



Cochrane
Library

Cochrane Database of Systematic Reviews

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B (Review)

Olasupo OO, Lowe MS, Krishan A, Collins P, Iorio A, Matino D

Olasupo OO, Lowe MS, Krishan A, Collins P, Iorio A, Matino D.

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B.

Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD014201.

DOI: [10.1002/14651858.CD014201](https://doi.org/10.1002/14651858.CD014201).

www.cochranelibrary.com

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B (Review)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	9
OBJECTIVES	9
METHODS	10
RESULTS	12
Figure 1.	14
Figure 2.	15
DISCUSSION	19
AUTHORS' CONCLUSIONS	21
ACKNOWLEDGEMENTS	21
REFERENCES	22
CHARACTERISTICS OF STUDIES	40
DATA AND ANALYSES	58
Analysis 1.1. Comparison 1: Comparison between two prophylaxis regimens, Outcome 1: Joint bleeds per year	58
Analysis 1.2. Comparison 1: Comparison between two prophylaxis regimens, Outcome 2: Joint bleeds per year (2)	58
Analysis 1.3. Comparison 1: Comparison between two prophylaxis regimens, Outcome 3: Spontaneous joint bleeds	59
Analysis 1.4. Comparison 1: Comparison between two prophylaxis regimens, Outcome 4: Joint bleeds per year (3)	59
Analysis 1.5. Comparison 1: Comparison between two prophylaxis regimens, Outcome 5: Total bleeds per year	59
Analysis 1.6. Comparison 1: Comparison between two prophylaxis regimens, Outcome 6: Overall bleeding frequency (bleeds per 100 days)	59
Analysis 1.7. Comparison 1: Comparison between two prophylaxis regimens, Outcome 7: Annualised bleeding rates	60
Analysis 1.8. Comparison 1: Comparison between two prophylaxis regimens, Outcome 8: Total bleeding frequency (HB)	60
Analysis 1.9. Comparison 1: Comparison between two prophylaxis regimens, Outcome 9: Overall bleeding frequency	60
Analysis 1.10. Comparison 1: Comparison between two prophylaxis regimens, Outcome 10: Total bleeds per year (2)	60
Analysis 1.11. Comparison 1: Comparison between two prophylaxis regimens, Outcome 11: Total treatment emergent adverse event	61
Analysis 1.12. Comparison 1: Comparison between two prophylaxis regimens, Outcome 12: Rate of adverse events	61
Analysis 2.1. Comparison 2: Standard prophylaxis versus investigational drug, Outcome 1: Annualised joint bleeding rate	61
Analysis 2.2. Comparison 2: Standard prophylaxis versus investigational drug, Outcome 2: Annualised total bleeding rate	62
Analysis 3.1. Comparison 3: Prophylaxis versus on-demand, Outcome 1: Mean total joint bleeds per year	62
Analysis 3.2. Comparison 3: Prophylaxis versus on-demand, Outcome 2: Mean change in joint health scores (CAJAS)	63
Analysis 3.3. Comparison 3: Prophylaxis versus on-demand, Outcome 3: Mean total bleeds per year	63
Analysis 3.4. Comparison 3: Prophylaxis versus on-demand, Outcome 4: Pain scores	63
Analysis 3.5. Comparison 3: Prophylaxis versus on-demand, Outcome 5: Radiologic measurements of joint damage (deterioration shown in eMRI)	63
Analysis 3.6. Comparison 3: Prophylaxis versus on-demand, Outcome 6: Participants with adverse events	64
APPENDICES	64
WHAT'S NEW	65
HISTORY	66
CONTRIBUTIONS OF AUTHORS	67
DECLARATIONS OF INTEREST	67
SOURCES OF SUPPORT	67
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	68
NOTES	68
INDEX TERMS	68

[Intervention Review]

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B

Omotola O Olasupo¹, Megan S Lowe², Ashma Krishan³, Peter Collins⁴, Alfonso Iorio¹, Davide Matino⁵

¹Department of Health Research Methods, Evidence and Impact (HEI), McMaster University, Hamilton, Canada. ²Department of Health Sciences, McMaster University, Hamilton, Canada. ³School of Health Sciences, Division of Population Health, Health Services Research & Primary Care, University of Manchester, Manchester, UK. ⁴Arthur Bloom Haemophilia Centre, Heath Park, School of Medicine, Cardiff University, Cardiff, UK. ⁵Department of Internal Medicine, McMaster University, Hamilton, Canada

Contact: Davide Matino, davide.matino@yahoo.it.**Editorial group:** Cochrane Cystic Fibrosis and Genetic Disorders Group.**Publication status and date:** New, published in Issue 8, 2021.**Citation:** Olasupo OO, Lowe MS, Krishan A, Collins P, Iorio A, Matino D. Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B. *Cochrane Database of Systematic Reviews* 2021, Issue 8. Art. No.: CD014201. DOI: [10.1002/14651858.CD014201](https://doi.org/10.1002/14651858.CD014201).

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

The hallmark of severe hemophilia (A or B) is recurrent bleeding into joints and soft tissues with progressive joint damage, despite on-demand treatment. Prophylaxis has long been used, but not universally adopted, because of medical, psychosocial, and cost controversies.

Objectives

To determine the effectiveness of clotting factor concentrate prophylaxis in managing previously-treated individuals with hemophilia A or B.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. In addition, we searched MEDLINE and Embase and online trial registries.

Most recent search of Group's Coagulopathies Trials Register: 24 February 2021.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs evaluating people with hemophilia A or hemophilia B, who were previously treated with clotting factor concentrates to manage their hemophilia.

Data collection and analysis

Two authors independently reviewed trials for eligibility, assessed risk of bias and extracted data. The authors used the GRADE criteria to assess the certainty of the evidence.

Main results

Ten trials (including 608 participants) were eligible for inclusion. Eight of the trials (477 participants) had arms comparing two or more prophylactic regimens to one another and four of the trials (n = 258) compared prophylaxis to on-demand treatment (two trials had multiple arms and were included in both comparisons).

Comparison of two or more prophylactic regimens

For trials comparing one prophylaxis regimen to another, given the heterogeneity of the data, none of the data were pooled for this comparison. Considering the individual trials, three trials reported the primary outcome of joint bleeding, and none showed a difference between dosing regimens (low-certainty evidence). For the secondary outcome of total bleeding events, prophylaxis with a twice-weekly regimen of FIX likely results in reduced total bleeds compared to a once-a-week regimen of the same dose, mean difference (MD) 11.2 (5.81 to 16.59) (one trial, 10 participants, low-certainty evidence).

Transient low-titer anti-FVIII inhibitors were reported in one of the trials. Blood-transmitted infections were not identified. Other adverse events reported include hypersensitivity, oedema, and weight gain. These were, however, rare and unrelated to study drugs (very low-certainty evidence).

Comparison of prophylactic and on-demand regimens

Four of the trials (258 participants) had arms that compared prophylaxis to on-demand treatment. Prophylaxis may result in a large decrease in the number of joint bleeds compared to on-demand treatment, MD -30.34 (95% CI -46.95 to -13.73) (two trials, 164 participants, low-certainty evidence). One of these trials (84 participants) also reported the long-term effects of prophylaxis versus on-demand therapy showing improved joint function, quality of life, and pain; but no differences between groups in joint structure when assessed by magnetic resonance imaging (MRI).

In one trial (84 participants) validated measures for joint health and pain assessment showed that prophylaxis likely improves joint health compared to an on-demand regimen with an estimated change difference of 0.94 points (95% CI 0.23 to 1.65) and improves total pain scores, MD -17.20 (95% CI -27.48 to -6.92 (moderate-certainty evidence).

Two trials (131 participants) reported that prophylaxis likely results in a slight increase in adverse events, risk ratio 1.71 (1.24 to 2.37) (moderate-certainty evidence). No inhibitor development and blood-transmitted infections were identified.

Overall, the certainty of the body of evidence was judged to be low because of different types of bias that could have altered the effect.

Authors' conclusions

There is evidence from RCTs that prophylaxis, as compared to on-demand treatment, may reduce bleeding frequency in previously-treated people with hemophilia. Prophylaxis may also improve joint function, pain and quality of life, even though this does not translate into a detectable improvement of articular damage when assessed by MRI.

When comparing two different prophylaxis regimens, no significant differences in terms of protection from bleeding were found. Dose optimization could, however, result in improved efficacy. Given the heterogeneity of the data, pooled estimates were not obtained for most comparisons.

Well-designed RCTs and prospective observational controlled studies with standardised definitions and measurements are needed to establish the optimal and most cost-effective treatment regimens.

PLAIN LANGUAGE SUMMARY

Regular clotting factor replacement therapy to prevent joint damage in people living with severe hemophilia A or B

Review question

Should people, who have previously been treated for joint bleeding, be given regular preventative treatment with clotting factor concentrates to manage their condition?

Background

Hemophilia A and B are X-linked inherited bleeding disorders in which bleeding into joints is a major problem. Repeated joint bleeds can lead to affected joints (commonly referred to as 'target joints') becoming damaged and painful, with limited movement. Currently, bleeding is treated and prevented with plasma-derived or recombinant clotting factor concentrates, and more recently non-clotting factor formulations. This review looked at how useful and effective different clotting factor treatment strategies are for preventing joint bleeding and other outcomes in previously treated people with hemophilia A or B.

Search date

Date of last search: 24 February 2021.

Study characteristics

This review includes 10 randomised controlled trials. Eight had treatment arms that compared the regular use of clotting factor concentrates to prevent joint bleeds with different dosing schemes to identify regimens that may be better; four had treatment arms that compared the regular use of factor concentrates to prevent bleeds to their 'on demand' use to treat bleeds once they occur (two trials had multiple arms and were included in both comparisons).

Key results

In people living with hemophilia A or B previously treated for joint bleeding or with existing joint damage, preventive therapy may reduce the number of joint bleeds compared to 'on-demand therapy'. This reduction in bleeds may lead to an improvement in joint function, pain, and quality of life. However, preventive therapy is linked to an increased use of factor concentrates and therefore higher treatment costs. Further studies are needed to establish the best preventive course of treatment in terms of starting time, frequency and dose level.

Certainty of the evidence

Overall, the certainty of the evidence was judged to be low because of different types of bias that could have affected the results. Future research might have an important role in changing our confidence in these results.

SUMMARY OF FINDINGS

Summary of findings 1. Comparison of two prophylaxis regimens

Prophylaxis regimen compared with another prophylaxis regimen for previously treated individuals with haemophilia A or B

Patient or population: children or adults with hemophilia A or B

Settings: outpatient

Intervention: secondary prophylaxis

Comparison: secondary prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis regimen	Prophylaxis regimen				
Number of joint bleeding episodes per year (AJBR)	No difference was seen between prophylaxis regimens in any of the studies. Thrice-weekly higher dose prophylaxis regimen compared to a twice-weekly lower dose regimen, MD -1.70 (95% CI -5.06 to 1.66) (LEOPOLD II 2015).		N/A	219 participants (3 trials)	⊕⊕⊕⊕ low ^a	We were unable to combine results in a meta-analysis due to the different prophylaxis regimens used in each trial.
Follow-up: 12 months	PK-guided prophylaxis targeting trough levels of 8% to 12% compared to targeting trough levels of 1% to 3%, MD -1.50 (95% CI -3.54 to 0.54) (n = 115 participants) (PROPEL III 2020). Low frequency prophylaxis (100 IU / kg once a week) compared to standard frequency regimen (50 IU / kg twice a week, MD of 1.70 (95% CI -1.09 to 4.49) (Valentino 2014).					
Number of total bleeds per year (ABR)	There was no difference in total number of bleeds between prophylactic regimens in five trials (Aronstam 1977; LEOPOLD II 2015; PROPEL III 2020; Valentino 2012; Valentino 2014).		N/A	310 participants (7 trials)	⊕⊕⊕⊕ low ^{b,c}	Due to heterogeneity of intervention and design, none of the trials we were unable to combine data from any of the trials (LEOPOLD II 2015).
Follow-up: 12 months	A twice-a-week regimen (7.5 IU/kg) was favoured over a once-a-week regimen (15 IU/kg), MD 11.20 (5.81 to 16.59) (Morfini 1976) and a prophylaxis group with dosing producing at least 0.25 IU/mL of factor VIII showed a significant reduction in overall bleed-					

	ing frequency compared to a dosing regimen producing at least 0.01IU/mL once weekly, MD 3.44 (95% CI 2.42 to 4.46) (Aronstam 1976).				
Treatment-related adverse events	One trial reported no difference in total treatment-emergent adverse events, MD 1.00 (95% CI 0.54 to 1.84) at 32 weeks (Valentino 2014). A further trial reported no difference between treatment regimens in mean rates of adverse events (Valentino 2012).	N/A	223 participants (3 trials)	⊕⊕⊕⊕ very low a,d	Three trials did not report the rate of adverse events by treatment groups (Aronstam 1977; LEOPOLD II 2015; Morfini 1976). The LEOPOLD II trial reported three treatment related adverse events but gave no further detail (LEOPOLD II 2015). There was no reported inhibitor development reported in six of the trials in this comparison (Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; Morfini 1976; Valentino 2012; Valentino 2014).
Follow-up: 32 weeks to 12 months	In the study targeting different trough levels, no serious adverse event was treatment-related in the arm targeting trough levels of 1% to -3%, and in the arm targeting trough levels of 8% to -12%, one serious adverse event was estimated to be treatment-related (PROPEL III 2020).				

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

ABR: annualised bleed rate; **AJBR:** annualised joint bleed rate; **CI:** confidence interval; **FIX:** factor IX; **RR:** risk ratio; **MD:** mean difference.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

- a. Downgraded twice due to risk of bias in the included trials, particularly across the domains of randomisation and allocation concealment. The trials were also considered at high risk of bias due to lack of blinding
- b. Downgraded once due to imprecision as a result of small sample sizes. Although the total number of participants included in this outcome is 390, none of the studies could be combined and so we have based our assessment on the numbers in individual trials. The two trials that showed a difference between regimens included nine and 10 participants.
- c. Downgraded twice due to an unclear or high risk of bias across many of the domains with particular concern around randomisation procedures, allocation concealment and blinding.
- d. Downgraded once due to imprecision from small sample size and low event rates. Although the total number of participants is reasonable, none of the trials could be combined and so we have based our judgement on the numbers in the individual trials.

Summary of findings 2. Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation

Prophylaxis with standard clotting factor concentrate compared with pegylated liposome FVIII formulation for previously treated individuals with haemophilia A

Patient or population: children or adults with hemophilia A

Settings: outpatient

Intervention: prophylaxis using investigational BAY 79-4980

Comparison: standard secondary prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis using investigational BAY 79-4980	Standard prophylaxis				
AJBR Follow-up: 12 months	The mean number of joint bleeding in the prophylaxis arm using investigational drug BAY 79-4980 was 12.2.	The mean number of joint bleeding in the standard prophylaxis regimen (5.0), was 7.20 lower (11.01 lower to 3.39 lower)	MD -7.20 (-11.01 to -3.39)	143 participants (1 trial)	⊕⊕⊕⊕ low a,b	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
ABR Follow-up: 12 months	The mean number of total bleeds in the prophylaxis arm using investigational drug BAY 79-4980 was 15.	The mean number of total bleeds in the standard prophylaxis regimen (5.8), was 9.20 lower (13.07 lower to 5.33 lower)	MD -7.20 (-13.07 to -5.33)	143 participants (1 trial)	⊕⊕⊕⊕ low a,b	More participants withdrew consent in the investigational drug arm. The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.
Any reported adverse effects Follow-up: 12 months	No specific information was given about the presence/absence of adverse events in the BAY 79-4980 group.	One participant in the prophylaxis group reported three serious adverse events, which were deemed to be drug related.	Not estimable	143 participants (1 trial)	⊕⊕⊕⊕ low a,b	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

ABR: annualised bleed rate; **AJBR:** annualised joint bleed rate; **CI:** confidence interval; **MD:** mean difference.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

- a. Downgraded once due to high risk of bias due to attrition bias from incomplete outcome data.
- b. Downgraded once due to premature study discontinuation.

Summary of findings 3. Prophylaxis regimen versus on-demand treatment

Prophylaxis regimen compared with on-demand treatment for previously treated individuals with haemophilia A or B

Patient or population: children and adults with haemophilia A or B

Settings: outpatient

Intervention: secondary prophylaxis

Comparison: on-demand treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	On-demand treatment	Prophylaxis regimen				
Number of joint bleeding episodes or joint bleeding frequency Follow-up: 12 months	The mean number of joint bleeding episodes in the on-demand treatment group was 34	The mean number of joint bleeding episodes in the prophylaxis regimen group was 30.34 lower (46.95 lower to 13.73 lower)	MD -30.34 (-46.95 to -13.73)	164 (2 trials)	⊕⊕⊕⊖ low a,b	The data from the A-LONG trial suggests the same; however, these data were reported with medians, hence could not be included in the analysis.
Number of total bleeds per year	The mean number of total bleeds in the	The mean number of total bleeds in the prophylaxis regimen group was	MD -40.24 (-64.04 to -16.44)	164 (2 trials)	⊕⊕⊕⊖ low a,b	The data from the A-LONG trial suggests the same effect; however, these data were reported

or bleeding frequency Follow-up: 12 months	on-demand treatment group was 44	40.24 lower (64.04 lower to 16.44 lower)				with medians, hence could not be included in the analysis (A-LONG 2014). When comparing the overall bleeding frequency in 9 participants in the Aronstam cross-over trial, there was a significant reduction in the overall bleeding frequency in the prophylaxis group
Any reported adverse events Follow-up: 12 months	415 per 1000 (27 per 65)	712 per 1000 (47 per 66) The number of participants with adverse events in the prophylaxis regimen group was 1.71 times higher (1.24 times higher to 2.37 times higher)	RR 1.71 (1.24 to 2.37)	131 (2 trials)	⊕⊕⊕⊖ moderate ^a	The 2 trials were open-label trials with unclear risk of bias for randomised sequence generation (A-LONG 2014; SPINART 2013). The LEOPOLD II trial did not give the distribution of adverse events across groups, but there were 3 reported treatment-related adverse events while no participant developed an inhibitor during the course of treatment (LEOPOLD II 2015). In the 1976 Aronstam trial, one participant developed antigen-negative hepatitis and was removed from the remaining duration of the trial (Aronstam 1976).

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **MD:** mean difference

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

a. Downgraded once due to high risk of bias due to performance and detection bias attributed to open-label studies.

b. Downgraded once due to high levels of heterogeneity across trials.

BACKGROUND

Description of the condition

Congenital hemophilia is a rare x-linked bleeding disorder caused by a deficiency in clotting factor VIII (FVIII) in hemophilia A and factor IX (FIX) in hemophilia B (Srivastava 2020). Severity of disease is classified according to level of clotting factor naturally present in the blood: severe (with a baseline coagulation factor level of less than 1% of normal); moderate (with clotting factor levels of 1% to 5%); and mild (6% to 49%) (Blanchette 2014).

The physical manifestation of hemophilia varies with the severity of disease. People with mild and moderate hemophilia rarely experience spontaneous bleeding episodes, and often only bleed abnormally following trauma or in association with invasive procedures. People with severe hemophilia are at highest risk for experiencing frequent and severe spontaneous bleeding incidents. This group is also prone to experiencing recurrent or chronic bleeding into joints and muscles, which can develop into haemophilic joint arthropathy and muscle atrophy.

Description of the intervention

While there is no routinely-available cure for hemophilia, symptoms of the disease can be effectively managed by the infusion of exogenous clotting factor concentrates (either FVIII or FIX). The availability of clotting factor concentrates has improved the morbidity, mortality and quality of life (QoL) of people with hemophilia (Lusher 1997; Tobase 2016). Availability of factor concentrate allows for early treatment of acute bleeding incidents, and has resulted in a decrease in joint deformities in untreated or minimally-treated individuals (Ahlberg 1965; Hilgartner 1974; Liddle 2017).

Factor concentrates are generally administered according to two treatment regimens:

1. on-demand (also termed episodic) treatment, where individuals receive clotting factor only in response to a bleeding event; or
2. prophylaxis treatment, where individuals receive regular infusions of clotting factor with the aim to prevent bleeds.

A 1994 study by Aledort, showed that prophylaxis treatment reduced the number of bleeding events and may reduce the incidence of bleeding-related adverse events, such as haemophilic arthropathy (Aledort 1994). This same study showed progressive joint deterioration over the six-year follow-up period in participants using on-demand treatment only (Aledort 1994). Given its preferable outcomes, prophylaxis treatment, in comparison to on-demand treatment, has been recommended for all children with severe hemophilia (Berntorp 2003; MASAC 2010; MASAC 2016; Rayment 2020; Richards 2010; Srivastava 2020).

How the intervention might work

There are two main categories of prophylactic treatment: primary prophylaxis, which is established before joint deterioration (before the second clinically-evident joint bleed and age three years); and secondary prophylaxis, which is established after some joint deterioration. Given the differences in starting times, the aims of primary and secondary prophylaxis differ. Primary prophylaxis aims to use regular infusions of factor concentrate to maintain the individuals' factor level above a desired target, usually in the mild

or moderate range (above 1% of clotting factor present in blood), to prevent spontaneous bleeding episodes and joint arthropathy. Secondary prophylaxis aims to slow the progression of existing arthropathy, prevent the development of new arthropathies, and prevent further spontaneous bleeding incidents (Hay 2007).

Secondary prophylaxis is generally started after some degree of joint arthropathy has already occurred (Hay 2007) and can theoretically be started at any time in life. The existing evidence shows that starting secondary prophylaxis in adulthood can reduce bleeding frequency, and delay the progression of joint arthropathy (Tagliaferri 2008). For these reasons, the Medical and Scientific Advisory Council of the US National Hemophilia Foundation (MASAC) has identified that individuals, especially those with severe hemophilia, may benefit from continuing prophylaxis throughout their life (MASAC 2010; MASAC 2016).

Why it is important to do this review

Despite the known benefits of prophylaxis, there are medical, psychosocial and cost barriers that preclude the universal use of prophylaxis (Blanchette 2004; Thornburg 2017). Such concerns may be balanced by strong evidence of the efficacy of prophylaxis treatment. Numerous studies exist citing the efficacy of primary prophylaxis and the previous systematic review (from which this review has been derived) showed that primary prophylaxis was significantly better at preserving joint function in children with hemophilia, in comparison to on-demand treatment (Iorio 2011). Similar evidence, including evidence from randomised controlled trials, for the efficacy of secondary prophylaxis started in adulthood is accumulating, but has not yet been systematically reviewed.

This review aims to clarify the efficacy and safety of secondary prophylaxis in adults by systematically reviewing and summarising the available evidence of prophylactic administration of factor concentrates in previously-treated individuals with hemophilia A or B.

OBJECTIVES

To determine the effectiveness of clotting factor concentrate prophylaxis in managing previously treated individuals with hemophilia A or B, for improving short- and long-term outcomes measured by one or more of the following.

Short-term outcomes

1. Number of joint bleeding episodes per year or bleeding frequency
2. Number of total bleeds per year or bleeding frequency
3. Clotting factor concentrate levels in plasma

Long-term outcomes

1. Clinical joint function
2. Orthopedic joint score
3. Radiologic joint score
4. QoL measurements

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials. All identified trials, unpublished or published as an article, an abstract or a letter, without any language limitations, were eligible for inclusion.

Types of participants

Trials including individuals with congenital haemophilia A or B, receiving secondary prophylaxis were eligible. We included all trials which enrolled adults (aged 18 or over) and those trials with participants under 18 years of age if the participants met one of the three following criteria:

1. proven haemophilic arthropathy;
2. presence of one or more target joint;
3. previous on-demand treatment.

We did not exclude based on degree of disease severity, type of previous treatment (if any), or presence of previous joint damage. Trials including participants with factor VIII or IX inhibitors at baseline were excluded.

Types of interventions

We compared intravenous clotting factor concentrates administered as prophylactic treatment in any formulation (e.g. fresh frozen plasma, cryoprecipitate, lyophilised plasma-derived clotting factor concentrate, or recombinant clotting factor concentrate), any concentration, any frequency and any dose, with no treatment, placebo, on-demand treatment, or with one or more different prophylaxis regimens. We did not include trials of a single treatment and at least one treatment must have been a clotting factor concentrate.

Therefore the anticipated comparison groups were as follows:

- prophylaxis versus prophylaxis with a different regimen;
- prophylaxis versus on-demand treatment;
- prophylaxis versus no treatment;
- prophylaxis versus placebo.

Types of outcome measures

The following primary and secondary outcomes were assessed based on clinical relevance.

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency during the trial
2. Orthopedic joint score or clinical joint function
3. QoL on validated scales (disease-specific where possible)

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency during the trial period
2. Pain scores
3. Radiologic joint score or radiologic measurements or descriptions of joint damage

4. Clotting factor concentrate plasma levels
5. Time loss to school or employment
6. Integration into society (i.e. absenteeism)
7. Scores on scales recording feeling of well-being and global functioning
8. Economic data: cost-effectiveness, cost-benefit, cost-utilisation, cost-minimisation
9. Any reported adverse effects or toxicity of clotting factor concentrates (e.g. inhibitors, reactions, transmission of infection)

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We identified relevant trials from the Group's Coagulopathies Trials Register using the term: prophylaxis and (haemophilia* or haemophilia*).

The Coagulopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE and the prospective handsearching of one journal - Haemophilia. Unpublished work is identified by searching the abstract books of major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Congress of the World Federation of Hemophilia; the European Association for Haemophilia and Allied Disorders, the American Society of Gene and Cell Therapy and the International Society on Thrombosis and Haemostasis. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of the most recent search of the Group's Coagulopathies Trials Register: 24 February 2021.

We also searched the following databases and trial registries:

1. MEDLINE Ovid (1946 to June 2016 – search carried out by authors of a previous version of this review)
2. Embase Ovid (1974 to June 2016 – search carried out by authors of a previous version of this review);
3. ISRCTN registry (www.isrctn.com/; searched 06 August 2020);
4. US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 06 August 2020);
5. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (<https://apps.who.int/trialsearch>; we were unable to carry out a search as access was temporarily unavailable due to the current COVID-19 pandemic. We will try and search this resource when the review is updated).

For details of the search strategies, please see ([Appendix 1](#)).

Searching other resources

We checked the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant trials.

The following conference proceedings were also hand searched:

1. International Society for Thrombosis and Haemostasis Biannual Meeting (2004 to 2016);
2. European Association for Haemophilia and Allied Disorders (2004 to 2016).

Data collection and analysis

Selection of studies

Two authors independently screened the titles and abstracts of the retrieved citations and retrieved all available complete manuscripts for potentially relevant trials. The same two authors assessed the full-text manuscripts to select the final trials to be included according to the review's inclusion criteria. A third-party arbitrator helped to settle any differences between the two authors.

Data extraction and management

Two authors independently extracted data using a pre-designed data extraction form. The structured data form included the following information.

- Inclusion criteria of the trial
- Characteristics of the trial (i.e. trial design, location and time frame)
- Participant number and demographics
- The intervention and co-interventions (including dosing and frequency of clotting factor concentrate)
- Outcomes (including primary and secondary outcome measures and description)
- Information regarding limitations and biases

We considered any outcome data recorded as either individual events or as events grouped by time periods.

Assessment of risk of bias in included studies

The authors used the tool in RevMan 5.4 to measure the risk of bias and to produce summary figures ([RevMan 2020](#)).

The authors assessed the risk of bias using the 'Risk of bias' assessment tool as documented in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). The following domains were assessed as having either a low, high, or unclear risk of bias:

- sequence generation;
- allocation concealment;
- blinding (of participants, personnel and outcome assessors);
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

To estimate selective outcome reporting, we identified original protocols and compared the results and outcomes reported in the final report to those proposed in the protocol.

Measures of treatment effect

We anticipated that the primary outcome (number of joint bleeding episodes or joint bleeding frequency during the trial) would be reported using mean and standard deviation (SD). For the secondary outcomes, we anticipated continuous outcomes to be reported as either a rate of event, mean and SD, or median and interquartile range (IQR). We anticipated dichotomous outcomes to be reported as the frequency of each option. Given these assumptions, we measured the treatment effect of the primary outcome using a mean difference (MD). We measured the treatment effects of secondary outcomes using the risk difference (RD) or MD for continuous outcomes and risk ratio (RR) for dichotomous outcomes. We reported the 95% confidence interval (CI) of each measure of treatment effect.

Unit of analysis issues

We anticipated that the unit of analysis would be the individual, as disease progression and treatment can vary between individuals. Given the chronic nature of the condition, as well as the rapid onset and short duration of the intervention (factor VIII and IX physiological half-lives are 12 and 24 hours respectively), we anticipated that some trials included would be cross-over in design. We used the generic inverse variance (GIV) method to include cross-over trials in any meta-analyses conducted, as reported in chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2021](#)). Whenever possible we have used individual patient data to analyze the results of cross-over trials ([Aronstam 1976](#); [Aronstam 1977](#); [Morfini 1976](#)). In the Leopold II trial ([LEOPOLD II 2015](#)) participants were randomised to receive on-demand or prophylactic therapy with FVIII (two different regimens); participants were crossed-over within their treatment groups, but only with respect to the methods for measuring the content of FVIII in the vials, therefore, we treated this trial as if it had a parallel design.

Dealing with missing data

We attempted to contact trial authors to provide any missing data. We reported the level of missing data and reason for missing data where possible.

Assessment of heterogeneity

Given the small number of trials that were included in a meta-analysis in this review, we did not assess for heterogeneity in most of the analyses. However, where sufficient trials were included in a meta-analysis, we identified the presence of statistical heterogeneity using the Chi² value. We also reported the I² value as a measure of heterogeneity in the meta-analysis. We applied the following thresholds, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2021](#)):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: represents considerable heterogeneity.

Assessment of reporting biases

In future versions of this review, if there are more than 10 trials in the same analysis, we will construct a funnel plot and assess it for symmetry.

Data synthesis

In comparisons where only one trial was assessed, we used the fixed-effect model in the analyses. We used a random-effects model in analyses including multiple trials to account for possible heterogeneity.

Subgroup analysis and investigation of heterogeneity

In future versions of this review, depending on data availability, we plan a subgroup analysis based on Pattersson scores and other measures indicating the extent of disease progression.

Sensitivity analysis

We were unable to aggregate data for a majority of outcomes in this review. However, if there are a sufficient number of eligible and included trials, we will undertake a sensitivity analysis by looking at trials with a low risk of bias versus a high risk of bias, as measured above.

Summary of findings and assessment of the certainty of the evidence

We presented a summary of findings table for each of the following comparisons.

1. Comparison between two prophylaxis regimens
2. Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation
3. Prophylaxis versus on-demand comparison.

The following outcomes were chosen based on relevance to clinicians and consumers and reported in the table.

1. Number of joint bleeding episodes per year or bleeding frequency;
2. Number of total bleeds per year or bleeding frequency;
3. Any reported adverse event.

We determined the certainty of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

Description of studies and results of the search are described below.

Results of the search

Our search strategies yielded 322 unique references, of which 68 articles reporting seven studies were included in this review (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014). A further three trials (three articles) (Aronstam 1976; Aronstam 1977; Morfini 1976) were accessed from a previous Cochrane Review (which this current review and one more Cochrane Review in progress, supersedes), and were also included in this review (lorio 2011). No additional articles were found from searching reference lists of included articles or conference proceedings.

We excluded a further 251 references to 89 trials.

Included studies

See [Characteristics of included studies](#) for a full description of each trial.

Trial design

10 trials, with a total of 608 participants were included in the review (A-LONG 2014 (n = 47); Aronstam 1976 (n = 9); Aronstam 1977 (n = 4); LEOPOLD II 2015 (n = 80); LipLong 2012 (n = 143); Morfini 1976 (n = 10); PROPEL III 2020 (n = 115); SPINART 2013 (n = 84); Valentino 2012 (n = 66); Valentino 2014 (n = 50). There was no disagreement between authors regarding trial relevance and inclusion.

One trial was conducted in Italy (Morfini 1976), two in England (Aronstam 1976; Aronstam 1977) and seven were multicentre trials (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014).

Four trials were cross-over in design (Aronstam 1976; Aronstam 1977; Morfini 1976; Valentino 2014). In these trials, the order of intervention was randomised, and all participants received both the control and active treatment. All of the cross-over trials included an adequate washout period before the second treatment intervention was administered. The remaining six trials were parallel in design, four trials were randomised open-label trials (A-LONG 2014; PROPEL III 2020; SPINART 2013; Valentino 2012), one was a randomised double-blind trial with an active control (LipLong 2012). The remaining randomised trial, the LEOPOLD II study, was reported as cross-over, with participants randomised to one of six treatment arms (two low-dose prophylaxis groups, two high-dose prophylaxis groups, and two on-demand treatment groups); participants received treatment based on CS/EP (chromogenic substrate assay per European Pharmacopoeia) or adjusted by a predefined factor to mimic results obtained with the one-stage assay (CS/ADJ) for six months each with an intraindividual cross-over after six months (LEOPOLD II 2015). However, since participants were crossed-over within their treatment groups but only with respect to the methods for measuring the content of FVIII activity in the vials (using the CS/EP or the CS/ADJ). This cross-over trial has been analysed as a parallel trial.

Types of participants

All trials included participants receiving secondary prophylaxis. Two trials included individuals with hemophilia B: the Morfini trial included individuals with severe hemophilia B (FIX levels < 1%) (Morfini 1976); and the 2014 Valentino trial included individuals with moderately severe and severe hemophilia B (FIX levels ≤ 2%) (Valentino 2014). Seven trials included individuals with severe haemophilia A only (FVIII levels < 1% of normal) (A-LONG 2014; Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013). One trial included participants with moderately severe to severe hemophilia A (FVIII levels ≤ 2% of normal) (Valentino 2012). All trials included participants who were previously exposed to FVIII or FIX, whether through on-demand treatment or through a prophylaxis regimen. All included participants were males and between five years and 65 years of age. None of the participants had an inhibitory antibody to FVIII or FIX at baseline.

There were some boys in the Aronstam 1976 trial who were also included in the 1977 trial: "Those boys who had been on the first double-blind controlled trial (Aronstam 1976) and were still available for a further two terms were selected. There were four such boys, patients 1, 3, 8, and 9 of that trial. The boys selected had each had at least one full school term off prophylaxis before entering the second trial" (Aronstam 1976; Aronstam 1977).

Types of interventions

Two of the trials had multiple arms where a prophylaxis regimen was compared to another prophylaxis regimen, as well as a comparison of a prophylaxis and on-demand regimen (LEOPOLD II 2015; Valentino 2014). Therefore, we included these two trials in two comparisons.

Comparison between two prophylaxis regimens

Eight trials compared two different prophylactic regimens (Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; LipLong 2012; Morfini 1976; PROPEL III 2020; Valentino 2012; Valentino 2014). Of these, four trials had a fixed prophylaxis dose in both arms (LEOPOLD II 2015; LipLong 2012; Morfini 1976; Valentino 2014). We describe the intervention and comparison in the included trials below.

Aronstam 1977: prophylaxis arm A: sufficient dose to increase the FVIII level to 10% of normal versus prophylaxis arm B: sufficient dose to raise the FVIII level to 30% of normal.

Aronstam 1976: prophylaxis arm A: sufficient dose to increase FVIII levels to ≥ 0.25 IU/mL versus prophylaxis arm B: sufficient dose to increase FVIII levels to ≥ 0.1 IU/mL once weekly.

Morfini 1976: prophylaxis arm A: FIX 7.5 U/kg twice per week versus prophylaxis arm B: FIX 15 U/kg once per week.

Valentino 2012: prophylaxis arm A: standard prophylactic treatment of 20 to 40 IU/kg FVIII every 48 hours versus prophylaxis arm B: PK-tailored prophylactic treatment of 20 to 80 IU/kg FVIII every 72 hours (dose-dependent on PK evaluation).

LEOPOLD II 2015: prophylaxis arm A: high-dose regimen (FVIII 30 to 40 IU/kg thrice-weekly versus prophylaxis arm B: low-dose regimen (FVIII 20 to 30 IU/kg twice-weekly). The factor concentrate used was an experimental full-length rFVIII product referred to as BAY 81-8973. This product was created to improve clinical efficacy by alterations in glycosylation and was also free of any human or animal-derived products. BAY 81-8973 was co-expressed with heat shock protein 70 to improve the in vivo viability of the product.

LipLong 2012: prophylaxis arm A: the investigational drug, BAY 79-4980 consisting of 35 IU/kg of rFVIII and 13 mg/kg of pegylated liposome, administered at a reduced frequency of once per week versus prophylaxis arm B: standard prophylaxis treatment with rFVIII at a dose of 25 IU/kg three times per week.

Valentino 2014: prophylaxis arm A: high-frequency schema (50 IU/kg twice-weekly) versus prophylaxis arm B: low-frequency schema (100 IU/kg once-weekly).

PROPEL III 2020: prophylaxis arm A: PK-guided prophylaxis to achieve FVIII trough levels of 1% to 3% versus treatment arm B: prophylaxis targeting trough levels of 8% to 12%.

Prophylaxis regimen compared to on-demand (episodic) treatment

Four trials compared on-demand treatment to prophylaxis treatment (A-LONG 2014; LEOPOLD II 2015; SPINART 2013; Valentino 2014).

SPINART 2013: on-demand treatment administered on the basis of investigator recommendations versus prophylaxis treatment administered at a dosage of 25 IU/kg three times per week. This amount could be increased to a maximum of 35 IU/kg over two years in participants with 12 or more bleeding episodes per year on the trial.

A-LONG 2014: on-demand treatment administered at a dose of 10 to 50 IU/kg FVIII as needed versus standard prophylaxis administered at a dose of 65 IU/kg rFVIII once weekly. Additionally, this trial also enrolled individuals who were previously on prophylaxis or on-demand therapy but not willing to be randomised (Arm 1) to be treated with an individualized prophylaxis regimen (N = 118). Since this was a non-randomised arm we did not include it in the analysis.

Valentino 2014: prophylaxis A: high-frequency schema (50 IU/kg twice-weekly) versus prophylaxis B: low-frequency schema (100 IU/kg once-weekly). These two regimens were compared to an on-demand treatment where FIX was given to treat bleeding events as needed. The factor product used for all study arms was nonacog alfa (BeneFIX).

LEOPOLD II 2015: on-demand treatment with BAY 81-8973, a recombinant factor VIII product, was compared with two arms of prophylaxis treatment (prophylaxis A: high-dose regimen (FVIII 30 to 40 IU/kg thrice-weekly and prophylaxis B: low-dose regimen (FVIII 20 to 30 IU/kg twice-weekly).

Types of outcomes

Our primary outcome of interest, joint bleeding events or joint bleeding frequency, was reported in seven out of the 10 studies (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014). Clinical joint function and radiologic measurements were reported in two trials (Morfini 1976; SPINART 2013). Two trials also reported conducting QoL measurements (SPINART 2013; Valentino 2012) and one trial (SPINART 2013) reported the results of pain assessment.

Overall bleeding events or overall bleeding frequency were reported in all 10 trials. The quantity of factor concentrate used was reported in four trials (LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012). Adverse event reporting, including the development of inhibitors, was reported in seven of the trials (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014).

Excluded studies

See [Characteristics of excluded studies](#) for more details of the excluded trials.

We excluded 89 trials (251 references) from this review. A total of 40 trials were excluded because they were not randomised studies, including 22 prospective and 18 retrospective observational studies. 15 trials had an intervention arm that included non-clotting factors, e.g. concizumab (n = 9), emicizumab (n = 5), investigational RNA interference therapeutic (n = 1). Six trials were excluded because they were conducted in participants with

inhibitors, 13 additional trials were not eligible because they included individuals on primary prophylaxis. 10 trials assessed pharmacokinetic parameters and four were reported in conference abstracts only and detailed descriptions of trial participants were not available. One trial was a feasibility study with no hypothesis

testing, no useable results and concluded that the trial lacked feasibility.

Risk of bias in included studies

We present an overall risk of bias assessment graphically in the figures section (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

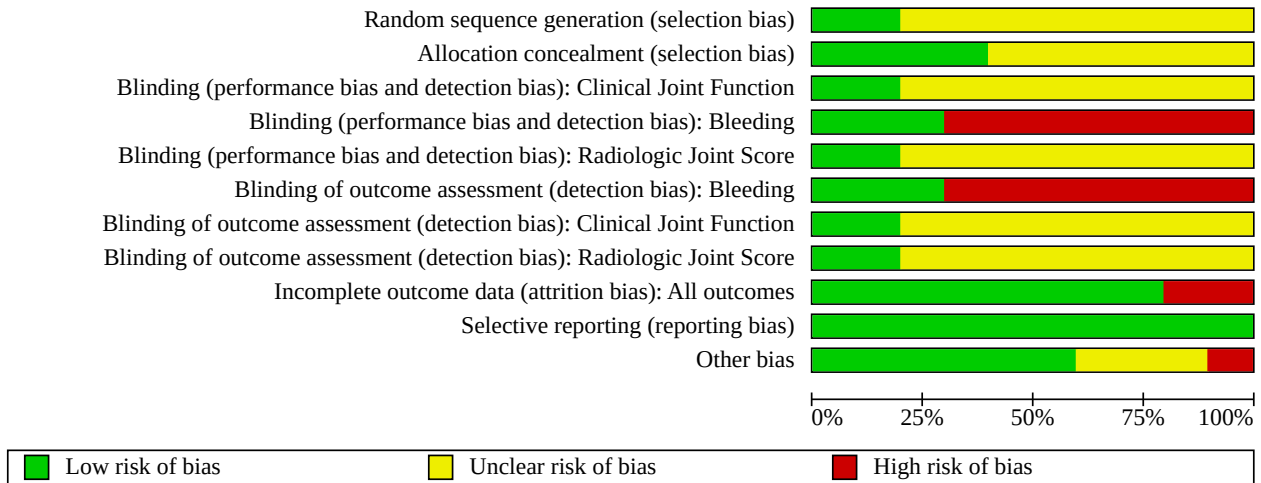


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Clinical Joint Function	Blinding (performance bias and detection bias): Bleeding	Blinding (performance bias and detection bias): Radiologic Joint Score	Blinding of outcome assessment (detection bias): Bleeding	Blinding of outcome assessment (detection bias): Clinical Joint Function	Blinding of outcome assessment (detection bias): Radiologic Joint Score	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
A-LONG 2014	?	?	?	-	?	-	?	?	+	+	+
Aronstam 1976	?	?	?	+	?	+	?	?	+	+	?
Aronstam 1977	?	?	?	+	?	+	?	?	+	+	?
LEOPOLD II 2015	?	+	?	-	?	-	?	?	+	+	+
LipLong 2012	?	?	?	+	?	+	?	?	-	+	-
Morfini 1976	?	+	+	-	+	-	+	+	+	+	?
PROPEL III 2020	+	?	?	-	?	-	?	?	+	+	+
SPINART 2013	?	+	+	-	+	-	+	+	+	+	+
Valentino 2012	+	+	?	-	?	-	?	?	-	+	+
Valentino 2014	?	?	?	-	?	-	?	?	+	+	+

Allocation

Random sequence generation

While all trial reports indicated that the trial was randomised, only four of the 10 included trials provided some detail of the method used for random sequence generation (LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012). In two of these trials, the method used was judged to be sound and of low risk of bias (PROPEL III 2020; Valentino 2012). Eight trials were judged to be of unclear risk of bias.

Allocation concealment

Four trials indicated the method for allocation concealment; these were judged to be at low risk of bias for this domain (LEOPOLD II 2015; Morfini 1976; SPINART 2013; Valentino 2012). The remaining six trials had an unclear risk of bias (A-LONG 2014; Aronstam 1976; Aronstam 1977; LipLong 2012; PROPEL III 2020; Valentino 2014).

Blinding

Performance and detection bias

Three of the included trials employed an appropriate method to blind participants and personnel to minimise performance bias (Aronstam 1976; Aronstam 1977; LipLong 2012). The remaining seven trials were open-label and we judged these to be at high risk of bias (A-LONG 2014; LEOPOLD II 2015; Morfini 1976; PROPEL III 2020; SPINART 2013; Valentino 2014; Valentino 2012). In the Manco-Johnson trial, bleeding events were patient-reported using an electronic diary, but for other outcomes such as the MRI evaluation of hemophilic arthropathy by radiologists and the joint physical examination performed by the physiotherapists, the assessors were blinded. The open-label trial design may also have influenced the results of the HRQoL (SPINART 2013). Similarly, in the Morfini trial, even though this is an open-label trial, it is reported that the assessors of orthopedic and radiological outcomes were blinded (Morfini 1976).

Incomplete outcome data

Eight of the 10 included trials either had no missing data or the losses to follow-up were balanced and explained. We judged these trials to be at low risk of bias (A-LONG 2014; Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; Morfini 1976; PROPEL III 2020; SPINART 2013; Valentino 2014). One included trial had dropouts not balanced across groups and with the reason cited as "PK results". Since this seems to be a treatment-related difference, we judged this to be at a high risk of bias (Valentino 2012). The LipLong trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board and was analysed per protocol (LipLong 2012). Also, higher consent withdrawal was reported in the investigational drug arm (N = 8 versus N = 2).

Selective reporting

We judged all included trials to have a low risk of bias for this domain. The protocols were not available in four of the 10 trials, but all expected outcomes were reported in these trials (Aronstam 1976; Aronstam 1977; Morfini 1976; Valentino 2014). We acquired the protocols for five trials and there was agreement between the outcomes outlined in the protocol and those presented in the final reports (A-LONG 2014; LEOPOLD II 2015; LipLong 2012; SPINART 2013; Valentino 2012). For one trial, authors provided

a three-month timeframe from the time of request to make the protocol available; all expected and stated outcomes in this trial were, however, reported (PROPEL III 2020).

Other potential sources of bias

In three of the cross-over trials, the washout period was unclear, therefore we judged these to have an unclear risk of bias (Aronstam 1976; Aronstam 1977; Morfini 1976). The LipLong trial is marked high risk for other potential sources of bias due to the possibility of over-estimation or "freezing-effect" that could arise from premature discontinuation of clinical trials (LipLong 2012; Wang 2016). In the remaining six trials, we did not identify any other potential sources of bias and so marked them as low risk for other potential sources of bias (A-LONG 2014; LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014).

Effects of interventions

See: **Summary of findings 1** Comparison of two prophylaxis regimens; **Summary of findings 2** Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation; **Summary of findings 3** Prophylaxis regimen versus on-demand treatment

Comparison between two prophylaxis regimens

The certainty of the evidence has been graded for those outcomes included in the summary of findings table (**Summary of findings 1**). For the definitions of these gradings, please refer to the summary of findings tables.

We included eight trials (477 participants) in this comparison (Aronstam 1976; Aronstam 1977; Morfini 1976; LEOPOLD II 2015; LipLong 2012; PROPEL III 2020; Valentino 2012; Valentino 2014). One of the included trials compared a standard prophylaxis treatment regimen to a PK-tailored regimen (Valentino 2012). One trial compared prophylaxis with a standard therapeutic factor concentrate to a pegylated liposome FVIII formulation (LipLong 2012), this comparison is reported separately below. Overall, given the heterogeneity in reporting these trials, we did not aggregate data.

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

Three included trials reported on joint bleeding (LEOPOLD II 2015; PROPEL III 2020; Valentino 2014). The LEOPOLD II trial found no difference in joint bleed prevention when a thrice-weekly, higher-dose prophylaxis regimen was compared to a twice-weekly (at 12 months follow-up) lower-dose prophylaxis, MD -1.70 (95% CI -5.06 to 1.66) (59 participants) (moderate-certainty evidence) (**Analysis 1.1**) (LEOPOLD II 2015). Comparing a PK-guided prophylaxis regimen targeting trough levels of 8% to 12% or 1% to 3% in the PROPEL III trial, no difference was also found between the two prophylaxis arms (at 12 months follow-up); MD -1.50 (95% CI -3.54 to 0.54) (115 participants) (moderate-certainty evidence) (**Analysis 1.2**) (PROPEL III 2020). No difference was also seen in spontaneous joint bleeds between the two regimens, MD -1.50 (95% CI -3.22 to 0.22) (**Analysis 1.3**) (PROPEL III 2020). In the Valentino 2014 trial, no difference was also reported in annualized joint bleeding in the low-frequency prophylaxis arm (100 IU/kg once weekly) compared to the standard frequency regimen (50 IU/kg twice weekly); MD of

1.70 (95% CI -1.09 to 4.49) (50 participants) ([Analysis 1.4](#)) ([Valentino 2014](#)).

2. Orthopedic joint score or clinical joint function

One included (cross-over) trial (10 participants) assessed joint function ([Morfini 1976](#)). While joint evaluations were conducted, data were not presented for individual treatment groups, rather results were presented that encompassed both arms. It was noted that through the 12 months of replacement therapy, range of motion was improved in 23 of 26 target joints. As well, there was also no deterioration in any joint, target or normal, over the course of treatment.

3. QoL on validated scales

One included trial (66 participants) assessed QoL using the SF36v1 scale ([Valentino 2012](#)). Data for individual treatment arms were not provided. Rather trial authors stated that there was no difference in overall QoL between prophylactic regimens.

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

Given the differences in treatment regimens and populations, we did not pool data for these trials and instead we report the results individually.

Seven trials reported on total bleeding. When comparing the use of a thrice-weekly, higher-dose prophylaxis with a twice-weekly, lower-dose prophylaxis regimen (at 12 months follow-up), results suggested no difference in overall bleeding rate, MD -1.40 (95% CI -4.91 to 2.11) (moderate-certainty evidence) ([Analysis 1.5](#)) ([LEOPOLD II 2015](#)). There was also no difference seen in total bleeding between prophylaxis to increase FVIII level to 30% or 15%, MD 10.20 (95% CI -1.29 to 21.69) ([Analysis 1.6](#)) ([Aronstam 1977](#)).

Comparing a standard prophylaxis regimen to a PK-tailored regimen, no reduction in bleeds across the comparison was indicated, MD -0.30 (95% CI -0.86 to 0.26) (66 participants) ([Analysis 1.7](#)) ([Valentino 2012](#)). When considering the effect of prophylaxis on 10 participants with haemophilia B, we see that the twice-a-week regimen (7.5 IU/kg) was favoured over the once-a-week regimen (15 IU/kg), MD 11.20 (5.81 to 16.59) (moderate-certainty evidence) ([Analysis 1.8](#)) ([Morfini 1976](#)). In the 2014 Valentino trial, comparing two different dosing frequencies in people with haemophilia B, only a P value of 0.22 was reported in the comparison of the two treatment regimens (50 IU/kg twice-weekly versus 100 IU/kg once-weekly) ([Valentino 2014](#)).

When comparing the overall bleeding frequency in nine participants in the Aronstam cross-over trial, there was a significant reduction in the overall bleeding frequency in the prophylaxis group with dosing producing at least 0.25 IU/mL of factor VIII compared to the dosing producing at least 0.01 IU/mL once weekly, MD 3.44 (95% CI 2.42 to 4.46) ([Analysis 1.9](#)) ([Aronstam 1976](#)).

In the comparison between the prophylactic arm targeting trough levels of 1% to 3% or 8% to 12% in the PROPEL III trial, no difference was seen in bleeding frequency between the two groups, MD 2.00 (95% CI -0.13, 4.13) (115 participants) ([Analysis 1.10](#)) ([PROPEL III 2020](#)).

2. Pain scores

None of the included trials reported this outcome.

3. Radiologic joint score or radiologic measurements or descriptions of joint damage

Only one trial (10 participants) reported this outcome ([Morfini 1976](#)). Trial authors stated that the 12 months of prophylaxis treatments improved the radiological picture in six cases with grade II or III arthropathy, but had no effect in those with grade IV arthropathy, but no numeric data were given.

4. Clotting factor concentrate plasma levels

One included trial (115 participants) assessed clotting factor concentrate plasma levels ([PROPEL III 2020](#)). In this trial, initial PK assessments showed mean (SD) plasma half-lives ($t_{1/2}$) of 15.3 (4.2) and 14.7 (5.1) hour in the 1% to 3% and 8% to 12% arms to be respectively. FVIII activity was a median (Q1 to Q3) 17.30 (15.2-21.7) and 35.0 (29.2 - 40.9) IU/dL during the first six months, and 17.30 (14.5 - 22.4) and 30.9 (24.9 - 41.2) IU/dL during the second six months for the 1% to 3% and 8% to 12% arms, respectively. Observed FVIII activity trough levels during the second six months were within the intended ranges of 1% to 3% and 8% to 12%; with median FVIII troughs ranging from 2.1 to 3.0 IU/dL and 10.7 to 11.7 IU/dL.

5. Time loss to school or employment

None of the included trials reported this outcome.

6. Integration into society

None of the included trials reported this outcome.

7. Scores on scales recording feeling of well-being and global functioning

None of the included trials reported this outcome.

8. Economic data

None of the included trials reported this outcome.

9. Any reported adverse effects or toxicity of clotting factor concentrates

There was no reported inhibitor development reported in six of the trials in this comparison ([Aronstam 1976](#); [Aronstam 1977](#); [LEOPOLD II 2015](#); [Morfini 1976](#); [Valentino 2012](#); [Valentino 2014](#)).

Transient low-titer anti-FVIII inhibitory antibodies, which resolved before the end of the trial, was reported in one out of 58 participants in the PROPEL III trial, in the arm targeting trough levels of 8% to 12% ([PROPEL III 2020](#)).

The Valentino trial reported (at 32 weeks follow-up) no differences in total treatment-emergent adverse events, MD 1.00 (95% CI 0.54, 1.84) ([Analysis 1.11](#)) ([Valentino 2014](#)).

Three trials did not report the rate of adverse events by treatment groups ([Aronstam 1977](#); [LEOPOLD II 2015](#); [Morfini 1976](#)). However, in the LEOPOLD II trial, there were three reported treatment-related adverse events, but no details regarding the type of event or group were given ([LEOPOLD II 2015](#)).

In the 2012 Valentino trial that compared standard prophylaxis to a PK-tailored regimen, there was no difference in mean rates of

adverse events between the two regimens at 12 months follow-up, MD 0.27 (95% CI -0.44 to 0.98) ([Analysis 1.12](#)) ([Valentino 2012](#)).

Serious and non-serious adverse events were reported in the PROPEL III trial. However, two out of 101 and two out of 103 of these events were estimated to be treatment-related in the arm targeting 1% to 3% and 8% to 12% respectively ([PROPEL III 2020](#)). In the arm targeting trough levels of 1% to 3%, no serious adverse event was treatment-related, and in the arm targeting trough levels of 8% to 12%, one serious adverse event was estimated to be treatment-related.

We assessed the certainty of the evidence as very low.

Prophylaxis with standard therapeutic factor concentrate compared to pegylated liposome FVIII formulation

The certainty of the evidence has been graded for those outcomes included in the summary of findings table ([Summary of findings 2](#)). For the definitions of these gradings, please refer to the summary of findings tables.

One trial was included in this comparison ([LipLong 2012](#)).

The 2012 LipLong trial (143 participants) compared a standard prophylaxis dose to a new investigational drug, pegylated liposome FVIII formulation (BAY 79-4980), given once-weekly ([LipLong 2012](#)); 73 participants were randomised to the prophylaxis group and 70 to the BAY79-4980 group. Four randomised participants did not receive the intervention drugs, leaving 139 participants (n = 67 in BAY 79-4980 and n = 72 in the prophylaxis group) for analysis. The sponsor halted the trial prematurely based on the recommendations of the data safety and monitoring board, indicating that the primary and secondary endpoints of non-inferiority with prophylaxis with rFVIII-FS three times/week would not be met. No safety issues were cited as the reason for early termination. The efficacy outcomes of this trial were reported as a per-protocol analysis set.

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

This outcome was reported in terms of annualised bleeding rates. This comparison showed fewer joint bleeding with the standard prophylaxis regimen compared to the investigational drug BAY 79-4980, MD -7.20 (95% CI -11.01 to -3.39) (low-certainty evidence) ([Analysis 2.1](#)) ([LipLong 2012](#)).

2. Orthopedic joint score or clinical joint function

This outcome was not reported.

3. QoL on validated scales

This outcome was not reported.

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

This outcome was reported in terms of annualised bleeding rates. There was a statistically significant difference favouring the prophylaxis regimen compared to the investigational drug BAY 79-4980, MD -9.20 (95% CI -13.07 to -5.33) (low-certainty evidence) ([Analysis 2.2](#)) ([LipLong 2012](#)).

2. Pain scores

This outcome was not reported.

3. Radiologic joint score or radiologic measurements or descriptions of joint damage

This outcome was not reported.

4. Clotting factor concentrate plasma levels

This outcome was not reported.

5. Time loss to school or employment

This outcome was not reported.

6. Integration into society

This outcome was not reported.

7. Scores on scales recording feeling of well-being and global functioning

This outcome was not reported.

8. Economic data

This outcome was not reported.

9. Any reported adverse effects or toxicity of clotting factor concentrates

One participant in the prophylaxis group reported three serious adverse events, which were deemed to be drug-related ([LipLong 2012](#)). No specific information was given about the presence of adverse events in the BAY 70-4980 group. No participant developed inhibitors to FVIII over the course of the trial. We judged the certainty of the evidence to be low.

Prophylaxis regimen compared to on-demand (episodic) treatment

The certainty of the evidence has been graded for those outcomes included in the summary of findings table ([Summary of findings 3](#)). For the definitions of these gradings, please refer to the summary of findings tables.

Four trials were reported on this comparison ([A-LONG 2014](#); [LEOPOLD II 2015](#); [SPINART 2013](#); [Valentino 2014](#)). In the Valentino 2012 trial, while comparing prophylaxis and on-demand treatments, the comparison was not across the randomised allocation and hence was not included in the following analyses ([Valentino 2012](#)). Of note, this trial found that any type of secondary prophylaxis (standard versus PK-adjusted) was significantly protective for total bleeding and joint bleeding when compared to episodic treatment (P < 0.0001). Also, this trial reported a significant improvement in QoL for the bodily pain (4.1, P = 0.0007) and physical component score (PCS) (3.6, P = 0.0002) domains as measured on the SF36v1 scale for prophylaxis (any type) versus on-demand treatment ([Valentino 2012](#)).

Primary outcomes

1. Number of joint bleeding episodes or joint bleeding frequency

All trials reported this outcome.

Data from two combined trials suggest that the use of a prophylaxis regimen significantly decreases the number of joint bleeds when compared to on-demand treatments, MD -30.34 (95% CI -46.95

to -13.73) (low-certainty evidence) ([Analysis 3.1](#)) ([LEOPOLD II 2015](#); [SPINART 2013](#)). Considerable heterogeneity was seen in this analysis ($I^2 = 87%$). The data from the A-LONG trial suggest the same effect; however, these data were reported with medians, hence could not be included in the above analysis ([A-LONG 2014](#)).

2. Orthopedic joint score or clinical joint function

The three-year follow-up of the SPINART trial measured the joint function using the Colorado Joint Assessment Scale (CAJAS) ([SPINART 2013](#)). The CAJAS provides a score taking into account nine items for knee and ankles and seven for elbows. Data from the original report showed a mild improvement in joint health in the prophylaxis group at year three, least square (LS) mean -0.31 (95% CI -0.79 to 0.18), while the on-demand group experienced a mild deterioration, LS mean 0.63 (95% CI 0.08 to 1.18). Comparing the two regimens, the estimated change difference was 0.94 points (95% CI 0.23 to 1.65) in favour of the prophylaxis regimen ([Analysis 3.2](#)) ([SPINART 2013](#)).

3. QoL on validated scales

The HAEMO-QoL-A and EQ-5D questionnaires were used in the SPINART trial ([SPINART 2013](#)). Questionnaires were completed at baseline, six months, years one, two and three. LS mean changes in HAEMO-QoL-A score from baseline to year three showed an improvement in the prophylaxis group and a deterioration in the on-demand group resulting in a 9.98 point (95% CI 3.42 to 16.54) difference in favour of prophylaxis. Similarly, the EQ-5D showed improved HRQoL in the prophylaxis group with a mean (SD) change of 0.06 (0.15), whereas almost no change was seen for the on-demand group with a mean (SD) change of -0.01 (0.16) in utility index score from baseline to year three.

Secondary outcomes

1. Number of total bleeding episodes or total bleeding frequency

Data from two combined trials suggest that the use of a prophylaxis regimen is significantly more protective than on-demand treatment when preventing bleeding episodes, MD -40.24 (95% CI -64.04 to -16.44) (low-certainty evidence) ([Analysis 3.3](#)) ([LEOPOLD II 2015](#); [SPINART 2013](#)). Considerable heterogeneity was also seen in this analysis ($I^2 = 93%$). Total bleeding rates in the A-LONG trial also suggest a similar effect and were also not included in this analysis as data were reported as medians ([A-LONG 2014](#)).

2. Pain scores

The SPINART trial reports the results for the Short-Form McGill Pain Questionnaire total score, determined at baseline and years one, two and three ([SPINART 2013](#)). At three years, the participants enrolled in the prophylaxis group reported a 50% decrease in pain for the previous four weeks, mean 17.2 (SD 22.9), whereas on-demand participants reported no change, mean 0.0 (SD 25.1), resulting in a MD of -17.20 (95% CI -27.48 to -6.92) in total score in favour of prophylaxis ([Analysis 3.4](#)) ([SPINART 2013](#)).

3. Radiologic joint score or radiologic measurements or descriptions of joint damage

The SPINART trial used the 45-item eMRI scale, previously validated with baseline data. Six index joints (knees, ankles, and elbows) were evaluated and each MRI was independently scored by three radiologists that were blinded to treatment allocation ([SPINART 2013](#)). Overall, the results at year three indicated detectable

deteriorations on eMRI from baseline in both the prophylaxis group and the on-demand group (mean (SD) 0.75 (1.59) and 0.92 (SD 1.15) respectively) and a total MD -18.39 (95% CI -21.55 to 15.23) ([Analysis 3.5](#)) ([SPINART 2013](#)). However, LS mean changes of -0.71 between the two regimens were not considered significantly different.

4. Clotting factor concentrate plasma levels

This outcome was not reported in any of the included trials for this comparison.

5. Time loss to school or employment

One trial reported the time spent under medical care ([Aronstam 1976](#)). In this trial, more than three hours under medical care were noted as one day. The authors reported that children on prophylaxis spent significantly less time confined to bed.

6. Integration into society

This outcome was not reported in any of the included trials for this comparison.

7. Scores on scales recording feeling of well-being and global functioning

This outcome was not reported in any of the included trials for this comparison.

8. Economic data

This outcome was not reported in any of the included trials for this comparison.

9. Any reported adverse effects or toxicity of clotting factor concentrates

When considering the number of individuals who experienced an adverse event, over two trials, more adverse events were reported in the participants on prophylaxis compared to those on on-demand therapy, RR 1.71 (95% CI 1.24 to 2.37) ([Analysis 3.6](#)) ([A-LONG 2014](#); [SPINART 2013](#)). The distribution of adverse events across groups was not given in the LEOPOLD II trial, and hence it was not included in the above analysis. Of note, there were three reported treatment-related adverse events, but no participant developed an inhibitor during the course of treatment ([LEOPOLD II 2015](#)). In the 1976 Aronstam trial, one participant developed antigen-negative hepatitis and was removed from the remaining duration of the trial ([Aronstam 1976](#)).

DISCUSSION

Summary of main results

This Cochrane Review included 10 trials with a total of 608 people with severe or moderate haemophilia A (n = 548) or B (n = 60), who had been previously treated for their disease. These trials yielded two different comparisons:

1. comparison between two prophylaxis regimens; including prophylaxis with a standard, commercial rFVIII and a new investigational drug; and
2. standard prophylaxis versus on-demand treatment.

Due to differences in treatment schedules and reporting methods, we were only able to aggregate data for our primary outcomes in one of the comparisons.

The data included in the review from the individual studies and the aggregated data suggest that secondary prophylaxis may be superior to on-demand treatment for preventing both joint bleeding incidents and overall bleeding (low-certainty evidence). Prophylaxis may also improve joint function, pain and QoL (low-certainty evidence). However, it seems that the regimens tested were not effective in halting or reversing the progression of arthropathy once structural joint damage has occurred. In fact, no detectable improvement, as assessed by MRI, of articular damage could be found at the three-year observation time-point in the SPINART trial.

When considering the comparison between two prophylaxis regimens, no individual prophylactic treatment schedule investigated proved to be superior at preventing total bleeding events in people in haemophilia A. Finally, standard prophylaxis may be more effective at preventing joint and total bleeding events than the experimental drug BAY 79-4980 (low-certainty evidence). Individuals with hemophilia B were included in two trials (Morfini 1976; Valentino 2014). The Morfina trial showed that a twice-weekly regimen of prophylaxis may be superior to a once-weekly regimen in decreasing total bleeding incidence, but these results should be interpreted cautiously given the small number of participants, the extremely low dose used and the fact that none of the participants were blinded to their treatment allocation (low-certainty evidence). The results of the Valentino 2014 trial did not establish a superior prophylaxis regimen; however, this trial did show that prophylaxis at any dosing schedule was superior to on-demand treatment to prevent spontaneous bleeds and joint bleeding incidence (Valentino 2014). When considering these data, it must be kept in mind that the bleeding data were aggregated for only 16 weeks, and the annualized bleeding rates were extrapolated from this time period.

Regarding the incidence of adverse events, when considering the comparison of prophylaxis versus on-demand treatment, the moderate-certainty evidence showed that on-demand treatment probably reduces the incidence of adverse events (131 participants, two trials) (A-LONG 2014; SPINART 2013). However, all individuals with a past history of an inhibitor were excluded from the trials and so information for this group is not available.

Of note, in the LEOPOLD II 2015 trial, participants were crossed over between groups to receive factor that was labelled in different ways (LEOPOLD II 2015). Each participant received six months of the trial drug labelled with a chromogenic substrate assay per European Pharmacopoeia, followed by six months of the trial drug labelled using a correction factor to simulate the results obtained with the one-stage assay. Because of this, trial authors report that participants likely received approximately 20% to 25% higher factor concentrate product in the time period when received FVIII based on the one-stage adjusted labelling method. Since all participants in the trial were given both the factor concentrate based on the two labelling methods, all participants were subject to the fluctuation in factor concentrate. Hence, we did not deem it necessary to alter our analyses to accommodate for the use of a substrate assay in this trial (LEOPOLD II 2015).

Since one of the goals of initiating secondary prophylaxis is to prevent further deterioration of target joints, we decided to use joint bleeds, rather than total bleeds, as our primary outcome. However, interestingly this outcome was infrequently reported

separately from total bleeding events. In addition, only two trials assessed joint function.

One limitation of this review was our inability to aggregate data for most of our outcomes. There were two main reasons for which we were unable to aggregate data:

1. diversity in participant characteristics and treatment regimens; and
2. diversity in reporting methods.

We hoped to be able to combine data from trials comparing different secondary prophylaxis regimens in order to give a more powerful estimate of the use of secondary prophylaxis. However, we found that the differences in participants and treatment arms between trials were too great to generate a reliable aggregate result. Many of the outcomes were reported as medians with ranges, while others were reported as means. Medians are often used when data are skewed, as might be the case with bleeding events, where individuals with a very high or very low number of bleeding events may pull an estimate in one direction. Often, a median can be used to approximate to mean values, but since our sample sizes were comparatively small, we decided against using this approach, as this may not have been an accurate approximation. We hope that as haemophilia treatment becomes increasingly optimised, and based on large randomised trials, the barriers that precluded us from aggregating data in this review will no longer exist.

Overall completeness and applicability of evidence

We conducted this review to investigate the effectiveness of clotting factor concentrate prophylaxis in managing previously-treated individuals with haemophilia A or B. In this Cochrane Review, we included only RCTs, and the primary outcome for this review, joint bleeding events or joint bleeding frequency, was reported in seven out of the 10 trials. Overall bleeding events or overall bleeding frequency were reported in all 10 trials. Other secondary outcomes such as clinical joint function and radiologic measurements were reported in two trials (Morfini 1976; SPINART 2013). Two trials also reported conducting QoL assessments (SPINART 2013; Valentino 2012) and one trial reported the results of pain assessment (SPINART 2013). Participants included people with haemophilia A and B and mostly characterised by FVIII or FIX levels < 1% of normal. Two trials included people with severe or moderately severe (factor levels \leq 2%) haemophilia A or B. The evidence summarised in this review is applicable to individuals with moderate-severe to severe hemophilia A and B on secondary prophylaxis.

Quality of the evidence

Overall, we found the included trials to be at low risk or unclear risk of bias for most domains. In particular, while all trial reports indicated that the trial was randomised, only four of the 10 included trials indicated the method used for random sequence generation (LEOPOLD II 2015; PROPEL III 2020; SPINART 2013; Valentino 2012), with only two were assessed as having a low risk of bias for the domain (LEOPOLD II 2015; PROPEL III 2020). When considering the method for allocation concealment four trials were judged to be at low risk of bias for this domain (LEOPOLD II 2015; Morfina 1976; SPINART 2013; Valentino 2012). The remaining six trials had an unclear risk of bias (A-LONG 2014; Aronstam 1976;

Aronstam 1977; LipLong 2012; (PROPEL III 2020; Valentino 2014). Also, three of the included trials used an appropriate method to blind participants and personnel to minimize performance bias (Aronstam 1976, Aronstam 1977, LipLong 2012). The remaining seven trials were open-label. Regarding the possibility of reporting bias, all included trials were judged to have a low risk of bias for this domain.

Overall, the certainty of the evidence was considered to be low because of different types of bias that could have altered the effect. In the comparison of two prophylaxis regimens, the certainty of the evidence was downgraded twice due to performance and detection bias as included studies were open-label and due to incomplete outcome data. The certainty of the evidence was also downgraded due to high levels of heterogeneity across trials. In the comparison of prophylaxis and on-demand regimens. Future research might have an important role in changing our confidence in the estimate of effect.

Potential biases in the review process

We attempted to minimise the possibility of bias in the review process and all the authors had access to all the data and critically reviewed the manuscript. Our search strategy has been as inclusive as possible, and no specific restrictions were placed on the language or date of publication when searching databases. It is unlikely that potentially relevant trials were missed, also considering that in addition to the search of the electronic databases the bibliographic references of all retrieved trials and reviews were assessed for additional reports of potential interest. We also handsearched the proceedings of the International Society for Thrombosis and Haemostasis bi-annual meeting and proceedings of the European Association for Haemophilia and Allied Disorders.

Agreements and disagreements with other studies or reviews

Overall the conclusions of this review are in substantial agreement with the recent literature assessing the importance of secondary prophylaxis in haemophilia (Haemophilia 2018). It is also interesting to consider that consistent results were obtained in a 2015 non-randomised study investigating the effects of long-term late secondary prophylaxis compared with on-demand treatment in haemophilia (POTTER 2015). Results from this study support the efficacy of late secondary and tertiary prophylaxis, which

ultimately significantly decreased the frequency of all bleeding episodes, including joint bleeds, and improved joint status.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence from randomised controlled trials that the use of prophylactic clotting factor concentrate may result in reduced frequency of total bleeds, and likely improves joint function and quality of life in people with severe or moderate haemophilia A and B.

Implications for research

Prophylaxis treatment is often considered the ideal treatment in high-resource countries. However, there are still knowledge gaps in the understanding of haemophilia treatment with respect to the ideal regimen and when to start prophylaxis. While the results of this review begin to shed light on the use of secondary prophylaxis in managing bleeding, there are still areas that require elucidation, namely the impact of late prophylaxis in people with varying degrees of arthropathy at baseline, the most cost-efficient dosage and frequency, the minimally effective dose and the role of individualised regimens to a person's bleeding pattern and activity. Further research should be undertaken to attempt to provide evidence-based data for these areas.

Future randomised controlled trials should address the following aspects:

1. comparative efficacy, safety, and effectiveness of different prophylactic regimens (escalating versus fixed-dose, pharmacokinetic-tailored versus fixed-dose);
2. standardised clinical and radiological outcome measures of efficacy;
3. long-term cost-effectiveness;
4. Individualisation of regimens.

ACKNOWLEDGEMENTS

The authors will like to acknowledge and thank Tracey Remington (Managing Editor) of the Cochrane Cystic Fibrosis and Genetic Disorders Group for providing comments and feedback on drafts of this review.

REFERENCES

References to studies included in this review

A-LONG 2014 {published data only}

Konkle B, Pasi K, Young G, Recht M, Quon D, Tsao E, et al. Long-term efficacy of recombinant factor VIII Fc fusion protein (rFVIII Fc) prophylaxis in adults, adolescents, and children with severe hemophilia A: longitudinal analysis of A-LONG and ASPIRE studies. *Haemophilia* 2017;**23** Suppl 3:21. [CENTRAL: CN-01602316] [CFGD REGISTER: HA114f]

Kulkarni R, Ragni MV, Baker RI, Pasi J, Manco-Johnson MJ, Potts J, et al. Analysis of clinical target joint bleeding on prophylactic regimens with recombinant Factor VIII Fc fusion protein in patients with severe hemophilia A. *Haemophilia* 2014;**20** Suppl 3:94. [CFGD REGISTER: HA114a]

Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood* 2014;**123**(3):317-25. [CFGD REGISTER: HA114a]

Mahlangu JN, Ragni M, Gupta N, Rangarajan S, Klamroth R, Oldenburg J, et al. Long-acting recombinant factor VIII Fc fusion protein (rFVIII Fc) for perioperative haemostatic management in severe haemophilia A. *Thrombosis and Haemostasis* 2016;**116**(1):1-8. [CENTRAL: CN-01414922] [CFGD REGISTER: HA114e / HA106b] [PMID: 26962852]

Shapiro AD, Ragni MV, Kulkarni R, Oldenburg J, Srivastava A, Quon DV, et al. Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels. *Journal of thrombosis and haemostasis : JTH* 2014;**12**(11):1788-800. [CFGD REGISTER: HA114c]

Wyrwich KW, Krishnan S, Auguste P, Poon JL, von Maltzahn R, Yu R, et al. Changes in health-related quality of life with treatment of longer-acting clotting factors: results in the A-LONG and B-LONG clinical studies. *Haemophilia* 2016;**22**(6):866-72. [CENTRAL: CN-01262866] [CFGD REGISTER: HA114d] [PMID: 27385432]

Aronstam 1976 {published data only}

Aronstam A, Arblaster PG, Rainsford SG, Turk P, Slattery M, Alderson MR, et al. Prophylaxis in haemophilia: a double-blind controlled trial. *British Journal of Haematology* 1976;**33**(1):81-90. [CENTRAL: 13878] [CFGD REGISTER: HA4] [PMID: 773416]

Aronstam 1977 {published data only}

Aronstam A, Kirk PJ, McHardy J, Culver-James JW, McLellan DS, Turk P, et al. Twice weekly prophylactic therapy in haemophilia A. *Journal of Clinical Pathology* 1977;**30**(1):65-7. [CENTRAL: CN-00462731] [CFGD REGISTER: HA80]

LEOPOLD II 2015 {published data only}

Church N, Ayyagari R, Pocoski J, Sajeev G, Sneha K, Du EX, et al. Bleed occurrence after Bay 81-8973 injection and characteristics of patients who respond to prophylaxis: analyses from Leopold I and II. *Haemophilia* 2016;**22** Suppl 2:78-9. [CENTRAL:

CN-01612491] [CFGD REGISTER: HA129j / HA111h] [EMBASE: 622470086]

Fujii T, Hanabusa H, Shima M, Morinaga T, Fukutake K. Analysis of the Japanese subgroup in LEOPOLD II: a phase 2/3 study of BAY 81-8973, a new recombinant factor VIII product. *International Journal of Hematology* 2017;**105**(3):280-6. [CENTRAL: CN-01215985] [CFGD REGISTER: HA111i] [PMID: 27832514]

Garmann D, McLeay S, Shah A, Vis P, Maas Enriquez M, Ploeger BA. Population pharmacokinetic characterization of BAY 81-8973, a full-length recombinant factor VIII: lessons learned - importance of including samples with factor VIII levels below the quantitation limit. *Haemophilia* 2017;**23**(4):528-37. [CENTRAL: CN-01395099] [CFGD REGISTER: HA111n / HA129q] [EMBASE: 614542165]

Kavakli K, Saxena K, Maas Enriquez M. Study design of 2 randomized, crossover, open-label trials to evaluate the pharmacokinetics, efficacy, and safety of plasma protein-free recombinant factor VIII formulated with sucrose (BAY 81-8973). *Haemophilia* 2012;**18** Suppl 3:25. [ABSTRACT NO.: PO-WE-057] [CENTRAL: CN-00883170] [CFGD REGISTER: HA111a / HA129a]

Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Enriquez MM. Superiority of prophylaxis versus on-demand therapy with plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973): LEOPOLD II study results. *Haemophilia* 2014;**20** Suppl 3:94-5. [CFGD REGISTER: HA111b]

* Kavakli K, Yang R, Rusen L, Beckmann H, Tseneklidou-Stoeter D, Maas Enriquez M. Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). *Journal of Thrombosis and Haemostasis* 2015;**13**:360-9. [CFGD REGISTER: HA111c]

Lalezari S, Tii F, Kwong YL, Delesen H, Shah A, Tuckmantel C, et al. Leopold trial results: correlation of von willebrand factor antigen level with bay 81-8973 pharmacokinetic parameters of patients with severe hemophilia A. *Journal of Thrombosis and Haemostasis* 2015;**13**:96-7. [CENTRAL: CN-01103566] [CFGD REGISTER: HA111f / HA129e] [EMBASE: 71944691]

Mahlangu JN, Kavakli K, Hvitfeldt Poulsen L, Tseneklidou-Stoeter D, Beckmann H, Enriquez MM, et al. Prophylactic efficacy of twice-weekly vs. 3-times-weekly bay 81-8973 in severe hemophilia A: results of the Leopold I and II clinical trials. *Journal of Thrombosis and Haemostasis* 2015;**13** Suppl 2:858. [CENTRAL: CN-01131775] [CFGD REGISTER: HA111d / HA129c] [EMBASE: 71946758]

Oldenburg J, Windyga J, Hampton K, Lalezari S, Tseneklidou-Stoeter D, Beckmann H, et al. Safety and efficacy of BAY 81-8973 for surgery in previously treated patients with haemophilia A: results of the LEOPOLD clinical trial programme. *Haemophilia* 2016;**22**(3):349-53. [CENTRAL: CN-01159190] [CFGD REGISTER: HA129l / HA111j] [EMBASE: 610446754]

Saxena K, Kavakli K, Kitchen S, Oldenburg J, Yang R, Beckmann H, et al. Bay 81-8973 demonstrates comparable efficacy during prophylaxis irrespective of the assay determining potency. *Haemophilia* 2015;**21**:31-2. [CENTRAL: CN-01077524] [CFGD REGISTER: HA111g / HA129g] [EMBASE: 71814436]

Shah A, Delesen H, Garger S, Lalezari S. Pharmacokinetic properties of BAY 81-8973, a full-length recombinant factor VIII. *Haemophilia* 2015;**21**(6):766-71. [CENTRAL: CN-01127144] [CFGD REGISTER: HA111e / HA129d] [PMID: 25952661]

Yang R, Sun J, Zhao Y, Wang X, Wu D, Tseneklidou-Stoeter D, et al. Efficacy and safety of prophylaxis with BAY 81-8973 in Chinese patients with severe haemophilia A enrolled in the LEOPOLD II trial. *Haemophilia* 2019;**25**(3):e153-8. [CENTRAL: CN-01943371] [CFGD REGISTER: HA111m] [EMBASE: 627325629] [PMID: 30993836]

LipLong 2012 {published data only}

Di Minno G, Cerbone AM, Coppola A, Cimino E, Di Capua M, Pamparana F, et al. Longer-acting factor VIII to overcome limitations in haemophilia management: The PEGylated liposomes formulation issue. *Haemophilia* 2010;**16** Suppl 1:2-6. [CFGD REGISTER: HA104c]

Lalezari S, Coppola A, Lin J, Enriquez MM, Tseneklidou-Stoeter D, Powell J, et al. Patient characteristics that influence efficacy of prophylaxis with rFVIII-FS three times per week: a subgroup analysis of the LIPLONG study. *Haemophilia* 2014;**20**(3):354-61. [CFGD REGISTER: HA104f]

Lalezari S, Coppola A, Lin J, Enriquez MM. Subgroup analyses of annualized number of bleeds with three-times-per-week prophylaxis with rFVIII-FS. *Journal of thrombosis and haemostasis : JTH* 2011;**9** Suppl 2:373. [ABSTRACT NO: P-TU-204] [CFGD REGISTER: HA104g]

Lalezari S, Martinowitz U, Windyga J, Enriquez MM, Delesen H, Schwartz L, et al. Correlation between endogenous VWF: ag and PK parameters and bleeding frequency in severe haemophilia A subjects during three-times-weekly prophylaxis with rFVIII-FS. *Haemophilia* 2014;**20**(1):e15-22. [CFGD REGISTER: HA104e]

Martinowitz U, Windyga J, Powell J, Maas Enriquez M, Scharer I. Pharmacokinetic results and correlations with intrinsic von Willebrand factor levels from a randomized, double-blind study of prophylaxis with once-weekly BAY 79-4980 vs. 3-times-weekly sucrose-formulated recombinant factor VIII. *Haemophilia* 2012;**18** Suppl 3:25. [ABSTRACT NO: PO-WE-061] [CFGD REGISTER: HA104a]

Powell J, Ingerslev J, Enriquez MM, Martinowitz U. Efficacy and safety of prophylaxis with once-weekly bay 79-4980 vs. three-times-weekly rFVIII-FS: a randomized, active-controlled, double-blind study. *Journal of thrombosis and haemostasis : JTH* 2011;**9** Suppl 2:726. [ABSTRACT NO: O-TH-016] [CFGD REGISTER: HA104h]

Powell J, Martinowitz U, Windyga J, Di Minno G, Hellmann A, Pabinger I, et al. Efficacy and safety of prophylaxis with once-weekly BAY 79-4980 compared with thrice-weekly rFVIII-FS in haemophilia A patients: a randomised, active-controlled,

double-blind study. *Blood Coagulation, Fibrinolysis and Cellular Haemostasis* 2012;**108**:913-22. [CFGD REGISTER: HA104d]

Schafer K, Tseneklidou-Stoeter D, Nelson L, Maas Enriquez M. Experience with electronic patient diaries in a randomized, double-blind study of prophylaxis with once-weekly BAY 79-4980 vs. 3-times-weekly sucrose-formulated recombinant factor VIII. *Haemophilia* 2012;**18** Suppl 3:25. [ABSTRACT NO: PO-WE-062] [CFGD REGISTER: HA104b]

Morfini 1976 {published data only}

Morfini M, Mannucci PM, Mariani G, Panicucci F, Petrucci F, Baicchi U, et al. Evaluation of prophylactic replacement therapy in haemophilia B. *Scandinavian Journal of Haematology* 1976;**16**(1):41-7. [CENTRAL: CN-00013490] [CFGD REGISTER: HB8] [EMBASE: 1977017603] [PMID: 1251139]

PROPEL III 2020 {published data only}

Collins P, Windyga J, Escobar M, Ibrahim HM, Lam JCM, Tangada SD, et al. Efficacy and target joint resolution with pharmacokinetic-guided ruriotocog alfa pegol prophylaxis targeting two factor VIII trough levels in patients with severe hemophilia A: post-hoc analysis of the phase 3 propel trial. *Research and Practice in Thrombosis and Haemostasis* 2020;**4** Suppl 1:455. [CFGD REGISTER: HA137j]

Escuriola-Ettingshausen C, Klamroth R, Escobar M, Mullins ES, Stasyshyn O, Tangada S, et al. Personalizing prophylaxis with ruriotocog alfa pegol in previously treated patients with severe hemophilia A: outcomes from the phase 3B continuation and phase 3 propel studies. *Research and Practice in Thrombosis and Haemostasis* 2020;**4**(Suppl 1):453-4. [CFGD REGISTER: HA137i]

Horling FM, Allacher P, Koppensteiner H, Engl W, Scheiflinger F, Abbuehl BE, et al. Immunogenicity of BAX 855 in previously treated patients with congenital severe hemophilia A. *Blood* 2016;**128**(22):2594. [CFGD REGISTER: HA137a]

Klamroth R, Windyga J, Radulescu V, Collins P, Stasyshyn O, Ibrahim HM, et al. PK-guided ruriotocog alfa pegol prophylaxis in patients with severe hemophilia A targeting two FVIII trough levels: results from the phase 3 propel study. *Research and practice in thrombosis and haemostasis* 2019;**3**:106-7. [CFGD REGISTER: HA137e]

Klamroth R, Windyga J, Radulescu V, Collins P, Stasyshyn O, Ibrahim HM, et al. Results from a phase 3, randomized, multicenter study of ruriotocog alfa pegol PK-guided prophylaxis targeting 2 FVIII trough levels in patients with severe hemophilia A (propel study). *Haemophilia* 2019;**25**:162. [CFGD REGISTER: HA137d]

* Klamroth R, Windyga J, Radulescu V, Collins PW, Stasyshyn O, Ibrahim HM, et al. Ruriotocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study. *Blood* 2021;**137**(13):1818-27. [CFGD REGISTER: HA137h] [DOI: [10.1182/blood.2020005673](https://doi.org/10.1182/blood.2020005673)]

NCT02585960. BAX 855 pk-guided dosing. clinicaltrials.gov/show/nct02585960 (first posted 26 October 2015). [CFGD REGISTER: HA137b]

Radulescu V, Klamroth R, Windyga J, Collins P, Stasyshyn O, Mohd Ibrahim H, et al. Results from a phase 3, randomized, multicenter study of Rurioctocog Alfa Pegol PK-guided prophylaxis targeting two FVIII trough levels in patients with severe hemophilia A (PROPEL Study). *Haemophilia* 2019;**25**:57-8. [CFGD REGISTER: HA137f]

Robert K, Jerzy W, Vlad R, Peter C, Oleksandra S, Mohd Hishamshah I, et al. Results from a phase 3, randomized, multicenter study of rurioctocog alfa pegol PK-guided prophylaxis targeting 2 FVIII trough levels in patients with severe hemophilia A (Propel Study). *Hamostaseologie* 2019;**39**(S1):S1-92. [CFGD REGISTER: HA137c]

Windyga J, Collins P, Escuriola-Ettingshausen C, Escobar M, Shapiro S, Zulfikar B, et al. Rurioctocog alfa pegol PK-guided prophylaxis targeting two FVIII trough levels in severe hemophilia a patients (PROPEL phase 3 study): impact of patient FVIII half-life on consumption and efficacy outcomes. *Haemophilia* 2020;**26**:25. [CFGD REGISTER: HA137g]

SPINART 2013 {published data only}

EUCTR2008-000985-21-BG. Trial to evaluate the effect of two treatment regimens for adults with severe hemophilia A [Randomized, controlled, parallel, prospective trial to evaluate the effect of secondary prophylaxis with rFVIII therapy in severe hemophilia A adult and/or adolescent subjects, as applicable, compared to that of episodic treatment. (SPINART) - SPINART]. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-000985-21-BG (date of registration 4 February 2008). [CENTRAL: CN-01847483] [CFGD REGISTER: HA105r]

Funk S, Lundin B, Hong W. Spinart 3-year analyses: patient- and joint-level changes in colorado adult joint assessment scale and magnetic resonance imaging scores with Bayer's sucrose-formulated recombinant factor VIII in adolescents and adults. *Journal of thrombosis and haemostasis : JTH* 2015;**13 Suppl 2**:244. [ABSTRACT NO: OR388] [CFGD REGISTER: HA105j]

Hong W, Raunig D, Funk S. 3-year joint outcomes in the SPINART trial: results using the Colorado adult joint assessment scale. *Haemophilia* 2014;**20 Suppl 3**:63-4. [CFGD REGISTER: HA105f]

Hong W, Raunig D, Funk S. Joint outcome evaluation by magnetic resonance imaging: results at the 3-year evaluation in the SPINART study. *Haemophilia* 2014;**20 Suppl 3**:63. [CFGD REGISTER: HA105e]

Hong W, Raunig D, Lundin B. SPINART study: validation of the extended magnetic resonance imaging scale for evaluation of joint status in adult patients with severe haemophilia A using baseline data. *Haemophilia* 2016;**22**(6):e519-26. [CENTRAL: CN-01289866] [CFGD REGISTER: HA105m] [EMBASE: 613346343] [PMID: 27642172]

Kempton C, Valluri S, Reding M, Lissitchkov T, Goranov S, Gercheva L, et al. Randomized, controlled, parallel-group trial of secondary prophylaxis vs on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A. *Haemophilia* 2012;**18**(5):830-1. [CENTRAL: CN-01027887] [CFGD REGISTER: HA105n] [EMBASE: 71024222]

Kempton C, Valluri S, Reding M, Lissitchkov T, Goranov S, Gercheva L, et al. Regional differences in baseline patient-reported outcomes in a randomized, controlled, prospective trial of secondary prophylaxis VS on-demand treatment in patients with severe hemophilia A. *Haemophilia* 2012;**18 Suppl 3**:25. [ABSTRACT NO: PO-WE-058] [CFGD REGISTER: HA105a]

Lundin B, Hong W, Raunig D, Engelen S, Peterfy C, Werk M, et al. 3-year analyses from spinart: Patient-and joint-level changes in magnetic resonance imaging scores with bayer's sucrose-formulated recombinant factor VIII (RFVIII-FS) in adolescents and adults previously treated on demand. *Haemophilia* 2015;**21**:40-1. [CFGD REGISTER: HA105l]

Lundin B, Hong W, Raunig D, Engelen S, Peterfy C, Werk M, et al. Effect on joint health of routine prophylaxis with Bayer's sucrose-formulated recombinant factor VIII (rFVIII-FS) in adolescents and adults previously treated on demand: MRI analyses from the 3-year Spinart Study. In: 56th ASH Annual Meeting and Exposition; 2014 Dec 6-9; San Francisco, California. 2014. [ABSTRACT NO: 2854] [CFGD REGISTER: HA105h]

Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L, et al. Corrigendum to Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *Journal of Thrombosis and Haemostasis* 2014;**12**(1):119-22. [CENTRAL: CN-00980287] [CFGD REGISTER: HA105o] [EMBASE: 372087709]

Manco-Johnson M, Kempton CL, Reding MT, Goranov S, Gercheva L, Rusen L, et al. 3-year results from SPINART: prophylaxis vs on-demand treatment with sucrose-formulated recombinant factor VIII. *Haemophilia* 2014;**20 Suppl 3**:96. [CFGD REGISTER: HA105d]

Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L, et al. Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *Journal of Thrombosis and Haemostasis* 2013;**11**(16):1119-27. [CFGD REGISTER: HA105c]

Manco-Johnson MJ, Lundin B, Funk S, Peterfy C, Raunig D, Werk M, et al. Effect of late prophylaxis in hemophilia on joint status: a randomized trial. *Journal of Thrombosis and Haemostasis* 2017;**15**(11):2115-24. [CFGD REGISTER: HA105p]

NCT00623480. Trial to evaluate the effect of secondary prophylaxis with rfVIII therapy in severe hemophilia a adult and/or adolescent subjects compared to that of episodic treatment [Randomized, controlled, parallel, prospective trial to evaluate the effect of secondary prophylaxis with rfVIII therapy in severe hemophilia a adult and/or adolescent subjects, AS applicable, compared to that of episodic treatment]. clinicaltrials.gov/show/NCT00623480 (first posted 26 February 2008). [CENTRAL: CN-01517226] [CFGD REGISTER: HA105q]

Pocoski J, Humphries TJ, Hong W. Spinart 3-year data: Patient-reported benefits of adult prophylaxis vs on-demand treatment with bayer's sucrose-formulated recombinant factor VIII. *Haemophilia* 2015;**21**:51-2. [CFGD REGISTER: HA105k]

Pocoski J, Silberman C, Humphries T, Walker D, Hong W. Spinart trial 3-year results: improved quality of life in adults using prophylaxis with Bayer's sucrose-formulated recombinant factor VIII. *Journal of thrombosis and haemostasis : JTH* 2013;**11 Suppl 2**:20. [ABSTRACT NO: COA34] [CFGD REGISTER: HA105g]

Reding MT, Kempton CL, Funk S, Engelen S, Walker D, Hong W. Spinart trial 3-year results with bayer's sucrose-formulated recombinant factor VIII: relationship between bleeding frequency and joint health in adults with severe hemophilia A using prophylaxis. *Journal of thrombosis and haemostasis : JTH* 2015;**13 Suppl 2**:132. [ABSTRACT NO: OR101] [CFGD REGISTER: HA105i]

Zarkova AG, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L, et al. Bleeding frequency subanalyses in a randomized controlled trial of prophylaxis vs on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A. *Haemophilia* 2013;**19 Suppl 2**:28. [ABSTRACT NO: PO032] [CFGD REGISTER: HA105b]

Valentino 2012 {published data only}

Chowdary P, Fischer K, Collins PW, Cotterill A, Konkle BA, Blanchette V, et al. Modeling to predict factor VIII levels associated with zero bleeds in patients with severe hemophilia a initiated on tertiary prophylaxis. *Thrombosis and Haemostasis* 2020;**120**(5):728-36. [CFGD REGISTER: HA107g]

NCT00243386. Prophylaxis study of recombinant factor VIII manufactured protein-free (rahf-pfm) in patients with hemophilia a. clinicaltrials.gov/show/NCT00243386 2005 (first posted 24 October 2005). [CFGD REGISTER: HA107f]

Quon DV, Shapiro AD, Santagostino E, Valentino LA. Impact of rAHF-PFM prophylactic treatment on annual bleeding rate and health-related quality of life of adults with severe hemophilia A. *Journal of thrombosis and haemostasis : JTH* 2013;**11 Suppl 2**:1081. [ABSTRACT NO: PO 160] [CFGD REGISTER: HA107c]

Shapiro AD, Santagostino E, Epstein JD, Schroth P, Wong WY. Significant improvement in health-related quality of life with prophylaxis in severe hemophilia A: results from the rAHF-PFM randomized, controlled prophylaxis study. *Journal of thrombosis and haemostasis : JTH* 2011;**9 Suppl 2**:827. [ABSTRACT NO: P-TH-184] [CFGD REGISTER: HA107d]

Valentino LA, Mamonov V, Hellmann A, Quon DV, Chybicka A, Schroth P, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *Journal of Thrombosis and Haemostasis* 2012;**10**:359-67. [CFGD REGISTER: HA107a]

Valentino LA, Reyes CM, Ewenstein B, Guzman-Becerra N, Wong WY, Schoenig-Diesing C, et al. ADVATE prophylaxis: post hoc analysis of joint bleeding episodes. *Haemophilia* 2014;**20**(5):630-8. [CENTRAL: CN-01002062] [EMBASE: 53024411] [HA107b]

Valentino LA, Reyes CM, Ewenstein B, Guzman-Becerra N, Wong WY, Schoenig-Diesing C, et al. ADVATE prophylaxis: post hoc analysis of joint bleeding episodes. *Haemophilia* 2014;**20**(5):630-8. [CFGD REGISTER: HA107e]

Valentino 2014 {published data only}

Korth-Bradley J, Smith L, Fuiman J, Rendo P. Pharmacokinetic (PK) and clinical data support for effectiveness of once-weekly recombinant coagulation factor IX (RFIX) dosing for prophylaxis in patients with moderately severe or severe hemophilia B. *Journal of thrombosis and haemostasis : JTH* 2015;**13 Suppl 2**:322. [ABSTRACT NO: PO167-MON] [CFGD REGISTER: HB21g]

Rendo P, Barrette-Grischow MK, Smith L, Korth-Bradley JM, Charnigo R, Shafer FE. Evaluation of two secondary prophylaxis regimens of recombinant factor IX (r-IX) in moderately severe to severe (FIX \leq 2%) hemophilia B patients. *Blood* 2012;**120**(21). [ABSTRACT NO: 4628] [CFGD REGISTER: HB21c]

Rendo P, Smith L, Korth-Bradley J, Charnigo R, Shafer F. Evaluation of two secondary prophylaxis regimens of recombinant factor IX (r-fix) in moderately severe to severe (fix a% \leq 2%) hemophilia B patients. *Haemophilia* 2013;**19 Suppl 2**:20. [ABSTRACT NO: PO018] [CFGD REGISTER: HB21a]

Shafer F, Smith L, Vendetti N, Rendo P, Carr M. Lack of seasonal variation in bleeding and patient-assessed pain patterns in patients with haemophilia B receiving on-demand therapy. *Haemophilia* 2014;**20**(3):349-53. [HB21e]

Shafer FE, Smith L, Vendetti N, Rendo P, Carr ME. Lack of seasonal variation in bleeding and patient-assessed pain patterns in patients with hemophilia b receiving on-demand therapy. *Blood* 2012;**120**(21). [ABSTRACT NO: 1136] [CFGD REGISTER: HB21d]

Valentino LA, Plushch O, Rusen L, Andreeva T, Elezovic I, Charnigo R, et al. A multicenter, open-label study to compare on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in subjects with hemophilia B. *Journal of thrombosis and haemostasis : JTH* 2011;**9 Suppl 2**:357. [ABSTRACT NO: P-TU-155] [CFGD REGISTER: HB21b]

Valentino LA, Rusen L, Elezovic I, Smith LM, Korth-Bradley JM, Rendo P. Multicentre, randomized, open-label study of on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in haemophilia B subjects. *Haemophilia* 2014;**20**(3):398-406. [CFGD REGISTER: HB21f]

References to studies excluded from this review

Aledort 1994 {published data only}

Aledort LM, Haschmeyer RH, Pattersson H. The orthopaedic outcome study group. A longitudinal study of orthopaedic outcomes for severe factor VIII deficient haemophiliacs. *Journal of Internal Medicine* 1994;**236**(4):391-9.

Ali 2018 {published data only}

Ali TM, Crea R, Wanek K, Cano V. Tolerability/safety of feiba reconstituted in regular or 50% reduced volume and faster infusion rates: rationale and study design in patients with hemophilia A or B with inhibitors. *Haemophilia* 2018;**24 Suppl 1**:119. [CENTRAL: CN-01467061] [CFGD REGISTER: HG107] [EMBASE: 621290942]

Andreeva 2015 {published data only}

Andreeva T, Zorenko VY, Davydkin I, Konstantinova V, Zalepukhina O, Klimova N, et al. Safety and efficacy of new nonacog alfa drug (innonafactor) in prophylactic treatment in patients with severe and moderate hemophilia B. *Blood* 2015;**126**(23):3532. [CENTRAL: CN-01199405] [CFGD REGISTER: HB27a] [EMBASE: 72174222]

Davydkin I, Andreeva T, Zorenko VY, Konstantinova V, Zalepukhina O, Klimova N, et al. Safety and efficiency of new nonacog alfa drug in the treatment of bleeding episodes in patients with severe and moderate hemophilia b. *Blood* 2015;**126**(23):4690. [CFGD REGISTER: HB27b]

Antunes 2013 {published data only}

Antunes S, Tangada S, Stasyshyn O, Mamonov V, Phillips J, Guzman-Becerra N, et al. A prospective, open-label, randomized, parallel study with AICC to evaluate the efficacy and safety of prophylactic vs. on-demand treatment in hemophilia A or B subjects with inhibitors. *Journal of Thrombosis and Haemostasis* 2013;**11** Suppl 2:982. [ABSTRACT NO: PB 4.58-6] [CFGD REGISTER: HG66c]

Antunes SV, Tangada S, Phillips J, Stasyshyn O, Mamonov V, Guzman-Becerra N, et al. Comparison of historic on-demand versus prospective on-demand and prophylaxis bleeding episodes in hemophilia A and B patients with inhibitors treated with FEIBA NF. *Haemophilia* 2014;**20**:96. [CENTRAL: CN-01063882] [CFGD REGISTER: HG66g] [EMBASE: 71475655]

Antunes SV, Tangada S, Stasyshyn O, Mamonov V, Phillips J, Guzman-Becerra N, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia* 2014;**20**(1):65-72. [CFGD REGISTER: HG66a]

Stasyshyn O, Antunes S, Mamonov V, Ye X, Xiong Y, Tangada S. Health-related quality of life in hemophilia patients with inhibitors receiving prophylaxis with anti-inhibitor coagulant complex (AICC): results from the AICC prophylaxis study. *Journal of thrombosis and haemostasis* 2013;**11** Suppl 2:719. [ABSTRACT NO: PB 2.58-5] [CFGD REGISTER: HG66d]

Stasyshyn O, Antunes S, Mamonov V, Ye X, Epstein J, Xiong Y, et al. Prophylaxis with anti-inhibitor coagulant complex improves health-related quality of life in haemophilia patients with inhibitors: results from FEIBA NF Prophylaxis Study. *Haemophilia* 2014;**20**(5):644-50. [CFGD REGISTER: HG66b]

Varadi K, Tangada S, Loeschberger M, Montsch P, Schrenk G, Ewenstein B, et al. Pro- and anticoagulant factors facilitate thrombin generation and balance the haemostatic response to FEIBA in prophylactic therapy. *Haemophilia* 2016;**22**(4):615-24. [CFGD REGISTER: HG66f]

Varadi K, Tangada S, Schrenk G, Doralt J, Ewenstein B, Turecek P. Evidence of APCC mode of action in a clinical study treating hemophilia A inhibitor patients with prophylaxis therapy. In: *Journal of Thrombosis and Haemostasis*. Vol. 13 Suppl 2. 2015. [ABSTRACT NO: PO223-TUE] [CFGD REGISTER: HG66e]

ASPIRE 2020 {published data only}

Nolan B, Mahlangu J, Pabinger I, Young G, Konkle BA, Barnes C, et al. Recombinant factor VIII Fc fusion protein for the treatment of severe haemophilia A: final results from the ASPIRE extension study. *Haemophilia* 2020;**26**(3):494-502.

Nolan B, Mahlangu J, Perry D, Young G, Liesner R, Konkle B, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIII Fc) in subjects with haemophilia A. *Haemophilia* 2016;**22**(1):72-80.

Astermark 1999 {published data only}

Astermark J, Petrini P, Tengbrorn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *British Journal of Haematology* 1999;**105**(4):1109-13.

Astermark 2019 {published data only}

Astermark J, Angchaisuksiri P, Benson G, Castaman G, Chowdary P, Eichler H, et al. Subcutaneous prophylaxis with the anti-TFPI monoclonal antibody concizumab in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results. *Research and Practice in Thrombosis and Haemostasis* 2019;**3**(Suppl 2):1. [CFGD REGISTER: HG119c]

EUCTR2016-000510-30-ES. A trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia a and b patients with inhibitors [A multi-Centre, randomised, open-label, controlled trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia a and b patients with inhibitors - explorer™4]. <http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-000510-30-ES> (date of registration 02 June 2017). [CFGD REGISTER: HG119b]

Lee XY, Cepo K, Porstmann T. Concizumab subcutaneous prophylaxis improves health-related quality-of-life measures in patients with congenital hemophilia with inhibitors: phase 2 trial results. *Blood* 2019;**134**. [CFGD REGISTER: HG119f]

NCT03196284. A trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia a and b patients with inhibitors. clinicaltrials.gov/show/NCT03196284 (first posted 22 June 2017). [CFGD REGISTER: HG119a]

Shapiro A, Castaman G, Cepo K, Hvitfeldt Poulsen L, Hollensen C, Matsushita T, et al. Efficacy and safety of subcutaneous prophylaxis with concizumab in patients with hemophilia A or B with inhibitors: results from explorer4, a phase 2, randomized, open-label, controlled trial. *Blood* 2019;**134**. [CFGD REGISTER: HG119e]

Shapiro AD, Angchaisuksiri P, Astermark J, Benson G, Castaman G, Chowdary P, et al. Subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results. *Blood* 2019;**134**(22):1973-82. [CFGD REGISTER: HG119d]

Bertolet 2020 {published data only}

Bertolet M, Brooks MM, Ragni MV. The design of a Bayesian platform trial to prevent and eradicate inhibitors in patients

with hemophilia. *Blood Advances* 2020;**4**(21):5433-41. [CFGD REGISTER: HA160b]

NCT04303559. The hemophilia inhibitor prevention trial. clinicaltrials.gov/show/NCT04303559 (first posted 11 March 2020). [CFGD REGISTER: HA160a]

Booth 2017 {published data only}

Booth J, Ito D, Lee H-Y, Abbuehl B. Health-related quality of life in previously treated severe haemophilia a patients with extended half-life, pegylated, full-length, recombinant factor VIII (BAX855) prophylaxis. *Haemophilia* 2017;**23**:75.

Brackmann 1992 {published data only}

Brackmann HH, Eickhoff HJ, Oldenburg J, Hammerstein U. Long-term therapy and on-demand treatment of children and adolescents with severe haemophilia A: 12 years of experience. *Haemostasis* 1992;**22**(5):251-8.

Carlsson 1997 {published data only}

Carlsson M, Berntorp E, Bjorkman S, Lethagen S, Lindvall K, Ljung R. Clinical experience of pharmacokinetic dosing of Factor VIII for prophylaxis. *Haemophilia* 1996;**2** Suppl 1:16. [CENTRAL: CN-00462741] [CFGD REGISTER: HA11b]

* Carlsson M, Berntorp E, Bjorkman S, Lethagen S, Ljung R. Improved cost-effectiveness by pharmacokinetic dosing of factor VIII in prophylactic treatment of haemophilia A. *Haemophilia* 1997;**3**(2):96-101. [CENTRAL: CN-00198032] [CFGD REGISTER: HA11a] [EMBASE: 27187173]

Chakraborty 2018 {published data only}

Chakraborty J, Bhattacharyya M, Sankar Ray S. Effect of low dose prophylaxis versus episodic treatment on joint events in severe hemophilia a patients above 2 years: a randomized open label pilot study in Eastern India. *Indian Journal of Hematology & Blood Transfusion* 2018;**34**(1):68. [CFGD REGISTER: HA158]

Chowdary 2013 {published data only}

Chowdary P, Friedrich U, Lethagen S, Angchaisuksiri P. A new treatment concept for haemophilia: Safety, pharmacokinetics and pharmacodynamics of single i.v. and s.c. Doses of a monoclonal anti-TFPI antibody in healthy males and haemophilia subjects. *Journal of thrombosis and haemostasis* 2013;**11** Suppl 2:460. [CFGD REGISTER: HG86b]

Chowdary P, Lethagen S, Friedrich U, Brand B, Hay C, Karim FA, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. *Journal of thrombosis and haemostasis : JTH* 2015;**13**(5):743-54. [CFGD REGISTER: HG86a]

Chowdary 2017 {published data only}

Chowdary P, Georgiev P, Mant T, Creagh MD, Lissitchkov T, Bevan D, et al. Phase 1 and phase 1/2 extension study of fitusiran, an investigational rnaI therapeutic targeting antithrombin for the treatment of hemophilia: updated results in patients without inhibitors. *Haemophilia* 2017;**23** Suppl 2:118-9. [CENTRAL: CN-01333721] [CFGD REGISTER: HG103a] [EMBASE: 614511018]

Pasi KJ, Georgiev P, Mant T, Creagh MD, Lissitchkov T, Bevan D, et al. Phase 1 and phase 1/2 extension study of fitusiran, an investigational rnaI therapeutic targeting antithrombin for the treatment of hemophilia: updated results in patients with inhibitors. *Haemophilia* 2017;**23** Suppl 2:88-9. [CFGD REGISTER: HG103b]

Chozie 2018 {published data only}

Chozie N, Primacakti F, Tulaar A, Setiabudy R, Prasetyo M, Gatot D. Low-dose prophylaxis versus on-demand treatment in Indonesian children with severe hemophilia A: an interim report. *Haemophilia* 2018;**24** Suppl 5:94. [CENTRAL: CN-01612434] [CFGD REGISTER: HA148a] [EMBASE: 622461495]

* Chozie NA, Primacakti F, Gatot D, Setiabudhy RD, Tulaar ABM, Prasetyo M. Comparison of the efficacy and safety of 12-month low-dose factor VIII tertiary prophylaxis vs on-demand treatment in severe haemophilia A children. *Haemophilia* 2019;**25**(4):633-9. [CENTRAL: CN-01937513] [CFGD REGISTER: HA148b] [EMBASE: 627554739] [PMID: 31044491]

Chuansumrit 1995 {published data only}

Chuansumrit A, Hathirat I, Hathirat P. Prophylactic treatment for haemophilia A patients: a pilot study. *Southeast Asian Journal of Tropical Medicine of Public Health* 1995;**26**(2):243-6.

Collins 2010 {published data only}

Collins P, Faradji A, Morfini M, Enriquez MM, Schwarz L. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13-month crossover study. *Journal of Thrombosis and Haemostasis* 2010;**8**(1):83-9.

Collins 2014 {published data only}

Chowdary P, Kearney S, Meunier J, Hoxer CS, Yee DL. Improvement in health status and quality of life in patients with haemophilia B treated with nonacog beta pegol, an extended half-life glycopegylated recombinant FIX product. *Haemophilia* 2016;**22** Suppl 4:119. [CENTRAL: CN-01409403] [CFGD REGISTER: HB25d] [EMBASE: 617734554]

Chowdary P, Kearney S, Regnault A, Hoxer CS, Yee DL. Improvement in health-related quality of life in patients with haemophilia B treated with nonacog beta pegol, a new extended half-life recombinant FIX product. *Haemophilia* 2016;**22**(4):e267-74. [CENTRAL: CN-01177257] [CFGD REGISTER: HB25e] [EMBASE: 611361168] [PMID: 27352908]

Collins PW, Colberg T, Young G, Abdul Karim F, Angchaisuksiri P, Gursel T, et al. Safety, efficacy and pharmacokinetics of nonacog beta pegol (N9-GP) for prophylaxis and treatment of bleeding episodes in patients with haemophilia B. *Journal of thrombosis and haemostasis : JTH* 2013;**11** Suppl:19. [ABSTRACT NO: AS 12.4] [CFGD REGISTER: HB25c]

* Collins PW, Young G, Knobe K, Karim FA, Angchaisuksiri P, Banner C, et al. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial. *Blood* 2014;**124**(26):3880-6. [CFGD REGISTER: HB25a]

Escobar M, Young G, Oldenburg J, Mahlangu J, Carcao M, Santagostino E, et al. Prophylactic efficacy of nonacog beta pegol once weekly in adult and pediatric patients

with hemophilia B: a pooled analysis. *American Journal of Hematology* 2016;**91**(9):E417. [CENTRAL: CN-01763712] [CFGD REGISTER: HB25j] [EMBASE: 611870302]

EUCTR2010-023069-24-NL. A multi-centre, single-blind trial evaluating safety and efficacy, including pharmacokinetics, of NNC-0156-0000-0009 when used for treatment and prophylaxis of bleeding episodes in patients with haemophilia B - Paradigm™2. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-023069-24-NL (date of registration 31 December 2010). [CENTRAL: CN-01859225] [CFGD REGISTER: HB25k]

NCT01333111. Safety and efficacy of NNC-0156-0000-0009 in haemophilia b patients [A multi-centre, single-blind trial evaluating safety and efficacy, including pharmacokinetics, of NNC-0156-0000-0009 when used for treatment and prophylaxis of bleeding episodes in patients with haemophilia b]. clinicaltrials.gov/show/NCT01333111 2011 (first posted 11 April 2011). [CFGD REGISTER: HB25n]

Negrier C, Karim FA, Hanabusa H, Collins P, Colberg T, Goldman B, et al. Recombinant long-acting glycopegylated factor IX (nonacog beta pegol) in hemophilia B: assessment of target joints in the multinational randomized phase 3 clinical trial. *Journal of thrombosis and haemostasis : JTH* 2015;**13** Suppl 2:316. [ABSTRACT NO: PO149-MON] [CFGD REGISTER: HB25b]

Negrier C, Young G, Abdul Karim F, Collins PW, Hanabusa H, Colberg T, et al. Recombinant long-acting glycoPEGylated factor IX (nonacog beta pegol) in haemophilia B: assessment of target joints in multinational phase 3 clinical trials. *Haemophilia* 2016 Jul;**22**(4):507-13. [CENTRAL: CN-01177260] [CFGD REGISTER: HB25f] [EMBASE: 611361075]

Oldenburg J, Carcao M, Lentz SR, Mahlangu J, Mancuso ME, Matsushita T, et al. Once-weekly prophylaxis with 40 IU/kg nonacog beta pegol (N9-GP) achieves trough levels of >15% in patients with haemophilia B: pooled data from the Paradigm™ trials. *Haemophilia* 2018;**24**(6):911-20. [CENTRAL: CN-01792027] [CFGD REGISTER: HB25i] [EMBASE: 624035558] [PMID: 30248217]

Santagostino E, Escobar M, Young G, Oldenburg J, Mahlangu J, Lapecorella M, et al. Prophylactic efficacy of nonacog beta pegol once weekly in adult and pediatric patients with hemophilia B: a pooled analysis. *Blood Transfusion* 2016;**14** Suppl 5:s741. [CENTRAL: CN-01469351] [CFGD REGISTER: HB25g] [EMBASE: 621220132]

Tiede A, Abdul-Karim F, Carcao M, Persson P, Clausen WH, Kearney S, et al. Pharmacokinetics of a novel extended half-life glycoPEGylated factor IX, nonacog beta pegol (N9-GP) in previously treated adult, adolescent, and paediatric patients with haemophilia B-Results from two phase 3 trials. *Haemophilia* 2016;**22**:100. [CFGD REGISTER: HB25o]

Walsh C, Chuansumrit A, Mauser-Bunschoten E, Colberg T, Young G. Nonacog beta pegol for the perioperative management of minor surgery in patients with hemophilia B: results from the Paradigm™4 clinical trial. *American Journal of*

Hematology 2016;**91**(9):E415-6. [CENTRAL: CN-01473385] [CFGD REGISTER: HB25l] [EMBASE: 611870292]

Young G, Carcao M, Kearney S, Seremetis S, Cooper DL. Beyond ABR: high fix activity translates into clinical benefits. *Haemophilia* 2018;**24** Suppl 1:79-80. [CENTRAL: CN-01467052] [CFGD REGISTER: HB25m] [EMBASE: 621291045]

Young G, Lentz SR, Kearney S, Escobar M, Seremetis S, Cooper D, et al. Safety and efficacy of N9-GP, A recombinant glycopegylated factor IX with extended half-life, in us vs global patients with hemophilia B: results from the Paradigm™ clinical program. *American Journal of Hematology* 2018;**93**(9):E75. [CENTRAL: CN-01654448] [CFGD REGISTER: HB25h] [EMBASE: 624570283]

Courter 2001 {published data only}

Courter SG, Bedrosian CL. Clinical evaluation of B-domain deleted recombinant factor VIII in previously untreated patients. *Seminars in Hematology* 2001;**38**(2 Suppl 4):52-9. [CENTRAL: CN-00385713] [CFGD REGISTER: HA62a]

Curry 2019 {published data only}

Carcao M, Clausen WH, Holme PA, Moss J, Tosetto A, Wheeler A, et al. Simple and fixed N8-GP dosing regimen associated with measurable trough levels and low annualised bleed rates in children and adolescents/adults treated with N8-GP prophylaxis. *Haemophilia* 2018;**24** Suppl 5:92-3. [CENTRAL: CN-01612439] [CFGD REGISTER: HA151b] [EMBASE: 622461441]

Chowdary P, Chitlur M, Clausen WH, Escobar M, Kearney S, Landorph A, et al. N8-GP treatment sustains low bleeding rates in patients with haemophilia A. *Research and Practice in Thrombosis and Haemostasis* 2019;**3**:266-7. [CENTRAL: CN-01980920] [CFGD REGISTER: HA151g] [EMBASE: 628813777]

Chowdary P, Hvitfeldt PL, Escobar MA, Kearney S, Chitlur MB, Klamroth R, et al. Efficacy of an extended half-life glycoPEGylated rFVIII (N8-GP): pooled analysis of ABR (results from two clinical trials). *Blood* 2018;**132** Suppl 1:1177. [CENTRAL: CN-01658795] [CFGD REGISTER: HA151a]

* Curry N, Albayrak C, Escobar M, Andre Holme P, Kearney S, Klamroth R, et al. Once-weekly prophylaxis with glycoPEGylated recombinant factor VIII (N8-GP) in severe haemophilia A: safety and efficacy results from Pathfinder 2 (randomized phase III trial). *Haemophilia* 2019;**25**(3):373-81. [CENTRAL: CN-01999995] [CFGD REGISTER: HA151e] [EMBASE: 626601436] [PMID: 30817066]

Curry N, Albayrak C, Escobar M, Holme PA, Kearney S, Klamroth R, et al. Once-weekly prophylaxis with GlycoPEGylated recombinant factor VIII (N8-GP) in severe haemophilia A: safety and efficacy results from a randomised phase 3 trial (Pathfinder™2). *Research and Practice in Thrombosis and Haemostasis* 2017;**1** Suppl 1:730. [CENTRAL: CN-01653696] [CFGD REGISTER: HA151c] [EMBASE: 624157645]

Curry NJ, Chowdary P, Clausen WH, Landorph A, Lentz SR, Meunier S, et al. Long-term safety of N8-GP (turoctocog alfa pegol) prophylaxis in patients with severe haemophilia A. *Research and Practice in Thrombosis and Haemostasis*

2019;**3**:420. [CENTRAL: CN-01976279] [CFGD REGISTER: HA151f] [EMBASE: 628813917]

Giangrande P, Lee XY, Curry N, Benchikh El Fegoun S. Prophylaxis with turoctocog alfa pegol (N8-GP) maintains improvements in health-related quality of life (HRQoL) and treatment satisfaction (TS) over ≥ 4.5 years in patients with haemophilia A (HA). *Research and practice in thrombosis and haemostasis* 2020;**4**(Suppl 1):434. [CFGD REGISTER: HA151h]

Tiede A, Meunier S, Chowdary P, Lentz SR, Kavakli K, Hampton K, et al. Efficacy and PK of turoctocog alfa pegol in patients with severe haemophilia A: results from 4 clinical trials. *Haemophilia* 2019;**25**:41. [CENTRAL: CN-01945768] [CFGD REGISTER: HA151d] [EMBASE: 626414554]

Davydkin 2015 {published data only}

Andreeva T, Zorenko VY, Davydkin I, Konstantinova V, Zalepukhina O, Klimova N, et al. Safety and efficacy of new nonacog alfa drug (innonafactor) in prophylactic treatment in patients with severe and moderate hemophilia b. *Blood* 2015;**126**(23):3532. [CFGD REGISTER: HB27a]

Davydkin I, Andreeva T, Zorenko VY, Konstantinova V, Zalepukhina O, Klimova N, et al. Safety and efficiency of new nonacog alfa drug in the treatment of bleeding episodes in patients with severe and moderate hemophilia b. *Blood* 2015;**126**(23):4690. [CFGD REGISTER: HB27b]

Dzinaj 1996 {published data only}

Dzinaj T, Funk M, Schimdt H, Bottger S, Ngor T, Klarmann D, et al. Radiological score in paediatric haemophilic patients with early and late onset of factor VIII-prophylaxis. *Thrombosis Haemostasis* 1996;**76**(4):630-1.

Eichler 2018 {published data only}

* Eichler H, Angchaisuksiri P, Kavakli K, Knoebl P, Windyga J, Jimenez-Yuste V, et al. A randomized trial of safety, pharmacokinetics and pharmacodynamics of concizumab in people with hemophilia A. *Journal of thrombosis and Haemostasis* 2018;**16**(11):2184-95. [CFGD REGISTER: HG120b]

Eichler H, Angchaisuksiri P, Kavakli K, Knoebl P, Windyga J, Jimenez-Yuste V, et al. Evaluation of safety and establishment of a PK/PD relationship of concizumab in hemophilia a patients. *Research and Practice in Thrombosis and Haemostasis* 2017;**1**(Suppl 2):1-2. [CFGD REGISTER: HG120c]

NCT02490787. Trial investigating safety, pharmacokinetics and pharmacodynamics of concizumab administered subcutaneously to haemophilia a subjects [A multi-centre, randomised, placebo controlled, double blinded, multiple dose trial investigating safety, pharmacokinetics and pharmacodynamics of concizumab administered subcutaneously to haemophilia a subjects (Explorer™3)]. clinicaltrials.gov/show/NCT02490787 2015. [CFGD REGISTER: HG120a]

ENJOIH 2010 {published data only}

EUCTR2009-010172-21-IT. An Investigator-sponsored study on rFVIIa prophylaxis in children with haemophilia A and inhibitors - ENJOIH 01. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-010172-21-IT (date of registration 25 June 2009). [CENTRAL: CN-01815265] [CFGD REGISTER: HA100c]

Santagostino E, Auerswald G, Jimenez-Yuste V, Ljung R, Morfini M, Rocino A, et al. European Initiative to prevent joint damage in haemophilia children with inhibitors (ENJOIH) - a prospective study. *Haemophilia* 2010;**16**(2):407. [CENTRAL: CN-01743918] [CFGD REGISTER: HA100d] [EMBASE: 70211995]

Santagostino E, Auerswald G, Jimenez-Yuste V, Ljung R, Morfini M, Rocino A, et al. European initiative to prevent joint damage in haemophilia children with inhibitors (ENJOIH) - a prospective study. *Haemophilia* 2010;**16** Suppl 4:78. [ABSTRACT NO: 17P63] [CFGD REGISTER: HA100a]

Santagostino E. European initiative to prevent joint damage in haemophilia children with inhibitors (ENJOIH) - a prospective study. *Haemophilia* 2012;**18** Suppl 1:4-5. [CFGD REGISTER: HA100b]

Escuriola 2019 {published data only}

Escuriola Ettingshausen C, Hegemann I, Simpson ML, Cuker A, Kulkarni R, Pruthi RK, et al. Favorable pharmacokinetics in hemophilia B for nonacog beta pegol versus recombinant factor IX-Fc fusion protein: a randomized trial. *Research and Practice in Thrombosis and Haemostasis* 2019;**3**(2):268-76. [CENTRAL: CN-01916204] [CFGD REGISTER: HB29] [EMBASE: 626889048] [PMID: 31011711]

ESPRIT 2011 {published data only}

Fusco F, Gringeri A, Riva S, Leissingner C, Mackensen S, Mannucci PM. Direct costs of children with haemophilia A undergoing prophylaxis or episodic treatment: results from the ESPRIT study. In: 16th Congress of the European Hematology Association; 2011 June 9-12; London, UK. 2011. [CENTRAL: CN-01017612] [CFGD REGISTER: HA63j]

Gringeri A, Fusco F, Riva A, von M, Mantovani LG. Direct costs of children with haemophilia A undergoing prophylaxis or episodic treatment: results from the ESPRIT study. *Journal of Thrombosis and Haemostasis* 2011;**9** Suppl 2:927. [ABSTRACT NO.: P-TH-510] [CENTRAL: CN-01015138] [CFGD REGISTER: HA63j]

Gringeri A, Lundin B, Von Mackensen S, Mantovani L, Mannucci P. A randomized clinical trial on prophylaxis Vs. episodic treatment in children with haemophilia A: the ESPRIT study. *Haemophilia* 2010;**16** Suppl 4:29. [ABSTRACT NO.: 07FP06] [CENTRAL: CN-00868063] [CFGD REGISTER: HA63g]

* Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM, ESPRIT SG. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *Journal of Thrombosis and Haemostasis* 2011;**9**(4):700-10. [CENTRAL: CN-00785003] [CFGD REGISTER: HA63f] [PMID: 21255253]

Gringeri A, Lundin B, von Mackensen S, Mantovani LG, Mannucci PM, Bianchi Bonomi A. Primary and secondary prophylaxis in children with haemophilia A reduces bleeding frequency and arthropathy development compared to on-demand treatment: a 10-year, randomized, clinical trial. In: XXII Congress of the International Society on Thrombosis and

- Haemostasis (ISTH); 2009 Jul 11-16; Boston, MA, USA. 2009. [ABSTRACT NO.: OC-MO-034] [CENTRAL: CN-00759023] [CFGD REGISTER: HA63e]
- Gringeri A. A randomized, controlled trial on prophylaxis in children with haemophilia a: the E.S.P.R.I.T. study. *Hematology Journal* 2002;**Suppl 1**:173. [ABSTRACT NO.: 575] [CENTRAL: CN-00417991] [CFGD REGISTER: HA63a]
- Gringeri A. Evaluation study on prophylaxis: a randomised Italian trial (ESPRIT). One year report. *Haemophilia* 1998;**4**(3):171. [CENTRAL: CN-00448691] [CFGD REGISTER: HA63c]
- Gringeri A. Prospective controlled studies on prophylaxis: An Italian approach. *Haemophilia* 2003;**9 Suppl 1**:38-43. [CENTRAL: CN-00431310] [CFGD REGISTER: HA63b] [EMBASE: 36622048]
- Gringeri A. The Italian randomized evaluation of prophylaxis. *Haemophilia* 2000;**6 Suppl 2**:19. [CENTRAL: CN-00462763] [CFGD REGISTER: HA63d]
- Riva S, Gringeri A, Fusco F, Mantovani L. Direct costs of children with haemophilia A undergoing prophylaxis or episodic treatment: results from the ESPRIT study. *Haemophilia* 2012;**18 Suppl 1**:19. [CENTRAL: CN-00868073] [CFGD REGISTER: HA63h] [18]
- Riva S, Gringeri A, Mantovani L, Mannucci PM, Von Mackensen S. HR-QoL in children with hemophilia A: results from the ESPRIT study. *Haemophilia* 2012;**18 Suppl 1**:29. [ABSTRACT NO.: 37] [CENTRAL: CN-00868076] [CFGD REGISTER: HA63i]
- von Mackensen S, Riva S, Fusco F, Mantovani L, Gringeri A. Quality of life of children with hemophilia A undergoing prophylaxis or episodic treatment: results from the ESPRIT study. *Journal of Thrombosis and Haemostasis* 2011;**9 Suppl 2**:745. [CENTRAL: CN-01020368] [CFGD REGISTER: HA63k] [EMBASE: 70614652]
- Feldman 2006** {published data only}
- Feldman BM, Pai M, Rivard GE, Israels S, Poon MC, Demers C, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *Journal of Thrombosis and Haemostasis* 2006;**4**(6):1228-36.
- Fernandez-Bello 2017** {published data only}
- Fernandez-Bello I, Stenmo C, Butta N, Lind V, Ezban M, Jimenez-Yuste V. The pharmacokinetics and pharmacodynamics of single-dose and multiple-dose recombinant activated factor VII in patients with haemophilia A or B. *Haemophilia* 2017;**23**(6):868-76. [CENTRAL: CN-01432152] [CFGD REGISTER: HG101] [EMBASE: 619311897] [PMID: 28851065]
- Fischer 2005** {published data only}
- Fischer K, Van Dijk K, Van Den Berg HM. Late prophylaxis for severe hemophilia: effects of prophylaxis started in adulthood. *Journal of Thrombosis and Haemostasis* 2005;**3 Suppl 1**:OR205.
- HAVEN 1 2017** {published data only}
- Adamkewicz JI, Schmitt C, Asikanius E, Xu J, Levy G, Kim B, et al. Factor VIII (FVIII) inhibitor testing using a validated chromogenic betesda assay (CBA) in HAVEN 1 (BH29884), a Phase 3 trial of emicizumab in persons with hemophilia a (PwHA) with inhibitors. *Research and Practice in Thrombosis and Haemostasis* 2017;**1 Suppl 1**:724-5. [CENTRAL: CN-01924804] [CFGD REGISTER: HA149l] [EMBASE: 624157307]
- Callaghan M, Negrier C, Young G, Khoo L, Mahlangu J, Windyga J, et al. Use of bypassing agents prior to and post bypassing agent dosing guidance during emicizumab prophylaxis: Analyses from the haven 1 study.. *British Journal of Haematology* 2018 Suppl 1;**181**:129. [CFGD REGISTER: HA149d]
- Callaghan MU, Kuebler PJ, Gao L, Ko RH, Devenport J, Liberman M. Characterization of the impact of prior iti on patient outcomes in haven1. *American Journal of Hematology* 2018;**93**(9):E10-1. [CENTRAL: CN-01654451] [CFGD REGISTER: HA149k] [EMBASE: 624570187]
- Callaghan MU, Negrier C, Young G, Khoo L, Mahlangu J, Windyga J, Oldenburg J, et al. Use of bypassing agents prior to and post bypassing agent dosing guidance during emicizumab prophylaxis: analyses from the HAVEN 1 study. *Blood* 2017;**130 Suppl 1**:3668. [CFGD REGISTER: HA149c]
- Kruse-Jarres R, Callaghan M, Croteau SE, JimenezYuste V, Khoo L, Liesner R, et al. Surgical experience in two multicentre, openlabel phase 3 studies of emicizumab in persons with haemophilia a with inhibitors (HAVEN 1 and HAVEN 2). *British Journal of Haematology* 2018;**181 Suppl 1**:128. [CFGD REGISTER: HA149f]
- Kruse-Jarres R, Callaghan MU, Croteau SE, Jimenez-Yuste V, Khoo L, Liesner R, et al. Surgical Experience in Two Multicenter, Open-Label Phase 3 Studies of Emicizumab in Persons with Hemophilia A with Inhibitors (HAVEN 1 and HAVEN 2). *Blood* 2017;**130 Suppl 1**:89. [CFGD REGISTER: HA149b]
- Levy GG, Asikanius E, Kuebler P, Benchikh El Fegoun S, Esbjerg S, Seremetis S. Safety analysis of rFVIIa with emicizumab dosing in congenital hemophilia A with inhibitors: experience from the HAVEN clinical program. *Journal of Thrombosis and Haemostasis : JTH* 2019;**17**(9):1470-7. [CFGD REGISTER: HA149n]
- Mancuso ME, Callaghan MU, Kruse-Jarres R, Kempton CL, Xu J, Catalani O, et al. Emicizumab prophylaxis in adolescent/adult patients with hemophilia a previously receiving episodic or prophylactic bypassing agent treatment: updated analyses from the haven 1 study. *Blood* 2017;**130 Suppl 1**:1071. [CENTRAL: CN-01453075] [CFGD REGISTER: HA149h] [EMBASE: 620384723]
- Mancuso ME, Oldenburg J, Callaghan M, Kruse-Jarres R, Kempton C, Xu J, et al. Emicizumab prophylaxis in adolescent/ adult patients with haemophilia a previously receiving episodic or prophylactic bypassing agent treatment: updated analyses from the HAVEN 1 study. *British Journal of Haematology* 2018;**181 Suppl 1**:127. [CFGD REGISTER: HA149e]
- NCT02622321. A study to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia a participants with inhibitors [A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of

prophylactic emicizumab versus no prophylaxis in hemophilia a patients with inhibitors]. www.clinicaltrials.gov/show/nct02622321 (first posted 04 December 2015). [CFGD REGISTER: HA149j]

Oldenburg J, Mahlangu J, Kim B, Schmitt C, Callaghan M, Young G, et al. Efficacy, safety and pharmacokinetics (PK) of emicizumab (ACE910) prophylaxis (Px) in persons with haemophilia A with inhibitors (PwHAWI): randomized, multicenter, open-label, phase 3 study (HAVEN 1). *Hamostaseologie* 2018;**38 Suppl 1**:A6. [CENTRAL: CN-01468283] [CFGD REGISTER: HA149i] [EMBASE: 621403798]

Oldenburg J, Mahlangu JN, Bujan W, Trask P, Callaghan MU, Young G, et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study. *Haemophilia* 2019;**25**(1):33-44. [CENTRAL: CN-01930036] [CFGD REGISTER: HA149m] [EMBASE: 624932949] [PMID: 30427582]

* Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *New England Journal of Medicine* 2017;**377**(9):809-18. [CENTRAL: CN-01410224] [CFGD REGISTER: HA149a] [PMID: 28691557]

Schmitt C, Adamkewicz J, Xu J, Chang T, Petry C, Calatzis A, et al. Pharmacokinetics (PK), PK/PD relationships of emicizumab in persons with haemophilia a (PWHA) with inhibitors from adolescent/adult (HAVEN 1) and paediatric (HAVEN 2) phase 3 studies. *Haemophilia* 2018;**24 Suppl 1**:27. [CFGD REGISTER: HA149g]

Hazendonk 2015 {published data only}

Goedhart MHJ, Bukkems LH, Van Moort I, Spence CC, Gouw SC, Mathot RAA, et al. Does variation between label and actual potency of factor VIII concentrate vials affect results of pharmacokinetic (PK)-guided dosing of replacement therapy in hemophilia A. *Research and Practice in Thrombosis and Haemostasis* 2020;**4 (Suppl 1)**:465. [CFGD REGISTER: HA133d]

* Hazendonk HC, van Moort I, Fijnvandraat K, Kruij MJ, Laros-van Gorkom BA, van der Meer FJ, et al. The "OPTI-CLOT" trial. A randomised controlled trial on periOperative Pharmacokinetic-guided dosing of CLOTting factor concentrate in haemophilia A. *Thrombosis and Haemostasis* 2015;**114**(3):639-44. [CFGD REGISTER: HA133a]

Van Moort I, Bukkems LH, Heijdra JH, Schutgens R, Laros-Van Gorkom B, Nieuwenhuizen L, et al. Von Willebrand factor and its effect on FVIII clearance in perioperative hemophilia a patients. *Haemophilia* 2020;**26**:84-5. [CFGD REGISTER: HA133c]

Van Moort I, Preijers T, Bukkems L, Hazendonk H, Laros-van Gorkom B, Beckers E, et al. A randomized controlled trial: pharmacokinetic-guided dosing of factor VIII concentrate versus standard replacement therapy in perioperative hemophilia A patients (OPTI-CLOT Trial). *Research and Practice in Thrombosis and Haemostasis* 2020;**4 Suppl 1**:438. [CFGD REGISTER: HA133b]

INHIBIT 2014 {published data only}

Ragni M, Kessler C, Fogarty P, Josephson N, Neff A, Raffini L. Phase III randomized, controlled trial of pre-emptive vs.

standard prophylaxis to prevent inhibitor formation in children with severe hemophilia A: The inhibit study. *Haemophilia* 2011;**17**(3):563. [CENTRAL: CN-01003693] [CFGD REGISTER: HA138a] [EMBASE: 70566586]

* Ragni MV, Malec LM. Design of the INHIBITOR trial: preventing inhibitors by avoiding 'danger', prolonging half-life and promoting tolerance. *Expert Review of Hematology* 2014;**7**(6):747-55. [CENTRAL: CN-01426920] [CFGD REGISTER: HA138b]

Ragni MV. Feasibility of the Hemophilia INHIBIT trial. grantome.com/grant/NIH/U34-HL114674-02 (accessed 04 December 2017). [CENTRAL: CN-01426921] [CFGD REGISTER: HA138c]

Kavakli 1997 {published data only}

Kavakli K, Nisli G, Aydinok Y, Oztop S, Cetingul N, Aydogdu S. Prophylactic therapy for hemophilia in a developing country, Turkey. *Pediatric Hematology and Oncology* 1997;**14**(2):151-9.

Khayat 2016 {published data only}

Auerswald G, Skotnicki A, Pompa MT, Lissitchkov T, Joch C, Seifert W, et al. Overview of the clinical development program swift for the VWF/FVIII concentrate voncento in haemophilia a and von willebrand disease. *Haemophilia* 2017;**23**:68. [CENTRAL: CN-01333741] [CFGD REGISTER: HA121d] [EMBASE: 614510871]

Khayat C, Iosava G, Romashevskaya I, Aleinikova O, Stasyshyn O, Vashchenko L, et al. Efficacy and safety results of a phase 3, open label, multicentre study with Voncento in paediatric haemophilia A subjects < 12 years of age (SWIFTLY-HA study). *Hamostaseologie* 2016;**36**:A54. [CENTRAL: CN-01364579] [CFGD REGISTER: HA121c] [EMBASE: 615222264]

Klukowska A, Skotnicki A, Lissitchkov T, Mamonov V, Buevich E, Kuliczowski K, et al. Efficacy, safety and pharmacokinetic results of a phase II/III, multicentre, double-blinded, randomized, cross-over study with a plasma-derived von Willebrand Factor (VWF)/factorVIII (FVIII) concentrate (Voncento®) in subjects with hemophilia A (the SWIFT-HA study). *Haemophilia* 2014;**20 Suppl 3**:16. [CFGD REGISTER: HA121a]

Pompa MT, Iosava G, Khayat C, Romashevskaya I, Aleinikova O, Stasyshyn O, et al. A phase III, open-label, multicentre study to evaluate efficacy and safety of a plasma-derived von Willebrand factor/ factor VIII concentrate in pediatric subjects with hemophilia A (Swiftly-HA study). *Journal of thrombosis and haemostasis : JTH* 2015;**13 Suppl 2**:841. [ABSTRACT NO: PO249-WED] [CFGD REGISTER: HA121b]

Kids B-LONG 2017 {published data only}

Fischer K, Kulkarni R, Nolan B, Mahlangu J, Rangarajan S, Gambino G, et al. Recombinant factor IX Fc fusion protein in children with haemophilia B (Kids B-LONG): results from a multicentre non-randomised phase 3 study. *Lancet Haematology* 2017;**4**(2):e75-e82.

Konkle 2016 {published data only}

Booth J, Ito D, Lee H-Y, Abbuehl B. Health-related quality of life in previously treated severe haemophilia a patients with extended half-life, pegylated, full-length, recombinant factor

VIII (BAX855) prophylaxis. *Haemophilia* 2017;**23**:75. [CFGD REGISTER: HA130h]

Epstein J, Schwartz E, Abbuehl B, Ewenstein B. Patient preferences for FVIII and BAX 855: results from the BAX 855 pivotal trial. *Journal of Thrombosis and Haemostasis* 2015;**13 Suppl 2**:364. [CENTRAL: CN-01131784] [CFGD REGISTER: HA130d] [EMBASE: 71945398] [PO281-MON]

Konkle B, Stasyshn O, Wynn T, Manco-Johnson M, Gruppo R, Chowdary P, et al. Bleeding patterns evaluated during prophylaxis with a full-length pegylated recombinant factor VIII (bax 855) with extended half-life in hemophilia A. *Journal of Thrombosis and Haemostasis : JTH* 2015;**13 Suppl 2**:356-7. [CFGD REGISTER: HA130b]

Konkle B, Stasyshn O, Wyn TT, Manco-Johnson MJ, Gruppo RA, Tran H, et al. Results of a pivotal clinical trial evaluating a full-length pegylated recombinant factor VIII (Peg-RFVIII) with extended half-life in haemophilia A. *Haemophilia* 2015;**21 Suppl 2**:30-31. [CFGD REGISTER: HA130c]

Konkle BA, Stasyshn O, Wynn TT, Manco-Johnson MJ, Gruppo R, Chowdary P, et al. Bleeding patterns during prophylaxis with a full-length pegylated recombinant factor VIII (Bax 855) with extended half-life in hemophilia a. *Haemophilia* 2016;**22 Suppl 2**:99. [ABSTRACT NO.: P128] [CENTRAL: CN-01216066] [CFGD REGISTER: HA130e]

Ma AD, Klamroth R, Manco-Johnson MJ, Engl W, Dyck-Jones JA, Abbuehl BE. Characteristics of patients without bleeding in a pivotal trial of extended half-life, pegylated, full-length recombinant factor VIII (BAX 855) in the treatment of hemophilia a. *Blood* 2015;**126**(23):1105. [CFGD REGISTER: HA130f]

Manco-Johnson M, Ma AD, Klamroth R, Engl W, Griparic L, Dyck-Jones JA, et al. Joint bleeding patterns in patients treated prophylactically with an extended half-life, pegylated, full-length recombinant factor VIII (BAX 855). *Blood* 2015;**126**(23):2300. [CENTRAL: CN-01216067] [CFGD REGISTER: HA130g]

Stasyshyn O, Engl W, Abbuehl BE, Empson VG, Ewenstein B. Factors influencing the pharmacokinetics of pegylated recombinant factor VIII (BAX 855) administered for prophylaxis in previously treated patients with severe hemophilia A. *Journal of Thrombosis and Haemostasis : JTH* 2015;**13 Suppl 2**:177. [ABSTRACT NO: OR215] [CFGD REGISTER: HA130a]

Kreuz 1998 {published data only}

Kreuz W, Escuriola-Ettinghausen C, Funk M, Schmidt H, Kornhuber B. When should prophylactic treatment in patients with haemophilia A and B start?- the German experience. *Haemophilia* 1998;**4**(4):413-7.

LEOPOLD I 2015 {published data only}

Church N, Ayyagari R, Pocoski J, Sajeev G, Kelkar SS, Du EX, et al. Patterns of prior treatment and bleeds among patients with severe hemophilia a: impact on frequency of dosing with bay 81-8973 in the Leopold I trial. *Blood* 2015;**126**(23):1103. [CENTRAL: CN-01199448] [CFGD REGISTER: HA129h] [EMBASE: 72171649]

Church N, Ayyagari R, Pocoski J, Sajeev G, Sneha K, Du EX, et al. Bleed occurrence after Bay 81-8973 injection and characteristics of patients who respond to prophylaxis: analyses from Leopold I and II. *Haemophilia* 2016;**22 Suppl 2**:78-9. [CENTRAL: CN-01612491] [CFGD REGISTER: HA129j] [EMBASE: 622470086]

Garmann D, McLeay S, Shah A, Vis P, Maas Enriquez M, Ploeger BA. Population pharmacokinetic characterization of BAY 81-8973, a full-length recombinant factor VIII: lessons learned - importance of including samples with factor VIII levels below the quantitation limit. *Haemophilia* 2017;**23**(4):528-37. [CENTRAL: CN-01395099] [CFGD REGISTER: HA129q] [EMBASE: 614542165]

Humphries TJ, Church N, Lalezari S, Poulsen LH, Yoon M, Enriquez MM. Rationale for investigator-assigned prophylaxis dosing frequency in the leopold I study. *Blood* 2016;**128**(22):4984. [CENTRAL: CN-01334930] [CFGD REGISTER: HA129o] [EMBASE: 614266476]

Kavakli K, Saxena K, Maas Enriquez M. Study design of 2 randomized, crossover, open-label trials to evaluate the pharmacokinetics, efficacy, and safety of plasma protein-free recombinant factor VIII formulated with sucrose (BAY 81-8973). *Haemophilia* 2012;**18 Suppl 3**:25. [ABSTRACT NO.: PO-WE-057] [CENTRAL: CN-00883170] [CFGD REGISTER: HA129a]

Lalezari S, Tii F, Kwong YL, Delesen H, Shah A, Tuckmantel C, et al. Leopold trial results: Correlation of von willebrand factor antigen level with bay 81-8973 pharmacokinetic parameters of patients with severe hemophilia A. *Journal of Thrombosis and Haemostasis* 2015;**13**:96-7. [CENTRAL: CN-01103566] [CFGD REGISTER: HA129e] [EMBASE: 71944691]

Mahlangu JN, Kavakli K, Hvitfeldt Poulsen L, Tseneklidou-Stoeter D, Beckmann H, Enriquez MM, et al. Prophylactic efficacy of twice-weekly vs. 3-times-weekly bay 81-8973 in severe hemophilia A: results of the Leopold I and II clinical trials. *Journal of Thrombosis and Haemostasis* 2015;**13 Suppl 2**:858. [CENTRAL: CN-01131775] [CFGD REGISTER: HA129c] [EMBASE: 71946758]

Mancuso ME, Beckmann H, Enriquez MM. BAY 81-8973 prophylaxis efficacy in patients with severe hemophilia A: analyses of annualized bleeding rate outcomes in the LEOPOLD I trial. *Journal of Thrombosis and Haemostasis* 2015;**13 Suppl 2**:177. [CENTRAL: CN-01103556] [CFGD REGISTER: HA129b] [EMBASE: 71944894]

Oldenburg J, Windyga J, Hampton K, Lalezari S, Tseneklidou-Stoeter D, Beckmann H, et al. Safety and efficacy of BAY 81-8973 for surgery in previously treated patients with haemophilia A: results of the LEOPOLD clinical trial programme. *Haemophilia* 2016;**22**(3):349-53. [CENTRAL: CN-01159190] [CFGD REGISTER: HA129l] [EMBASE: 610446754]

Pocoski J, Ayyagari R, Church N, Sajeev G, Shi S, Maas Enriquez M, et al. History of sucrose-formulated recombinant factor VIII (rFVIII-FS) use and reduction in bleeds following Bay 81-8973 prophylaxis in Leopold I. *Haemophilia* 2016;**22 Suppl 2**:77. [CENTRAL: CN-01612492] [CFGD REGISTER: HA129i] [EMBASE: 622469987]

Sajeev G, Ayyagari R, Shah A, Wang Y, Church N, Guerin A, et al. Pharmacokinetic parameters, prophylaxis frequency and bleed outcomes of severe hemophilia A patients treated with BAY 81-8973. *Haemophilia* 2017;**23** Suppl 3:34-6. [CENTRAL: CN-01616863] [CFGD REGISTER: HA129m] [EMBASE: 615338000]

Saxena K, Kavakli K, Kitchen S, Oldenburg J, Yang R, Beckmann H, et al. Bay 81-8973 demonstrates comparable efficacy during prophylaxis irrespective of the assay determining potency. *Haemophilia* 2015;**21**:31-2. [CENTRAL: CN-01077524] [CFGD REGISTER: HA129g] [EMBASE: 71814436]

Saxena K, Lalezari S, Oldenburg J, Tseneklidou-Stoeter D, Beckmann H, Yoon M, et al. Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial. *Haemophilia* 2016;**22**(5):706-12. [CENTRAL: CN-01215987] [CFGD REGISTER: HA129k] [PMID: 27339736]

Saxena K, Sajeev G, Ayyagari R, Dua A, Church N, Sanabria M, et al. Bay 81-8973 prophylaxis frequency and long-term bleed outcomes in the leopold i extension study. *Blood* 2017;**130** Suppl 1:1076. [CENTRAL: CN-01453070] [CFGD REGISTER: HA129p] [EMBASE: 620384796]

Shah A, Delesen H, Garger S, Lalezari S. Pharmacokinetic properties of BAY 81-8973, a full-length recombinant factor VIII. *Haemophilia* 2015;**21**(6):766-71. [CENTRAL: CN-01127144] [CFGD REGISTER: HA129d] [PMID: 25952661]

Solms A, Delesen H, Maas Enriquez M, Kenet G, Lalezari S. Intra-individual cross-study comparison of pharmacokinetics of rFVIII-FS, bay 81-8973 and bay 94-9027 in patients with severe haemophilia A. *Haemophilia* 2020;**26**:48-9. [CFGD REGISTER: HA129r]

Windyga J, Maas Enriquez M, Beckmann H, Tseneklidou-Stoeter D, Yoon M. Prophylaxis with bay 81-8973, a full-length plasma-protein-free recombinant factor viii product: Efficacy results in leopold I by baseline patient characteristics. *Haemophilia* 2015;**21**:64-5. [CENTRAL: CN-01077523] [CFGD REGISTER: HA129f] [EMBASE: 71814490]

Liesner 1996 {published data only}

Liesner RJ, Khair K, Hann IM. The impact of prophylactic treatment in children with severe haemophilia. *British Journal of Haematology* 1996;**92**(4):973-8.

Lofqvist 1997 {published data only}

Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients - a long-term follow-up. *Journal of Internal Medicine* 1997;**241**(5):395-400.

Ma 2015 {published data only}

Ma AD, Klamroth R, Manco-Johnson MJ, Engl W, Dyck-Jones JA, Abbuehl BE. Characteristics of patients without bleeding in a pivotal trial of extended half-life, pegylated, full-length recombinant factor VIII (BAX 855) in the treatment of hemophilia a. *Blood* 2015;**126**(23):1105.

Manco-Johnson 1994 {published data only}

Manco-Johnson MJ, Nuss R, Geraghty S, Funk S, Kilcoyne R. Results of secondary prophylaxis in children with severe hemophilia. *American Journal of Hematology* 1994;**47**(2):113-7.

Manco-Johnson 2007 {published data only}

Hacker MR, Page JH, Shapiro AD, Rich-Edwards JW, Manco-Johnson MJ. Central venous access device infections in children with hemophilia: a comparison of prophylaxis and episodic therapy. *Journal of Pediatric Hematology/oncology* 2007;**29**(7):458-64. [CENTRAL: CN-01714304] [CFGD REGISTER: HA65e] [EMBASE: 47026247] [PMID: 17609623]

Manco-Johnson MJ, Abshire TC, Brown D, Buchanan GR, Cohen AR, DiMichele D, et al. Initial results of a randomized, prospective trial of prophylaxis to prevent joint disease in young children with factor VIII (FVIII) deficiency. *Blood* 2005;**106** Suppl. [ABSTRACT NO: 3] [CFGD REGISTER: HA65c]

Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *New England Journal of Medicine* 2007;**357**(6):535-44. [CFGD REGISTER: HA65d]

Manco-Johnson MJ, Blanchette VS. North American prophylaxis studies for persons with severe haemophilia: background, rationale and design. *Haemophilia* 2003;**9** Suppl 1:44-9. [CFGD REGISTER: HA65a]

Manco-Johnson MJ, Manco-Johnson ML, Blades TA, Funk S, Lane H, Dunn AL, et al. What is the cost of delaying prophylaxis until the school years? Results from the joint outcome study continuation project. *Haemophilia* 2014;**20**:99-100. [CFGD REGISTER: HA65i]

Manco-Johnson MJ, Manco-Johnson ML, Blades TA, Funk S, Lane H, McRedmond K, et al. Long-term orthopedic effects of delaying prophylaxis in severe hemophilia a until age 6 years: Results of the Joint Outcome Study Continuation (JOSc). *Blood* 2013;**122**(21):210. [CFGD REGISTER: HA65h]

Manco-Johnson MJ, Nuss R, Riske B, Jacobson L, Murphy J, Roberts M, et al. Optimal therapy for severe factor VIII deficiency: study design considerations for a U.S. prospective, randomized controlled trial. *Haemophilia* 1998;**4**(3):179. [CFGD REGISTER: HA65b]

NCT00207597. Joint outcome study [A clinical trial of primary prophylaxis against joint disease in children with severe hemophilia]. clinicaltrials.gov/show/NCT00207597 (first posted 21 September 2005). [CFGD REGISTER: HA65g]

Warren BB, Jacobsen L, Villalobos-Menuy E, Abshire TC, Shapiro AD, Recht M, et al. Non-factor VIII coagulation proteins fail to predict joint outcome in severe hemophilia A. *Blood* 2015;**126**(23):2289. [CENTRAL: CN-01134731] [CFGD REGISTER: HA65f] [EMBASE: 72172585]

NCT03315455 {published data only}

NCT03315455. Efficacy, safety, and pharmacokinetic study of prophylactic emicizumab versus no prophylaxis in hemophilia a participants [A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia a patients]. clinicaltrials.gov/show/NCT03315455 (first posted 20 October 2017). [CFGD REGISTER: HA159a]

Wang S, Zhao X, Wang X, Sun J, Chuansumrit A, Zhou J, et al. A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in persons with hemophilia A in the Asia-pacific region (HAVEN 5). *Research and Practice in Thrombosis and Haemostasis* 2020;**4**(Suppl 1):480. [CFGD REGISTER: HA159b]

NCT04303559 {published data only}

NCT04303559. The hemophilia inhibitor prevention trial [Multicenter, randomized phase III inhibitor prevention trial, comparing eloctate vs. emicizumab to prevent inhibitor formation in severe hemophilia a]. clinicaltrials.gov/show/NCT04303559 (first posted 11 March 2020). [CFGD REGISTER: HA160a]

Nemes 2007 {published data only}

Abbuehl B, Lissitchkov T, Dobaczewski G, Nemes L, Klukowska A, Komrska V, et al. Interim analysis of a phase 3, prospective, multicenter study to evaluate the pharmacokinetics, immunogenicity, safety, and efficacy of Immunate solvent detergent (Immunate S/D) in previously treated patients with severe or moderately severe hemophilia A. *Haemophilia* 2004;**10** Suppl 3:02 PO 07. [CENTRAL: 593077] [CFGD REGISTER: HA86a]

Nemes L, Lissitchkov T, Dobaczewski G, Klukowska A, Komrska V, Zimmermann R, et al. Pharmacokinetics, efficacy and safety of IMMUNATE solvent/detergent (IMMUNATE S/D) in previously treated patients with severe hemophilia A: results of a prospective, multicenter, open-label phase III study. *Acta Haematologica* 2008;**119**(2):89-97. [CENTRAL: 714803] [CFGD REGISTER: HA86c]

Nemes L, Lissitchkov T, Klukowska A, Dobaczewski G, Komrska V, Zimmermann R, et al. Evaluation of pharmacokinetics, efficacy and safety of Immunate solvent detergent in previously treated patients with severe hemophilia A. *Haemophilia* 2007;**13**(1):9-11. [CENTRAL: CN-00609089] [CFGD REGISTER: HA86b] [PMID: 17212718]

Nilsson 1970 {published data only}

Nilsson IM, Blomback M, Ahlberg A. Our experience in Sweden with prophylaxis on haemophilia. *Bibliotheca Haematologica* 1970;**34**:111-24.

Nilsson 1976 {published data only}

Nilsson IM, Hedner U, Ahlberg A. Hemophilia prophylaxis in Sweden. *Acta Paediatrica Scandinavica* 1976;**65**(2):129-35.

Nilsson 1992 {published data only}

Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years experience of prophylactic treatment in severe haemophilia A and B. *Journal of Internal Medicine* 1992;**232**(1):25-32.

PERSEPT 1 2017 {published data only}

Wang M, Lawrence J, Quon D, Reding M, Ducore J, Simpson M, et al. The global, multi-center, phase III, randomized, efficacy, pharmacokinetic and safety cross-over study (PERSEPT 1) of two dose regimens of eptacog beta (rhFVIIa) in congenital hemophilia A and B patients with inhibitors to factor VIII or

IX (HABI). *Haemophilia* 2016;**22** Suppl 4:151-2. [CENTRAL: CN-01409384] [CFGD REGISTER: HG91a] [EMBASE: 617734708]

* Wang M, Lawrence JB, Quon DV, Ducore J, Simpson ML, Boggio LN, et al. PERSEPT 1: a phase 3 trial of activated eptacog beta for on-demand treatment of haemophilia inhibitor-related bleeding. *Haemophilia* 2017;**23**(6):832-43. [CENTRAL: CN-01614346] [CFGD REGISTER: HG91b] [EMBASE: 617649074] [PMID: 28776894]

Petrini 1991 {published data only}

Petrini P, Lindvall N, Egberg N, Blomback M. Prophylaxis with factor concentrates in preventing hemophilic arthropathy. *American Journal of Pediatric Hematology/Oncology* 1991;**13**(3):280-7.

Pettersson 1981 {published data only}

Pettersson H, Nilsson IM, Hedner U, Norehn K, Ahlberg A. Radiologic evaluation of prophylaxis in severe haemophilia. *Acta Paediatrica of Scandinavia* 1981;**70**(4):565-70.

PRO-FEIBA 2010 {published data only}

Fusco F, Gringeri A, Leissinger C, Cortesi PA, Mantovani LG. Bleeding prophylaxis with an anti-inhibitor coagulant complex (AICC) in patients with hemophilia A and inhibitors can improve quality of life: results of the PRO-FEIBA Study. In: 16th Congress of the European Hematology Association; 2011 June 9-12; London, UK. 2011. [CFGD REGISTER: HA99k]

Gringeri A, Leissinger C, Cortesi P, Matovani LG. Bleeding prophylaxis with an anti-inhibitor coagulant complex (AICC) in patients with hemophilia a and inhibitors can improve quality of life: results of the pro-FEIBA study. *Journal of Thrombosis and Haemostasis* 2011;**9** Suppl 2:927. [ABSTRACT NO: P-TH-509] [CFGD REGISTER: HA99j]

Gringeri A, Leissinger C, Cortesi PA, Jo H, Fusco F, Riva S, et al. Health-related quality of life in patients with haemophilia and inhibitors on prophylaxis with anti-inhibitor complex concentrate: results from the Pro-FEIBA study. *Haemophilia* 2013;**19**(5):736-43. [CFGD REGISTER: HA99i]

Gringeri A, Leissinger CA, Cortesi P, Jo H, Mantovani L. Cost-effectiveness of prophylaxis with anti-inhibitor complex concentrate in patients with hemophilia A and inhibitors: results from the Pro-FEIBA study. *Blood* 2011;**118**(21). [ABSTRACT NO: 4187] [HA99g]

Gringeri A, Lessinger C, Santagostino E, Cortesi P, Mantovani L. Pharmacoeconomic evaluation with an activated prothrombin complex concentrate (APCC) in patients with hemophilia and inhibitors (PRO-FEIBA Study). *Haemophilia* 2012;**18** Suppl 3:70. [ABSTRACT NO: PO-MO-052] [CFGD REGISTER: HA99e]

Jo H, Gringeri A, Leissinger C, Mantovani L, Cortesi P, Gemmen E. Evaluating the cross-over effect on health-related quality of life in a randomized cross-over study of hemophilia-a patients. *Value in Health* 2011;**14**(7):A418-9. [CENTRAL: CN-01020853] [CFGD REGISTER: HA99l] [EMBASE: 70575231]

Leissinger C, Gringeri A, Antmen B, Berntorp E, Biasoli C, Carpenter S, et al. Anti-inhibitor coagulant complex prophylaxis

in hemophilia with inhibitors. *New England Journal of Medicine* 2011;**365**(18):1684-92. [CFGD REGISTER: HA99b]

Leissinger C, Negrier C, Berntorp E, Windyga J, Serban M, Bulent A, et al. A prospective, randomized, and crossover study of an activated prothrombin complex concentrate for secondary prophylaxis in patients with hemophilia A and inhibitors (Pro-FEIBA): subject demographics and safety data. *Haemophilia* 2010;**16 Suppl 4**:31. [ABSTRACT NO: 07P13] [CFGD REGISTER: HA99a]

Leissinger CA, Berntorp E, Biasioli C, Carpenter S, Jo H, Kavakli K, et al. Prophylactic dosing of anti-inhibitor coagulant complex (FEIBA) reduces bleeding frequency in hemophilia a patients with inhibitors: results of the pro-FEIBA study. *Blood* 2010;**116**(21):720. [CENTRAL: CN-01005244] [CFGD REGISTER: HA99f] [EMBASE: 70774357]

Leissinger CA, Berntorp E, Biasioli C, Carpenter S, Jo H, Kavakli K, et al. Prophylactic dosing of anti-inhibitor coagulant complex (FEIBA) reduces bleeding frequency in hemophilia a patients with inhibitors: Results of the pro-FEIBA study. *Blood* 2010;**116**(21):720. [CFGD REGISTER: HA99m]

Leissinger CA, Gringeri A, Valentino LA, Cortesi PA. Joint disease and the potential for improved joint health in inhibitor patients who have a good response to aPCC prophylaxis: data from the profeiba study. *Blood* 2012;**120**(21). [ABSTRACT NO: 3374] [CFGD REGISTER: HA99h]

Riva S, Fusco F, Cortesi P, Fasulo M, Gringeri A. Health-related quality of life (HRQOL) in bleeding prophylaxis with an activated prothrombin complex concentrate (APCC): results from the Pro-FEIBA study. *Haemophilia* 2012;**18 Suppl 3**:179. [ABSTRACT NO: PO-TU-227] [CFGD REGISTER: HA99d]

Riva S, Fusco F, Cortesi P, Mantovani L, Lessinger C, Gringeri A. Quality of life in pro-FEIBA study. *Haemophilia* 2012;**18 Suppl 1**:28. [ABSTRACT NO: 36] [CFGD REGISTER: HA99c]

PROTECT VIII 2017 *[published data only]*

Boggio LN, Hong W, Wang M, Eyster ME, Michaels LA. Bleeding protection using phenotype-guided bay 94-9027 prophylaxis: Protect VIII study subanalyses. *Haemophilia* 2015;**21 Suppl 2**:65. [CENTRAL: CN-01077522] [CFGD REGISTER: HA122b] [EMBASE: 71814491]

Ducore J, Holme PA, Lalezari S, Mancuso M-E, Maas Enriquez M, Bayh I, et al. Consistent control of bleeds among patients with haemophilia A aged >40 years treated with prophylactic bay 94-9027 in the protect VIII study and its extension. *Haemophilia* 2020;**26**:101-2. [CFGD REGISTER: HA122cc]

Ducore JM, Lalezari S, Santagostino E, Ahuja SP, Enriquez MM, Tueckmantel C, et al. Improvement in quality of life outcomes and bleeding rates among patients switching from on-demand FVIII to prophylactic bay 94-9027 in the protect VIII study. *Blood* 2019:134. [CFGD REGISTER: HA122bb]

EUCTR2011-005210-11-AT. A clinical trial investigating safety and efficacy of a long-acting factor VIII in severe hemophilia A [A Phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY 94-9027 in Severe Hemophilia

A - PROTECT VIII]. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-005210-11-AT (date of registration 28 March 2012). [CENTRAL: CN-01876552] [CFGD REGISTER: HA122t]

EUCTR2011-005210-11-Outside-EU/EEA. A clinical trial investigating safety and efficacy of a long-acting factor VIII in severe hemophilia A [A phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY94-9027 in severe hemophilia a]. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-005210-11-Outside-EU/EEA (date of registration 28 March 2012). [CFGD REGISTER: HA122jj]

EUCTR2011-005210-11-Outside-EU/EEA. A clinical trial investigating safety and efficacy of a long-acting factor VIII in severe hemophilia A [A Phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY 94-9027 in Severe Hemophilia A - PROTECT VIII]. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-005210-11-Outside-EU/EEA (date of registration 12 December 2020). [CENTRAL: CN-01814355] [CFGD REGISTER: HA122s]

Goerisch S, Walsch R, Kerschgens B, Lederman M, Deisem D, Bassiri B, et al. Clinical development program for bay 94-9027, a long acting pegylated b-domain-deleted recombinant factor VIII for patients with hemophilia A. *Haemophilia* 2013;**19 Suppl 2**:29. [ABSTRACT NO.: PO034] [CFGD REGISTER: HA122gg]

Holme PA, Klamroth R, Miesbach W, Wang M, Mancuso ME, Reding MT. Efficacy and safety of bay 94-9027 prophylaxis for ≥ 5 years: outcomes in 36 patients from the protect VIII extension study. *Research and Practice in Thrombosis and Haemostasis* 2020;**4**(Suppl 1):450-1. [CFGD REGISTER: HA122ee]

Holme PA, Poulsen L, Simpson M, Liu T, Maas Enriquez M, Pabinger-Fasching I. Overall annualised bleeding rates <2 in patients with haemophilia A treated with every-5-day or every-7-day BAY 94-9027 prophylaxis for ≥100 exposure days. *Haemophilia* 2019;**25**:151. [CENTRAL: CN-01791302] [CFGD REGISTER: HA122q] [EMBASE: 626414929]

Holme PA, Wang M, Saxena K, Caicedo J, Michaels LA. Predictors of patients with 0 bleeds during every-7-days prophylaxis with bay 94-9027 in protect VIII. *Research and Practice in Thrombosis and Haemostasis* 2017;**1 Suppl 1**:786-7. [CENTRAL: CN-01653693] [CFGD REGISTER: HA122n] [EMBASE: 624157884]

Holme PA, Wang M, Saxena K, Musi E, Michaels L. Bleeding phenotype and target joints predict patients with zero bleeds given once-weekly prophylaxis with bay 94-9027. *Blood Transfusion* 2017;**15 Suppl 3**:s489. [CENTRAL: CN-01437735] [CFGD REGISTER: HA122j] [EMBASE: 619752398]

Kerlin B, Kenet G, Saxena K, Caicedo J, Wang M, Afonja O. Baseline characteristics and bleeding outcomes in patients with severe hemophilia a administered bay 94-9027 prophylaxis every 5 or every 7 days. *Pediatric Blood & Cancer* 2017;**64**:S17. [CENTRAL: CN-01409492] [CFGD REGISTER: HA122i] [EMBASE: 617687803]

Liu T, Reding M, Chalasani P, Ahuja S, Eyster E. Bleeding outcomes during the last 90 days of treatment with BAY 94-9027: results from a post-hoc analysis of the PROTECT VIII

study. *Haemophilia* 2019;**25**:42. [CENTRAL: CN-01979290] [CFGD REGISTER: HA122w] [EMBASE: 628858381]

Miesbach WA, Di Minno G, Santagostino E, Klamroth DR, Bayh I, Soto A, et al. Efficacy and safety of bay 94-9027 (damoctocog alfa pegol) prophylaxis in patients with severe hemophilia A and comorbidities: a post hoc analysis of protect VIII data. *Blood* 2019;**134 Suppl 1**:1117. [CFGD REGISTER: HA122ff]

NCT01580293. A trial investigating safety and efficacy of treatment with BAY94-9027 in severe hemophilia a [A phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY94-9027 in severe hemophilia a]. clinicaltrials.gov/show/NCT01580293 (first posted 19 April 2012). [CFGD REGISTER: HA122aa]

Negrier C, Chambost H, Poulsen LH, Maas Enriquez M, Lalezari S, Pabinger I, et al. Protect VIII: effective protection with BAY 94-9027 prophylaxis given twice weekly, every 5 days, or every 7 days. *Haemophilia* 2017;**23 Suppl 2**:100-1. [CENTRAL: CN-01333738] [CFGD REGISTER: HA122d] [EMBASE: 614510879]

Oldenburg J, Holme P, Ducore J, Maas Enriquez M, Wang M. Annualised bleeding rates ≤ 2 with every-5-day and every-7-day dosing of BAY 94-9027 in the protect VIII study. *Haemophilia* 2019;**25**:114-5. [CENTRAL: CN-01788291] [CFGD REGISTER: HA122p] [EMBASE: 626414517]

Oldenburg J, Michaels LA, Wang M, Afonja O. Protect VIII: can patient characteristics predict eligibility for less frequent prophylaxis dosing regimens? *Research and Practice in Thrombosis and Haemostasis* 2017;**1 Suppl 1**:807-8. [CENTRAL: CN-01653662] [CFGD REGISTER: HA122m] [EMBASE: 624159232]

Pabinger I, Oldenburg J, Huth-Kuhne A, Liu T, Enriquez Maas M. Prophylaxis with extended dosing of BAY94-9027 decreases overall and joint bleeding rates with consistent consumption for over 4 years of treatment. *Hamostaseologie* 2019;**39 Suppl 1**:S1-S92. [CENTRAL: CN-01941115] [CFGD REGISTER: HA122u] [EMBASE: 627605272]

Reding M, Hvitfeldt PL, Tian L, Holme PA. Efficacy and safety of Bay 94-9027 is sustained for 5 years: outcomes in 33 patients in the Protect VIII extension study. *Blood* 2018;**132 Suppl 1**:2492. [CFGD REGISTER: HA122f]

Reding M, Poulsen L, Holme PA, Lalezari S, Wang M, Tarango C. Efficacy and safety of BAY 94-9027 is sustained for 5 years: outcomes in 36 patients in the protect VIII extension study. *Research and Practice in Thrombosis and Haemostasis* 2019;**3**:122-3. [CENTRAL: CN-01980928] [CFGD REGISTER: HA122y] [EMBASE: 628812507]

Reding M, Poulsen L, Liu T, Holme PA. Bay 94-9027 efficacy/safety sustained for 5 years: data from 33 patients (Protect VIII extension). *Pediatric Blood & Cancer* 2019;**66 Suppl**:S276. [CENTRAL: CN-01941574] [CFGD REGISTER: HA122v] [EMBASE: 627305522]

Reding M, Powell J, Santagostino E, Ng MJ, Lederman M, Wang M, et al. Safety and efficacy of prophylaxis and on-demand treatment with BAY 94-9027: results of a phase 2/3

multicentre, partially randomized, open-label trial. *Haemophilia* 2014;**20 Suppl 3**:20. [CFGD REGISTER: HA122a]

Reding M, Simpson M, Tarango C, Tockmantel C, Maas Enriquez M. Characteristics of patients successfully treated on every-7-day dosing in the PROTECT VIII extension (BAY 94-9027) study. *Haemophilia* 2019;**25**:59. [CENTRAL: CN-01981529] [CFGD REGISTER: HA122x] [EMBASE: 628859499]

Reding MT, Lalezari S, Pabinger I, Enriquez MM, Ducore JM. Decrease in overall and joint bleeding rates with extended-interval dosing: > 4 years of bay 94-9027 prophylaxis in the protect VIII extension. *Blood* 2018;**132 Suppl 1**:1206. [CENTRAL: CN-01792871] [CFGD REGISTER: HA122r] [EMBASE: 626460735]

* Reding MT, Ng HJ, Poulsen LH, Eyster ME, Pabinger I, Shin H-J, et al. Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII. *Journal of Thrombosis and Haemostasis* 2017;**15**(3):411-9. [CFGD REGISTER: HA122e]

Reding MT, Ng HJ, Tseneklidou-Stoefler D, Linardi C, Lalezari S. Safety of long-term prophylaxis with BAY 94-9027: interim results of >5 years of treatment in the PROTECT VIII extension trial. *Haemophilia* 2018;**24 Suppl 5**:17-8. [CENTRAL: CN-01920369] [CFGD REGISTER: HA122i] [EMBASE: 622461466]

Santagostino E, Kerlin BA, Negrier C, Tian L, Ducore JM. Characteristics of bleed-free patients on every-5-day dosing in the protect VIII (BAY 94-9027) study. *Blood* 2018;**132 Suppl 1**:2486. [CENTRAL: CN-01792865] [CFGD REGISTER: HA122g] [EMBASE: 626460703]

Santagostino E, Saxena K, Kenet G, Fischer K, Biss T, Radke S, et al. PROTECT VIII Kids trial results: BAY 94-9027 safety and efficacy in previously treated children with severe hemophilia A. *Haemophilia* 2016;**22 Suppl 4**:41. [CENTRAL: CN-01409379] [CFGD REGISTER: HA122c] [EMBASE: 617734747]

Shah A, Coyle T, Lalezari S, Fischer K, Kohlstaedde B, Delesen H, et al. BAY 94-9027, a PEGylated recombinant factor VIII, exhibits a prolonged half-life and higher area under the curve in patients with severe haemophilia A: comprehensive pharmacokinetic assessment from clinical studies. *Haemophilia* 2018;**24**(5):733-40. [CFGD REGISTER: HA122hh]

Shah A, Coyle T, Lalezari S, Kohlstaedde B, Fischer K, Radke S, et al. Pharmacokinetics of BAY 94-9027, a PEGylated B-domain-deleted recombinant factor VIII with an extended half-life, in children, adolescents, and adults with severe hemophilia A. *Haemophilia* 2016;**22**:99. [CFGD REGISTER: HA122kk]

Shah A, Solms A, Wiegmann S, Ahsman M, Berntorp E, Zhivkov T, et al. BAY 94-9027 and recombinant factor VIII Fc fusion protein: a head-to-head, randomized, crossover, pharmacokinetic study in patients with severe haemophilia A. *Haemophilia* 2019;**25**:45. [CFGD REGISTER: HA122ii]

Simpson M, Ahuja S, Tseneklidou-Stoeter D, Lalezari S. Extended interval prophylaxis with bay 94-9027 for > 4 years leads to median spontaneous annualized bleeding rates ≤ 1 in the Protect VIII extension. *Blood* 2018;**132 Suppl 1**:1189. [CENTRAL: CN-01788340] [CFGD REGISTER: HA122h] [EMBASE: 626460640]

- Simpson ML, Lalezari S, Chalasani P, Tseneklidou-Stoeter D, Afonja O, Enriquez MM. Bay 94-9027 prophylaxis improves activity and work productivity: data from the protect VIII study. *American Journal of Hematology* 2018;**93**(9):E60. [CENTRAL: CN-01654453] [CFGD REGISTER: HA122o] [EMBASE: 624570176]
- Solms A, Delesen H, Maas Enriquez M, Kenet G, Lalezari S. Intra-individual across-study comparison of pharmacokinetics of rFVIII-FS, bay 81-8973 and bay 94-9027 in patients with severe haemophilia A. *Haemophilia* 2020;**26**:48-9. [CFGD REGISTER: HA122dd]
- Thomson G, Holme PA, Wang M, Maas Enriquez M. Effective protection for >5 years with bay 94-9027 prophylaxis: interim results from the protect VIII extension trial. *Haemophilia* 2018;**24 Suppl 1**:114. [CENTRAL: CN-01656647] [CFGD REGISTER: HA122k] [EMBASE: 621290885]
- Wells JR, Gater A, Marshall C, Tritton T, Vashi P, Kessabi S. Exploring the impact of infusion frequency in hemophilia A: exit interviews with patients participating in BAY 94-9027 extension studies (PROTECT VIII). *Patient* 2019;**12**(6):611-9. [CFGD REGISTER: HA122z]
- Ragni 2017** {published data only}
- Ragni MV, Yabes JG, Fogarty PF, Josephson NC, Kessler CM, Neff AT, et al. Pilot randomized, non-inferiority, cross-over trial of once-weekly vs. three times-weekly recombinant factor VIII prophylaxis in adults with severe haemophilia A. *Haemophilia* 2017;**23**(1):e43-6. [CENTRAL: CN-01216068] [CFGD REGISTER: HA97b] [EMBASE: 613828270] [PMID: 27943502]
- Ragni MV. Rationale for a randomized controlled trial comparing two prophylaxis regimens in adults with severe hemophilia A: the Hemophilia Adult Prophylaxis Trial. *Expert Review of Hematology* 2011;**4**(5):495-507. [CFGD REGISTER: HA97a]
- Ramsay 1973** {published data only}
- Ramsay DM, Parker AC. A trial of prophylactic replacement therapy in haemophilia and Christmas disease. *Journal of Clinical Pathology* 1973;**26**(4):243-7.
- Royal 2002** {published data only}
- Royal S, Schramm W, Berntorp E, Giangrande P, Gringeri A, Ludlam C, et al. Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. *Haemophilia* 2002;**8**(1):44-50.
- Santagostino 2016** {published data only}
- Santagostino E, Martinowitz U, Lissitchkov T, Pan-Petes B, Hanabusa H, Oldenburg J, et al. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. *Blood* 2016;**127**(14):1761-9.
- Schimpf 1977** {published data only}
- Schimpf KI, Fisher B, Rothmann P. Hemophilia A prophylaxis with factor VIII concentrate in a home-treatment program: a controlled study. *Scandinavian Journal of Haematology. Supplementum* 1977;**30**:1979-80.
- Schobess 2008** {published data only}
- Schobess R, Kurnik K, Friedrichs F, Halimeh S, Krümpel A, Bildingmaier C. Effect of primary and secondary prophylaxis on the clinical expression of joint damage in children with severe haemophilia A. *Thrombosis and Haemostasis* 2008;**99**(1):71-6.
- Shah 2019** {published data only}
- NCT03364998. BAY94-9027 PK Study Comparing to Another Long Acting Product [Single dose, open label, randomized, crossover study in subjects with severe hemophilia a comparing pharmacokinetic parameters of BAY 94 9027 and Elocta]. clinicaltrials.gov/show/NCT03364998 2017 (first posted 07 December 2017). [CFGD REGISTER: HA154b]
- Shah A, Solms A, Wiegmann S, Ahsman M, Berntorp E, Tiede A, et al. Direct comparison of two extended-half-life recombinant FVIII products: a randomized, crossover pharmacokinetic study in patients with severe hemophilia A. *Annals of Hematology* 2019;**98**(9):2035-44. [CENTRAL: CN-01959432] [CFGD REGISTER: HA154a] [EMBASE: 628342728] [PMID: 31236667]
- Solms A, Shah A, Berntorp E, Delesen H, Lissitchkov T, Zhivkov T. Intra-individual across-study comparison of the pharmacokinetics of four recombinant factor VIII products in patients with severe haemophilia A. *Haemophilia* 2020;**26 Suppl 2**:74. [CFGD REGISTER: HA154c]
- Shapiro 2018** {published data only}
- Astermark J, Angchaisuksiri P, Benson G, Castaman G, Chowdary P, Eichler H, et al. Subcutaneous prophylaxis with the anti-TFPI monoclonal antibody concizumab in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results. *Research and practice in thrombosis and haemostasis* 2019;**3**(Suppl 2):1. [CFGD REGISTER: HG119c]
- EUCTR2016-000510-30-ES. A trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia a and b patients with inhibitors [A multi-Centre, randomised, open-label, controlled trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia a and b patients with inhibitors - explorer™4]. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-000510-30-ES (date of registration 02 June 2017). [CFGD REGISTER: HG119b]
- Lee XY, Cepo K, Porstmann T. Concizumab subcutaneous prophylaxis improves health-related quality-of-life measures in patients with congenital hemophilia with inhibitors: phase 2 trial results. *Blood* 2019;**134 Suppl 1**:2419. [CFGD REGISTER: HG119f]
- NCT03196284. A trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia a and b patients with inhibitors (explorer™4) [A Multi-Centre, Randomised, Open-Label, Controlled Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients With Inhibitors]. clinicaltrials.gov/show/NCT03196284 (first posted 22 June 2017). [CFGD REGISTER: HG119a]
- Shapiro A, Castaman G, Cepo K, Hvitfeldt Poulsen L, Hollensen C, Matsushita T, et al. Efficacy and safety of subcutaneous prophylaxis with concizumab in patients with

- hemophilia A or B with inhibitors: results from explorer4, a phase 2, randomized, open-label, controlled trial. *Blood* 2019;**134** Suppl 1:1139. [CFGD REGISTER: HG119e]
- Shapiro AD, Angchaisuksiri P, Astermark J, Benson G, Castaman G, Chowdary P, et al. Subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors: phase 2 trial results. *Blood* 2019;**134**(22):1973-82. [CFGD REGISTER: HG119d]
- Smith 1996** {published data only}
- Smith PS, Teutsch SM, Shaffer PA, Rolka H, Evatt B. Episodic versus prophylactic infusions for hemophilia A: a cost-effectiveness analysis. *Journal of Pediatrics* 1996;**129**(3):424-31.
- Smith 2018** {published data only}
- Smith MP, Rupon J, Wali Y, Remawi H, Korth-Bradley J, Smith L, et al. Impact of treatment regimen with moroctocog alfa (AF-CC) on bleeding frequency in pediatric aged subjects with moderately severe to severe hemophilia a. *Blood* 2018;**132** Suppl 1:1205. [CENTRAL: CN-01792868] [EMBASE: 626460727] [HA152a]
- Solms 2020** {published data only}
- Solms A, Shah A, Berntorp E, Tiede A, Iorio A, Linardi C, et al. Direct comparison of two extended half-life PEGylated recombinant FVIII products: a randomized, crossover pharmacokinetic study in patients with severe hemophilia A. *Annals of Hematology* 2020;**99**(11):2689-98. [CFGD REGISTER: HA157]
- Song 2012** {published data only}
- Quon DV, Dolan G, Recht M, Guzman-Becerra N, Epstein JD, Song CK, et al. Access to prophylaxis benefits hemophilia a subjects in both low and high IU/capita countries: adult subset analysis of a multicenter, open-label, randomized, phase 4 clinical study of rAHF-PFM. *American Journal of Hematology* 2012;**87** Suppl:S164. [CENTRAL: CN-01027885] [CFGD REGISTER: HA101b] [EMBASE: 71024379]
- Song CK, Quon DV, Dolan G, Recht M, Guzman-Becerra N, Epstein JD, et al. Access to prophylaxis benefits hemophilia A subjects in both low and high IU/capita countries: adult subset analysis of a multi-center, open-label, randomized, phase 4 clinical study of rAHF-PFM. *Haemophilia* 2012;**18** Suppl 1:19-20. [ABSTRACT NO: 19] [CFGD REGISTER: HA101a]
- Szucs 1996** {published data only}
- Szucs TD, Öffner A, Schramm W. Socioeconomic impact of haemophilia care: results of a pilot study. *Haemophilia* 1996;**2**(4):211-7.
- Tagliaferri 2008** {published data only}
- Tagliaferri A, Franchini M, Coppola A, Rivolta GF, Santoro C, Rossetti G, et al. Effect of secondary prophylaxis started in adult and haemophiliacs. *Haemophilia* 2008;**14**(5):945-51.
- Van den Berg 2001** {published data only}
- Van den Berg HM, Fisher K, Mauser-Bunschoten EP, Beek FJ, Roosendaal G, van der Bom JG, et al. Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *British Journal of Haematology* 2001;**112**(3):561-5.
- Verma 2016** {published data only}
- * Verma SP, Dutta TK, Mahadevan S, Nalini P, Basu D, Biswal N, et al. A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia - a success story from a resource limited country. *Haemophilia* 2016;**22**(3):342-8. [CENTRAL: CN-01158555] [CFGD REGISTER: HA120a] [EMBASE: 20160227673] [PMID: 26987935]
- Verma SP, Dutta TK, Mahadevan S, Nalini P, Basu D, Biswal N, et al. A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia - A success story from a resource limited country. *Haemophilia* 2016;**22**(3):342-8. [CFGD REGISTER: HA120c]
- Verma SP, Dutta TK, Mahadevan S, Nalini P, Biswal N, Basu D, et al. Low dose factor VIII prophylaxis in children with severe hemophilia. *Indian Journal of Hematology & Blood Transfusion* 2013;**29**(4):345. [ABSTRACT NO.: 200] [CENTRAL: CN-01024487] [CFGD REGISTER: HA120b] [EMBASE: 71223241]
- Windyga 2014** {published data only}
- Solano Trujillo MH, Stasyshyn O, Rusen L, Serban M, Lamas JL, Perina FG, et al. Safe switching from a pdFIX (Immunine®) to a rFIX (Bax326). *Haemophilia* 2014;**20**(5):674-81. [CFGD REGISTER: HB23e]
- Windyga J, Lin VW, Epstein JD, Ito D, Xiong Y, Abbuehl BE, et al. Improvement in health-related quality of life with recombinant factor IX prophylaxis in severe or moderately severe haemophilia B patients: results from the BAX326 Pivotal Study. *Haemophilia* 2014;**20**(3):362-8. [CFGD REGISTER: HB23c]
- Windyga J, Lissitchkov T, Stasyshyn O, Mamonov V, Ghandehari H, Chapman M, et al. Efficacy and safety of a recombinant factor IX (Bax326) in previously treated patients with severe or moderately severe haemophilia B undergoing surgical or other invasive procedures: a prospective, open-label, uncontrolled, multicentre, phase III study. *Haemophilia* 2014;**20**(5):651-8. [CFGD REGISTER: HB23d]
- Windyga J, Lissitchkov T, Stasyshyn O, Mamonov V, Rusen L, Lamas JL, et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicenter study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) hemophilia B. *Blood* 2012;**120**(21). [ABSTRACT NO: 2222] [CFGD REGISTER: HB23a]
- Windyga J, Lissitchkov T, Stasyshyn O, Mamonov V, Rusen L, Lamas JL, et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. *Haemophilia* 2014;**20**(1):15-24. [CFGD REGISTER: HB23b]
- Windyga J, Lissitchkov T, Stasyshyn O, Mamonov V, Rusen L, Lamas JL, et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: A prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. *Haemophilia* 2013;**20**(1):15-24. [CFGD REGISTER: HB23f]

Wu 2011 {published data only}

Wu R, Luke KH, Poon M, Wu X, Zhang N, Zhao L, et al. Low dose secondary prophylaxis reduces joint and severe bleeding in severe and moderate hemophilia children: A pilot study in China. *Haemophilia* 2011;**17**(1):70-4.

Young 2015 {published data only}

Young G, Mahlangu J, Kulkarni R, Nolan B, Liesner R, Pasi J, et al. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *Journal of Thrombosis and Haemostasis* 2015;**13**(6):967-77.

Young 2017 {published data only}

Chowdary P, Kearney S, Yee D, Meunier J, Slothuus U, Hoxer CS. Improved health-related quality of life (QoL) of haemophilia B patients treated with a weekly 40 IU kg⁻¹ dose of a new long-acting recombinant factor IX (FIX) product, nonacog beta pegol. *Journal of Thrombosis and Haemostasis : JTH* 2015;**13** Suppl 2:229. [ABSTRACT NO: OR349] [CFGD REGISTER: HB26a]

Chowdary P, Kearney S, Yee DL, Meunier J, Slothuus U, Hoxer CS. Improved health status of haemophilia b patients treated with nonacog beta pegol, a new glycopegylated recombinant fix product with prolonged half-life. *Value in Health* 2015;**18**(3):A300. [ABSTRACT NO: PSY49] [CFGD REGISTER: HB26b]

Young G, Clausen WH, Negrier C, Santagostino E, Ronn BB, Oldenburg J. Comparison of the relationship between factor IX activity and bleeding risk during prophylaxis with nonacog beta pegol (N9-GP). *Journal of Thrombosis and Haemostasis* 2017;**1** Suppl 1:793. [CENTRAL: CN-01653678] [CFGD REGISTER: HB26c] [EMBASE: 624158323]

Additional references
Ahlberg 1965

Ahlberg A. Haemophilia in Sweden VII. Incidence, treatment and prophylaxis of arthropathy and other musculoskeletal manifestations of haemophilia A and B. *Acta Orthopedic Scandinavian* 1965;**77** Suppl 1:7-80.

Berntorp 2003

Berntorp E, Astermark J, Bjorkman S, Blanchette VS, Fisher K, Giangrande PL, et al. Consensus perspectives in prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2000;**9** Suppl 1:1-4.

Blanchette 2004

Blanchette VS, Manco-Johnson M, Santagostino E, Ljung R. Optimizing factor prophylaxis for the haemophilia population: where do we stand? *Haemophilia* 2004;**10** Suppl 4:97-104.

Blanchette 2014

Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A, Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. Definitions in hemophilia: communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis* 2014;**12**(11):1935-9.

Deeks 2021

Deeks JJ, Higgins JP, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Haemophilia 2018

Nugent D, O'Mahony B, Dolan G, International Haemophilia Access Strategy Council. Value of prophylaxis vs on-demand treatment: application of a value framework in hemophilia. *Haemophilia* 2018;**24**(5):755-65.

Hay 2007

Hay CR. Prophylaxis in adults with haemophilia. *Haemophilia* 2007;**13** Suppl 2:10-5.

Higgins 2017

Higgins JP, Altman DG, Sterne JA on behalf of the Cochrane Statistical Methods Group, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.2 (updated June 2017). The Cochrane Collaboration, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Higgins 2021

Higgins JP, Eldridge S, Li T (editors). Higgins JP, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Hilgartner 1974

Hilgartner MW. Hemophilic arthropathy. *Advances in Pediatrics* 1974;**21**:139.

Iorio 2011

Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AKC. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No: CD003429. [DOI: [10.1002/14651858.CD003429.pub4](https://doi.org/10.1002/14651858.CD003429.pub4)]

Liddle 2017

Liddle AD, Rodriguez-Merchan EC. Evidence-based management of the knee in hemophilia. *JBJS Reviews* 2017;**5**(8):e12.

Lusher 1997

Lusher JM. Prophylaxis in children with hemophilia: is it the optimal treatment? *Thrombosis Haemostasis* 1997;**78**(1):726-9.

MASAC 2010

National Hemophilia Foundation MASAC. MASAC recommendation concerning prophylaxis (regular administration of clotting factor concentrate to prevent bleeding). Document 107. www.hemophilia.org/NHFWeb/

MainPgs/MainNHF.aspx?menuid=57&contentid=582 (accessed 01 July 2010).

MASAC 2016

National Hemophilia Foundation MASAC. MASAC Recommendation Concerning Prophylaxis. Document 241. www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-241-recommendation-concerning-prophylaxis (accessed July 6, 2021).

POTTER 2015

Tagliaferri A, Feola G, Molinari AC, Santoro C, Rivolta GF, Cultrera DB, et al. Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thrombosis and Haemostasis* 2015;**114**(1):35-45.

Rayment 2020

Rayment R, Chalmers E, Forsyth K, Gooding R, Kelly AM, Shapiro S, et al. Guidelines on the use of prophylactic factor replacement for children and adults with haemophilia A and B. *British Journal of Haematology* 2020;**190**(5):684-95.

RevMan 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richards 2010

Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V, et al. A United Kingdom Haemophilia Centre Doctors'

Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. *British Journal of Haematology* 2010;**149**(4):498-507.

Srivastava 2020

Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020;**26**(Suppl 6):1-158.

Thornburg 2017

Thornburg CD, Duncan NA. Treatment adherence in hemophilia. *Patient Prefer Adherence* 2017;**11**:1677-86.

Tobase 2016

Tobase P, Lane H, Siddiqi AE, Ingram-Rich R, Ward RS, Universal Data Collection Joint Outcome Working Group, Hemophilia Treatment Center Network (HTCN) Study Investigators. Declining trends in invasive orthopedic interventions for people with hemophilia enrolled in the Universal Data Collection program (2000-2010). *Haemophilia* 2016;**22**(4):604-14.

Wang 2016

Wang H, Rosner GL, Goodman SN. Quantifying over-estimation in early stopped clinical trials and the "freezing effect" on subsequent research. *Clinical Trials* 2016;**13**(6):621-31.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

A-LONG 2014

Study characteristics

Methods	<p>Open-label parallel trial. Partially randomised trial.</p> <p>3-armed trial - 2 arms were randomised.</p> <p>The study enrolled 165 participants into 1 of 3 treatment arms:</p> <ul style="list-style-type: none"> • Arm 1, individualized prophylaxis (25 - 65 IU/kg every 3 - 5 days, n = 118) (not randomised); • Arm 2, weekly prophylaxis (65 IU/kg, n = 24); or • Arm 3, episodic (on-demand) treatment as needed for bleeding episodes (10 - 50 IU/kg, depending on bleeding severity, n = 23). <p>All participants on a prophylactic regimen prior to trial entry were enrolled into arm 1; those on an episodic regimen prior to trial entry had the option to enter into arm 1 or be randomised into either arm 2 or arm 3, with randomisation stratified based on individual bleeding episodes in the past 12 months.</p> <p>Trial termination occurred after completion of the specified pharmacokinetic assessments and achievement of the prespecified rFVIII Fc exposure required to ensure acceptable inhibitor detection (e.g. a minimum of 104 participants from any arm with ≥ 50 exposure days to rFVIII Fc).</p>
Participants	Previously treated males aged 12 years or more with severe haemophilia A.

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B (Review)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

A-LONG 2014 (Continued)

Number of participants randomised: 47.

Interventions	<p>Type of prophylaxis: secondary prophylaxis; treatment arm A: sufficient dose to increase FVIII levels to ≥ 0.25 IU/mL versus treatment arm B: sufficient dose to increase FVIII levels to ≥ 0.1 IU/mL.</p> <p>1. weekly prophylaxis: 65 IU/kg (n = 24).</p> <p>2. episodic treatment: 10 - 50 IU/kg (n = 23).</p> <p>Trial visits occurred at screening (≤ 8 weeks), baseline, week 7, week 14, week 28, week 38, and week 52.</p>
Outcomes	<p>Annualised bleeding rate.</p> <p>Rate of inhibitor development.</p> <p>Adverse events.</p>
Notes	<p>Only randomised arms were included in this review. This trial also included an arm that used individualized prophylaxis regimen, which was not randomised.</p> <p>Dates of study: November 2010 - August 2012.</p> <p>Source of funding: Biogen Idec.</p> <p>ClinicalTrials.gov identifier: NCT01181128.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...subjects on an episodic regimen prior to study entry had the option to enter into arm 1 or be randomised into either arm 2 or arm 3, with randomization stratified based on individual bleeding episodes in the past 12 months." Methods of randomisation are not stated. However, since patients were given a choice to enter arm 1, which was an individualized prophylaxis regimen or be randomised, there may have been certain characteristics of individuals that predisposed them to choose to be randomised or not.
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment are not stated.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	The trial was open-label, with the primary endpoint of annualized bleeding rates. It is not stated how bleeding episodes were measured.
Blinding of outcome assessment (detection bias)	Unclear risk	Not assessed.

A-LONG 2014 (Continued)
Clinical Joint Function

Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts were discussed and were likely not due to allocated treatment.
Selective reporting (reporting bias)	Low risk	2 outcomes, which were listed in the protocol were not reported in the final paper: 1. participants with abnormal vital signs; and 2. participants with abnormal laboratory values.
Other bias	Low risk	Data analysis was conducted by the trial sponsor, Biogen Idec. As well, the initial draft was written by employees of the sponsor.

Aronstam 1976

Study characteristics

Methods	Single-centre RCT. Cross-over trial. Boys were studied for a total of 27 boy-school terms. A 'boy-school term' is defined as the whole or any part of any school term during which an individual boy was under observation; the whole study took place during five school terms. Note: there are 3 school terms per annum in the UK.
Participants	Country: England. Participants: males with haemophilia A (factor VIII < 1%). Age range: 13 - 17 years. Number enrolled: 9.
Interventions	Factor VIII concentrate. (Blood Products Laboratory - UK). Arm A: sufficient dose to increase FVIII levels to at least 0.25 IU/mL once weekly. Arm B: sufficient dose to increase FVIII levels to no more than 0.01 IU/mL once weekly. Follow-up duration: at least 2 school terms.
Outcomes	Bleeding events or frequency.
Notes	Source of funding: National Fund for Research into Crippling Diseases, the Lord Mayor Treloar Trust and the Department of Health and Social Security.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Specifics about random sequence generation methods were not given.

Aronstam 1976 (Continued)

Allocation concealment (selection bias)	Unclear risk	Participants were allocated, "... at the beginning of each trial term.. by the Wessex Medical Information Unit." but no specific details were given.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	Low risk	Participants were blinded to the allocation. Further, concentrate products were made to be indistinguishable, and were covered during infusion. Staff interacting with participants were also unaware of allocation.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Clinicians assessing bleeding were unaware of allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing outcome data - all participants were included in analyses and there were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	While the study protocol was not available, all expected outcomes were reported for all participants.
Other bias	Unclear risk	Unclear washout period between trial arms.

Aronstam 1977
Study characteristics

Methods	Single-centre RCT. Cross-over trial. Trial conducted over 2 school terms. Note: there are 3 school terms per annum in the UK.
Participants	Country: England. Participants: males with haemophilia A (factor VIII < 1%). Age range: 13 - 17 years. Number enrolled: 4 All participants completed the trial.

Aronstam 1977 (Continued)

Those boys who had been on the first double-blind controlled trial (Aronstam 1976) and were still available for a further 2 terms were selected. There were 4 such boys, patients 1, 3, 8, and 9 of that trial. The boys selected had each had at least one full school term off prophylaxis before entering the second trial.

Interventions	Cryoprecipitate (prepared by Wessex Regional Transfusion Centre) or Kryobulin (prepared by Serological Products, UK). Type of prophylaxis: 2 prophylaxis arms; Arm A: raise factor VIII to 15% twice weekly. Arm B: raise factor VIII to 30% twice weekly. Follow-up duration: 2 school terms
Outcomes	Bleeding events or frequency.
Notes	Source of funding: Sir William Coxon Trust and the Lord Mayor Treloar Trust.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	While authors indicated that random sequence generation was used to allocate participants to groups, no details were given.
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	Low risk	Participants and personnel were unaware of allocation.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Outcome assessors were blinded to allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data are present for all participants.
Selective reporting (reporting bias)	Low risk	While the trial protocol was not available, all expected outcomes were reported for all participants.

Aronstam 1977 (Continued)

Other bias	Unclear risk	Washout period between arms is unclear.
------------	--------------	---

LEOPOLD II 2015

Study characteristics

Methods	Multicentre RCT. Open label. Cross-over trial (see 'Notes'). Trial period:12 months. Conducted at 30 centres in 11 countries in Europe, South Africa, North America, South America, and Asia.
Participants	Males aged 12 – 65 years with severe haemophilia A who had not received regular prophylaxis treatment for > 6 consecutive months in the previous 5 years. Number randomised: 83; number included in the analysis: 80.
Interventions	1. Twice-weekly prophylaxis (20 – 30 IU/kg). 2. Thrice-weekly prophylaxis (30 – 40 IU/kg). 3. On-demand treatment with BAY 81-8973: a recombinant factor VIII product. Participants were randomised to 1 of 6 treatment arms (2 low-dose prophylaxis groups, 2 high-dose prophylaxis groups, and 2 on-demand treatment groups; participants received treatment based on CS/EP or CS/ADJ for 6 months each with an intra-individual cross-over after 6 months. Follow-up duration: 3 to 8 weeks of screening and 52 weeks of follow-up on either high- or low-dose prophylaxis.
Outcomes	Annualised number of all bleeding events and adverse events.
Notes	ClinicalTrials.gov identifier: NCT01233258. This is not a traditional cross-over trial. Participants were randomised to receive on demand or prophylactic therapy with FVIII (2 different regimen); patients were crossed-over within their treatment groups but only with respect to the methods for measuring the content of FVIII in the vials (CS/EP or CS/ADJ) therefore this study has been treated as a parallel trial for the analysis, "Study drug was labeled using the chromogenic substrate assay per European Pharmacopoeia (CS/EP) or adjusted by a predefined factor to mimic results obtained with the one-stage assay (CS/ADJ). Because of differences in the detection of FVIII activity between the two potency assays, the difference in the actual amount of FVIII received for prophylaxis injections in the CS/EP and CS/ADJ periods was ~20–25%, with higher amounts received during the CS/ADJ period. Patients received treatment based on CS/EP or CS/ADJ for 6 months each with an intraindividual crossover after 6 months (Fig. 1)." Date of trial: Between January 2011 and December 2012. Source of funding: Bayer HealthCare AG, Leverkusen, Germany.

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

LEOPOLD II 2015 (Continued)

Random sequence generation (selection bias)	Unclear risk	"...system generated by the sponsor's randomization management."
Allocation concealment (selection bias)	Low risk	"Patient assignment was performed using a centralized telephone interactive voice response system or interactive web response system".
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial where participants and outcome assessors were aware of the allocation.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial. It was unclear how the primary end-point of bleeding events was assessed.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 3 participants who were randomised but did not complete the study. Reasons for dropout were given for all of these participants.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the protocol were explored in the final study report.
Other bias	Low risk	3 of the trial authors are employees of the funding body, Bayer Healthcare AG.

LipLong 2012
Study characteristics

Methods	Double-blind, 2-arm, parallel, RCT. Trial duration: 52 weeks.
Participants	Males aged 12 - 70 years with severe haemophilia A (< 1% FVIII) who were currently using on-demand treatment with any FVIII product. Number randomised = 143.
Interventions	1. Once-weekly prophylaxis with BAY 79-4980 (35 IU/kg).[N=70] 2. Thrice-weekly prophylaxis with FVIII-FS (25 IU/kg).[N=73]

LipLong 2012 (Continued)

Outcomes	1. total bleeding episodes. 2. joint bleeding episodes.
----------	--

Notes	<p>The study Sponsor halted the study prematurely based on the recommendations of the DSMB, indicating that the primary and secondary endpoints of non-inferiority with prophylaxis with rFVIII-FS 3 times/week would not be met.</p> <p>Dates of study: From June 30, 2008 through to October 5, 2010, consisting of a three- to eight-week screening period and a 52-week treatment period for each enrolled participant.</p> <p>Source of funding: Bayer HealthCare Pharmaceuticals, Inc.</p>
-------	--

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not stated.
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	Low risk	This was a double-blind trial. Investigators employed a similar looking solvent for the different prophylaxis products to blind participation and outcome assessors.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	Low risk	Outcome assessors were unaware of allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Efficacy outcome analyzed per protocol.</p> <p>Participants lost to follow-up (n = 36; 51.4% in the investigational drug arm and n = 32; 43.8% in the comparison arm) where described with higher consent withdrawal reported in the investigational drug arm (N = 8 vs N = 2).</p>
Selective reporting (reporting bias)	Low risk	All reported outcomes in protocol were reported in paper.
Other bias	High risk	The trial was prematurely discontinued by the sponsor based on the recommendation of an independent data and safety monitoring board.

Morfini 1976
Study characteristics

Methods	RCT. Cross-over trial. Trial period: 1 year. Time unit: 3-month cycles (A-B-A-B versus B-A-B-A).
Participants	Country: Italy. Participants: males with haemophilia B (factor IX < 1%). Age range: 5 - 45 years. Number enrolled: 10.
Interventions	Two secondary prophylaxis treatment arms. Factor IX concentrate (Bebulin). Arm A: 7.5 U/kg twice weekly. Arm B: 15 U/kg weekly. Follow-up duration: 6 months per arm.
Outcomes	Bleeding events or frequency, joint deterioration.
Notes	Study involved participants of the Research Committee of the Fondazione dell'Emofilia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to treatment protocols was made on the basis of random envelopes..."
Blinding (performance bias and detection bias) Clinical Joint Function	Low risk	The personnel involved in the orthopedic examinations was blinded.
Blinding (performance bias and detection bias) Bleeding	High risk	No blinding.
Blinding (performance bias and detection bias) Radiologic Joint Score	Low risk	Radiological examinations were carried out in a blinded fashion.
Blinding of outcome assessment (detection bias) Bleeding	High risk	Haematologists were aware of patients' treatment.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Low risk	Quote: "Orthopedic and radiological examinations were carried out by staff who were unaware of the trial details."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Orthopedic and radiological examinations were carried out by staff who were unaware of the trial details."

Morfini 1976 (Continued)
 Radiologic Joint Score

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data for primary outcome and minimal missing data for secondary outcomes.
Selective reporting (reporting bias)	Low risk	Protocol was not available but all expected outcomes were reported.
Other bias	Unclear risk	Washout period between arms was not clear.

PROPEL III 2020
Study characteristics

Methods	<p>Open-label, phase 3, prospective, randomized, multi-centre clinical study comparing the safety and efficacy of BAX 855 following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe haemophilia A.</p> <p>Trial conducted at 62 study sites in 19 countries from November 2015 to August 2018.</p> <p>Participants underwent a 72- to 96-hour washout period followed by initial PK parameter evaluation. Blood samples were taken within 30 minutes before a single intravenous infusion of 60 ± 5 IU/kg rurioctocog alfa pegol and at 7 time points up to 96 ± 4 hours post-infusion.</p>
Participants	<p>Participants 12 - 65 years old with severe haemophilia A (FVIII level < 1%), and</p> <ul style="list-style-type: none"> • an ABR ≥ 2 during the 12 months before study entry; • had either completed a previous rurioctocog alfa pegol study or were naïve to rurioctocog alfa pegol; and • had received prophylaxis or on-demand treatment (for breakthrough bleeds) with plasma-derived or recombinant FVIII for ≥ 150 documented exposure days. <p>Number randomised: 115</p>
Interventions	<p>PwHA were randomly assigned (1:1) to 12 months of PK-guided prophylaxis with rurioctocog alfa pegol targeting FVIII troughs of either 1% - 3% (reference arm) or ~10% (8% - 12%).</p> <p>Targeting trough levels of 1% - 3%; N = 57.</p> <p>Targeting trough levels of 8% - 12%; N = 58.</p>
Outcomes	<ol style="list-style-type: none"> 1. Pharmacokinetic parameters 2. Hemostatic efficacy; <ul style="list-style-type: none"> • Presence or absence of any bleeds in the second 6-month study period reported as proportion of patients with zero total bleeds. • Proportions of PwHA who achieved zero spontaneous bleeds and zero spontaneous joint bleeds during the second 6-months. • Total ABR, spontaneous ABR, spontaneous joint ABR, joint ABR, ABR in joints with ≥ 4 spontaneous bleeds in 6 consecutive months, and injury-related ABR. • Total ABR during the 12-month trial period was compared with historical ABR during the 12 months before enrollment. • Change from baseline in the number of joints with ≥ 4 spontaneous bleeds. 3. Adverse events (inhibitor development, immunogenicity).

PROPEL III 2020 (Continued)

Notes ClinicalTrials.gov NCT02585960; EudraCT 2014-005477-37

Dates of study; November 2015 to August 2018

Source of funding: Baxalta US Inc., a Takeda company, and Baxalta Innovations GmbH, a Takeda company, Vienna, Austria.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was stratified according to pre-study treatment regimen and ABR (prophylaxis with ABR < 5 vs prophylaxis with ABR ≥ 5 vs on-demand) and was independent of the patient's PK profile."
Allocation concealment (selection bias)	Unclear risk	"The investigator and patient chose the dosing interval and dose was selected from the sponsor's dosing recommendation table."
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	Outcome assessment was by patient self-report. "Each patient was provided with a diary in electronic/paper format to record details of their infusions, bleeds and response to treatment, physical activity, unexpected events, and patient reported outcomes."
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts were discussed and were likely not due to allocated treatment. Both intention-to-treat (full analysis set) and per protocol analysis done.
Selective reporting (reporting bias)	Low risk	While the original protocol was not assessed (authors provided a 3-month time frame to make this assessable), all expected outcomes were reported in the trial results.
Other bias	Low risk	No other potential sources of bias identified.

SPINART 2013
Study characteristics

Methods	<p>Open-label, parallel, multicentre RCT.</p> <p>Conducted in 31 centres (USA, 23; Bulgaria, 3; Romania, 3; Argentina, 2).</p> <p>Treatment period: 1 year (of a planned 3-year trial).</p>
Participants	<p>Males aged 12 – 50 years (aged 18 – 50 years in Bulgaria and Romania) with severe haemophilia A with no prophylaxis for > 12 consecutive months in the past 5 years and 6 – 24 bleeding episodes in the preceding 6-month period.</p> <p>Number randomised: 84.</p>
Interventions	<p>1. rFVIII-FS prophylaxis thrice weekly (25 IU/kg) (n = 42).</p> <p>2. on-demand treatment (n = 42).</p>
Outcomes	Total number of bleeding episodes.
Notes	<p>ClinicalTrials.gov identifier: NCT00623480.</p> <p>Dates of trial: March 2008 to September 2011</p> <p>Source of funding: Bayer HealthCare AG, Leverkusen, Germany.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of the methods for the generation of the randomisation not given.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centralized and managed by use of a customized interactive voice response system."
Blinding (performance bias and detection bias) Clinical Joint Function	Low risk	The physiotherapists performing the joint physical examination were unaware of participants' treatment and bleeding history.
Blinding (performance bias and detection bias) Bleeding	High risk	This was an open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Low risk	Radiologists that examined the MRI were blinded.
Blinding of outcome assessment (detection bias) Bleeding	High risk	Open-label trial. However, the physiotherapists performing the joint physical examination were unaware of participants' treatment and bleeding history. The open-label trial design may also have influenced the results of the HRQoL.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Low risk	The physiotherapists performing the joint physical examination were unaware of participants' treatment and bleeding history.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Low risk	Radiologists that examined the MRI were blinded.

SPINART 2013 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of patients who dropped out were balanced across groups, and reasons for dropout were well documented.
Selective reporting (reporting bias)	Low risk	All listed outcomes in protocol were reported or addressed.
Other bias	Low risk	No other potential sources of bias identified.

Valentino 2012
Study characteristics

Methods	<p>Open-label, multicentre, randomised, 2-arm, parallel trial.</p> <p>Enrolled participants at 9 USA and 21 European sites between January 2006 and June 2010.</p> <p>Participants completed the 6-month on-demand period and were randomised to a 12-month prophylaxis period (32 on standard and 34 on PK-tailored prophylaxis).</p>
Participants	<p>Participants aged 7 to 65 years with moderately severe or severe haemophilia A, receiving on-demand treatment.</p> <p>Baseline FVIII: < 1%</p> <p>Number of participants enrolled: 82. Number of participants randomised: 66.</p>
Interventions	<p>2 secondary prophylaxis arms:</p> <ol style="list-style-type: none"> Standard prophylaxis (20 – 40 IU/kg) every other day.(N = 32) PK-tailored prophylaxis (20 – 80 IU/kg) every third day.(N = 34) <p>Follow-up duration: 6 months on-demand treatment followed by 12 months prophylaxis</p>
Outcomes	Annualized bleeding rate.
Notes	<p>Of note, this trial had a non-randomised longitudinal cross-over portion that compared prophylaxis versus on demand.</p> <p>Dates of trial: January 2006 to June 2010</p> <p>Source of funding: Baxter Healthcare Corporation.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was created using SAS version 8.2 (Cary, NC, USA), stratified by 0, 1–2 or ‡ target joints (defined as a joint in which ‡ 4 hemorrhages occurred within a period of 6 months, or > 20 lifetime hemarthroses)...".
Allocation concealment (selection bias)	Low risk	Quote: "...1:1 allocation to treatment regimens using a random block size of 2, and provided to the investigator via an automated assignment system as the subject neared completion of on-demand treatment."

Valentino 2012 (Continued)

Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Unbalanced dropout rate across groups (N = 2 in standard prophylaxis arm; N = 11 in PK-tailored prophylaxis arm). Reasons for dropout were included.
Selective reporting (reporting bias)	Low risk	Outcomes reported in protocol are present in report.
Other bias	Low risk	No other potential sources of bias identified.

Valentino 2014
Study characteristics

Methods	<p>Randomised, multicentre, open-label, four-period cross-over trial.</p> <p>Trial conducted between May 2007 and October 2010 at 18 centres in the USA, Canada and Europe.</p> <p>Treatment period: 56 weeks.</p>
Participants	<p>Males aged 6 – 65 years with severe or moderately severe haemophilia B with 12 or more bleeding episodes in the prior 12 months.</p> <p>Baseline FIX: < 2%</p> <p>Number randomised = 47. 50 participants were included in the ITT analysis (including three who dropped out prior to randomisation)</p>
Interventions	<ol style="list-style-type: none"> 1. On demand (2 separate periods). 2. Prophylaxis with FIX once weekly (100 IU/kg). 3. Prophylaxis with FIX twice weekly (50 IU/kg). <p>Participants received nonacog alfa (BeneFIX®; Pfizer, Philadelphia, PA, USA) as on-demand treatment for 16 weeks (Period 1), followed by randomisation to a prophylaxis regimen (Period 2) comprising</p>

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B (Review)

53

Valentino 2014 (Continued)

nonacog alfa at 100 IU kg⁻¹ once weekly or 50 IU kg⁻¹ twice weekly for 16 weeks. During the following 8-week period, participants received on-demand treatment only (Period 3). Participants then crossed over to the alternate prophylaxis treatment regimen for 16 additional weeks (Period 4).

Follow-up duration: total 59 weeks/participant to complete the entire study course.

Outcomes	Annualised bleeding rate.
Notes	Dates of trial: between May 2007 and October 2010. Source of funding: Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Specific methods used to conduct randomisation are unclear: "Randomization to treatment sequence utilized an electronic assignment system."
Allocation concealment (selection bias)	Unclear risk	No details were given regarding allocation concealment.
Blinding (performance bias and detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding (performance bias and detection bias) Bleeding	High risk	An open-label trial.
Blinding (performance bias and detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Bleeding	High risk	An open-label trial, outcome assessors were aware of allocation.
Blinding of outcome assessment (detection bias) Clinical Joint Function	Unclear risk	Not assessed.
Blinding of outcome assessment (detection bias) Radiologic Joint Score	Unclear risk	Not assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were balanced between groups (N = 3 in both allocation arms) and reasons for dropout noted.
Selective reporting (reporting bias)	Low risk	While the original protocol could not be located all expected trial results were reported.
Other bias	Low risk	No other potential sources of bias identified.

ABR: annualised bleed rate

HRQoL: health-related quality of life

MRI: magnetic resonance imaging

ITT: intention-to-treat
 IU: international units
 PK: pharmacokinetic
 PwHA : people with haemophilia A
 RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aledort 1994	Prospective observational study.
Ali 2018	Includes participants with inhibitors.
Andreeva 2015	Unclear if participants were previously treated (conference abstract only).
Antunes 2013	Includes participants with inhibitors.
ASPIRE 2020	Prospective observational study.
Astermark 1999	Retrospective observational study.
Astermark 2019	Intervention includes the anti-Tissue Factor Pathway Inhibitor (TFPI), concizumab, which is not a clotting factor therapy. This could be eligible for the subsequent review on non-clotting factor therapies.
Bertolet 2020	Intervention includes emicizumab, which is not a clotting factor therapy.
Booth 2017	Prospective observational study
Brackmann 1992	Retrospective observational study.
Carlsson 1997	Includes children previously on prophylaxis.
Chakraborty 2018	Includes children on primary prophylaxis.
Chowdary 2013	Intervention includes the anti-Tissue Factor Pathway Inhibitor (TFPI), concizumab, which is not a clotting factor therapy.
Chowdary 2017	Intervention is an investigational RNA interference (RNAi) therapeutic, not a clotting factor therapy.
Chozie 2018	Includes children on primary prophylaxis.
Chuansumrit 1995	Retrospective observational study.
Collins 2010	Prospective observational cross-over study.
Collins 2014	Includes children on primary prophylaxis.
Courter 2001	Prospective observational study.
Curry 2019	Includes people on primary prophylaxis.
Davydkin 2015	Unclear if participants were children or previously treated (conference abstract only).
Dzinaj 1996	Prospective observational study.

Study	Reason for exclusion
Eichler 2018	Intervention includes concizumab, which is not a clotting factor therapy.
ENJOIH 2010	Includes participants with inhibitors.
Escuriola 2019	Pharmacokinetics evaluated.
ESPRIT 2011	Pediatric population on primary prophylaxis.
Feldman 2006	Prospective observational single-arm dose-escalation study.
Fernandez-Bello 2017	Pharmacokinetics evaluated in participants with inhibitors.
Fischer 2005	Retrospective observational study.
HAVEN 1 2017	Includes participants with inhibitors.
Hazendonk 2015	Pharmacokinetic parameters evaluated.
INHIBIT 2014	Children on primary prophylaxis.
Kavakli 1997	Prospective observational study.
Khayat 2016	Children on primary prophylaxis.
Kids B-LONG 2017	Prospective observational study in children.
Konkle 2016	Retrospective observational study.
Kreuz 1998	Prospective observational study.
LEOPOLD I 2015	Participants on primary prophylaxis
Liesner 1996	Retrospective observational study.
Lofqvist 1997	Retrospective observational study.
Ma 2015	Retrospective observational study.
Manco-Johnson 1994	Prospective observational study.
Manco-Johnson 2007	Children on primary prophylaxis.
NCT03315455	Intervention includes emicizumab, which is not a clotting factor therapy.
NCT04303559	Intervention includes emicizumab, which is not a clotting factor therapy.
Nemes 2007	Prospective observational single-arm study.
Nilsson 1970	Retrospective observational study with historical control.
Nilsson 1976	Prospective observational study with historical control.
Nilsson 1992	Retrospective observational study.
PERSEPT 1 2017	Includes participants with inhibitors.

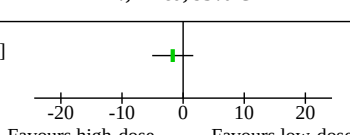
Study	Reason for exclusion
Petrini 1991	Retrospective observational study.
Pettersson 1981	Retrospective observational study with historical control.
PRO-FEIBA 2010	Includes participants with inhibitors.
PROTECT VIII 2017	Includes participants on primary prophylaxis.
Ragni 2017	Pilot feasibility study with cross-over design.
Ramsay 1973	Prospective observational study.
Royal 2002	Retrospective observational study with parallel groups.
Santagostino 2016	Prospective observational single-arm study.
Schimpf 1977	Prospective observational cross-over study.
Schobess 2008	Prospective observational study.
Shah 2019	Pharmacokinetic parameters evaluated.
Shapiro 2018	Intervention includes concizumab, which is not a clotting factor therapy.
Smith 1996	Retrospective observational switch study.
Smith 2018	Includes children on primary prophylaxis
Solms 2020	Pharmacokinetic parameters evaluated.
Song 2012	Ad-hoc analysis of a randomized controlled trial. Protocol or full study with results not found on trial registries. Also, the comparison focused on the degree of availability of factor concentrates per country i.e. low versus high IU/capita countries.
Szucs 1996	Prospective observational study.
Tagliaferri 2008	Retrospective observational switch study.
Van den Berg 2001	Retrospective observational single-arm study.
Verma 2016	Includes children on primary prophylaxis
Windyga 2014	No randomization in the comparison arm assessing outcome of interest (hemostatic efficacy).
Wu 2011	Prospective observation with historical control.
Young 2015	Prospective observational study in children.
Young 2017	Prospective dose and dose-interval comparison study (conference abstract only).

DATA AND ANALYSES

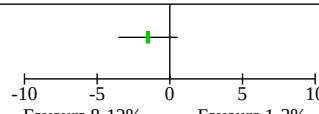
Comparison 1. Comparison between two prophylaxis regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Joint bleeds per year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Joint bleeds per year (2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Spontaneous joint bleeds	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Joint bleeds per year (3)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Total bleeds per year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Overall bleeding frequency (bleeds per 100 days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Annualised bleeding rates	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Total bleeding frequency (HB)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Overall bleeding frequency	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 Total bleeds per year (2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11 Total treatment emergent adverse event	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.12 Rate of adverse events	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

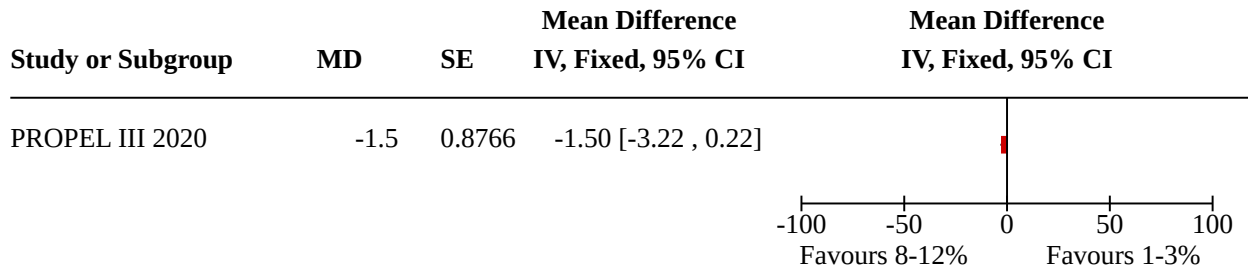
Analysis 1.1. Comparison 1: Comparison between two prophylaxis regimens, Outcome 1: Joint bleeds per year

Study or Subgroup	High-dose			Low-dose			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
LEOPOLD II 2015	3.5	6.2	31	5.2	6.9	28	-1.70 [-5.06 , 1.66]	

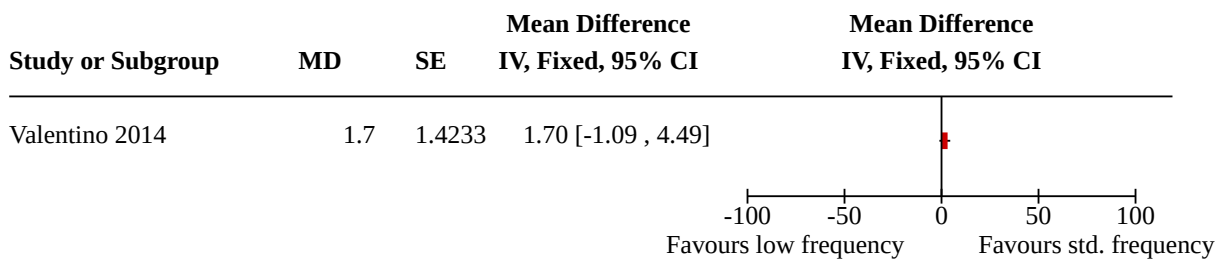
Analysis 1.2. Comparison 1: Comparison between two prophylaxis regimens, Outcome 2: Joint bleeds per year (2)

Study or Subgroup	Targeting trough of 8-12%			Targeting trough of 1-3%			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
PROPEL III 2020	1.1	2.6	53	2.6	7.4	57	-1.50 [-3.54 , 0.54]	

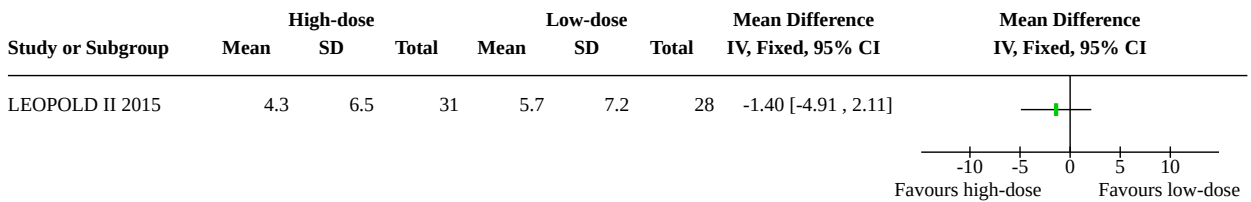
Analysis 1.3. Comparison 1: Comparison between two prophylaxis regimens, Outcome 3: Spontaneous joint bleeds



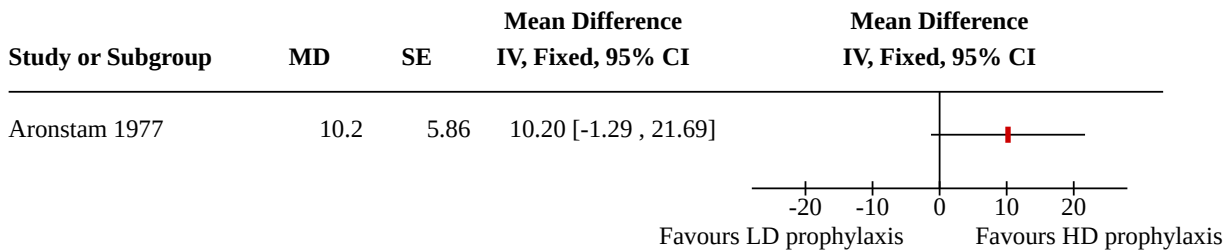
Analysis 1.4. Comparison 1: Comparison between two prophylaxis regimens, Outcome 4: Joint bleeds per year (3)



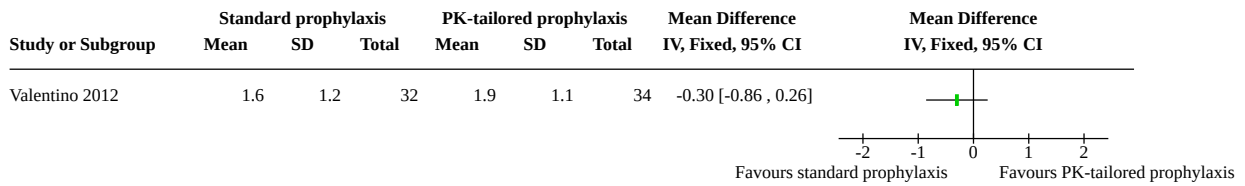
Analysis 1.5. Comparison 1: Comparison between two prophylaxis regimens, Outcome 5: Total bleeds per year



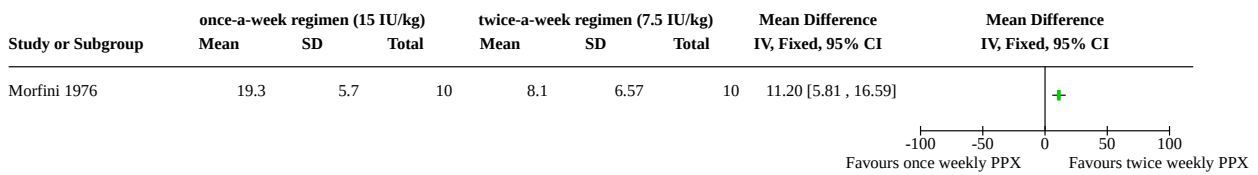
Analysis 1.6. Comparison 1: Comparison between two prophylaxis regimens, Outcome 6: Overall bleeding frequency (bleeds per 100 days)



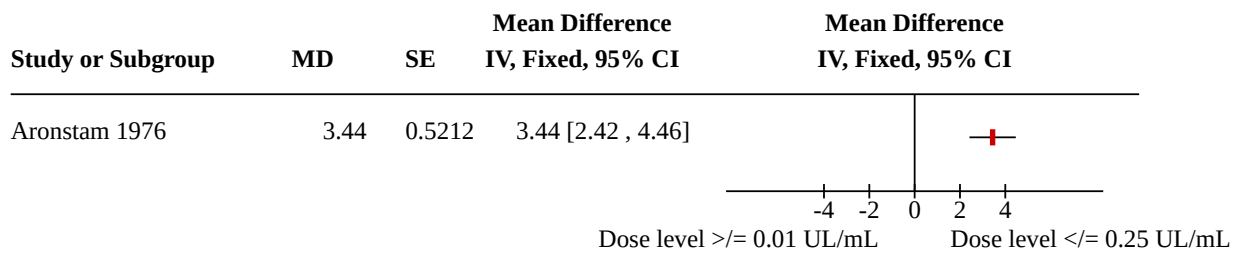
Analysis 1.7. Comparison 1: Comparison between two prophylaxis regimens, Outcome 7: Annualised bleeding rates



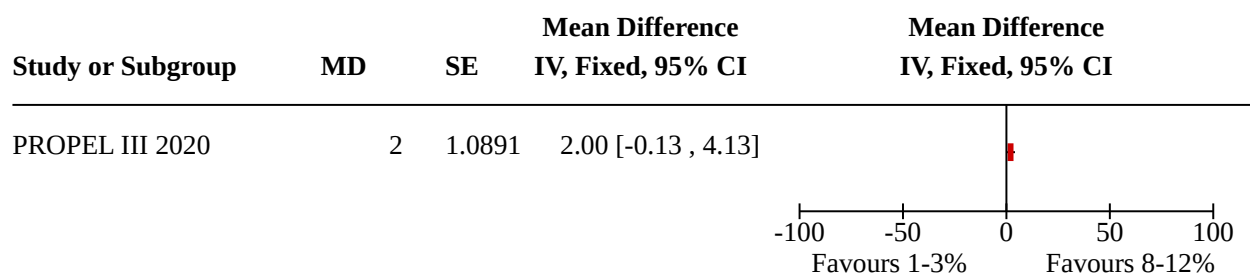
Analysis 1.8. Comparison 1: Comparison between two prophylaxis regimens, Outcome 8: Total bleeding frequency (HB)



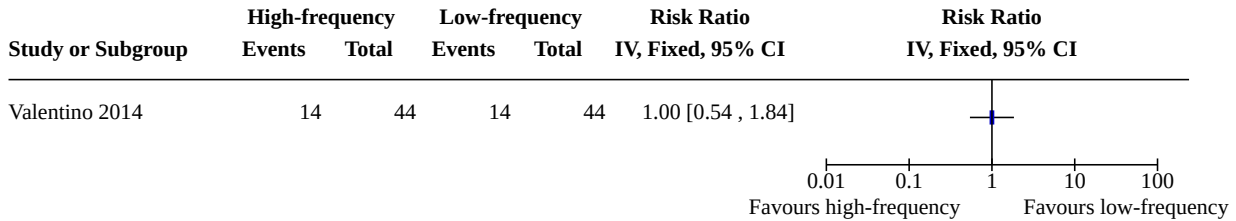
Analysis 1.9. Comparison 1: Comparison between two prophylaxis regimens, Outcome 9: Overall bleeding frequency



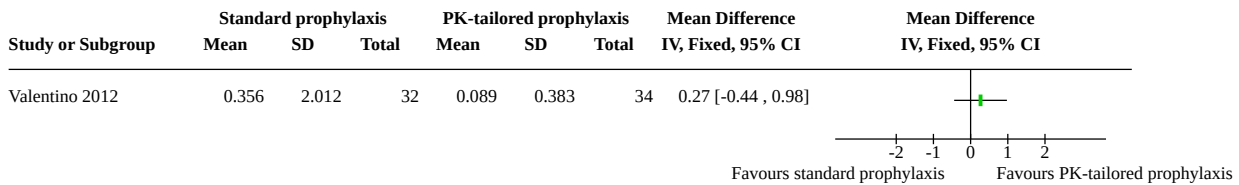
Analysis 1.10. Comparison 1: Comparison between two prophylaxis regimens, Outcome 10: Total bleeds per year (2)



Analysis 1.11. Comparison 1: Comparison between two prophylaxis regimens, Outcome 11: Total treatment emergent adverse event



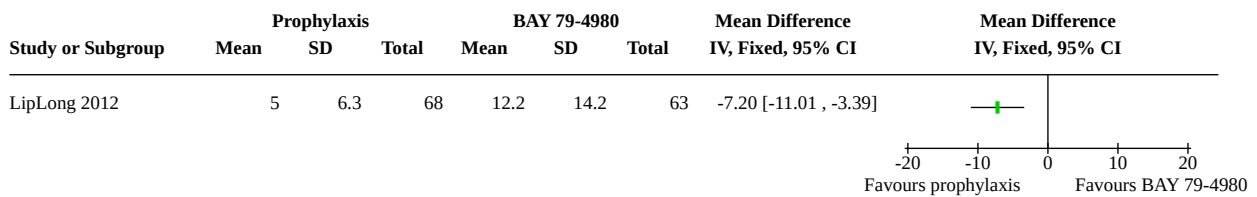
Analysis 1.12. Comparison 1: Comparison between two prophylaxis regimens, Outcome 12: Rate of adverse events



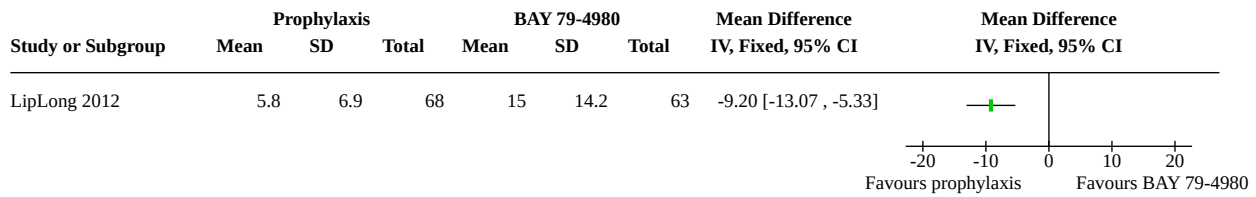
Comparison 2. Standard prophylaxis versus investigational drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Annualised joint bleeding rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Annualised total bleeding rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Standard prophylaxis versus investigational drug, Outcome 1: Annualised joint bleeding rate



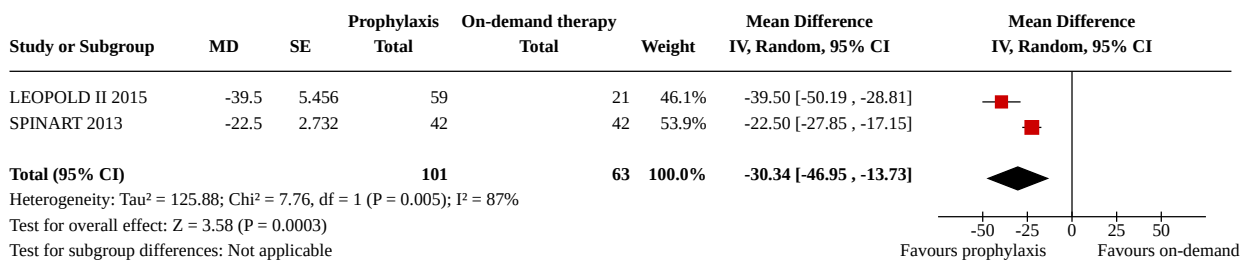
Analysis 2.2. Comparison 2: Standard prophylaxis versus investigational drug, Outcome 2: Annualised total bleeding rate



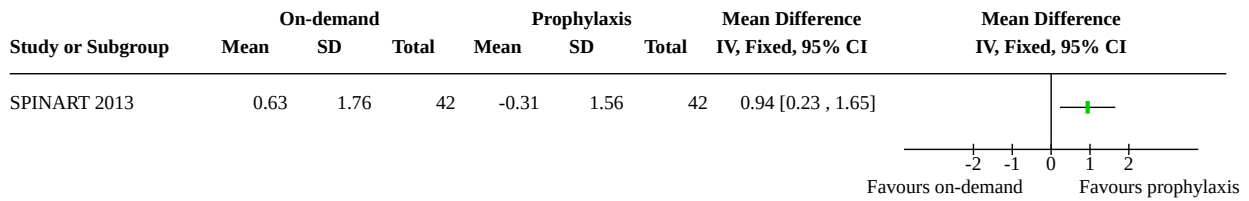
Comparison 3. Prophylaxis versus on-demand

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mean total joint bleeds per year	2	164	Mean Difference (IV, Random, 95% CI)	-30.34 [-46.95, -13.73]
3.2 Mean change in joint health scores (CAJAS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3 Mean total bleeds per year	2	164	Mean Difference (IV, Random, 95% CI)	-40.24 [-64.04, -16.44]
3.4 Pain scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5 Radiologic measurements of joint damage (deterioration shown in eMRI)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6 Participants with adverse events	2	131	Risk Ratio (IV, Fixed, 95% CI)	1.71 [1.24, 2.37]

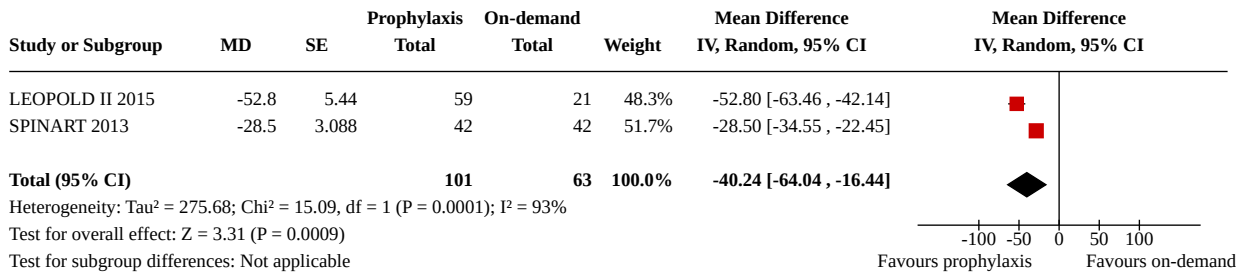
Analysis 3.1. Comparison 3: Prophylaxis versus on-demand, Outcome 1: Mean total joint bleeds per year



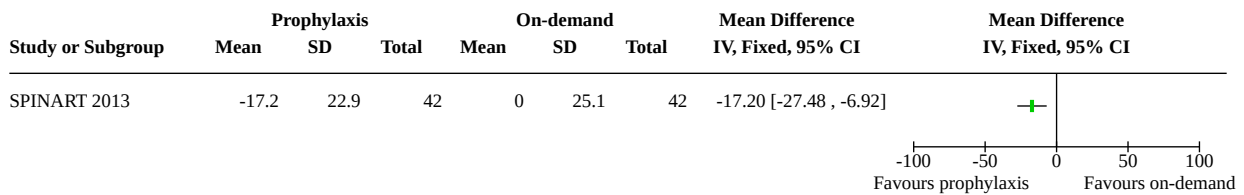
Analysis 3.2. Comparison 3: Prophylaxis versus on-demand, Outcome 2: Mean change in joint health scores (CAJAS)



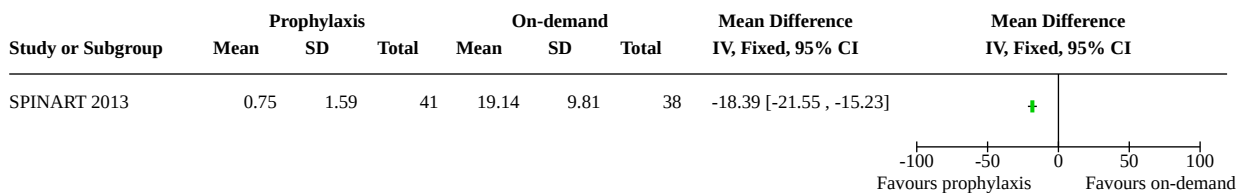
Analysis 3.3. Comparison 3: Prophylaxis versus on-demand, Outcome 3: Mean total bleeds per year



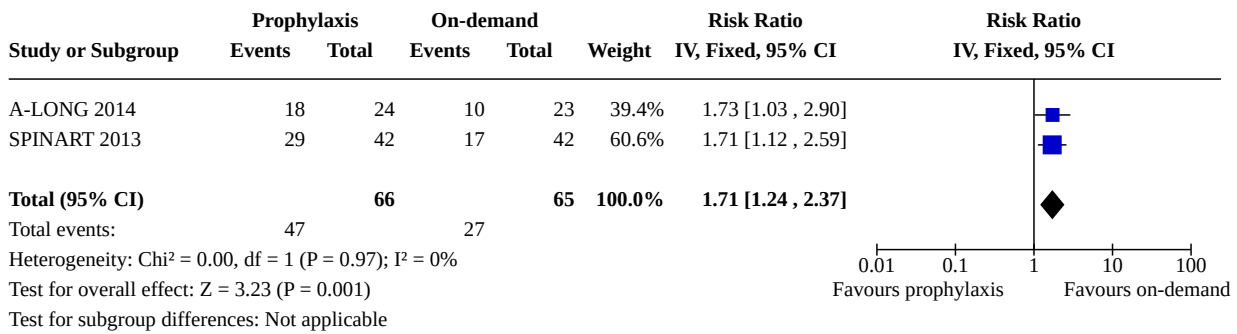
Analysis 3.4. Comparison 3: Prophylaxis versus on-demand, Outcome 4: Pain scores



Analysis 3.5. Comparison 3: Prophylaxis versus on-demand, Outcome 5: Radiologic measurements of joint damage (deterioration shown in eMRI)



Analysis 3.6. Comparison 3: Prophylaxis versus on-demand, Outcome 6: Participants with adverse events



APPENDICES

Appendix 1. Search strategies

Search engine or registry	Search terms
Medline OVID (2010 - June 2016)	1 exp Hemophilia/ 2 Haemophilia.mp. 3 hemophilia.mp. or exp Hemophilia/ 4 Inherit:.mp. 5 Heredit:.mp. 6 Congenital.mp. 7 4 or 5 or 6 8 1 or 2 or 3 9 7 and 8 10 factor concentrat:.mp. 11 Factor Product:.mp. 12 recombinant factor:.mp. 13 plasma\$ factor\$.mp. 14 clot\$ factor\$.mp. 15 Factor\$ VIII.mp. 16 Factor eight.mp. 17 FVIII.mp. 18 FIX.mp. 19 Factor nine.mp. 20 Factor\$ IX.mp.

(Continued)

21 cryoprecipitat\$.mp.
 22 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
 23 Prophyla:.mp.
 24 prevent:.mp.
 25 23 or 24
 26 Secondar:.mp.
 27 Adult.mp.
 28 26 or 27
 29 25 and 28
 30 9 and 22 and 29

 ISRCTN www.isrctn.com/

[Basic Search]

(haemophilia OR hemophilia) AND (prophylactic OR prophylaxis)

 Clinicaltrials.gov ClinicalTrials.gov

[Advanced Search]

Condition or disease: haemophilia OR haemophilia

Other terms: prophylactic OR prophylaxis

Study type: Interventional Studies (Clinical Trials)

WHO ICTRP

[Advanced Search]

Condition: haemophilia OR haemophilia

AND

Intervention: prophylactic OR prophylaxis

Recruitment status is: All

WHAT'S NEW

Date	Event	Description
12 August 2021	New citation required and conclusions have changed	<p>This review of previously treated individuals is one of two set to replace the original 2011 published review - <i>Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B (Iorio 2011)</i>. The original review is currently still available on the Cochrane Library, but when this is next updated (currently in production), will only include previously untreated individuals.</p> <p>The conclusions of this new review have changed from the original review. Previously we identified evidence that the use of these concentrates was effective in decreasing the frequency of joint bleeds and in partially preventing or slowing down the development of arthropathy. Currently, in relation to people previously treated with clotting factor concentrates, we have found evidence that the use of these concentrates may be effective in</p>

Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B (Review)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Date	Event	Description
		decreasing the frequency of total bleeds and joint bleeds and improve joint function, pain and quality of life, even though this does not translate into a detectable improvement of articular damage when assessed by radiologic assessment.
12 August 2021	New search has been performed	<p>The review 'Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with haemophilia A or B' has been split into two reviews, of which this is the first to be published. The second review is in production: Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously untreated individuals with haemophilia A or B.</p> <p>The previous review (which included both people previously and not previously treated for bleeding and related complications) included six studies, of which three were regarded as not eligible for this review (Carlsson 1997; ESPRIT 2011; Manco-Johnson 2007).</p> <p>10 trials (32 references) are included in this review (A-LONG 2014; Aronstam 1976; Aronstam 1977; LEOPOLD II 2015; LipLong 2012; Morfini 1976; PROPEL III 2020; SPINART 2013; Valentino 2012; Valentino 2014). The number of participants included in the review has increased from 142 to 608.</p>

HISTORY

Date	Event	Description
10 July 2011	New citation required and conclusions have changed	<p>The conclusions of the review have changed from there being insufficient evidence assessing the use of prophylactic clotting factor concentrates, to there being evidence that the use of these concentrates is effective in decreasing the frequency of joint bleeds and in partially preventing or slowing down the development of arthropathy.</p> <p>The number of participants included in the review has increased from 37 to 142, with two new studies added.</p> <p>Alfonso Iorio (previously a co-author) is now lead author on this review and Kent Stobart (previously lead-author) is now a co-author. John Wu has stepped down from the review and Emanuela Marchesini, Maura Marcucci and Anthony Chan are new co-authors.</p>
10 July 2011	New search has been performed	Two new trials have been incorporated into the review (Gringeri 2011; Manco-Johnson 2007).
7 October 2009	Amended	<p>Please note:</p> <p>We are aware that the update of this review is overdue. The original review team has stepped down and a new review team is in place and working on the update. The updated version of this review will be published in 2010.</p>
31 October 2008	Amended	Converted to new review format.

Date	Event	Description
1 February 2006	New search has been performed	The text of the Reviewers' Conclusions in the abstract has been altered to make clear that there is a lack of evidence from randomised controlled trials for the use of prophylaxis. No new references were found in the latest search for this review.

CONTRIBUTIONS OF AUTHORS

Omotola Olasupo assessed eligibility of studies, conducted data extraction and risk of bias assessment, performed and interpreted analyses, constructed the summary of findings tables and drafted the review text.

Alfonso Iorio drafted the original protocol, assessed eligibility of studies and risk of bias, interpreted analyses, drafted the review text, and commented on the final draft version.

Ashma Krishan performed and interpreted initial analyses.

Peter Collins reviewed and commented on the final draft version.

Megan Lowe conducted risk of bias assessment and data extraction.

Davide Martino assessed eligibility of studies, conducted data extraction and risk of bias assessment, interpreted analyses, and reviewed the review text.

DECLARATIONS OF INTEREST

Omotola Olasupo: has no conflict of interest.

Megan Lowe: has no conflict of interest.

Peter Collins has acted as a paid consultant, received lecture fees and support to attend meetings from Novo Nordisk, Bayer, Baxter, CSL Behring. Grant support has been received from CSL Behring.

Ashma Krishan: none known.

Alfonso Iorio does not perceive any relevant conflict of interest, while his institution receives grants from pharmaceutical companies, he does not benefit from these, nor does he have control over the use of the funds.

Davide Martino reports research grants paid directly to the Institution from Bayer, Pfizer, Novo Nordisk, Sanofi, Spark, Octapharma; personal fees outside the submitted work from Sanofi, Sobi, Novo Nordisk, Bayer, Pfizer, Octapharma for participation in advisory boards, lectures and preparation of educational material.

SOURCES OF SUPPORT

Internal sources

- Alberta Research Centre for Child Health Evidence, Canada

This support was received for the original version of this review (now withdrawn).

External sources

- Association of Hemophilia Clinic Directors of Canada, Canada

This support was received for the original version of this review (now withdrawn).

- National Institute for Health Research, UK

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is one of two set to replace the original review - *Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B* (lorio 2011) - which has now been withdrawn from the Cochrane Library. This new review focuses on people previously treated with clotting factor concentrates.

NOTES

This review of previously treated individuals is one of two set to replace the original 2011 published review - *Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B* (lorio 2011). The original review is currently still available on the Cochrane Library, but when this is next updated (currently in production), will only include previously untreated individuals.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Coagulation Factors [*therapeutic use]; Factor VIII [*therapeutic use]; Hemarthrosis [*prevention & control]; Hemophilia A [*complications]; Hemophilia B [*complications]; *Pharmaceutical Preparations

MeSH check words

Humans