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Clinical evidence review of emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors

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About this clinical evidence review

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Summary

This evidence review considers emicizumab for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in people with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. The evidence review was undertaken in line with NHS England's methods for undertaking clinical evidence reviews.

A literature search was done, which identified 167 references (see appendix 1 for search strategy). The company also provided a submission of evidence. One published study was included in this review.

Overview of included studies

Evidence of the effect of emicizumab comes from one 24-week open-label, randomised trial including a total of 109 participants (53 randomised and 56 non-randomised; Oldenburg et al. 2017). The key efficacy results for the study were only reported for the 53 randomised participants. Participants in the study had a confirmed diagnosis of congenital haemophilia A, a history of factor VIII inhibitors and were receiving episodic (on-demand) or prophylactic treatment with bypassing agents at recruitment.

Effectiveness

Evidence from the 24-week randomised trial suggests that in people who had previously received episodic treatment with a bypassing agent, emicizumab (n=35) is associated with a significant reduction in bleeds requiring treatment per year compared with no prophylactic treatment (n=18, 2.9 events versus 23.3 events, risk ratio [RR] 0.13, p<0.001). This outcome suggests that people with haemophilia A with factor VIII inhibitors who take emicizumab can expect to have fewer bleeds each year that require treatment with a bypassing agent, than if they did not take emicizumab.

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Evidence from the same trial also suggest that people taking emicizumab prophylaxis had significant improvements in their quality of life and health status compared with people receiving no prophylaxis.

Some people in the study by Oldenburg et al. (2017) had previously been involved in an unpublished non-interventional study that assessed efficacy and safety outcomes in people with haemophilia A receiving standard clinical care (NCT02476942). These people had a lower annualised bleeding rate while treated with emicizumab in the Oldenburg et al. (2017) study compared with that observed during standard care in the non-interventional study. However, since the non-interventional is not yet published conclusions on the relative effectiveness of emicizumab compared with standard care cannot be made.

Safety and tolerability

Evidence from the randomised trial by Oldenburg et al. (2017) found that 73/103 people (70.9%) treated with emicizumab reported at least 1 adverse event. The most common adverse events were injection-site reactions, upper respiratory tract infection, headache, fatigue and arthralgia (joint pain). Adverse events were only reported for people receiving emicizumab; not reported for the no prophylaxis group while receiving no treatment.

There were 3 cases of thrombotic microangiopathy, 1 case of cavernous sinus thrombosis and 1 case of superficial thrombophlebitis in people receiving emicizumab. All participants who experienced these adverse events were also receiving activated prothrombin complex concentration (a bypassing agent) at doses of more than 100 U/kg for more than 1 day. The authors concluded that the combination of emicizumab and activated prothrombin complex concentrate appears to be associated with an increased risk of toxic effects, limiting the usefulness of this bypassing agent for the management of bleeds in people receiving emicizumab prophylaxis.

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No participants in the Oldenberg et al. (2017) study developed anti-drug antibodies for emicizumab. Declining exposure to emicizumab was observed in the pharmacokinetic profiles of 2 participants, which may indicate the development of antibodies. These participants are being followed up.

Evidence gaps

Emicizumab prophylaxis has not been directly compared with bypassing agent prophylaxis in a pair-wise comparison randomised controlled trial.

The primary efficacy endpoint of the Oldenburg et al. (2017) study was reported at week 24, data beyond this time-point are currently lacking.

The efficacy and safety of emicizumab prophylaxis in people aged less than 12 years has not been demonstrated in a published trial, although a trial has been conducted in this population and is likely to publish in the future.

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Abbreviations

Term	Definition
aPCC	Activated prothrombin complex concentrate, a bypassing agent for managing bleeding
dL	Decilitre
EQ-5D-5L	EuroQol group 5-Dimension Self-Report Questionnaire (5-level version)
Haem-A-QoL	Haemophilia Quality of Life Questionnaire
ITI	Immune Tolerance Induction
IU	International unit
rFVIIa	Recombinant activated factor VII, a bypassing agent for managing bleeding

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Medical definitions

Term	Definition
Antibody	A type of protein produced by the body's immune system, which combines with foreign material in the body (such as bacteria or viruses) to act against it
Bethesda units	The Bethesda assay is used to quantify the concentration of factor VIII inhibitor. One Bethesda unit (BU) is the amount of inhibitor required to neutralise 50% of a unit of factor VIII in normal plasma after incubation at 37°C for 2 hours
Factor VIII	A protein involved in blood clotting
Haemophilia A	An inherited condition, affecting predominately males, in which there is excessive bleeding which can follow trauma or can occur spontaneously due to insufficient production of factor VIII, an essential blood-clotting protein.
Inhibitor	An antibody produced by the immune system which neutralises and de-activates factor VIII
Inhibitor titres	Measured in Bethesda units (BU). The higher the number of Bethesda units, the more inhibitors are present.
Recombinant	Recombinant material (such as genes, proteins or cells) is formed by genetic engineering, by combining genetic material from more than 1 place. Susoctocog alfa is a recombinant protein that is genetically engineered using the factor VIII gene from pigs
Target joint	A joint in the body where there are recurrent bleeds
Titre	The concentration of a substance (such as an antibody) in solution, which is worked out by a method called titration

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Introduction

Disease background

Haemophilia is an inherited genetic condition of which there are two main types. The most common is haemophilia A, a deficiency of coagulation factor VIII, which causes increased bleeding and usually affects males with a prevalence of between 1 in 5,000 and 1 in 10,000 in males. Recurrent bleeds lead to progressive joint damage and other complications (NHS England Clinical Commissioning Policy: Immune Tolerance Induction [ITI] for haemophilia A).

Diagnosis is normally made in early childhood. People diagnosed with haemophilia A require prophylactic treatment with recombinant factor VIII in order to prevent bleeds. Up to 4% of people with haemophilia A will form antibodies against administered factor VIII after commencing treatment. These antibodies are known as inhibitors. The inhibitors neutralise the circulating factor VIII, causing it to be broken down and removed from the blood stream. The level of risk of developing inhibitors to factor VIII depends upon the specific inherited genetic mutation, and this will vary from family to family. Generally speaking, the risk is higher in people with severe haemophilia, and usually occurs within the first 10-20 exposure days to administered factor VIII. However, inhibitors can develop even after many years of treatment (NHS England Clinical Commissioning Policy: Immune Tolerance Induction [ITI] for haemophilia A).

Immune tolerance induction (ITI), also known as immune tolerance therapy (ITT), involves administration of factor VIII in increased doses so that the person's immune system learns to tolerate the factor VIII and ceases to produce inhibitors. Immune induction therapy is routinely commissioned by NHS England and is the only proven method for the eradication of inhibitors (NHS England Clinical Commissioning Policy: Immune Tolerance Induction [ITI] for haemophilia A). ITI must be initiated soon after the presence of

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factor VIII inhibitors are confirmed for it to work. ITI works for most people who have it (approximately 70%), but for some people ITI will not get rid of the factor VIII inhibitor (approximately 30%),

To control bleeding, patients with inhibitors have to be treated with agents which bypass it. The two products currently available for this are recombinant factor VIIa (rFVIIa, Novoseven) and factor VIII bypassing agent (FEIBA, anti-inhibitor coagulant complex; an activated prothrombin complex concentrate, aPCC).

Focus of review

In line with the anticipated marketing authorisation, the focus of this review is on the routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

Epidemiology and needs assessment

The UK National Haemophilia Database Bleeding Disorder Statistics for 2015-2016 reports that between April 2015 and March 2016 there were 5,930 people in the UK with mild, moderate or severe forms of haemophilia A (not including low-level carriers; factor VIII level ≥40 IU/dL). Of these, 230 people (3.9%) have current inhibitors, the majority of whom have severe haemophilia A (164 people; 71%), followed by moderate (42 people; 18%) and mild (24 people; 10%).

Table 1 Patient numbers

Estimates	Data source	Number of people
People with haemophilia A (excluding low-level carriers)	UK National Haemophilia Database Bleeding Disorder Statistics for 2015-2016	**Total = 5,930** Severe = 1,845 Moderate = 882 Mild = 3,203
People with haemophilia A and current inhibitors (excluding low-level carriers) – approximately 4%		**Total = 230** Severe = 164 Moderate = 42

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of people with haemophilia A		Mild = 24
People with haemophilia A and newly reported inhibitors (excluding low-level carriers)		**Total = 29** Severe = 19 Moderate = 4 Mild = 6
Definitions Severe = Factor VIII level <1 IU/dL, or <1% of normal Moderate = Factor VIII level 1 to 5 IU/dL, or 1-5% of normal Mild = Factor VIII level >5 to <40 IU/dL, or >5 to <40% of normal Low level carriers = Factor VIII level ≥40 IU/dL, or ≥40% of normal Not all patients will be eligible for ITI as it is has to be initiated soon after the inhibitors are identified. ITI does not work for approximately 30% of patients		

Product overview

Mode of action

Emicizumab (ACE910) is a bispecific monoclonal antibody designed to mimic factor VIII activity. Emicizumab bridges activated factor IX and factor X to restore the function of activated factor VIII, which is needed for effective haemostasis (Oldenburg et al. 2017).

Regulatory status

Emicizumab does not currently have a UK marketing authorisation. It has been studied in clinical trials in people aged 12 years and over with congenital haemophilia A with a history of factor VIII inhibitors who are receiving episodic or prophylactic treatment with bypassing agents.

Treatment pathway and current practice

The NHS England commissioning policy Immune Tolerance Induction (ITI) for haemophilia A (all ages) states that infants and children with severe haemophilia (and adults who are initiating treatment) should be tested for an inhibitor at least every third exposure day until 20 exposure days and subsequently every 3-6 months until 150 exposure days to ensure that an

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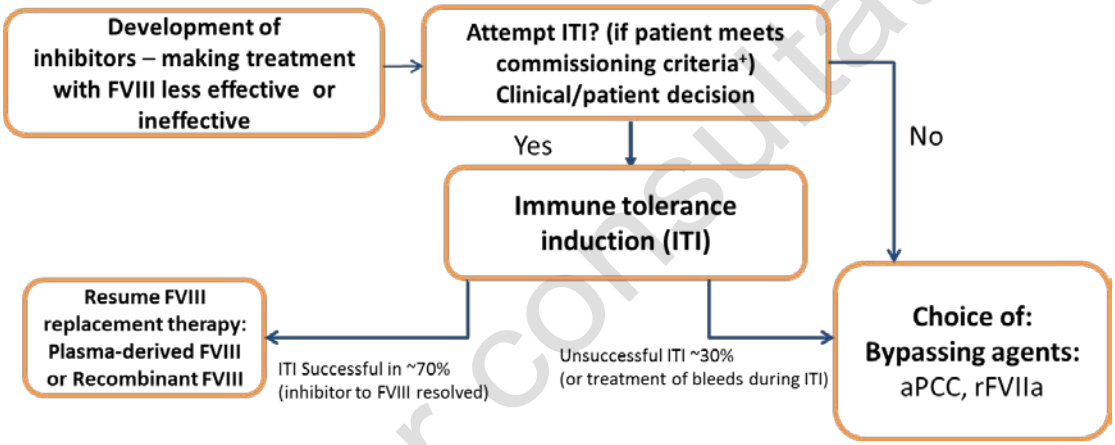
inhibitor is detected and treated early. When an inhibitor is detected, ITI should be considered as an option to optimise the chances of inhibitor eradication. The commissioning policy states that where there is an inadequate sustained downward trend in the inhibitor titre, the specialist team would be expected to consider alternative strategies.

In their submission, the company provided the following current treatment pathway for people with haemophilia A with factor VIII inhibitors (see figure 1).

Figure 1 Current treatment pathway for people with haemophilia A with factor VIII inhibitors (submitted by company).



The company has suggested that emicizumab could be a treatment option for people who cannot undergo ITI and those for whom ITI was unsuccessful. A proposed treatment pathway was provided.

Figure 2 Proposed treatment pathway for people with haemophilia A with factor VIII inhibitors, including emicizumab (submitted by company)

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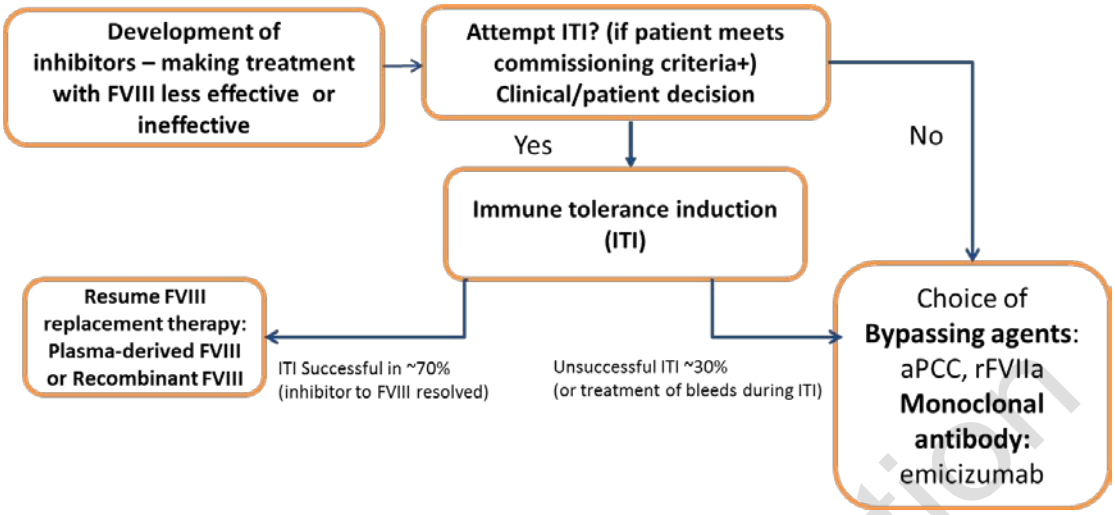

Evidence base

A literature search was done, which identified 167 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 13 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 1 study was included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

The company submission identified 6 references to published studies in their submission. All of these studies were identified in the literature search, and as such no additional unique references were identified.

Clinical evidence

Overview of included studies

One open-label, phase III, randomised trial identified from the search (Oldenburg et al. 2017) was included in this evidence summary. A summary of the characteristics of the included study is shown in table 2 (see evidence tables for full details).

Table 2 Summary of included studies

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Study	Population	Intervention and comparison	Primary outcome
Oldenburg et al. 2017 (HAVEN 1) Open-label, phase III, randomised trial	People aged 12 years and over with congenital haemophilia A (only men included), a history of factor VIII inhibitors and receiving episodic or prophylactic treatment with bypassing agents (53 randomised participants and 56 non-randomised participants; total n=109)	Emicizumab subcutaneous injection, 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly thereafter No treatment	Number of bleeds requiring treatment

Key outcomes

The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 3 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence table and results for the study can be found in appendices 3 and 4.

Study design

There were 4 treatment arms in the study (Oldenburg et al. 2017), 2 were randomised and 2 non-randomised. People who had previously received episodic (on-demand) treatment with a bypassing agent were randomised to emicizumab (Group A, n=35) or no prophylaxis (Group B, n=18). The study also included people who had previously received prophylactic treatment with a bypassing agent who were allocated to receive emicizumab (in a non-randomised fashion, Group C, n=49). A fourth treatment group included people who were unable to enrol in the other 3 groups before they were

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closed for enrolment; these people all received emicizumab (non-randomised, Group D, n=7).

One participant randomised to group A withdrew before receiving the first dose of emicizumab; this person is included in the efficacy intention to treat (ITT) population, but not included in the safety analysis. After data on the primary efficacy treatment were collected in week 24, participants randomised to the no prophylaxis group (group B) could be switched to emicizumab treatment. In total 13 out of 18 participants started taking emicizumab at this point.

The primary outcome and most of the secondary outcomes of the study were based on comparisons between these 2 groups.

Effectiveness

Bleeding outcomes

The primary efficacy outcome in the study by Oldenburg et al. (2017) was number of bleeds requiring treatment with a bypassing agent. People previously treated with episodic bypassing agents who received emicizumab had a lower annualised treated bleed rate (Group A, 2.9 events, 95% CI 1.7 to 5.0) compared with no prophylaxis (Group B, 23.3 events, 95% CI 12.3 to 43.9; risk ratio [RR] 0.13, 95% CIs not reported; p<0.001). These results suggest that compared with no prophylaxis treatment, emicizumab reduced the number of bleeds requiring treatment per year by 87%.

For people who had previously received prophylactic treatment with a bypassing agent (group C, n=49) the annualised treated bleed rate was 5.1 events (95% CI 2.3 to 11.2), although this study was not designed to compare this group to the no prophylaxis group and no statistical analysis is reported.

Statistically significant reductions in annualised bleeding rates for emicizumab (group A) compared with no prophylaxis (group B) were also observed for the

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secondary bleeding-related outcomes: all bleeds (RR 0.20), spontaneous bleeds (RR 0.08) and joint bleeds (RR 0.11, all p<0.01).

Quality of life and health status outcomes

Health-related quality of life was reported using the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale and total score. The Haem-A-QoL assesses health-related quality of life in people with haemophilia A and B. The questionnaire consists of 46 items and is composed of 10 subscales; all subscales are combined to get a total score. Subscale scores are transformed to a 0 to 100 scale, with lower scores suggesting better health-related quality of life. A reduction of 10 points on the physical health subscale and 7 points in total score represent a clinically meaningful improvement in health-related quality of life (Wyrwich et al. 2015).

At week 25 the adjusted mean difference in the Haem-A-QoL physical health subscale between emicizumab (group A) and no prophylaxis (group B) was 21.6 points (95% CI 7.9 to 35.2, p=0.003). This mean reduction is greater than the minimal clinically meaningful difference (MCID) of 10 points, although the lower limit of the 95% CI falls below the MCID. Similar results were observed for the Haem-A-QoL total score, with a mean reduction greater than the MCID of 7 points observed, but with the lower limit of 95% CI falling below the MCID (adjusted mean difference 14.0 points, 95% CI 5.6 to 22.4, p=0.002).

Health status was reported using the 5-level version of the EuroQol group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) visual analogue scale and index utility score. EQ-5D is a standardised instrument for measuring health status that can be used in a wide range of health conditions and treatments. The EQ-5D-5L visual-analogue scale ranges from 0 to 100, with higher scores indicating better health status and a change of 7 points is considered a clinically meaningful difference (Pickard et al. 2007). The EQ-5D-5L index utility score ranges from −0.4 to 1.0, with higher scores indicating better health status and a change of 0.07 points is considered a clinically meaningful difference (Pickard et al. 2007).

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At week 25 the adjusted mean difference in the EQ-5D-5L visual-analogue scale between emicizumab (group A) and no prophylaxis (group B) was −9.7 points (95% CI −17.6 to −1.8, p=0.02). The mean reduction was greater than the MCID of 7 points, although the lower limit of the 95% falls below the MCID. Significant reductions were also reported for the EQ-5D-5L index utility score (−0.16 points, 95% CI −0.25 to −0.07, p=0.001). The mean reduction is greater than the MCID of 0.07 points, although the lower limit of the 95% CI falls below the MCID.

Before-and-after comparison

Oldenburg et al. (2017) also reported intra-individual comparisons of emicizumab with standard care in a sub-set of participants previously recruited into a non-interventional study. In total 24 participants in group A and 24 participants in group C had previously been recruited into a prospective, non-interventional study that collected real-world data on bleeding events and safety outcomes in people with haemophilia A who received episodic or prophylactic treatment with bypassing agents (given according to local, routine clinical practice). This non-interventional study has not been published in a peer-reviewed journal (NCT02476942), although some comparison results are reported by Oldenburg et al. (2017).

Among the people in group C who took part in the non-interventional study (n=24), the intra-individual comparison showed a significantly lower annualised bleeding rate with emicizumab (3.3 events, 95% CI 1.3 to 8.1) compared with previous prophylactic bypassing agents (15.7 events, 95% CI 11.1 to 22.3). This is a 79% reduction in bleeding rate (p<0.001, 95% CIs not reported).

Among the 24 people in group A who took part in the non-interventional study, the annualised bleeding rate was significantly lower with emicizumab (1.7 events, 95% CI 0.7 to 4.1) compared with previous episodic bypassing

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agents (21.6 events, 95% 15.4 to 30.2). This is a 92% reduction in bleeding rate (p<0.001, 95% CI not reported).

The results of this intra-individual comparison need to be interpreted with care. The non-interventional study has not been published in a peer-reviewed journal, meaning there are no details on baseline characteristics and the treatments the participants received. It is not clear from the report by Oldenburg et al. how participants were selected from the non-interventional study, and whether selection bias may be present. In addition to this, care must be taken when comparing the results of a 'real-world' study using standard-care with the results of a more rigidly controlled clinical trial. In the absence of a published study these results cannot be critically appraised.

Safety and tolerability

Adverse events

In total, 198 adverse events were reported in 103 participants receiving emicizumab in the study by Oldenburg et al. (2017); this includes people in the no prophylaxis group who were switched to emicizumab after week 25 (n=13). Across the 4 treatment arms, during treatment with emicizumab 73 out of 103 people (70.9%) reported 1 or more adverse events. The most common adverse event was injection-site reactions (28 events in 15 people). In addition to this 9 people reported an upper respiratory tract infection, 12 people reported headache, 6 people reported fatigue and 6 people reported arthralgia (number of actual events not reported). These common adverse events were all mild in intensity and resolved, except for 1 case of moderate injection-site haematoma occurring on day 2 of the trial, which resolved on day 28.

Serious adverse events during emicizumab treatment were reported in 9 out of 103 (8.7%) people. Cases of thrombotic microangiopathy (in 2 participants), skin necrosis, superficial thrombophlebitis and cavernous sinus thrombosis (in 1 participant each) were reported in people who had received multiple

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infusions of activated prothrombin complex concentration while receiving emicizumab. The cases of thrombotic microangiopathy resolved after the activated prothrombin complex concentrate was stopped, and neither thrombotic events required anticoagulation. The authors report that after data cut-off for the primary analysis, thrombotic microangiopathy developed in 1 additional participant. This occurred 5 days after their previous emicizumab dose and after 4 consecutive days of treatment with activated prothrombin complex concentration which was given for a rectal haemorrhage. This rectal bleeding was recurrent and eventually fatal; although the investigators assessed that the thrombotic microangiopathy was resolved at the time of death. Other serious adverse events reported during emicizumab prophylaxis included skin necrosis, iron deficiency anaemia, sepsis, haemarthrosis, muscle haemorrhage, gastric ulcer haemorrhage, headache and haematuria (occurring in 1 participant each).

The investigators report that of 104 participants receiving emicizumab, 28 people (27%) used activated prothrombin complex concentrate, 34 people (33%) used recombinant factor VIIa, and 13 people (12%) used both bypassing agents. A range of doses for recombinant factor VIIa were used, and most treatment episodes lasted for 1 day. Most people treated with activated prothrombin complex concentrate received doses less than 100 U/kg for 1 day, although in 19 treatment events a dose of more than 100 U/day was given for more than 1 day. All of the 5 people who had thrombotic microangiopathy or thrombosis had received activated prothrombin complex concentration at a dose of more than 100 U/kg for more than 1 day.

The investigators note that synergistic thrombin generation has been shown with aPCC in combination with emicizumab in vitro and in vivo. Substrates for emicizumab to form the intrinsic tenase complex are supplied by aPCC, along with other activated and non-activated coagulation factors that have half-lives of up to 60 hours and can accumulate with multiple doses. The authors conclude that the combination of emicizumab and activated prothrombin

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complex concentrate appears to be associated with an increased risk of adverse effects, which may limit the usefulness of this bypassing agent for managing bleeds in people receiving emicizumab prophylaxis.

Pharmacokinetics and antibodies

No participants tested positive for anti-drug antibodies for emicizumab. However, the pharmacokinetic profiles of 2 participants showed declining exposure to emicizumab over-time, which may be suggestive of anti-drug antibodies. One of these participants experienced no bleeding events while on emicizumab prophylaxis, and the other is being monitored after having their dose of emicizumab increased to 3 mg/kg at week 24 (shortly before the primary analysis). Both participants remained in the trial and are being followed up.

Evidence gaps

No RCTs were identified that directly compared prophylaxis with emicizumab to prophylaxis with a bypassing agent using a pair-wise comparison study design. Comparisons of emicizumab with bypassing agents are limited to intra-individual comparisons for a sub-group of participants who had previously been enrolled in an unpublished, non-interventional study.

All participants involved in the study by Oldenburg et al. (2017, HAVEN 1) were aged 12 years and over; the median age was 28 years (range 12 to 75) and 29% of participants were aged less than 18 years. A separate study is investigating emicizumab in children with haemophilia A and inhibitors, although at the time of this review this study had not published in a peer-reviewed journal, meaning the efficacy, safety and pharmacokinetics in this population is not known.

The primary efficacy outcome for Oldenburg et al. (2017) was reported at week 24; the effectiveness of emicizumab prophylaxis beyond this time-point is not known.

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Table 3 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Bleeding rate Reported using annualised rate of treated bleeding events Primary efficacy outcome	Oldenburg et al. 2017 (HAVEN 1)	7	Directly applicable	B	A 'treated' bleed is any bleeding event that required treatment with a haemophilia medication used to treat bleeds. In the study this was a bypassing agent (either recombinant activated factor VII or active prothrombin complex concentration). The investigators calculated the bleeding rate per day, and converted this to an annual bleeding rate. The study by Oldenburg and colleagues included 53 randomised participants who had previously received episodic treatment with bypassing agents. People treated with emicizumab (n=35) had an annual treated bleeding rate of 2.9 events (95% CI 1.7 to 5.0), compared with 23.3 events (95% CI 12.3 to 43.9) in the no prophylaxis group (n=18), risk ratio 0.13 (95% CI not reported, p<0.001). This is an 87% reduction in treated bleeds (statistically significant difference p<0.001) These results suggest that people who were previously treated with episodic bypassing agents who received emicizumab had an 87% reduction in treated bleeds compared to people who received no treatment. The results of 1 study suggest that treatment with emicizumab produces a large and statistically significant reduction in treated bleeds compared with no treatment. These results should be interpreted with a degree of caution as the study was open-label,

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					which may have introduced bias.
Quality of life Reported used the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale and total score	Oldenburg et al. 2017 (HAVEN 1)	7	Directly applicable	B	The Haem-A-QoL is a tool for assessing quality of life in people with haemophilia. The questionnaire has 2 main parts which look at 'physical health' and 'sports and leisure'. Scores range from 0 to 100, with lower scores indicating better quality of life. In Oldenburg et al. (2017), compared with those receiving no prophylaxis (n=18), people treated with emicizumab (n=35) had a significantly greater reduction in Haem-A-QoL physical health subscale score (adjusted mean difference 21.6 points (95% CI 7.9 to 35.2, p=0.003) and Haem-A-QoL total score (adjusted mean difference 14.0 points, 95% CI 5.6 to 22.4, p=0.002). The mean reductions in both scores were greater than the minimal clinically meaningful difference (MCID) reported in the literature (10 and 7 points respectively), however it should be noted that the lower 95% CI limit falls below the MCID. These results suggest that people who have previously been treated with episodic bypassing agents who receive emicizumab prophylaxis experienced a statistically significant improvement in quality of life which may be clinically meaningful. These results should be interpreted with caution as the people in the study knew which treatment they were receiving, which may have affected their perception of quality of life.
Health status Reported using the EQ-5D-5L visual analogue scale	Oldenburg et al. 2017 (HAVEN 1)	7	Directly applicable	B	The EQ-5D-5L is a standardised questionnaire used to measure health status. There are 2 parts, the EQ-5D-5L visual analogue scale (scored from 0 to 100) and the EQ-5D-5L index utility score (scored from −0.4 to 1.0); higher scores in both parts indicate better health status.

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and index utility score					In Oldenburg et al. (2017) people treated with emicizumab prophylaxis (n=35) had a significantly greater reduction in EQ-5D-5L visual analogue scale score (adjusted mean difference −9.7 points (95% CI −17.6 to −1.8, p=0.02) and EQ-5D-5L index utility score (adjusted mean difference −0.16 points, 95% CI −0.25 to −0.07, p=0.001) compared with those receiving no prophylaxis (n=18). All participants in this comparison had previously received episodic bypassing agents. The mean reductions in both scores were greater than the published MCID reported in the literature (7 and 0.07 points respectively), however it should be noted that the lower 95% CI limit falls below the MCID. Results from Oldenburg et al. suggest treatment with emicizumab prophylaxis improves health status compared with no prophylaxis. The results were statistically significant and possibly clinically meaningful. These results should be interpreted with caution as the people in the study knew which treatment they were receiving, which may have affected how they responded to the questionnaire.
Adverse events	Oldenburg et al. 2017 (HAVEN 1)	7	Directly applicable	B	A total of 198 adverse events were reported in 103 participants who received emicizumab in Oldenburg et al. (2017). The majority of participants reported at least one adverse event (73/103, 70.9%). The most common adverse events were injection-site reactions, upper respiratory tract infection, headache, fatigue and arthralgia (joint pain). Adverse events are only reported for people taking emicizumab,

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					those that occurred while people were taking no prophylaxis were not reported.
Thromboembolic and thrombotic microangiopathy events	Oldenburg et al. 2017 (HAVEN 1)	7	Directly applicable	B	In Oldenburg et al. (2017) there were 3 cases of thrombotic microangiopathy, 1 case of cavernous sinus thrombosis and 1 case of superficial thrombophlebitis in people receiving emicizumab. In all cases participants had received multiple infusions of activated prothrombin complex concentration while receiving emicizumab. Two of the cases of thrombotic microangiopathy resolved after the activated prothrombin complex concentrate was stopped, and neither thrombotic events required anticoagulation. The third case of thrombotic microangiopathy (that occurred after data cut-off for the primary analysis) happened 5 days after the person's last emicizumab dose and 4 days treatment with activated prothrombin complex concentration for a rectal haemorrhage. The rectal bleed was recurrent and ultimately fatal. Investigators assessed that the thrombotic microangiopathy had resolved at the time of death.
Development of anti-drug antibodies	Oldenburg et al. 2017 (HAVEN 1)	7	Directly applicable	B	No participants tested positive for antibodies to emicizumab. A reduction in emicizumab levels in 2 participant's over-time (which may suggest anti-drug antibodies) were observed- these participants are being followed up.

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Related NICE guidance and NHS England clinical policies

There are no specific NICE guidelines on this topic.

NHS England has published a Clinical Commissioning Policy of Immune Tolerance Induction [ITI] for haemophilia A.

A service specification for haemophilia services (all ages) commissioned by NHS England has been developed (B05/S/a).

References

Oldenburg J, Mahlangu JN, Kim B et al. (2017) Emicizumab prophylaxis in hemophilia A with inhibitors. New England Journal of Medicine 377(9), 809-818

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Appendix 1 Search strategy

Databases

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily Update and Ovid MEDLINE(R)
Platform: Ovid
Version: <1946 to September Week 1 2017>, Ovid MEDLINE(R) Epub Ahead of Print <September 14, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 14, 2017>, Ovid MEDLINE(R) Daily Update <September 14, 2017>
Search date: 15/09/2017
Number of results retrieved: 66
Search strategy:

Database: Ovid MEDLINE(R) <1946 to September Week 1 2017>, Ovid MEDLINE(R) Epub Ahead of Print <September 14, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 14, 2017>, Ovid MEDLINE(R) Daily Update <September 14, 2017>
Search Strategy:
---
1 (emicizumab* or ACE910 or ACE-910 or RG6013 or RG-6013).tw. (22)
2 emicizumab/ (0)
3 or/1-2 (22)
4 (monoclonal or mono-clonal or hybridom* or humani#ed).tw. (228282)
5 Antibodies, Monoclonal/ (186601)
6 Antibodies, Monoclonal, Humanized/ (32890)
7 ("immunoglobulin G4" or "immunoglobulin G 4").tw. (993)
8 ("IgG4" or "gamma g4" or "gamma g 4" or "igg" or "igg 4" or "igg4" or "igG4").tw. (134102)
9 or/4-6 (314787)
10 or/7-8 (134402)
11 9 and 10 (17294)
12 ("haemophilia A" or "hemophilia A").tw. (7299)
13 ("haemophilia type A" or "hemophilia type A").ti,ab. (36)
14 Hemophilia A/ (19713)
15 Factor XIII Deficiency/ (617)
16 ((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight or FVIII) adj4 deficien*).tw. (88)
17 or/12-16 (21654)
18 11 and 17 (53)
19 3 or 18 (73)
20 Animals/ not Humans/ (4550116)
21 19 not 20 (70)
22 limit 21 to english language (66)

Database: Embase

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Platform: Ovid
Version: 1974 to 2017 September 13
Search date: 15/09/2017
Number of results retrieved: 146
Search strategy:

Database: Embase <1974 to 2017 September 14>
Search Strategy:
---
1 (emicizumab* or ACE910 or ACE-910 or RG6013 or RG-6013).tw. (75)
2 emicizumab/ (40)
3 or/1-2 (85)
4 (monoclonal or mono-clonal or hybridom* or humani#ed).tw. (265777)
5 monoclonal antibody/ (190626)
6 human monoclonal antibody/ (2687)
7 ("immunoglobulin G4" or "immunoglobulin G 4").tw. (1171)
8 ("IgG4" or "gamma g4" or "gamma g 4" or "igg" or "igg 4" or "igg4" or "igG4").tw. (169168)
9 immunoglobulin G4/ (7684)
10 or/4-6 (322556)
11 or/7-9 (171314)
12 10 and 11 (20414)
13 ("haemophilia A" or "hemophilia A").tw. (12284)
14 ("haemophilia type A" or "hemophilia type A").ti,ab. (65)
15 Hemophilia A/ (18832)
16 ((heredit* or inherit* or congen*) adj4 ("8" or VIII or eight or FVIII) adj4 deficien*).tw. (137)
17 or/13-16 (20450)
18 12 and 17 (85)
19 3 or 18 (165)
20 nonhuman/ not human/ (4063322)
21 19 not 20 (150)
22 limit 21 to english language (146)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR –9 of 12, September 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 8 of 12, August 2017
HTA –4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 15/09/2017

Number of results retrieved: CDSR 0; DARE 0; CENTRAL 8 ; HTA 0 ; NHS EED 0 .
Search strategy:

ID Search Hits
Search Name: CSD - 8 September 2017 - v3

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Date Run: 15/09/17 09:17:40.53
Description: FINAL 14 Sept 217

ID	Search	Hits
#1	emicizumab* or ACE910 or ACE-910 or RG6013 or RG-6013:ti,ab	7
#2	MeSH descriptor: [Antibodies, Monoclonal, Humanized] this term only	3073
#3	MeSH descriptor: [Antibodies, Monoclonal] this term only	4612
#4	monoclonal or mono-clonal or hybridom* or humani?ed:ti,ab	11058
#5	"immunoglobulin G4" or "immunoglobulin G 4":ti,ab	226
#6	"IgG4" or "gamma g4" or "gamma g 4" or "igg" or "igg 4" or "igg4" or "igG4":ti,ab	4338
#7	{or #2-#4}	11058
#8	{or #5-#6}	4395
#9	#7 and #8	398
#10	"haemophilia A" or "hemophilia A":ti,ab	461
#11	("haemophilia type A" or "hemophilia type A"):ti,ab	0
#12	MeSH descriptor: [Hemophilia A] this term only	310
#13	MeSH descriptor: [Factor XIII Deficiency] this term only	4
#14	((heredit* or inherit* or congen*) near/4 ("8" or VIII or eight or FVIII) near/4 deficien*):ti,ab	3
#15	{or #10-#14}	613
#16	#9 and #15	2
#17	#1 or #16	8

Note: Further duplicate reference in EPPI-R removed while sifting – 31931899 was deleted; 31931901 retained. Details: Nogami, K (2016) A bispecific antibody mimicking factor VIII in hemophilia A therapy.

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Trials registries

Clinicaltrials.gov

Search date: 11 September 2017
Number of results retrieved: 5
Search strategy and link to results page:

Search: emicizumab OR ACE910 OR ACE-910 OR RG6013 OR RG-6013 | Phase 2, 3, 4
Link to search results page:

Clinicaltrialsregister.eu

Search date: 13 September 2017
Number of results retrieved: 5 (all found in the clinicaltrials.gov search)

- 2015-002866-21: “Trial protocol: DE (temporarily halted); ES (Restarted); GB (ongoing); PL (ongoing)”
- 2016-000073-21: “Trial protocol: ES (ongoing); DE (temporarily halted)”
- 2016-001094-33: “Trial protocol: ES (Temporarily Halted) PL (Ongoing) BE (Ongoing)”
- 2016-004366-25: PT () DE (Ongoing) HU (Ongoing) ES (Ongoing) FI (Ongoing)”

Search strategy and link to results page:

Search: emicizumab OR ACE910 OR ACE-910 OR RG6013 OR RG-6013
Link to results page

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Appendix 2 Study selection

The search strategy presented in Appendix 1 yielded 169 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Sifting criteria	Inclusion	Exclusion
Population	People with haemophilia A (congenital factor VIII deficiency)	Non-humans
Intervention	Emicizumab (ACE910)	
Comparator	Any	
Outcomes	N/A	
Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, epidemiological studies, burden of disease studies

Table 4 Studies excluded at full text

Study reference	Reason for exclusion
Adamkewicz J, Kim B, Steinbuesch D, and Calatzis A (2017) Measurement of FVIII inhibitor titer using a chromogenic bethesda assay (CBA) in the presence of emicizumab (ACE910), a humanized bispecific antibody mimicking FVIIIa cofactor function. Haemophilia 23, 3-4	Excluded on outcomes Study investigated methods for measuring factor VIII levels in the presence of emicizumab – not directly relevant to decision problem.
Hartmann R, Knappe S, Goldstein B, Ewenstein Bm, Valentino L, and Scheiflinger F (2017) Synergistic effects of a procoagulant bispecific antibody and FEIBA or factor VIIA on thrombin generation. Haemophilia. Conference: 10th annual congress of the European association for haemophilia And allied disorders. France. Conference start: 20170201. Conference end: 20170203 23, 26	Excluded on study type In vitro study
Kanematsu T, Suzuki N, Sanda N, Ogawa M,	Excluded on study type

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Study reference	Reason for exclusion
Kishimoto M, Suzuki A, Kiyoi H, Kasai R, and Matsushita T (2015) Clinical course and management of surgical emergency in a severe hemophilia a patient under weekly subcutaneous administration of a bispecific antibody to factors IXA and X (ACE910). Blood 126(23), 1099	Single case report
Klamroth R (2017) A new era of treatment for patients with haemophilia A?. Hamostaseologie 37(3), 216-218	Excluded on study type Narrative review
Nogami K, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Kasai R, Yoneyama K, Yoshida H, and Shima M (2016) Updated results of an ongoing long-term phase 1/2 study of emicizumab (ACE910) in hemophilia A patients with or without inhibitors. Haemophilia 22, 76	Abstract only
Nogami K, Taki M, Matsushita T, Sato T, Fukutake K, Kasai R, Yoneyama K, Yoshida H, and Shima M (2017) Updated results of a long-term phase 1/2 study of emicizumab (ACE910) in haemophilia A patients. British Journal of Haematology 176, 112	Abstract only
Ogiwara K, Nogami K, Yada K, Furukawa S, Minami H, Haku J, Kitazawa T, Hattori K, and Shima M (2013) A novel bispecific antibody (ACE910) against coagulation factors IXa and X improves procoagulant activity of patients with hemophilia A ex vivo to hemostatic level. Journal of Thrombosis and Haemostasis 11, 169	Abstract only
Shima M (2015) The potential of bispecific antibodies for treatment of hemophilia A. Journal of Thrombosis and Haemostasis 13, 5-6	Excluded on population Healthy volunteers
Shima M (2015) How to treat patients with severe haemophilia A without FVIII concentrates? New concepts in haemophilia therapy (bi-specific antibody mimicking VIII). Haemophilia 21, 7-8	Abstract only
Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Fukazawa N, Yoneyama K, Yoshida H, and Nogami K (2016) Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. New England Journal of Medicine 374(21), 2044-2053	Excluded on evidence Study included participants who did not have inhibitors, used different doses to the anticipated license and focussed on pharmacokinetic and pharmacodynamics outcomes (bleeding events used as an exploratory end point). No control or comparator arm. Better evidence available.

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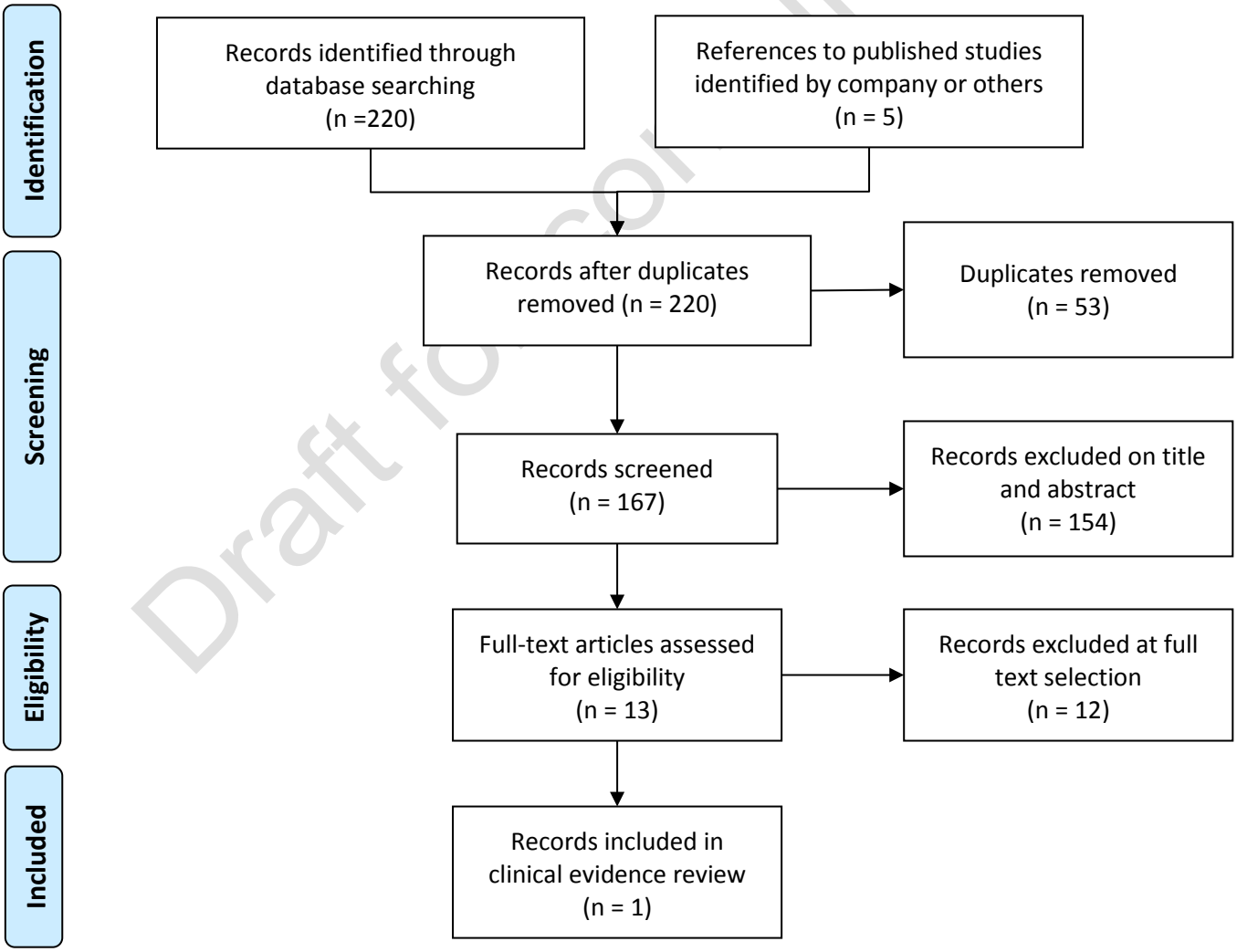
Study reference	Reason for exclusion
Yada K, Nogami K, Shida Y, Takeyama M, Kasai R, and Shima M (2015) Enhanced global hemostatic potentials with a bispecific antibody to factors IXa and X (ACE910) in the whole blood by rotation thromboelastometry (ROTEM). Blood 126(23), 3503	Excluded on outcomes Study investigated viscoelastmetric parameters in the whole blood.
Yoneyama A K, Schmitt C, Kotani N, Fukazawa N, Levy G G, Iida S, Shima M, and Kawanishi T (2016) Repeated time-to-event modeling to characterize the bleeding-prophylactic efficacy of ACE910, a bispecific antibody to factors IXA and X, in patients with hemophilia. Clinical Pharmacology and Therapeutics 99, S33	Excluded on study type Analysis of phase I and phase I/II studies

Figure 3 Flow chart of included studies



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Appendix 3 Evidence tables

Table 5 Oldenburg et al. 2017 (HAVEN 1)

Study reference	Oldenburg J, Mahlangu JN, Kim B et al. (2017) Emicizumab Prophylaxis in Hemophilia A with Inhibitors. The New England Journal of Medicine 377:809–18
Unique identifier	NCT02622321
Study type (and NSF-LTC study code)	Open-label, phase III, randomised trial P1 Primary research using quantitative approaches
Aim of the study	To assess the efficacy, safety, and pharmacokinetics of once weekly subcutaneous emicizumab prophylaxis in people with haemophilia A with inhibitors
Study dates	Started: November 2015 Primary completion date: October 2016 (final data collection date for primary outcome measure) Estimated study completion date: August 2018
Setting	43 centres in 14 countries (including 3 centres in the UK)
Number of participants	109 in total 53 in the randomised groups (group A and group B; see below) 56 in the non-randomised groups (group C and group D; see below)
Population	People aged 12 and over with congenital haemophilia A (all men) and a history of factor VIII inhibitors who are receiving episodic or prophylactic treatment with bypassing agents at recruitment. **Randomised groups** Participants receiving episodic (on-demand) treatment with bypassing agents were randomised to either: • Group A – emicizumab, or • Group B – no prophylaxis **Non-randomised groups** Participants who had previously received prophylactic (regular) treatment with bypassing agents were assigned to: • Group C – emicizumab Participants who were unable to enrol in groups A, B, or C before they were closed to enrolment were assigned to: • Group D – emicizumab The proportion of participants in each group who had previously undergone induction of immune tolerance was: • Group A – 40% • Group B – 39%

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	• Group C – 67% • Group D – 43% Most participants (70%) had target joints, with 49% having more than 1 target joint.
Inclusion criteria	Congenital haemophilia A (any severity) History of a high titre of factor VIII inhibitor (≥5 Bethesda units per ml) Episodic or prophylactic treatment with bypassing agents for at least the last 24 weeks 6 or more bleeds in the last 24 weeks prior to screening (if on an episodic bypassing agent regimen) or 2 or more bleeds in the last 24 weeks prior to screening (if on a prophylactic bypassing agent regimen)
Exclusion criteria	People with an inherited or acquired bleeding disorder other than haemophilia A People with ongoing (or plan to receive during the study) immune tolerance induction therapy or prophylaxis with factor VIII, with the exception of people who have received a treatment regimen of factor VIII prophylaxis with concurrent bypassing agent prophylaxis
Intervention(s)	Emicizumab subcutaneous injections, 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly thereafter The median exposure to emicizumab in group A was 29.5 weeks (range 3.3 to 47.9), and 24 weeks (range 3.0 to 47.9) across all groups.
Comparator(s)	No prophylaxis (no subcutaneous control injections, Group B)
Length of follow-up	24 weeks
Outcomes	Primary outcome (for Group A compared with Group B): • Number of bleeds over time (from baseline up to 24 weeks [or study discontinuation]). Presented as annualised bleeding rate.

	Secondary outcomes:
	• Additional bleeding-related outcomes, including:
	  o all bleeding events (both treated and not treated with bypassing agents)
	  o spontaneous bleeding
	  o joint bleeding
	  o target joint
	  o bleeding
	• Health-related quality of life (Haemophilia Quality of Life Questionnaire for Adults [Haem-A-QoL]) physical health subscale and total score at week 25
	• Health status (the five-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire [EQ-5D-5L]) visual-

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	analogue scale and index utility score at week 25
	Safety outcomes: • Adverse events, including: o Injection-site reactions o Serious adverse events o Thromboembolic events o Antidrug antibodies o Abnormal laboratory values
Source of funding	F. Hoffmann–La Roche and Chugai Pharmaceutical

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear and appropriate for study type, but the study is limited by the open-label design, lack of placebo control and the inclusion of non-randomised groups. This may have introduced bias, particularly for the subjective outcomes.
3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Results partially support author's conclusions. The authors conclude that emicizumab is associated with lower bleed rates compared with no prophylaxis. Although the study included people who had previously received prophylactic treatment with a bypassing agent who received emicizumab, these people were not randomised and the study was not designed to compare these people receiving no treatment. Firm conclusions cannot be made on the relative effectiveness of emicizumab in

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		people previously treated with a prophylactic bypassing agent.
5. Are the results generalisable?	1/2	Although the study included people previously treated with episodic and prophylactic bypassing agents, the study was not designed to assess the efficacy of emicizumab in people previously treated with prophylactic bypassing agents. The results for people previously treated with episodic bypassing agents may not be generalisable to those people who had taken prophylactic bypassing agents.
Total	7/10	
Applicability	Directly	The intervention and indication are directly relevant to the decision problem

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Appendix 4 Results tables

Table 6 Oldenburg et al. 2017 (HAVEN 1)

Group	Emicizumab prophylaxis (Group A)	No prophylaxis (Group B)	Emicizumab prophylaxis (Group C, not randomised)	Analysis (Group A versus Group B only)
Primary outcome				
N	**35**	**18**	**49**	
Annualised rate of bleeds treated with bypassing agents (95% CI)	2.9 events (1.69 to 5.02)	23.3 events (12.33 to 43.89)	5.1 events (2.28 to 11.22)	Significantly lower annualised bleeding rate - risk ratio 0.13 (p<0.0001, 95% CI not reported)
Secondary outcomes				
N	**35**	**18**	**49**	
Annualised rate of all bleeds, both treated and not treated with bypassing agents (95% CI)	5.5 events (3.58 to 8.60)	28.3 events (16.79 to 47.76)	6.5 events (3.43 to 12.43)	Significantly lower annualised bleeding rate - risk ratio 0.20 (p<0.0001, 95% CI not reported)
Annualised rate of spontaneous bleeds treated with bypassing agents (95% CI)	1.3 (0.73 to 2.19)	16.8 (9.94 to 28.30)	3.1 (1.20 to 8.02)	Significantly lower annualised bleeding rate - risk ratio 0.08 (p<0.0001, 95% CI not reported)
Annualised rate of joint bleeds treated with bypassing agents (95% CI)	0.8 (0.26 to 2.20)	6.7 (1.99 to 22.42)	0.6 (0.21 to 1.48)	Significantly lower annualised bleeding rate - risk ratio 0.11 (p=0.005, 95% CI not reported)
Percentage of participants with no bleeds over	62.9% (44.9 to 78.5)	5.6% (0.1 to 27.3)	69.4% (54.6 to 81.7)	No statistical analysis reported

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Group	Emicizumab prophylaxis (Group A)	No prophylaxis (Group B)	Emicizumab prophylaxis (Group C, not randomised)	Analysis (Group A versus Group B only)
study period (95% CI)				
Haem-A-QoL physical health subscale at week 25	Not reported	Not reported	Not reported	Adjusted mean difference between Group A and Group B = 21.6 points (95% CI 7.9 to 35.2; p=0.003) The mean difference is greater than the minimal clinically meaningful difference (MCID) of 10 points, although the lower limit of the 95% CI is below the MCID.
Haem-A-QoL physical health total score at week 25	Not reported	Not reported	Not reported	Adjusted mean difference between Group A and Group B = 14.0 points (95% CI 5.6 to 22.4; p=0.002) The mean difference is greater than the MCID of 7 points, although the lower limit of the 95% CI is below the MCID.
EQ-5D-5L visual analogue scale	Not reported	Not reported	Not reported	Adjusted mean difference between Group A and Group B = −9.7 points (95% CI −17.6 to −1.8, p=0.02). The mean difference is greater than the MCID of 7 points,

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Group	Emicizumab prophylaxis (Group A)	No prophylaxis (Group B)	Emicizumab prophylaxis (Group C, not randomised)	Analysis (Group A versus Group B only)
				although the lower limit of the 95% CI is below the MCID.
EQ-5D-5L index utility score	Not reported	Not reported	Not reported	Adjusted mean difference between Group A and Group B = −0.16 points (95% CI −0.25 to −0.07, p=0.001). This is greater than the MCID of 0.07 points.
Intra-individual comparisons (only includes people who had participated in the non-interventional study				
N	**24**		**24**	
Annualised bleeding rate	Bleeding rate on previous episodic bypassing agent = 21.6 events (95% CI 15.4 to 30.2) Bleeding rate on emicizumab prophylaxis = 1.7 events (95% CI 0.7 to 4.1)		Bleeding rate on previous bypassing-agent prophylaxis = 15.7 events (95% CI 11.1 to 22.3) Bleeding rate on emicizumab prophylaxis = 3.3 events (95% CI 1.3 to 8.1)	Statistically significant differences observed in Group A (92% lower bleed rate, p<0.001) and Group C (79% lower bleed rate, p<0.001). Indirect comparisons of treatments should be interpreted with caution. Data on previous bleeding rate on bypassing agent from an unpublished study.

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Safety (only reported in participants receiving emicizumab)					
Group	**Group A**	**Group B**	**Group C**	**Group D**	**Total**
Median emicizumab exposure (range)	**29.5 weeks (3.3 to 47.9)**	**8.0 weeks (4.0 to 16.0)**	**19.0 weeks (5.9 to 45.0)**	**5.8 weeks (3.0 to 14.0)**	**24.0 weeks (3.0 to 47.9)**
N	**34**	**13**	**49**	**7**	**103**
Participants with 1 or more adverse events	29/34 (85.3%)	7/13 (53.8%)	35/49 (71.4%)	2/7 (28.6%)	73/103 (70.9%)
Participants with 1 or more serious adverse events	4/34 (11.8%)	1/13 (7.7%)	4/49 (8.2%)	0/7 (0%)	9/103 (8.7%)
Common adverse events					
Injection-site reaction	8/34 (23.5%)	1/13 (7.7%)	5/49 (10.2%)	1/7 (14.3%)	15/103 (14.6%)
Headache	3/34 (8.8%)	1/13 (7.7%)	6/49 (12.2%)	2/7 (28.6%)	12/103 (12.6%)
Fatigue	3/34 (8.8%)	1/13 (7.7%)	2/49 (4.1%)	0/7 (0%)	6/103 (5.8%)
Upper respiratory tract infection	7/34 (20.6%)	0/13 (0%)	2/49 (4.1%)	0/7 (0%)	9/103 (8.7%)
Arthralgia (joint pain)	2/34 (5.9%)	1/13 (7.7%)	3/49 (6.1%)	0/7 (0%)	6/103 (5.8%)
Abbreviations	CI, confidence interval; EQ-5D-5L, EuroQol group 5-Dimension Self-Report Questionnaire (5-level version); Haem-A-QoL, Haemophilia Quality of Life Questionnaire;				

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Appendix 5 Grading of the evidence base

[NHS England has requested that NICE use the following system for grading the evidence:]

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

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- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.

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