# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Clinical evidence review of vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease

## NHS England unique reference number URN1709 / NICE ID018

First published: March 2020

Prepared by: NICE on behalf of NHS England Specialised Commissioning

**About this clinical evidence review**

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

# Summary

This evidence review considers vonicog alfa for treating adults with von Willebrand disease (VWD), when desmopressin treatment alone is ineffective or not indicated for the:

- treatment of haemorrhage and surgical bleeding
- prevention of surgical bleeding.

People with VWD lack von Willebrand factor, a protein needed for the blood to clot normally. This means that people with VWD have difficulty forming a blood clot and, as a result, bleed more after events such as injury, childbirth, or during surgery. The symptoms of VWD may start at any age. They can range from very mild and barely noticeable to frequent and severe. Symptoms can include nosebleeds, bleeding from the gums, easy bruising and heavy menstrual bleeding. Inherited VWD is classified according to whether the predominant defect is a reduction in level of VWF (types 1 and 3) or abnormality of function of VWF (type 2), each with differing degrees of severity and inheritance patterns.

Vonicog alfa works in the body in the same way as natural von Willebrand factor. It replaces the missing or dysfunctional protein, thereby helping the blood to clot and giving temporary control of the bleeding disorder.

This evidence review considers the results from 2 phase 3, non-comparative, open-label and prospective studies that included people with severe VWD. Gill et al. (2015) was a part-randomised study that included 37 participants (n=22 for efficacy) who were given vonicog alfa for the treatment of bleeding episodes. Peyvandi et al. (2018) was a non-randomised study that included 15 participants who were given vonicog alfa to prevent and treat bleeding during surgery. Vonicog alfa was co-administered with recombinant factor 8 (rFVIII) in some participants in both studies to ensure haemostasis.

## *Effectiveness*

Evidence from Gill et al. (2015) found that treatment with vonicog alfa was successful in 100% of the participants for stopping the bleeding episode (Clopper-Pearson exact 90% confidence interval [CI]: 87.3 to 100.0%). A total of 192 bleeding

episodes were recorded, and vonicog alfa was rated as excellent or good for treating 100% of bleedings (Clopper-Pearson exact 95% CI: 98.1 to 100%). Most bleeding episodes were controlled with 1 infusion of vonicog alfa.

Evidence from Peyvandi et al. (2018) found treatment with vonicog alfa was rated as excellent or good for controlling bleeding in all 15 major and minor surgeries that occurred during the study (100%, 90% CI: 81.9 to 100%).

This evidence suggests that vonicog alfa is effective for stopping bleeding episodes and for stopping and preventing bleeding during surgery in people with VWD.

### *Safety and tolerability*

No deaths, severe allergic reactions or discontinuations were reported in either study. Most of the treatment-related adverse events reported in the studies were mild to moderate in severity.

Gill et al. (2015) reported that 6.4% (8/125) of the adverse events seen were considered to be related to treatment with vonicog alfa. Two of these were reported to be serious: chest discomfort and increased heart rate in 1 participant. Peyvandi et al. (2018) reported 12 treatment-emergent adverse events in 6 participants. Two of these participants each had 1 serious adverse event: diverticulitis (a digestive condition) that was not thought to be treatment related and DVT that was considered to be possibly related to vonicog alfa treatment. One participant had a positive result for anti-von Willebrand factor binding antibodies (which were reported to be non-inhibitory), but no adverse events were reported for this participant.

There were no other findings of thromboembolic events, anti-von Willebrand factor neutralising or binding antibodies, factor 8 (FVIII) neutralising antibodies, or antibodies against rFurin, Chinese hamster ovary (CHO) host cell proteins, or murine immunoglobulin G.

The European public assessment report (EPAR) for vonicog alfa states that most of the reported adverse events are expected for treatment with von Willebrand factor products or blood coagulation factors, and were mostly regarded as infusion or hypersensitivity reactions.

### *Evidence gaps and limitations*

The main limitations of the studies included their small size (n=22 for efficacy analysis and n=37 for safety analysis in Gill et al. 2015 and n=15 in Peyvandi et al. 2018), the design of the study (open-label and non-comparative), co-administration with other treatments (such as rFVIII) and subjective outcome measures. However, these limitations are as expected for studies investigating treatment in people with bleeding conditions given that: the indications of interest were episodic and recruitment was limited to severe types of VWD; it would be impractical and unethical to blind participants who are bleeding and treating them with placebo; plasma-derived concentrates commonly contain both VWF and FVIII in practice; and subjective assessments are commonly used for assessing treatment efficacy in this population.

Both studies included people with severe VWD who previously needed plasma-derived VWF, and most (but not all) included people with type 3 VWD. Therefore, results are limited to these populations who need plasma-derived VWF.

# Table of contents

# Abbreviations

| Term | Definition |
|---|---|
| FVIII | factor 8 |
| FVIII:C | factor 8 activity |
| rFVIII | recombinant factor 8 |
| rVWF | recombinant von Willebrand factor (or vonicog alfa) |
| VWD | von Willebrand disease |
| VWF | von Willebrand factor |
| VWF:Ag | von Willebrand factor antigen |
| VWF:RCo | von Willebrand factor: ristocetin cofactor activity |

# Medical definitions

| Term | Definition |
|---|---|
| Angiodysplasia | A condition where a number of dilated blood vessels develop within the inner wall of the bowel |
| Autosomal dominant inheritance | 1 gene that is mutated is inherited from either parent causing a genetic disorder The phenotype of the disorder is produced by a variant in only one allele of the gene. |
| Autosomal recessive inheritance | 2 alleles of a gene that have mutated are inherited, with 1 coming from each parent, causing a genetic disorder. Both alleles of the gene must contain a variant in order to produce the phenotype of the disorder |
| Factor 8 (or factor VIII, FVIII) | A blood clotting protein |
| Plasma-derived products | Products that are derived from human plasma and include von Willebrand factor in combination with factor 8. |
| Recombinant factor 8 (rFVIII) | FVIII made in a cell line using recombinant DNA techniques. (therefore not from human plasma) |
| Recombinant von Willebrand factor | VWF made in a cell line using recombinant DNA techniques. (therefore not from human plasma) |
| Von Willebrand factor | This is a large protein essential for normal haemostasis. It binds to damaged blood vessel walls and captures platelets, to form a platelet plug which is the first step in stopping bleeding. It also binds FVIII and prolongs its survival in the circulation. |
| von Willebrand factor: ristocetin cofactor | This is a measure of the platelet binding function of VWF in the presence of ristocetin |
| Von Willebrand disease | The disorder due to a deficiency or functional abnormality of von Willebrand factor |

# 1 Introduction

## *Disease background*

1.1 Von Willebrand disease (VWD) is an inherited genetic disorder caused by missing or defective von Willebrand factor (VWF), a clotting protein. VWF binds factor 8, a key clotting protein, and captures platelets on damaged blood vessel walls, which helps form a platelet plug during the clotting process (National Haemophilia Foundation: Von Willebrand disease). People with VWD have difficulty forming a blood clot and often have bleeding from the mucous membranes. The symptoms of VWD may start at any age. They can range from very mild and barely noticeable to frequent and severe. Symptoms can include nosebleeds, bleeding from the gums, easy bruising, and heavy menstrual bleeding. People with severe VWD may experience bleeding from joints or soft tissue. This can cause chronic musculoskeletal damage and may require joint replacement surgery. In addition, people with the condition may bleed easily after injury, childbirth, and surgery.

1.2 Inherited VWD has been classified as 3 main types (known as VWD types 1, 2, and 3) each with differing degrees of severity and inheritance patterns. Type 1 is the mildest and most common type, transmitted as an autosomal dominant trait (Franchini et al. 2016). People with type 1 VWD have a reduced level of VWF in their blood. In people with type 2, VWF doesn't work properly. Type 2 is inherited mainly with an autosomal dominant pattern (Franchini et al. 2016). Bleeding tends to be more frequent and heavier than in type 1. Type 2 has 4 subtypes (2A, 2B, 2M and 2N). Type 3 is the most severe and rarest type and is inherited as an autosomal recessive trait (Franchini et al. 2016). People with type 3 VWD have very low levels of VWF, or none at all (NHS choices: von Willebrand disease). In addition to the genetic cause, VWD can be acquired during life (known as acquired von Willebrand syndrome), often in relation to a separate underlying condition (National organisation for rare disorders [NORD]: von Willebrand disease).

## *Focus of review*

1.3 In line with the marketing authorisation, the focus of this review is on vonicog alfa for treating adults (aged 18 years and over) with von Willebrand disease, when desmopressin treatment alone is ineffective or not indicated for the:

- treatment of haemorrhage and surgical bleeding
- prevention of surgical bleeding.

## *Epidemiology and needs assessment*

1.4 Based on the UK National Haemophilia Database Bleeding Disorder Statistics for April 2017 to March 2018, it is estimated that 7,374 adults have von Willebrand disease in England. A total of 542 adults were treated with desmopressin or with plasma-derived VWF. Of the adults treated with plasma-derived VWF, around 10% (54) used them for prophylaxis, and so would not be eligible for treatment with vonicog alfa. The eligible patient population for vonicog alfa in England is considered equivalent to the adults with all types of VWD who are currently treated with plasma concentrates but excluding those using the concentrates for prophylaxis. This is equivalent to 488 adults.

1.5 Bleeding can be severe and life-threatening in people with VWD. For example gastrointestinal bleeding from angiodysplasia (enlarged blood vessels within the inner lining of the colon) is a serious and life-threatening complication in older people with VWD. Joint bleeding occurs in a considerable number of severely affected people and can lead to joint disease and reduced joint function (Leebeek et al. 2016). Post-partum haemorrhage frequently occurs in women mainly with type 2A and 2B and type 3 VWD. Most people with VWD will require treatment before surgery, In addition people with VWD with more severe forms of VWD (severe type 1, some type 2 and type 3) will require regular prophylaxis or targeted prophylaxis (for example during pregnancy or menstruation). In people with type 3 VWD who have surgery, prophylactic treatment is always required (Castaman et al. 2013). According to Leebeek et al. (2016)

people with VWD have a lower health-related quality of life compared with the general population.

1.6 For people with VWD, the key outcome is preventing the bleed and having fewer infusions for treating the bleed, therefore less time spent in hospital for managing the bleeding episode or after surgery. Replacement therapy includes plasma-derived VWF/factor 8 and VWF concentrates to treat and/or prevent bleeds in people with VWD. Most VWF containing concentrates currently used also contain factor 8. Historically in the UK, recombinant factor concentrates (when available) have been used in preference to plasma derived products on account of historical problems with transfusion transmitted infection. Gill et al. 2015 describes issues such as plasma donor availability, theoretical risk of pathogen transmission, variation in composition of clotting factors depending on the plasma source and manufacturing process, and external plasma proteins that may cause allergic responses, which are sometimes severe and may limit their use. Plasma-derived VWF/factor 8 concentrates show variable deficiency of ultra-large multimers (large proteins) of VWF because of proteolysis (Gill et al. 2015). Although the safety record of modern plasma derived factor concentrates is excellent, it is anticipated that the principle of 'recombinant for all' will be an important consideration in choice of product. There is currently no evidence from clinical studies that vonicog alfa has any other advantage over plasma derived VWF concentrate.

1.7 Vonicog alfa would be an alternative treatment option to plasma-derived concentrates for a person with VWD. Vonicog alfa is the only purified recombinant human VWF for adults with VWD. It is not plasma derived, and is produced and formulated without the addition of any exogenous human or animal materials. Treatment with vonicog alfa avoids the risk of factor 8 accumulation during dosing and risk of thrombosis, which may be the case with plasma-derived concentrates containing VWF/factor 8. In addition, it contains ultra large multimers, contributing to a greater specific activity of vonicog alfa compared with plasma-derived concentrates containing VWF.

## *Product overview*

### Mode of action

1.8 Vonicog alfa is a recombinant human von Willebrand factor that works in the same way as naturally occurring VWF in the body. People with VWD have missing or dysfunctional VWF, a protein needed for normal clotting of the blood, and, as a result, bleed much more than the general population. Vonicog alfa replaces the missing or dysfunctional protein, helping the blood to clot and giving temporary control of bleeding.

### Regulatory status

1.9 Vonicog alfa received a marketing authorisation for the treatment of adults (18 years or more) with VWD, when desmopressin treatment alone is ineffective or not indicated for the:

- treatment of haemorrhage and surgical bleeding
- prevention of surgical bleeding.

### Dosing information

1.10 Dosage and frequency of administration must be individualised according to clinical judgement and based on the person´s weight, type and severity of the bleeding episodes/surgical intervention and based on monitoring of appropriate clinical and laboratory measures. See summary of product characteristics (SPC) for dosing details.

1.11 The summary of product characteristics for vonicog alfa states that if the baseline plasma factor 8 coagulant activity (FVIII:C) level is less than 40% of normal activity or unknown and in all situations where a rapid correction of haemostasis is needed, such as treating an acute haemorrhage, severe trauma or emergency surgery, it is necessary to administer recombinant factor 8 with the first infusion of vonicog alfa in order to achieve a haemostatic plasma level of FVIII:C. The product information also states that if an immediate rise in FVIII:C is not necessary or if the baseline level is sufficient to ensure haemostasis (40% or more of normal activity) then

the physician may decide to omit the co-administration of recombinant factor 8 with the first infusion of vonicog alfa.

1.12 Based on experience from clinical studies, once VWF has been replaced, endogenous factor 8 levels will remain normal or near normal as long as sufficient dose of vonicog alfa continues to be administered (SPC: vonicog alfa).

### *Treatment pathway and current practice*

1.13 According to the European public assessment report (EPAR), treatment of VWD depends on type and severity. Treatment aims to correct the deficiency in the clotting process and reduce the prolonged bleeding time in people with VWD. Minor bleeds such as nosebleeds, small bruises, and minor cuts may not need treatment. In mild cases, people with VWD may only need treatment before undergoing surgery or a dental procedure, or following trauma or injury (National organisation for rare disorders [NORD]: von Willebrand disease).

1.14 The UK Haemophilia Centre Doctors Organisation (UKHCDO) have developed guidance (Laffan et al. 2014) on the diagnosis and management of VWD. Treatments to stop or prevent bleeds in people with VWD include tranexamic acid, desmopressin or plasma-derived concentrates containing either high-purity VWF alone or intermediate-purity concentrates containing factor 8 and VWF.

- Desmopressin works by temporarily increasing factor 8 and VWF levels in people with VWD with adequate stores of functionally effective VWF. It is used to treat bleeding complications or prophylactically before surgery in mild or moderate type 1 VWD and may occasionally be of some benefit in type 2 VWD. Desmopressin can be administered intravenously, subcutaneously or intranasally. According to Laffan et al. (2014), a trial of desmopressin should be carried out in people with type 1, 2A, 2M and 2N VWD and if sufficiently effective for the severity of bleeding or the planned procedure, should be used in preference to plasma-derived concentrates when possible. Desmopressin is

contraindicated in people with cardiovascular disease, and fluid restriction is necessary to avoid hyponatremia and the risk of seizures, especially in young children (Gill et al. 2015).

- Tranexamic acid is an antifibrinolytic agent, which stops the breakdown of blood clots. It can be used (topically, as a mouthwash, orally or intravenously) as a treatment for minor bleeding or given before surgery. It is either given on its own or combined with desmopressin or plasma-derived concentrates.
- For prophylaxis in major surgery or for the treatment of serious bleeding episodes, plasma-derived VWF-containing factor 8 concentrates are the treatment of choice (Laffan et al. 2014).
- In people who do not respond to plasma-derived VWF concentrate or when anaphylaxis occurs (because of the development of VWF inhibitors), Laffan et al. (2014) recommend considering high-dose recombinant factor 8 infusion, recombinant factor 7a (VIIa), platelet transfusion and tranexamic acid as treatment options.

# 2 Evidence

## *Literature search*

2.1 A literature search was done, which identified 489 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 8 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 2 studies were included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

2.2 The company submission highlighted 2 published studies that were identified in the literature search and included in the clinical evidence review.

2.3 During the scoping phase, 4 papers were also highlighted of which 2 papers had already been identified from the literature search. The

remaining 2 papers did not fall within the search parameters and were not relevant.

## *Overview of included studies*

2.4 Two phase 3, non-comparative studies identified from the search (Gill et al. 2015 and Peyvandi et al. 2018) are included in this clinical evidence review.

2.5 Doses of vonicog alfa are expressed as IU/kg von Willebrand factor: ristocetin cofactor (VWF:RCo). For the purpose of this evidence review, where doses of vonicog alfa are mentioned, this will be referred to as vonicog alfa IU/kg.

2.6 Gill et al. (2015) is a part-randomised study in adults with severe VWD that assessed the pharmacokinetics, safety and efficacy of vonicog alfa for the treatment of a bleeding episode. Thirty-seven participants were exposed to vonicog alfa during the study, however, only 22 of the participants experienced 1 or more bleeding episode and were analysed for efficacy outcomes. Gill et al. (2015) had 4 treatment arms (data from arms 1, 3 and 4 were used to analyse efficacy). Participants were randomised within the first 2 arms (1 and 2):

- (1) pharmacokinetics 50 (PK50) plus treatment: this involved a crossover pharmacokinetics phase at a dose of 50 IU/kg vonicog alfa (with recombinant factor 8 or placebo) followed by 12 months of on-demand bleed treatment
- (2) PK50 only: this involved a crossover pharmacokinetics phase at a dose of 50 IU/kg vonicog alfa (with recombinant factor 8 or placebo)
- (3) pharmacokinetics 80 (PK80) plus treatment: this involved a pharmacokinetics phase at a dose of 80 IU/kg vonicog alfa followed by 6 months of on-demand treatment, another pharmacokinetic phase at the same dose of vonicog alfa and then another 6 months of on-demand bleed treatment

- (4) treatment only: this involved 12 months of on-demand treatment.

2.7 Bleeding episodes (on demand treatment) were treated with an initial infusion of 40 to 60 IU/kg vonicog alfa for minor to moderate bleeds such as epistaxis and up to 80 IU/kg vonicog alfa for major bleeds, which included bleeds such as severe or refractory epistaxis. Vonicog alfa was co-administered with recombinant factor 8 for the initial infusion. For subsequent dosing, vonicog alfa was administered without recombinant factor 8, as long as the therapeutic plasma factor 8 coagulant activity (FVIII:C) levels were maintained. In major bleeding episodes, subsequent doses were to be administered every 8 to 12 hours for 3 days to maintain the trough level of vonicog alfa activity of more than 50 IU/dL and then as deemed necessary by the investigator for up to 7 days.

2.8 Peyvandi et al. (2018) is a non-randomised study in adults with severe VWD undergoing elective major, minor, or oral surgery, and treated with vonicog alfa to prevent excessive bleeds during surgery. The study involved giving vonicog alfa (40 to 60 IU/kg) 12 to 24 hours before surgery, to allow FVIII:C levels to rise to 30 IU/dL or more (minor/oral surgery) or 60 IU/dL or more (major surgery), which were assessed within 3 hours of starting surgery. If target FVIII:C levels were achieved, vonicog alfa was administered on its own within 1 to 2 hours before surgery to achieve peak levels. If target FVIII:C levels were not achieved, vonicog alfa was co-administered with recombinant factor 8 within 1 to 2 hours before surgery to meet peak levels.

A summary of the characteristics of the included studies is shown in table 2 (see evidence tables for full details in appendix 3).

**Table 1 Summary of included studies**

| Study | Population | Intervention and comparison | Primary outcome |
|---|---|---|---|
| Gill et al. (2015), prospective, non-comparative part-randomised open- | People aged 18 to 65 years with type 1 (n=2), 2A (n=5), 2N (n=1) | Intervention: vonicog alfa with or without rFVIII | Extent of control of the bleeding episodes |

| | | | |
|---|---|---|---|
| label phase 3 study | and 3 (n=29) VWD who had a bleed[a]<br>N=37 | No comparator | |
| Peyvandi et al. (2018) prospective, non-comparative, non-randomised open-label phase 3 study | People aged 18 years or more with type 1 (n=3), 2A (n=2), 2B (n=1), 2M (n=1) and 3 (n=8) VWD undergoing elective surgery[b]<br>N=15 | Intervention: vonicog alfa with or without rFVIII<br><br>No comparator | Overall investigator assessed haemostatic efficacy of vonicog alfa at 24 hours after the last perioperative infusion or at completion of the study, whichever occurred earlier |
| [a] Bleeds were classed as minor to moderate bleeds such as nose bleeds, oral bleeding, or heavy menstrual bleeding and major bleeds such as severe or refractory nose bleeds or heavy menstrual bleeding, gastrointestinal bleeding, central nervous system trauma, bleeding into the joint, or post-traumatic haemorrhage.<br>[b] Major surgeries were defined as those that carried a significant risk of large volume blood loss or blood loss into a confined anatomical space, such as major orthopaedic, abdominal, gynaecologic, head and neck, intracranial, cardiovascular or spinal surgery, and extraction of impacted third molars. Minor surgical procedures included placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy, or conization. Oral surgeries included extractions of less than 3 non-molar teeth with no bony involvement. | | | |
| **Abbreviations:**<br>rFVIII, recombinant factor 8; VWD, von Willebrand disease | | | |

## *Key outcomes*

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

2.10 **Grade of evidence:** the grade of evidence for all of the efficacy outcomes is C because the evidence for each outcome is based on 1 study scoring 4 to 6 points and directly applicable. For the safety outcome of adverse events, the grade of evidence is B because the evidence is based on more than 1 study scoring 4 to 6 points, which are directly applicable to people with the indication of interest.

## Effectiveness

2.11 The primary and secondary outcomes varied between the 2 studies depending on the indication for treatment with vonicog alfa.

### *Treatment of bleeding episodes (Gill et al. 2015)*

**2.12** **Extent of control of the bleeding episode (primary outcome):** This outcome looked at how many participants had their bleeding episode stopped with vonicog alfa. It was defined as the number of participants with a mean haemostatic efficacy rating score of less than 2.5. The rating score was measured using a 4-point scale based on the actual number of infusions administered compared with the estimated (by the treating doctor) number of infusions needed to control the bleed. A score of 1 indicated excellent control and a score of 4 indicated no control of the bleeding episode. A score of less than 2.5 indicated excellent or good control of the bleeding episode.

**2.13** All participants who experienced 1 or more bleeding episodes treated with vonicog alfa in the study (n=22) reported an efficacy score of less than 2.5, with an overall treatment success rate of 100% (Clopper-Pearson exact 90% confidence interval [CI]: 87.3 to 100.0%). The results suggest that all participants had excellent or good control of bleeding episodes with vonicog alfa (with or without recombinant factor 8).

**2.14** **Number of treated bleeding episodes with an efficacy rating of excellent or good:** This outcome looked at how many of the bleeding episodes controlled by vonicog alfa (with or without recombinant factor 8) were rated as excellent or good.

2.15 A total of 192 bleeding episodes (minor: n=122, moderate: n=61, major/severe: n=7 and unknown severity: n=2) in 22 participants were treated successfully (100%; Clopper-Pearson exact 95% CI: 98.1 to 100%), with results rated as excellent in 96.9% and good in 3.1% of bleeds. The cause of bleed appeared not to have an impact on efficacy, with excellent efficacy ratings in 97.5% (160/165) of spontaneous and 100% (26/26) of traumatic bleeds.

2.16 **Number of infusions and units of vonicog alfa/rFVIII and/or vonicog alfa per bleeding episode:** This outcome looked how many infusions and units (or dose) were needed to stop a bleeding episode based on the severity and location of the bleed.

2.17 Most bleeds (81.8%, [157/192]) were stopped by a single infusion (median 1 infusion, range 1 to 4 infusions). The median dose of vonicog alfa and recombinant factor 8 administered per bleed was 46.5 IU/kg (range 23.8 to 139.6 IU/kg (data taken from EPAR]) and 33.6 IU/kg (range 16.6 to 129.3 IU/kg), respectively.

2.18 One bleed (in the genital tract and oral cavity concomitantly, participant with type 3 VWD) required 4 infusions, which was the maximum number of infusions administered to treat a bleed during the study. A median of 2 infusions (range 1 to 3) was required to control major bleeds. The amount of vonicog alfa administered per bleed was generally higher for bleeds of greater severity. However, the authors report that 1 major gastrointestinal tract bleed was controlled after a single infusion of vonicog alfa and recombinant factor 8 at a dose of 57.5 IU/kg and 41.5 IU/kg, respectively.

***Treatment/prophylaxis during elective surgery (Peyvandi et al. 2018)***

2.19 **Overall investigator-assessed haemostatic efficacy (primary outcome):** This outcome looked at how well vonicog alfa controlled bleeding at 24 hours after the last perioperative infusion or at completion of the study, whichever occurred earlier. This was assessed by using a 4-point rating scale (excellent, good, moderate or none) based on haemostasis relative to a person who does not have VWD undergoing the same surgery.

2.20 All participants (n=15) had excellent or good overall control of bleeding with vonicog alfa during and after surgery. Overall haemostatic efficacy was rated as excellent or good in 100% (15/15) of participants (90% CI: 81.9 to 100%) who had surgery (major: n=10, minor: n=4 and oral: n=1).

### Safety and tolerability

2.21 **Adverse events:** This outcome looked at how many adverse events were considered to be caused by vonicog alfa (treatment-related) and also how many of these events occurred during treatment with vonicog alfa (treatment-emergent).

2.22 Gill et al. (2015) reported that 6.4% (8/125) of the total number of adverse events were considered to be related to treatment with vonicog alfa. Two of these were reported to be serious treatment-related adverse events of chest discomfort and increased heart rate that occurred in 1 participant who was hospitalised for observation. These symptoms improved after 10 minutes of oxygen treatment. The participant had a history of allergic responses to cryoprecipitate and a plasma-derived VWF concentrate. Six treatment-related adverse events in 4 participants were reported to be not serious. These were tachycardia (fast heart rate), infusion-site paraesthesia (burning/prickling sensation), ECG T-wave inversion, dysgeusia (unpleasant taste in mouth), generalised pruritus (itchy skin) and hot flush.

2.23 Peyvandi et al. (2018) reported 12 treatment-emergent adverse events in 6 participants, including acne, anaemia, deep vein thrombosis (DVT), diverticulitis, dizziness, dry skin, headache, joint swelling, nasopharyngitis, pelvic pain and peripheral swelling. Two participants each had 1 serious adverse event, diverticulitis (a digestive condition) that was thought not to be treatment-related and DVT. The participant with DVT was reported to have a number of additional risk factors for DVT, but the authors stated that despite the existence of these confounding factors, the continued administration of treatment in the postoperative period led the study sponsor to reassess this event as “possibly related” to treatment. The DVT was reported to be asymptomatic, proximal and non-occlusive and was picked up as part of standard care that included imaging at day 4 after the surgery (despite the participant receiving thromboprophylaxis with dabigatran [an anticoagulant] beginning on the day of surgery). One participant with type 3 VWD had a positive result for anti-VWF binding

antibodies, but no adverse events were reported for this participant. The authors report that these antibodies were non-inhibitory and had no effect on vonicog alfa.

2.24 No deaths, severe allergic reactions or discontinuations were reported in either study. There were also no other findings of thromboembolic events, anti-VWF neutralising or binding antibodies, factor 8 neutralising antibodies, or antibodies against rFurin, Chinese hamster ovary host cell proteins, or murine immunoglobulin G.

2.25 The EPAR states that overall, a sufficient number of participants have been exposed to vonicog alfa for the treatment of bleeding episodes with a total duration of 12 months, during surgical procedures and for pharmacokinetic assessments, to adequately evaluate the safety profile. Most of the reported adverse events are expected for treatment with VWF products or blood coagulation factors, and were mostly regarded as infusion or hypersensitivity reactions (EPAR: vonicog alfa). Most of the treatment-related adverse events reported in the studies were mild to moderate in severity.

### *Evidence gaps and limitations*

2.26 There were no comparative, randomised controlled trials of vonicog alfa treatment in people with VWD, which is consistent with studies looking at VWF plasma-derived concentrates. This evidence review includes data on the efficacy and safety of vonicog alfa for treating bleeding episodes, and for treating and preventing surgical bleeding, in people with severe VWD from 2 uncontrolled prospective studies undertaken in multiple centres that included the UK.

2.27 The main limitations of the studies included their small size (n=22 for efficacy analysis and n=37 for safety analysis in Gill et al. 2015 and n=15 in Peyvandi et al. 2018), the study design (open-label and non-comparative), co-administration with other treatments (such as recombinant factor 8) and subjective outcome measures.

2.28 Although both studies recruited people with VWD across multiple study sites in up to 15 countries, the criteria of only including severe types of VWD may have limited the numbers recruited, particularly with most of the participants having type 3 VWD which is the rare type. In addition, bleeding episodes and surgery are episodic which may have contributed to the small size. Therefore, limited data are available for clinical efficacy and safety.

2.29 The design of both studies was as expected and considered acceptable for investigating treatments for bleeding conditions. It would be impractical and unethical to blind participants to treatment when they are bleeding or to compare with placebo. However, the open-label nature of the studies is subject to bias and confounding. Vonicog alfa was not compared with active treatment such as plasma-derived concentrates containing VWF and factor 8 and so no comparative data are available to show if vonicog alfa works better than an active treatment, and its place in therapy.

2.1 In both studies, vonicog alfa could be given with recombinant factor 8. Also an antifibrinolytic agent (such as tranexamic acid) was given (at the discretion of the physician) during 45 of 192 (23.4%) treated bleeding episodes in 7 (31.8%) participants in the study by Gill et al. (2015). Although using a combination of 2 treatments and/or giving recombinant factor 8 may be considered as standard practice, this may have confounded the results. However, Gill et al. (2015) reported that 10 bleeding episodes (n=3) were treated with the first infusion of vonicog alfa without recombinant factor 8 and the efficacy was rated as excellent for all these bleeds. In the study by Peyvandi et al. (2018), out of a total of 104 surgical infusions of vonicog alfa, 93 infusions (89.4%) of vonicog alfa were given alone (80% of participants were not given any preoperative rFVIII and 67% of participants and 70% of the major surgeries performed used vonicog alfa alone). Of the 11 infusions of vonicog alfa (10.6%) co-administered with recombinant factor 8 in 5 participants, 2 infusions of recombinant factor 8 were given when the FVIII:C level was less than 60 IU/dL, and the remaining 9 were given despite the FVIII:C level being

above the target level (30 IU/dL or more for minor/oral surgery, or 60 IU/dL or more for major surgery). Co-administration with other treatments may have masked the true effect of vonicog alfa.

2.2 Most of the outcomes were assessed subjectively, which may have introduced investigator or surgeon bias. It was not clear in the studies whether or not validated tools or measures were used to assess the outcomes. Gill et al. (2015) used a predefined 4-point scale, that has previously been used to assess a commonly used VWF concentrate in people with VWD (Lillicrap et al. 2002). An estimated (by the treating physician) number of infusions needed to control the bleed and also predicted blood loss based on a person of the same gender, age, stature and co-morbidities who does not have VWD were used to compare with actual values found in people with VWD in the studies by Gill et al. (2015) and Peyvandi et al. (2018), respectively. It is difficult to predict blood loss because it depends on the nature of the surgical procedure, the extent of incision(s) and individual variability. However, the haemostatic efficacy rating scale used in the studies are thought to be commonly used for assessing treatment efficacy in people with bleeding conditions.

2.3 Both studies included people with severe VWD who previously needed plasma-derived VWF, and most (but not all) included people with type 3 VWD. Therefore, results are limited to these populations who need plasma-derived VWF. There were no quality of life outcomes reported in the studies. Also, no evidence was found for the following standard outcomes included in the scope: survival; progression-free survival; health-related quality of life (including mobility; self-care; usual activities; anxiety/depression); dependency on care giver/supporting independence; and delivery of the medicine.

2.4 The licensed indication for vonicog alfa does not include continued treatment for the prevention of bleeding episodes, and the EPAR states that the indication to include prevention of bleeding episodes could not be granted because no studies or data were provided to support the claim for prophylaxis.

## Table 2 Grade of evidence for key outcomes

| Outcome measure | Study | Critical appraisal score | Applicability | Grade of evidence | Interpretation of evidence |
|---|---|---|---|---|---|
| Extent of control of the bleeding episode (primary outcome) | Gill et al (2015) | 6/10 | Directly applicable | C | This outcome measured how well vonicog alfa stopped a bleeding episode based on a 4-point scale of 1 (excellent), 2 (good), 3 (moderate), or 4 (none) in participants. The rating score was based on the actual number of infusions given compared with the estimated (by the treating doctor) number of infusions needed to control the bleed. An average score of less than 2.5 treatment success.<br><br>Gill et al. (2015) (n=22) reported an overall treatment success rate of 100% (Clopper-Pearson exact 90% CI: 87.3 to 100.0%).<br><br>The result suggests that all participants had excellent or good control of their bleeding episode with vonicog alfa. The probability that the true value is contained within the range of 87.3% to 100% is 90%.<br><br>This result should be interpreted with caution because it is based on a small and non-comparative, study. Therefore this study does not provide evidence that vonicog alfa is any better or worse than other treatments for this outcome. Also, this outcome was subjectively assessed by the treating doctor using a predefined scale rather than by using a validated tool, which may introduce bias. The results are limited to people with severe types of VWD, however the licensed indications do not differentiate between severe and less severe types of VWD suggesting that people with different severities of VWD can be treated with vonicog alfa. |

| | | | | | |
|---|---|---|---|---|---|
| Overall investigator-assessed haemostatic efficacy during/after surgery (primary outcome) | Peyvandi et al (2018) | 6/10 | Directly applicable | C | This outcome looked at how well vonicog alfa controlled bleeding 24 hours after the last infusion (which may have been before or during surgery, or at completion of the study). This was assessed by the investigator using a 4-point scale of excellent, good, moderate, or none.<br><br>Peyvandi et al. (2018) (n=15) reported an overall haemostatic efficacy rating of excellent or good in 100% of the participants who had surgery (Clopper-Pearson exact 90% CI: 81.9 to 100.0%).<br><br>The result suggests that all participants who had surgery had control of bleeding as good or better than that expected, or as good as that expected relative to a person who does not have VWD undergoing the same surgery, The probability that the true value is contained within the range of 81.9% to 100% is 90%.<br><br>The limitations in the Peyvandi et al. (2018) study were similar to the Gill et al. (2015) study, see outcome on 'extent of control of the bleeding episode'. |

| | | | | | |
|---|---|---|---|---|---|
| Number of treated bleeding episodes with an efficacy rating of excellent or good | Gill et al (2015) | 6/10 | Directly applicable | C | This outcome looked at how many bleeding episodes treated with vonicog alfa rated the treatment as giving excellent or good control of the bleed. This was assessed by the treating doctor using a 4-point scale of excellent, good, moderate, or none.<br><br>Gill et al. (2015) (n=22) reported that all 192 bleeding episodes were rated as either excellent or good (100% [Clopper-Pearson exact 95% CI: 98.1 to 100.0%]).<br><br>The result suggests that all the bleeding episodes had either an excellent or good control with vonicog alfa. The probability that the true value is contained within the range of 98.1% to 100% is 95%.<br><br>For limitations see outcome on 'extent of control of the bleeding episode'. |
| Number of infusions and units of vonicog alfa/ rFVIII and/or vonicog alfa per bleeding episode | Gill et al (2015) | 6/10 | Directly applicable | C | This outcome looked at how many infusions and units of vonicog alfa were required to stop a bleeding episode. Vonicog alfa was given with rFVIII at the first infusion to maintain baseline plasma FVIII coagulant activity (FVIII:C), and subsequently without rFVIII as long as therapeutic FVIII:C levels were maintained.<br><br>Gill et al. (2015) (n=22) reported that 81.8% of the bleeding episodes were stopped by 1 infusion (median 1, range 1 to 4 infusions) of vonicog alfa. The median dose of vonicog alfa needed to stop a bleed was 46.6 IU/kg (range 23.8 to 139.6 IU/kg) and for rFVIII was 33.6 IU/kg (range 16.6 to 129.3 IU/kg).<br><br>The results suggest that most of the bleeds were stopped with 1 infusion of vonicog alfa. The most number of infusions needed to stop a bleed was 4. The dose of vonicog alfa needed to control a bleeding episode was a minimum of 23.8 IU/kg and a maximum of 139.6 IU/kg when given with rFVIII.<br><br>This result should be interpreted with caution because it is based on a small and non-comparative, study. Therefore this study does not provide evidence that vonicog alfa is any better or worse than other treatments for this outcome. The |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | results are limited to people with severe types of VWD, however the licensed indications do not differentiate between severe and less severe types of VWD suggesting that people with different severities of VWD can be treated with vonicog alfa. |
| Adverse events | Gill et al (2015) | 6/10 | Directly applicable | B | This outcome looked at how many adverse events were thought to be caused by vonicog alfa (treatment-related) and also how many adverse events occurred during treatment with vonicog alfa (treatment-emergent).<br><br>Gill et al. (2015) (n=37 participants with bleeding episodes) reported that 6.4% (8/125) of the adverse events seen were thought to be related to vonicog alfa. This included 2 adverse events of chest discomfort and increased heart rate in 1 participant that were reported as serious (the participant was hospitalised).<br><br>Peyvandi et al. (2018) (n=15 participants undergoing elective surgery) reported 12 adverse events in 6 participants during treatment with vonicog alfa. This included 2 participants each reporting 1 serious adverse event of diverticulitis (a digestive condition) or deep vein thrombosis (DVT). Only the DVT was considered to be possibly related to vonicog alfa treatment.<br><br>The results suggest that people who are given vonicog alfa for either a bleeding episode or surgery may experience some adverse events that are mostly of a mild or moderate severity.<br><br>For limitations see outcome on ‘extent of control of the bleeding episode’. |
| | Peyvandi et al (2018) | 6/10 | Directly applicable | | |

# 3 Related NICE guidance and NHS England clinical policies

NHS England and NICE have not issued any guidelines or policies for treating haemorrhage and surgical bleeding, or preventing surgical bleeding, for people with VWD.

# 4 References


Castaman G, Goodeve A, Eikenboom J et al. (2013) Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica 98(5): 667–74

Franchini M and Mannucci P (2016) Von Willebrand factor (Vonvendi®): the first recombinant product licensed for the treatment of von Willebrand disease. Expert Review of Hematology volume 9 (9): 825–30

Gill J, Castaman G, Windyga J et al. (2015) Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. Blood 126 (17): 2038–46

Laffan M, Lester W, O'Donnell JS et al. (2014) The diagnosis and management of von Willebrand disease; United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. British Journal of Haematology 167(4): 453–65

Leebeek W and J Eikenboom (2016) Von Willebrand's Disease. New England Journal of Medicine 375: 2067–80

Lillicrap D, Poon MC, Walker I et al. (2002) Efficacy and safety of the factor VIII/von Willebrand factor concentrate, haemate-P/humate-P: ristocetin cofactor unit dosing in patients with von Willebrand disease. Journal of Thrombosis and Haemostasis 87(2): 224–30.

Peyvandi F, Mamaev A, Wang J D et al (2018) Phase 3 Study of Recombinant von Willebrand Factor in Patients With Severe von Willebrand Disease Who Are Undergoing Elective Surgery. Journal of thrombosis and haemostasis 17: 52–62

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

# Appendix 1 Search strategy

## Databases

**Database:** Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Version: 1946 - date
Search date: 8 Nov 18
Number of results retrieved: 238

Database: Ovid MEDLINE(R) ALL <1946 to November 07, 2018>
Search Strategy:
---
1 von willebrand diseases/ or von willebrand disease, type 1/ or von willebrand disease, type 2/ or von willebrand disease, type 3/ (5447)
2 (vwd or vws or avws or avwd).ti,ab. (2327)
3 ((willebrand* or vonwillebrand*) adj3 (disease* or syndrome* or deficien* or defect*)).ti,ab. (5372)
4 or/1-3 (7157)
5 von Willebrand Factor/ and recombinant.ti,ab. (732)
6 (Recombinant adj5 (willebrand* or vonwillebrand)).ti,ab. (134)
7 rVWF.ti,ab. (86)
8 Vonicog.ti,ab. (1)
9 Veyvondi.ti,ab. (0)
10 ("BAX 111" or BAX111 or "SHP-677" or SHP677 or "SHP 677" or Vonvendi).ti,ab. (4)
11 or/5-10 (773)
12 4 and 11 (255)
13 limit 12 to english language (251)
14 animals/ (6293745)
15 humans/ (17375728)
16 14 not 15 (4479922)
17 13 not 16 (242)
18 limit 17 to (comment or editorial or letter) (4)
19 17 not 18 (238)

**Database: Embase**
Platform: Ovid
Version: 1974 to 2018 November 07
Search date: 8 Nov 18
Number of results retrieved: 240

Database: Embase <1974 to 2018 November 07>
Search Strategy:
---
1 von willebrand disease/ (9178)
2 (vwd or vws or avws or avwd).ti,ab. (4436)
3 ((willebrand* or vonwillebrand*) adj3 (disease* or syndrome* or deficien* or defect*)).ti,ab. (7992)
4 or/1-3 (11063)
5 von Willebrand Factor/ and recombinant.ti,ab. (1744)
6 (Recombinant adj5 (willebrand* or vonwillebrand)).ti,ab. (215)
7 rVWF.ti,ab. (209)
8 Vonicog.ti,ab. (6)

9 Veyvondi.ti,ab. (0)
10 ("BAX 111" or BAX111 or "SHP-677" or SHP677 or "SHP 677" or Vonvendi).ti,ab. (19)
11 or/5-10 (1826)
12 4 and 11 (507)
13 limit 12 to english language (499)
14 Nonhuman/ (5598328)
15 human/ (18865004)
16 14 not 15 (4253245)
17 13 not 16 (465)
18 limit 17 to (conference abstract or conference paper or editorial or letter or note) (225)
19 17 not 18 (240)

**********

**Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL, NHS EED**
Platform: Wiley
Version:
CDSR – Issue 11 of 12, November 2018
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – Issue 10 of 12, October 2018
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 8 Nov 18
Number of results retrieved: CDSR –0 ; DARE –0 ; CENTRAL –10 ; *HTA – 1 (see below);* NHS EED –0 .

Date Run: 08/11/2018 18:10:48
Search strategy *NB the strategy export from Cochrane is still not functioning properly, this is the printout which at least gives the terms and numbers.*

ID Search Hits
#1 MeSH descriptor: [von Willebrand Diseases] explode all trees 38
#2 MeSH descriptor: [von Willebrand Disease, Type 1] explode all trees 1
#3 MeSH descriptor: [von Willebrand Disease, Type 2] explode all trees 1
#4 MeSH descriptor: [von Willebrand Disease, Type 3] explode all trees 0
#5 (vwd or vws or avws or avwd):ti,ab 64
#6 ((willebrand* or vonwillebrand*) near/3 (disease* or syndrome* or deficien* or defect*)):ti,ab 118
#7 #1 or #2 or #3 or #4 or #5 or #6 130
#8 MeSH descriptor: [von Willebrand Factor] explode all trees 393
#9 recombinant:ti,ab 11253
#10 #8 and #9 9
#11 (Recombinant near/5 (willebrand* or vonwillebrand)):ti,ab 9
#12 rVWF:ti,ab 7
#13 Vonicog:ti,ab 2
#14 Veyvondi:ti,ab 0
#15 ("BAX 111" or BAX111 or "SHP-677" or SHP677 or "SHP 677" or Vonvendi):ti,ab 3
#16 #10 or #11 or #12 or #13 or #14 or #15 17
#17 #7 and #16 11
#18 clinicaltrials.gov:so 127836
#19 #17 not #18 10

*HTA searched separately through the CRD website (so records ending 31 March 17), using BAX 111 OR Vonicog OR Veyvondi OR Vonvendi OR rVWF.af.*

*1 record found, a duplicate from other searching: NIHR HSRIC. Vonicog alfa for severe von Willebrand disease. Birmingham: NIHR Horizon Scanning Research&Intelligence Centre. Horizon Scanning Review. 2016*

## Trials registries

## Clinicaltrials.gov

Search date: 20181109
Number of results retrieved: 6 (including 1 phase I trial, not included)
Search strategy and link to results page: BAX 111 OR Vonicog OR Veyvondi OR Vonvendi OR rVWF

NCT02606045 Prospective, Randomized, Crossover Trial Comparing Recombinant Von Willebrand Factor (rVWF) vs. Tranexamic Acid (TA) to Minimize Menorrhagia in Women With Type 1 Von Willebrand Disease: The VWD Minimize Study.
Status: not yet recruiting. Estimated study start date: October 2018. Estimated primary completion date: August 2022.
Phase III, "outpatient, 24-week Phase III prospective, randomized, crossover trial comparing recombinant von Willebrand factor (rVWF) and tranexamic acid (TA, Lysteda®) to minimize menorrhagia in women with type 1 von Willebrand disease (VWD)."

NCT02973087 A prospective, phase 3, open-label, international multicenter study on efficacy and safety of prophylaxis with rVWF in severe von Willebrand disease.
Status: recruiting. Study start date: December 2017. Estimated primary completion date: May 2019.
Phase III study " …to investigate the efficacy and safety, including immunogenicity and thrombogenicity of prophylactic treatment with recombinant von Willebrand factor (rVWF) in subjects with severe von Willebrand disease (VWD)."

NCT02932618 A Phase 3, Prospective, Multicenter, Uncontrolled, Open-Label Clinical Study to Determine the Efficacy, Safety, and Tolerability of rVWF With or Without ADVATE in the Treatment and Control of Bleeding Episodes, the Efficacy and Safety of rVWF in Elective and Emergency Surgeries, and the Pharmacokinetics (PK) of rVWF in Children Diagnosed With Severe Von Willebrand Disease.
Status: recruiting. Study start date: December 2017. Estimated primary completion date: May 2020.
"The purpose of this study in pediatric participants (<18 years of age) with severe hereditary von Willebrand disease (VWD) is:
1.To assess the efficacy, safety, and tolerability of recombinant von Willebrand Factor (rVWF), with or without ADVATE, in the treatment and control of nonsurgical bleeding events
2.To assess the efficacy and safety of rVWF with ADVATE during elective or emergency surgery
3.To determine the pharmacokinetic (PK) profile of rVWF"

NCT01410227 A Phase 3 Clinical Study to Determine the Pharmacokinetics, Safety and Efficacy of Recombinant Von Willebrand Factor : Recombinant Factor VIII (rVWF:rFVIII) and rVWF in the Treatment of Bleeding Episodes in Subjects Diagnosed With Von Willebrand Disease. *Completed 2014, with results, also with a publication attached to the record.*

NCT02283268 A Phase 3, Prospective, Multicenter Study to Evaluate Efficacy and Safety of Recombinant Von Willebrand Factor (rVWF) With or Without ADVATE in Elective Surgical Procedures in Subjects With Severe Von Willebrand Disease. *Completed 2016, with results*

## Clinicaltrialsregister.eu

Search date: 20181109
Number of results retrieved: 4
Search strategy and link to results page: Vonicog OR Veyvondi OR Vonvendi

*All captured above from Clinicaltrials.gov*

# Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 489 studies (excluding the 4 references identified during the scoping phase). These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

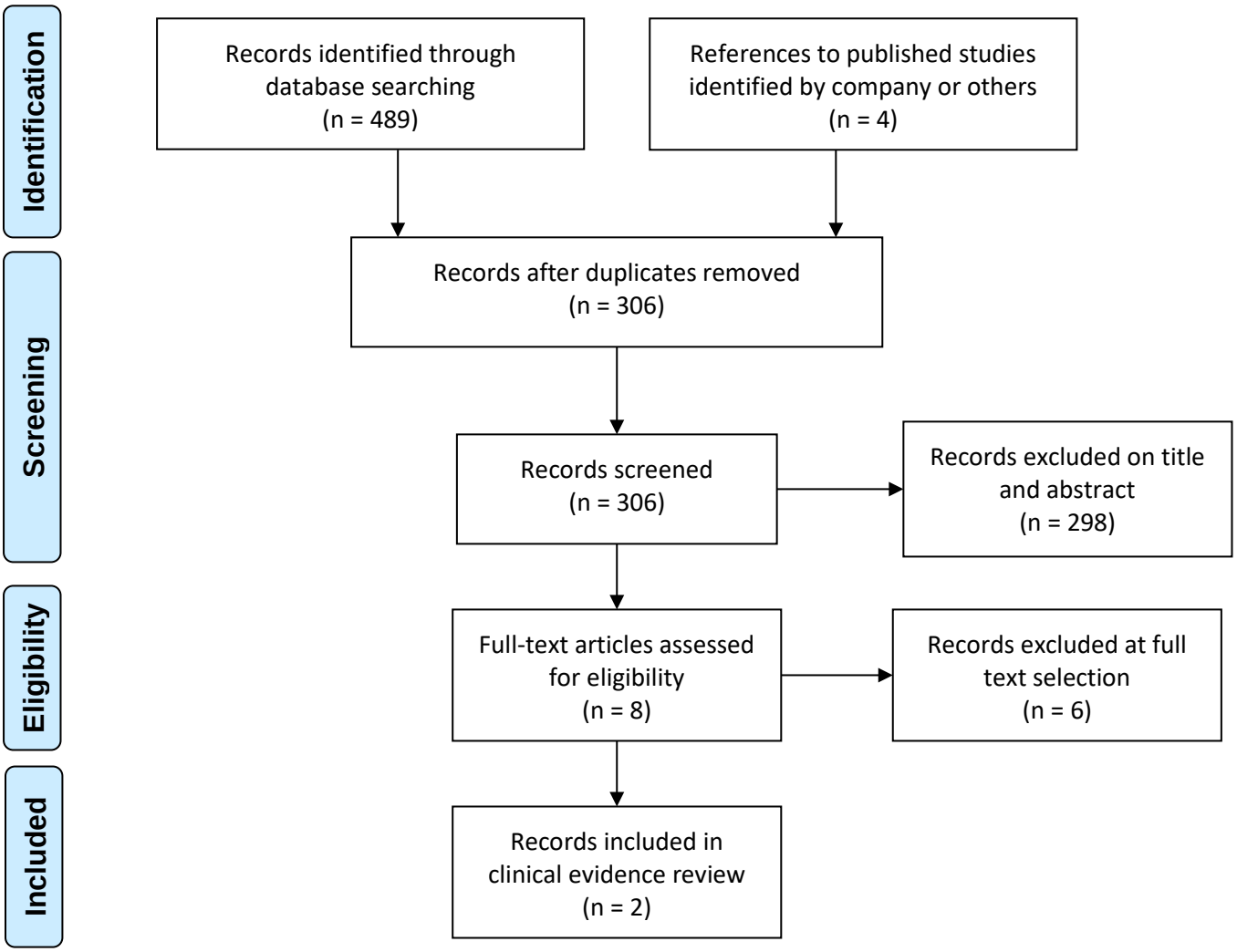
| **Sifting criteria** | **Inclusion** | **Exclusion** |
|---|---|---|
| Population | Adults aged 18 years and over with von Willebrand disease | Non-humans |
| Intervention | Vonicog alfa (Veyvondi) | |
| Comparator | • Desmopressin<br>• Replacement therapy with plasma derived VWF-FVIII complex or plasma derived VWF with/without a recombinant FVIII<br>• Antifibrinolytics such as tranexamic acid<br>• Platelet transfusion<br>• Hormonal contraceptives (for people who have menstrual cycles) | |
| Outcomes | • Control of the bleeding episodes<br>• Treatment response/success of each bleeding episode (rated by participant or investigator)<br>• Number of infusions and units/dose of rVWF (vonicog alfa)/rFVIII or rVWF required to control a bleed<br>• Time taken to achieve resolution of a bleed<br><br>The following outcomes are included as standard and will be considered where evidence allows: survival; progression-free survival; health-related quality of life (including mobility; self-care; usual activities; anxiety/depression); replacement of more toxic treatment; dependency on care giver/supporting independence; safety (including adverse effects); and delivery of the medicine. | None |
| Other | | Abstracts<br>Non-English language<br>Duplicates |

| | | |
|---|---|---|
| | | Opinion pieces, commentaries, epidemiological studies, burden of disease studies |

## Table 3 Excluded Studies following full text review

| Study reference | Reason for exclusion |
|---|---|
| Castaman G, and Linari S (2016) Vonicog alfa for the treatment of von Willebrand disease. Expert Opinion on Orphan Drugs 4(5), 549-554 | Narrative/expert review |
| Franchini Massimo, and Mannucci Pier Mannuccio (2016) Von Willebrand factor (Vonvendi): the first recombinant product licensed for the treatment of von Willebrand disease. Expert review of hematology 9(9), 825-30 | Narrative/expert review that includes the main study that has been included as part of the clinical evidence review |
| Lyseng-Williamson K A (2016) Recombinant von Willebrand factor (vonicog alfa) in von Willebrand disease: a guide to its use. Drugs and Therapy Perspectives 32(11), 456-462 | Review paper |
| Singal M, and Kouides P A (2016) Recombinant von Willebrand factor: a first-of-its-kind product for von Willebrand disease. Drugs of today (Barcelona, and Spain : 1998) 52(12), 653-664 | Review paper |
| Suiter Tobias, Laffan Michael, Mannucci Pier et al. (2010) Recombinant human von Willebrand factor (RHVWF): first-in-human study evaluating pharmacokinetics, demonstrating safety and tolerability in type 3 von Willebrand disease. Blood 116(21), | Abstract |
| Tahata S, Ragni M V, and Kadosh J (2017) Feasibility of A smartphone application (APP) pictorial blood assessment chart (PBAC) as an endpoint in A von willebrand disease trial. Blood. Conference: 59th annual meeting of the american society of hematology, and ASH 2017. United states 130(Supplement 1) (no pagination), | Conference report |

**Figure 1 Flow chart of included studies**



# Appendix 3 Evidence tables

### Table 4 Gill et al. (2015)

| | |
|---|---|
| **Study reference** | Gill JC, Castaman G, Windyga J et al. (2015) Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. Blood 126 (17): 2038–46 |
| **Unique identifier** | NCT01410227 |
| **Study type (and NSF-LTC study code)** | Prospective, part-randomised open-label phase 3 study[a]<br>P1 Primary research using quantitative approaches |
| **Aim of the study** | To evaluate the, pharmacokinetics, safety and haemostatic efficacy of a vonicog alfa for treatment of bleeds in severe von Willebrand disease. |
| **Study dates** | November 2011 to February 2014 |
| **Setting** | The trial was conducted in 30 study sites in 15 countries that included the UK<br>Participants had the opportunity to qualify for home treatment |
| **Number of participants** | N=37 |
| **Population** | The median age was 37 years (range 18 to 64 years) and 54% were female. The median weight was 73 kg (range 44 to 143 kg). Of the participants, 78% (n=29) had type 3 VWD, whereas 5.4% (n=2), 13.5% (n=5) and 2.7% (n=1) had types 1, 2A and 2N respectively.<br>Treatments received within 24 months before enrolment were on-demand in 73%, prophylaxis in 8.1% and a combination of on-demand and prophylaxis in 18.9% of participants.<br>The median number of bleeding episodes per year before enrolment in 36 participants was 0.7 (range 0 to 6). |
| **Inclusion criteria** | Male and females aged 18 to 65 years with type 3 or severe type 1 and type 2A (VWF:RCo less than 20 IU/dL), type 2B (as diagnosed by genotype), type 2N (FVIII:C less than 10 IU/dL and historically documented genetics), type 2M, or type 3 (VWF:Ag less than or equal to 3 IU/dL) and treated for 1 or more bleeds with a VWF concentrate within 12 months before enrolment. |
| **Exclusion criteria** | People with a history of VWF or FVIII inhibitors, immunologic disorders, or thromboembolic events. |
| **Intervention(s)** | Vonicog alfa (rVWF) with or without rFVIII[b,c] |
| **Comparator(s)** | No comparator for clinical efficacy assessment |
| **Length of follow-up** | Part A comprised a treatment period of 6 months; during Part B participants continued treatment for a further 6 months, to provide a total of 12 months of treatment (including Part A).<br>The total study duration was 27 months |
| **Outcomes** | Primary outcome<br>• Extent of control of the bleeding episode[d] |

| | |
|---|---|
| | Secondary outcomes:<br>• The number of treated bleeding episodes with a haemostatic efficacy rating of 'excellent' or 'good'[d]<br>• The number of infusions and units of rVWF/rFVIII or rVWF required to control a bleed |
| | Safety outcomes:<br>• Number of adverse events |
| **Abbreviations** | FVIII, factor 8; FVIII:C, factor VIII activity; rFVIII, recombinant factor 8; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor: ristocetin cofactor; |
| **Comments** | [a] This study has 2 parts and 4 arms. Part A consisted of pharmacokinetic assessments alone (arm 2: PK50 only [without treatment of bleeding episodes]), or pharmacokinetic assessments (arm 1: PK50 and arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes, or arm 4: on-demand treatment for bleeding episodes only. Participants receiving treatment for pharmacokinetic assessments and/or bleeding episodes in part A were entered into part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.<br>[b] Bleeding episodes were treated with an initial infusion of 40 to 60 IU/kg vonicog alfa for minor to moderate bleeds (for example oral bleeding) and up to 80 IU/kg vonicog alfa for major bleeds, such as severe or refractory gastrointestinal bleeding. To ensure an immediate haemostatic level of FVIII:C, the initial dose of vonicog alfa was to be administered together with rFVIII at a ratio of 1.3:1 ± 0.2 VWF:RCo/FVIII:C and subsequently without rFVIII as long as therapeutic FVIII:C levels were maintained.<br>[c] Dosage was based on the participants' weight, type and severity of bleeding episode and based on clinical monitoring.<br>[d] Defined as the number of subjects with a mean haemostatic efficacy rating score of less than 2.5. This rating score was based on a predefined 4-point scale based on the actual number of infusions administered to control the bleed versus the treating physician's estimate of the number of infusions required (according to the EPAR, this was based on different types of bleeds at various anatomical locations and using published literature data). A score of 1 indicated excellent control and a score of 4 indicated no control of the bleeding episode. |
| **Source of funding** | Baxalta (part of Shire) |

**NSF-LTC**

| Criteria | Score | Narrative description of study quality |
|---|---|---|
| **1. Are the research questions/aims and design clearly stated?** | 2/2 | The research questions are stated and the design is clearly stated. |

| | | |
|---|---|---|
| **2. Is the research design appropriate for the aims and objectives of the research?** | 1/2 | This was an open-label and part-randomised cross-over study, therefore the design of the study and use of clinical judgement to assess the primary endpoint may be susceptible to bias. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution. |
| **3. Are the methods clearly described?** | 1/2 | The methods are described for the intervention, However, there is no further information on methods for handling bias, and confounding. Also, it is not clear if validated tools were used to assess outcomes. |
| **4. Are the data adequate to support the authors' interpretations / conclusions?** | 1/2 | The study was open-label and part-randomised, and subject to bias and confounding. However, the design of the study is common for assessing treatment efficacy in this population and so the data are adequate to support conclusions. |
| **5. Are the results generalisable?** | 1/2 | The results are generalisable to the decision problem. However, the study includes few people with types 1 (n=2) and 2 (n=6) VWD and so the generalisability is limited to these types. |
| **Total** | 6/10 | |
| **Applicability** * | Directly applicable | The intervention and indication are directly relevant to the decision problem. |

## Table 5 Peyvandi et al. (2018)

| | |
|---|---|
| **Study reference** | Peyvandi F, Mamaev A, Wang JD et al. (2018) Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery. Journal of Thrombosis and Haemostasis 17: 52–62 |

| | |
|---|---|
| **Unique identifier** | NCT02283268 |
| **Study type (and NSF-LTC study code)** | Prospective, non-randomised, open-label, uncontrolled phase 3 study<br>P1 Primary research using quantitative approaches |
| **Aim of the study** | To evaluate the haemostatic efficacy and safety profile of rVWF (vonicog alfa), with/without rFVIII, in people with severe VWD undergoing elective surgery |
| **Study dates** | April 2015 to July 2016 |
| **Setting** | The trial was conducted in 14 study sites in 10 countries that included the UK |
| **Number of participants** | N=15 |
| **Population** | The median age was 40 years (range 20 to 70 years) and 53.3% were female. The median weight was 73.5 kg (range 52 to 127 kg). Of the participants, 53.3% (n=8) had type 3 VWD, whereas 20% (n=3), 13.3% (n=2), 6.7% (n=1) and 6.7% (n=1) had types 1, 2A, 2B and 2M respectively.<br>Major surgeries were performed in 10 participants (66.7%), minor surgeries in 4 participants (26.7%), and oral surgery in 1 participant (6.7%).<br>Although thromboprophylaxis was allowed at the discretion of the investigator, only 1 participant received it. |
| **Inclusion criteria** | Participants aged 18 years or more with severe[a] VWD of all types who had planned elective surgery were eligible for the study.<br>Participants with type 3 VWD had to have a history of 20 or more exposure days to VWF/FVIII concentrates (including cryoprecipitate or fresh frozen plasma). For participants with type 1 or type 2 VWD, a minimum of 5 exposure days or a past major surgery requiring VWF/FVIII-containing products (including cryoprecipitate or fresh frozen plasma) was required. |
| **Exclusion criteria** | Participants were excluded if they tested positive for VWF or FVIII inhibitors or had a history of a thromboembolic event, hypersensitivity to VWF, or any immunologic disorder. |
| **Intervention(s)** | Participants received 40–60 IU/kg vonicog alfa 12 to 24 hours before surgery. If endogenous FVIII:C target levels were achieved 3 hours before surgery (30 IU/dL or more for minor/oral surgery[b], or 60 IU/dL or more for major surgery[c]), vonicog alfa was administered alone 1 to 2 hours before surgery. If target endogenous FVIII levels were not achieved, rVWF was co-administered with rFVIII.<br>Vonicog alfa was also infused intra- and post-operatively to maintain target trough levels. |
| **Comparator(s)** | None |
| **Length of follow-up** | 14 days post-surgery |
| **Outcomes** | Primary outcome<br>• Overall investigator-assessed haemostatic efficacy of vonicog alfa at 24 hours after the last perioperative infusion or at completion of the study, whichever occurred earlier, using a 4-point rating scale[d] |

| | |
|---|---|
| | Secondary outcomes:<br>• Intraoperative haemostatic efficacy was assessed by the surgeon using the 4-point efficacy rating scale[d]<br>• Intraoperative actual versus predicted blood loss (surgeon evaluated)[d] |
| | Safety outcomes[e]<br>• Incidence/severity of adverse events, thromboembolic events, and severe allergic reactions |
| **Abbreviations** | FVIII, factor 8; FVIII:C, factor VIII activity; rFVIII, recombinant factor 8; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor: ristocetin cofactor |
| **Comments** | [a] Severe VWD was defined as follows: type 1 (VWF:Ag and VWF:RCo <20 IU/dL), type 2A (lack of high molecular-weight multimers and VWF:RCo/VWF:Ag <0.6), type 2B (identification of specific genotype), type 2M (presence of all multimers and VWF:RCo/VWF:Ag <0.6), type 2N (FVIII:C levels <10% with documented genetics), and type 3 (VWF:Ag ≤3 IU/dL).<br>[b] Minor surgical procedures included placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy, or conization. Oral surgeries included extractions of less than 3 non-molar teeth with no bony involvement.<br>[c] Major surgeries were defined as those that carried a significant risk of large volume blood loss or blood loss into a confined anatomical space, such as major orthopaedic, abdominal, gynaecologic, head and neck, intracranial, cardiovascular or spinal surgery, and extraction of impacted third molars.<br>[d] Assessment was done by the investigator/surgeon using an ordinal scale of haemostatic efficacy ('excellent', 'good', 'moderate', or 'none'). Observations were compared to expected rates in a haemostatically normal subject if having undergone the same surgical procedure.<br>[e] Safety evaluations were based on the criteria outlined in the guideline on the clinical investigation of human plasma derived von Willebrand factor products. |
| **Source of funding** | Baxalta (part of Shire) |

**NSF-LTC**

| Criteria | Score | Narrative description of study quality |
|---|---|---|
| **1. Are the research questions/aims and design clearly stated?** | 2/2 | The research questions are stated and the design is clearly stated. |
| **2. Is the research design appropriate for the aims and objectives of the research?** | 1/2 | This was an open-label, non-randomised study therefore the design of the study and use of clinical judgement to assess the primary endpoint are known |

| | | |
|---|---|---|
| | | to be susceptible to bias. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution. |
| **3. Are the methods clearly described?** | 1/2 | The methods are described for the intervention, However, there is no further information on methods for handling bias, and confounding. Outcomes were also subjectively assessed. |
| **4. Are the data adequate to support the authors' interpretations / conclusions?** | 1/2 | The study was open-label and non-randomised, and subject to bias and confounding. However, the design of the study is common for assessing treatment efficacy in this population and so the data are adequate to support conclusions. |
| **5. Are the results generalisable?** | 1/2 | The results are generalisable to the decision problem. However, the study includes few people overall, particularly people with types 1 (n=3) and 2 (n=4) VWD and so the generalisability is limited to these types |
| **Total** | 6/10 | |
| **Applicability** * | Directly applicable | The intervention and indication are directly relevant to the decision problem. |

# Appendix 4 Results tables

### Table 6 Gill et al. (2015)

| | On-demand vonicog alfa treatment of BEs in study arm 1,3 and 4[a] | Statistical analysis |
|---|---|---|
| **N** | **22** [b,c] | |
| **Primary outcome** | | |
| Number of participants with a treatment success for treated BEs[d] | 22/22 | 100% (Clopper-Pearson exact 90% CI: 87.3 to 100%) |
| **Secondary outcomes** | | |
| Number of treated BEs with an efficacy rating of excellent or good[e] | 192/192[f]<br>Excellent = 186/192 (96.9%)<br>Good = 6/192 (3.1%) | 100% (Clopper-Pearson exact 95% CI: 98.1 to 100%) |
| Number of **infusions** of rVWF:rFVIII and/or rVWF per BE[g] | One infusion was adequate to treat 157/192 bleeds (81.8%)[h] | median 1 infusion (range 1 to 4 infusions) |
| Median number of **units** of rVWF:rFVIII and/or rVWF per BE[g] | rVWF: 46.5 IU/kg VWF:RCo<br>rFVIII: 33.6 IU/kg | n/a |
| **Safety outcomes** | | |
| N | 37 | |
| Number of adverse events | 125 | n/a |
| Number of treatment-related adverse events | 8[i] | n/a |

[a] The initial dose of vonicog alfa was administered together with rFVIII at a ratio of 1.3:1 ± 0.2 VWF:RCo/FVIII:C and subsequently without rFVIII as long as therapeutic FVIII:C levels were maintained.

[b] A total of 49 participants were enrolled and assessed for eligibility, and 37 were exposed to vonicog alfa during the study. Twenty two participants (n=17 type 3, n=4 type 2A, and n=1 type 2N VWD) experienced 1 or more bleeding episodes that were treated with vonicog alfa, and 9 of 31 participants allocated for bleed treatment did not experience a bleed during the study.

[c] Most bleeding episodes (several of which occurred in multiple locations) were mucosal (epistaxis, menorrhagia, mouth/oral cavity; n=106, 55.2%), followed by 59 (30.7%) joint bleeds, 37 (19.3%) bleeding episodes in other sites including soft tissue and superficial bleeds, and 6 (3.1%) gastrointestinal bleeds.

[d] Treatment success was defined as a mean efficacy rating score of less than 2.5 for a participant's vonicog alfa-treated BEs during the study. The extent of control of the BEs was assessed using the following scores: Excellent = 1; Good = 2; Moderate = 3; None = 4. This included participants with or without rFVIII. Assessments were made prospectively and excluded gastrointestinal bleeds.

[e] This rating score was based on a predefined 4-point scale based on the actual number of infusions administered to control the bleed versus the treating physician's estimate of the number of infusions required. The rating was scored as stated in footnote d above.

[f] Of these 192 BEs,122 were minor, 61 moderate, 7 major/severe, and 2 unknown severity.

[g] This was determined by the investigator based on the severity and location of the bleed. The EPAR provides further details on the guidance used by the investigator.

[h] For 10 of these infusions in 3 participants, the first infusion of vonicog alfa was inadvertently administered without rFVIII, all with excellent efficacy. Four infusions, which was the maximum number of infusions administered during the trial, were required for 1 mucosal bleed (in the genital tract and oral cavity simultaneously).

[i] Six of these adverse events were reported to be not serious (n=4). One participant experienced mild infusion site paraesthesia (burning/prickling sensation), moderate dysgeusia (unpleasant taste in the mouth), and moderate tachycardia (increased heart rate), 1 participant showed a mild ECG T-wave inversion, 1 participant experienced mild generalised pruritus (itchy skin) and 1 participant had a mild hot flush. One participant experienced 2 simultaneous serious adverse events, chest discomfort and increased heart rate.

**Abbreviations**

BE, bleeding episode; CI, confidence interval; FVIII, factor 8; FVIII:C, factor VIII activity; rFVIII, recombinant factor 8; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor: ristocetin cofactor

## Table 7 Peyvandi et al. (2018)

| | **Vonicog alfa with or without rFVIII[a]** | **Statistical analysis** |
|---|---|---|
| **N** | **15** | |
| **Primary outcome** | | |
| Overall assessment of haemostatic efficacy, rated as excellent or good by the investigator[b,c] | 15/15<br>Excellent = 11/15 (73.3%)<br>Good = 4/15 (26.7%) | 100% (Clopper-Pearson 90% CI: 81.9 to 100%) |
| **Safety outcomes** | | |
| N | 15 | |
| Number of treatment-emergent adverse events | 12 (n=6)[d] | n/a |
| Number of serious adverse events | 2 (n=2)[e] | n/a |

| | | |
|---|---|---|
| Deaths | 0 | n/a |
| Severe allergic reactions | 0 | n/a |

[a] Participants received a priming dose of vonicog alfa (40 to 60 IU/kg VWF:RCo) to raise endogenous FVIII levels to at least 30 IU/dL for minor/oral surgery or to 60 IU/dL for major surgery. rFVIII was co-administered if required FVIII levels were not achieved.

[b] Assessed 24 hours after last perioperative vonicog alfa infusion or at completion of day 14 visit, whichever occurred earlier (assessed by the investigator using a 4-point efficacy rating scale (excellent, good, moderate, or none).

[c] Assessment was done by the investigator/surgeon using an ordinal scale of haemostatic efficacy ('excellent', 'good', 'moderate', or 'none'). Observations were compared to expected rates in a haemostatically normal subject if having undergone the same surgical procedure. Excellent rating was given when intraoperative blood loss was less than or equal to the maximum expected for the type of procedure performed in a haemostatically normal participant (less than 100%). Good rating was given when intraoperative blood loss was up to 50% more than the maximum expected blood loss for the type of procedure performed in a haemostatically normal participant (101 to 150%).

[d] These were dizziness, dry skin, headache, joint swelling, nasopharyngitis, pelvic pain, and peripheral swelling.

[e] One participant had diverticulitis and 1 participant had a DVT. None of these events were considered treatment-related by the investigator. For the participant with a DVT, there were a number of additional risk factors for the DVT. However, the authors state that despite the existence of these confounding factors, the continued administration of treatment in the postoperative period led the study sponsor to reassess this event as 'possibly related' to treatment.

**Abbreviations**

CI, confidence interval; DVT, deep vein thrombosis; FVIII, factor 8; rFVIII, recombinant factor 8;

# Appendix 5 Grading of the evidence base

Each study is assigned one of the following codes:

**NSF-LTC Categories of research design**

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

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

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

Applicability should be classified as:

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