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Horizon Scanning Research & Intelligence Centre

Vonicog alfa for severe von Willebrand disease

LAY SUMMARY

People with von Willebrand disease either have a deficiency of a blood protein called von Willebrand factor, or this protein doesn't work properly. This means that their blood cannot clot properly and they are prone to prolonged or excessive bleeding. There are three different types of von Willebrand disease – types 1, 2, and 3. Type 3 is rare and people with this type have very low levels of von Willebrand factor in their blood, or none at all.

Vonicog alfa is a new drug that is given in a drip (directly into a vein). It is being studied to see whether it reduces bleeding in people with severe von Willebrand disease, and that it is safe to use. If vonicog alfa is licensed for use in the UK, it could provide a new treatment for people with severe von Willebrand disease.

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TARGET GROUP

Von Willebrand disease (VWD): severe – first line.

TECHNOLOGY

DESCRIPTION

Vonicog alfa (Bax-111; BAX 111; recombinant von Willebrand factor; rVWF) is a recombinant form of von Willebrand factor (VWF) intended for the treatment of bleeding episodes in patients with severe VWD. In a phase III clinical trial, vonicog alfa was administered via intravenous (IV) infusion at 40-80 IU/kg[1].

Vonicog alfa does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, vonicog alfa will offer an additional treatment option for patients with severe VWD. Vonicog alfa has the potential to improve safety as not being derived from human plasma, it is plasma- and albumin-free which eliminates the potential risk of transmitting blood-borne pathogens. Vonicog alfa contains only VWF, offering the flexibility to administer FVIII when needed.

DEVELOPER

Baxalta.

AVAILABILITY, LAUNCH OR MARKETING

In phase III trials.

PATIENT GROUP

BACKGROUND

VWD is an inherited genetic disorder caused by missing or defective VWF, a clotting protein[2]. VWF binds factor VIII (FVIII), a key clotting protein, collagen and platelets in blood vessel walls, which help form a platelet plug during the clotting process. There are three main types of VWD described based on the amount and function of VWF in the blood[3]. Type 1 is the mildest and most common type of VWD, occurring in up to 80% of patients with the disorder[2,3]. Type 3 is the most severe form of VWD and is found in approximately 5-10% of patients[2,3]. Type 3 is inherited in an autosomal recessive manner[3].

Symptoms of VWD include easy bruising, bleeding from mouth, nose and bowel, prolonged bleeding from cuts, excessive bleeding after surgery, menorrhagia, and postpartum bleeds[3]. In addition, joints and muscle bleeds are common in patients with severe VWD. However only a small minority have symptoms that may require medical attention[3]. The severity of bleeding tendency in VWD is usually proportional to the degree of the deficiency of VWF and therefore the deficiency of FVIII as VWF is the carrier of FVIII in circulating plasma[4].

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

- NHS England. 2013/14 NHS Standard Contract for Haemophilia (all ages). B05/S/a.

CLINICAL NEED and BURDEN OF DISEASE

VWD is the most common inherited bleeding disorder, with an estimated prevalence of 1% of the UK population[4]. Clinically relevant cases are thought to have a 10-fold lower prevalence[4]. There were 2 deaths from von Willebrand disease registered in England and Wales during 2014 (ICD-10 D68.0)[5]. In 2014-15, there were 939 admissions for von Willebrand disease (ICD-10 D68.0) in England, resulting in 1,015 bed days and 353 finished consultant episodes[6]. In the UK in 2014-2015, there were 155 patients with type 3 VWD, 1,248 patients with type 2 VWD, 4,614 patients with type 1VWD and 4,415 patients with an unreported type[7].

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- No relevant guidance identified.

Other Guidance

- NHS Clinical Knowledge Summary. Bruising. 2010[8].
- United Kingdom Haemophilia Centre Doctors Organisation Guideline. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organisation guideline approved by the British Committee for Standards in Haematology. 2014[9].

CURRENT TREATMENT OPTIONS

The aim of treatment in VWD is to correct the duel defect of haemostasis; the abnormal platelet adhesion-aggregation and the abnormal intrinsic coagulation due to low FVIII levels[5], as well as to treat patients prophylactically in preparation for high risk surgical or dental procedures.

Bleeding episodes in patients with type 3 VWD are treated with plasma derived concentrates containing FVIII/vWF[10,11]. Patient with type 3 VWD are unresponsive to desmopressin acetate, which is the mainstay of treatment for types 1 and 2[4]. Factor VIII fraction, dried (human coagulation factor VIII dried) is the only product currently licensed for use in patients with VWD type 3[12].

EFFICACY and SAFETY

Trial	NCT01410227; 2010-024108-84; recombinant von Willebrand factor; phase III.	NCT02283268; 2014-003575-38; recombinant von Willebrand factor; phase III.
Sponsor	Baxalta US Inc.	Baxalta US Inc.
Status	Complete and published.	Ongoing.
Source of information	Publication[13], trial registry[14], manufacturer.	Trial registry[1], manufacturer.
Location	EU (incl UK), USA, Canada and other countries.	EU (incl UK), USA, Canada and other countries.
Design	Non-randomised, uncontrolled.	Non-randomised, uncontrolled.
Participants	n=49; aged 18-65 years; VWD disease; Karnofsky score ≥ 60%; one documented bleed requiring VWF coagulation factor replacement therapy during previous 12 months.	n=15 (planned); aged 18 years and older; severe VWD; elective surgical procedure planned; history of requiring VWF therapy.
Schedule	Subjects allocated into one of four arms as follows: PK80+treatment arm (severe VWD) – subjects receive a single dose of 80IU/kg recombinant VWF (rVWF) followed by on-demand treatment for 6 months, then repeated. PK50+treatment arm (type 3 VWD) – subjects randomised to receive a single dose of 50IU/kg rVWF IV with rFVIII (Advate) IV or placebo IV, followed by cross-over to the opposite treatment, then a further 12 months on-demand treatment. PK50 only arm (type 3 VWD) – subjects randomised to receive a single dose of 50IU/kg rVWF IV with rFVIII (Advate) IV or placebo IV. Treatment only arm (any VWD subtype) – subjects receive rVWF IV as an on-demand treatment for 12 months.	Subjects receive single 50±5IU/kg rVWF IV bolus infusion.
Follow-up	Active treatment for 12 months.	Follow up for up to 72 hours ± 2 hours post-infusion.
Primary outcome/s	Number of participants with treatment success for treated bleeding episodes in 12 months, rated as excellent (=1), good (=2), moderate (=3), or none (=4).	Haemostatic efficacy as assessed by the investigator - scale of excellent, good, moderate, or none.
Secondary outcome/s	Number of treated bleeding episodes with an efficacy rating of "excellent" or "good"; number of infusions and number of units of rVWF; development of inhibitory and total binding antibodies to VWF; development of inhibitory antibodies to FVIII; occurrence of thrombotic events; AEs; pharmacokinetics.	Intraoperative actual versus predicted blood loss; AEs; occurrence of thrombotic events; occurrence of severe allergic reactions; development of inhibitory and total binding antibodies to VWF; development of inhibitory antibodies to FVIII; pharmacokinetics.

Key results	192 bleeding episodes were treated with rVWF and all were rated as excellent (96.9%) or good (3.1%). 1 infusion was adequate to treat 157 out of 192 bleeds (81.8%). No subject developed anti-VWF neutralising or binding antibodies, FVIII neutralising antibodies, or antibodies against rFurin, CHO host cell proteins, or murine IgG.	-
Adverse effects (AEs)	125 AEs were observed, of which 8 (6.4%) were considered to have a causal relationship to rVWF. Six of these AEs in 4 subjects were not serious. One subject experienced mild infusion site paresthesia, moderate dysgeusia, and moderate tachycardia, 1 subject showed mild ECG T-wave inversion, 1 subject experienced mild generalised pruritus, and 1 subject had a mild hot flush. One subject experienced 2 simultaneous serious AEs (chest discomfort and increased heart rate).	-
Expected reporting date	-	July 2016.

ESTIMATED COST and IMPACT

COST

The cost of vonicog alfa is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

☐ Reduced mortality/increased length of survival

☑ Reduced symptoms or disability: *expert opinion states that the United Kingdom Haemophilia Centre Doctors Organisation generally favours the use of recombinant products, cost permitting, over plasma derived products because of theoretical safety/infection concerns. Currently no recombinant VWF available therefore this product would theoretically improve patient outcomes (however it should be noted that currently available VWF plasma derived concentrates have an excellent safety record)*[a].

☐ Other

☐ No impact identified

[a] Expert personal communication

Impact on Health and Social Care Services

- ☐ Increased use of existing services
- ☐ Decreased use of existing services
- ☑ Re-organisation of existing services: *expert opinion states that initial staff training required*[b].
- ☐ Need for new services
- ☐ Other
- ☐ None identified

Impact on Costs and Other Resource Use

- ☑ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☑ Other increase in costs: *expert opinion states that additional staff training required but this would be a short term issue, and haemophilia networks should have the existing infrastructure to deliver this*[b].
- ☐ Other reduction in costs
- ☐ Other
- ☐ None identified

Other Issues

- ☑ Clinical uncertainty or other research question identified: *expert opinion states that there is uncertainty around its use to treat a bleed or provide haemostasis prior to emergency surgery, as in some patients there would be a delayed rise in Factor VIII which might delay haemostasis being achieved. In these situations it may be necessary to also infuse a separate dose of recombinant Factor VIII. Its use is more logical in prophylaxis*[b].
- ☐ None identified

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[b] Expert personal communication

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