants. Both participants had no bleeds, no injection-site reactions, hypersensitivity, or anaphylactic reactions. No thrombotic microangiopathies; 1/72 (1%) had grade 1 thrombosed haemorrhoids which was classified as a thrombotic event (deemed unrelated to emicizumab). No deaths, no adverse events led to treatment withdrawal, modification, or interruption. No systemic hypersensitivity, anaphylactic, or anaphylactoid reactions. No clinically significant changes from baseline in vital signs or ECG parameters. In participants with moderate haemophilia A, 42/51 (82%) had an adverse event and 6/51 (12%) had a serious adverse event. Injection-site reactions were reported by 8/51 (16%).	

Abbreviations

ABR, annualised bleed rate; BU, Bethesda unit; CATCH, the Comprehensive Assessment Tool of Challenges in Haemophilia; CI, confidence interval; HJHS, Haemophilia Joint Health Score; IQR, interquartile range; SD, standard deviation.

Appendix F Quality appraisal checklists

The National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) studies with no (concurrent) control group

1. Was the study question or objective clearly stated?

2. Were eligibility/selection criteria for the study population prespecified and clearly described?

3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?

4. Were all eligible participants that met the prespecified entry criteria enrolled?

5. Was the sample size sufficiently large to provide confidence in the findings?

6. Was the test/service/intervention clearly described and delivered consistently across the study population?

7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?

8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?

9. Was the loss to follow up after baseline 20% or less? Were those lost to follow up accounted for in the analysis?

10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?

11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?

12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Appendix G GRADE profiles

Table 2: Question In people with moderate haemophilia A without inhibitors, what is the clinical effectiveness and safety of emicizumab prophylaxis compared with current standard care?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Emicizumab	No comparator	Result (95%CI)		
Rate of treated bleeding events (1 single-arm study)									
Model-based ABR for treated bleeds in participants with mild or moderate haemophilia A without inhibitors over a median follow-up of 55.6 weeks (IQR 52.3 to 61.6 weeks)[A]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	0.9 (95% CI 0.55 to 1.52) Baseline ABR for treated bleeds not provided	CRITICAL	VERY LOW
Model-based ABR for treated bleeds in participants with moderate haemophilia A without inhibitors over a median follow-up of 55.6 weeks (IQR 52.3 to 61.6 weeks)[A]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=51	-	0.9 (95% CI 0.50 to 1.78) Baseline ABR for treated bleeds not provided	CRITICAL	VERY LOW
Rate of all bleeding events (1 single-arm study)									
Model-based ABR for all bleeds in participants with mild or moderate haemophilia A without inhibitors over a median follow-up of 55.6 weeks (IQR 52.3 to 61.6 weeks)[A]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	2.3 (95% CI 1.67 to 3.12) compared with 10.1 (95% CI 6.93 to 14.76) pre-study (measured in the 24 weeks before study entry) Bleed data self-reported Bleed data for the 24 weeks before the study was collected retrospectively	CRITICAL	VERY LOW
Model-based ABR for all bleeds in participants with moderate haemophilia A without inhibitors over a median follow-up of 55.6 weeks (IQR 52.3 to 61.6 weeks)[A]									
Single-arm study	Serious[1]	Serious[2]	Not applicable	Not reported	N=51	-	2.2 (95% CI 1.57 to 3.20) compared with 6.0 (95% CI 4.33 to 8.22) pre-study	CRITICAL	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Emicizumab**	**No comparator**	**Result (95%CI)**		
1 study Négrier et al. 2023							(measured in the 24 weeks before study entry) Bleed data self-reported Bleed data for the 24 weeks before the study was collected retrospectively		
Joint health (1 single-arm study)									
Target joint resolution in participants with mild or moderate haemophilia A without inhibitors who had target joints at baseline and were in the study for at least 52 weeks[B]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=21		20/21 (95%)	CRITICAL	VERY LOW
Mean total Haemophilia Joint Health Score from baseline to week 49 in participants with mild or moderate haemophilia A without inhibitors[C]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=65	-	7.20 (SD 10.37) at baseline in 65 participants 6.48 (SD 8.96) in 56 participants at week 49 mean change from baseline of −1.25 (SD 3.95) in 52 participants	CRITICAL	VERY LOW
Health related quality of life (1 single-arm study)									
Mean CATCH domain scores from baseline to week 49 and week 61 in participants aged 8 and over with mild or moderate haemophilia A without inhibitors[D]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=60	-	The mean CATCH score in the treatment burden domain was reported to show a trend to improvement although results only presented graphically (up-to week 61) Other domains were reported to be stable, with baseline values maintained until week 49 although no specific results presented	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Emicizumab**	**No comparator**	**Result (95%CI)**		
Patient treatment preference (1 single-arm study)									
Number of participants 12 years and over who preferred emicizumab to their previous treatment assessed by EmiPref questionnaire conducted at week 17[E]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	52	-	50/52 (96%)	IMPORTANT	VERY LOW
Number of caregivers responding to EmiPref questionnaire conducted at week 17 who preferred emicizumab to their child's previous treatment[E]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	28	-	24/28 (86%)	IMPORTANT	VERY LOW
Rate of joint bleeding events (1 single-arm study)									
Model-based ABR for treated joint bleeds in participants with mild or moderate haemophilia A without inhibitors over a median follow-up of 55.6 weeks (IQR 52.3 to 61.6 weeks)									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[1]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	0.2 (95% CI 0.09 to 0.57) Baseline ABR for treated joint bleeds not provided	IMPORTANT	VERY LOW
Model-based ABR for treated target joint bleeds in participants with target joints at baseline over a median follow-up of 55.6 weeks (IQR 52.3 to 61.6 weeks)[B]									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[1]	Not applicable	Not reported	N=24	-	0.1 (95% CI 0.03 to 0.40) Baseline ABR for treated target joint bleeds not provided	IMPORTANT	VERY LOW
Activities of daily living (1 single-arm study)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Emicizumab**	**No comparator**	**Result (95%CI)**		
Change from baseline to week 49 in mean daily step count in participants aged 5 and over with mild or moderate haemophilia A without inhibitors									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=not reported	-	Mean daily step counts reported to be stable from baseline to week 49 Results only presented graphically	IMPORTANT	VERY LOW
Change from baseline to week 49 in moderate-to-vigorous activity in participants aged 5 and over with mild or moderate haemophilia A without inhibitors									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=not reported	-	Duration of time spent in moderate-to-vigorous activity reported to be stable from baseline to week 49 Results only presented graphically	IMPORTANT	VERY LOW
Safety (1 single-arm study)									
Number of participants with mild or moderate haemophilia A without inhibitors with an adverse event over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks)									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	60/72 (83%) The most common adverse events were headache (12/72, 17%), injection-site reaction (12/72, 17%), and arthralgia (11/72, 15%)	IMPORTANT	VERY LOW
Number of participants with mild or moderate haemophilia A without inhibitors with an adverse event considered related to emicizumab over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks)									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	15/72 (21%) Most treatment-related adverse events were local injection-site reactions	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Emicizumab**	**No comparator**	**Result (95%CI)**		
Number of participants with moderate haemophilia A without inhibitors with an adverse event over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks)									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=51	-	42/51 (82%)	IMPORTANT	VERY LOW
Number of participants with mild or moderate haemophilia A without inhibitors with a serious adverse event over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks)									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	8/72 (11%) No deaths No systemic hypersensitivity, anaphylactic, or anaphylactoid reactions. No clinically significant changes from baseline in vital signs or ECG parameters.	IMPORTANT	VERY LOW
Number of participants with moderate haemophilia A without inhibitors with a serious adverse event over a median follow up of 55.6 weeks (IQR 52.3 to 61.6 weeks)									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=51	-	6/51 (12%)	IMPORTANT	VERY LOW
Number of participants with mild or moderate haemophilia A without inhibitors with an adverse event leading to treatment withdrawal, modification, or interruption									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	0/72	IMPORTANT	VERY LOW
Number of participants with mild or moderate haemophilia A without inhibitors who had a Grade 3 or above adverse event									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Emicizumab**	**No comparator**	**Result (95%CI)**		
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	4/72 (6%)	IMPORTANT	VERY LOW
Number of participants with mild or moderate haemophilia A without inhibitors who had thrombotic microangiopathies or thrombotic events									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	No thrombotic microangiopathies 1/72 (1%) had grade 1 thrombosed haemorrhoids which was classified as a thrombotic event (deemed unrelated to emicizumab)	IMPORTANT	VERY LOW
Number of participants with mild or moderate haemophilia A without inhibitors who had treatment-induced anti-drug antibodies detected									
Single-arm study 1 study Négrier et al. 2023	Serious[1]	Serious[2]	Not applicable	Not reported	N=72 (moderate haemophilia A, n=51; mild haemophilia A, n=21)	-	2/72 (3%) Both participants had no bleeds, no injection-site reactions, hypersensitivity or anaphylactic reactions	IMPORTANT	VERY LOW

Abbreviations

ABR, annualised bleed rate; BU, Bethesda unit; CATCH, the Comprehensive Assessment Tool of Challenges in Haemophilia; CI, confidence interval; IQR, interquartile range; SD, standard deviation.

1 No blinding of investigators or participants. Statistical methods did not examine changes in outcome measures from before to after the intervention, p values for the pre-to-post changes not provided.
2 Single-arm study. No comparison group. Study population mixed population of mild and moderate haemophilia A without inhibitors.

A Moderate Haemophilia A defined as FVIII activity ≥1% to ≤5%, and mild >5% to <40%. Model-based ABR accounts for different follow-up times. Treated bleeds were defined as bleeds in which coagulation factors were given to treat signs or symptoms of bleeding. Two bleeds of the same type and at the same anatomical location were considered to be 1 bleed if the second bleed occurred within 72 hours from the last treatment for the first bleed.
B Target joints were defined as joints with 3 or more bleeds occurring in the same joint during the last 24 weeks or unresolved target joints, defined as a target joint that does not fulfil the criterion of 2 or less bleeds into this joint within a consecutive 12-month period. Resolved target joints were classed as reporting fewer than three bleeds over a 52-week period.
C Haemophilia Joint Health Score (HJHS). The HJHS measures joint health, in the domain of body structure and function (impairment), of the joints most commonly affected by bleeding in haemophilia: the knees, ankles, and elbows. It is primarily designed for children with haemophilia aged 4 to 18 with mild joint impairment. The maximum total score is 124. Higher scores indicate worse joint health.

D CATCH (the Comprehensive Assessment Tool of Challenges in Haemophilia) is a tool to assess outcomes important to children, young people and adults with haemophilia. It includes domains related to quality of life, lifestyle restrictions, physical activity and treatment burden.
E EmiPref Questionnaire – a questionnaire to assess treatment preference. Participants or caregivers were asked to report what treatment regimen they preferred: emicizumab or their pre-study treatment.

Glossary

Haemophilia A	Haemophilia is an inherited genetic condition of which there are 2 main types (haemophilia A and B). The most common is haemophilia A, a deficiency of coagulation factor VIII (FVIII) which causes increased bleeding.
FVIII inhibitors	In up-to a third of patients with haemophilia A treated with long-term replacement factor VIII, alloantibodies against the replacement factor develop and render this treatment ineffective. These antibodies are referred to as FVIII inhibitors (or inhibitors) and can be detected via a blood test.
Severe, moderate and mild haemophilia A	The condition can be classified depending on the FVIII level as a percentage of the normal level: severe (<1% of normal levels), moderate (≥1% to ≤5%), and mild (>5% to <40%).
Target joints	When there is recurrent bleeding into a certain joint. In the Négrier et al. 2023 study target joints were defined as joints with 3 or more bleeds occurring in the same joint during the last 24 weeks or unresolved target joints, defined as a target joint that does not fulfil the criterion of 2 or less bleeds into this joint within a consecutive 12-month period.

References

Included study:

- Négrier et al. (2023) Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study. Lancet Haematology. 10 (3): e168-e177. doi: 10.1016/S2352-3026 (22)00377-5

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