19 July 2018
EMA/329068/2017
Committee for Orphan Medicinal Products

Withdrawal Assessment Report - Orphan Maintenance

Veyvondi (recombinant human von Willebrand factor)
Treatment of von Willebrand disease
EU/3/10/814 (EMA/OD/055/10)
Sponsor: Baxalta Innovations GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Product and administrative information

Product	
Active substance	Recombinant human von Willebrand factor
International Non-Proprietary Name	Vonicog alfa
Orphan indication	Treatment of von Willebrand disease
Pharmaceutical form	Powder and solvent for solution for injection
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	B02BD10
Sponsor's details:	Baxalta Innovations GmbH Industriestrasse 67 A – 1221 Vienna Austria
Orphan medicinal product designation procedural history	
Sponsor/applicant	Baxter Innovations GmbH
COMP opinion date	9 September 2010
EC decision date	26 November 2010
EC registration number	EU/3/10/814
Post-designation procedural history	
Sponsor's name change	Name change from Baxter Innovations GmbH to Baxalta Innovations GmbH – EC letter of 28 May 2015
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Jan Mueller-Berghaus, Andrea Laslop
Applicant	Baxalta Innovations GmbH
Application submission date	22 May 2017
Procedure start date	15 June 2017
Procedure number	EMA/H/C/004454/0000
Invented name	Recombinant human von Willebrand factor
Therapeutic indication	Prevention and treatment of haemorrhage or surgical bleeding in adults diagnosed with von Willebrand Disease (VWD) Further information on Veyvondi can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/ European public assessment reports
CHMP opinion date	28 June 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	F. Naumann-Winter/ K. Penttila
Sponsor's report submission date	22 May 2017 and 12 October 2017
COMP discussion and adoption of list of questions	22-24 May 2018
Oral explanation	17 July 2018
Sponsor's removal request	18 July 2018

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 18 July 2018, prior to final opinion

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

- von Willebrand disease (hereinafter referred to as “the condition”) was estimated to be affecting less than 2 in 10,000 persons in the European Union, at the time the application was made;
- the condition is associated with prolonged bleeding times which can result in significant morbidity for a proportion of VWF disease patients and in some cases, the complications can be considered as life-threatening;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that recombinant human von Willebrand factor may be of significant benefit to those affected by the condition. This rationale was based on a pharmacokinetic data which indicated that the product could potentially offer a sustained effect over time versus current available formulations. The product would not undergo degradation specific to plasma derived vWF which could potentially mean that the product delivered would have better consistent therapeutic effects. The concentration of ultra high weight multimer vWF in the recombinant formulation may lead to improved control of bleeding as compared to the plasma derived product.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Von Willebrand’s disease is the most common inherited bleeding disorder and has an autosomal inheritance pattern mucosa-associated bleeding and bleeding after surgery and trauma. The diagnosis is based on history of bleeding and laboratory evidence of abnormalities in von Willebrand factor, factor VIII, or both. Von Willebrand’s disease is subdivided into three types. Type 1, which accounts for 70 to 80% of cases, is characterized by a quantitative deficiency of von Willebrand factor. Type 2, accounting for approximately 20% of cases, is caused by dysfunctional von Willebrand factor, resulting in a normal or reduced von Willebrand factor antigen concentration but a large reduction in von Willebrand factor function. Type 3 (accounting for <5% of cases), is the most severe form, and is caused by the absence of circulating von Willebrand factor. (Leegbeek and Eikenboom, N Engl J Med. 2016 Nov 24;375(21):2067-2080.)

The proposed therapeutic indication is “prevention and treatment of haemorrhage or surgical bleeding in adult patients diagnosed with VWD, when desmopressin treatment alone is ineffective or contraindicated”. This falls entirely within the orphan designated indication which is worded broadly as “treatment of von Willebrand disease”.

Intention to diagnose, prevent or treat

Conditional to a positive CHMP assessment, the intention to treat, prevent or diagnose the condition may be considered justified. The sponsor discusses 3 clinical studies in subjects with severe VWD, supporting the orphan indication of treatment of VWD: a Phase 1 study (Study 070701 [Phase 1 VWD]), a Phase 3 study in the treatment of bleeding episodes (Study 071001 [Phase 3 VWD on demand]), and a Phase 3 study in subjects undergoing elective surgery (Study 071101 [Phase 3 VWD Surgery]). The studies were performed in the primary target patient population that is expected to receive treatment with rhVWF (ie, severe VWD).

Table 1. Clinical Studies with rhVWF to Support the Orphan Indication (adopted from the sponsor's maintenance report)

	Study 070701 (Phase 1 VWD)	**Study 071001 (Phase 3 VWD-on demand)**	**Study 071101 (Phase 3 VWD-Surgery)**
Study design	Controlled, randomised, single-blind, prospective 3-step, dose escalation study to investigate safety, tolerability and PK of rhVWF combined at a fixed ratio with ADVATE (rFVIII)	Open-label, part-randomised clinical study to assess the PK, safety and efficacy of rhVWF:rFVIII and rhVWF in the treatment of bleeding episodes	Open-label, nonrandomised study to evaluate the efficacy and safety of rhVWF with or without ADVATE (rFVIII) in adults with severe VWD undergoing major and minor elective surgical procedures
Subject population	Adult subjects with severe VWD 32 subjects	Adult subjects with severe type 3 and severe non-type 3 VWD 37 subjects	Adult subjects with severe VWD 15 surgical procedures
Efficacy results	Not applicable	All subjectsa met the protocol-defined criterion for treatment success. All treated bleeding events had an efficacy rating of "excellent" or "good"	All subjects had "excellent" or "good" overall and intraoperative haemostatic efficacy and "excellent" or "good" intraoperative blood loss
Safety results	rhVWF was safe and well tolerated	rhVWF was safe and well tolerated	rhVWF was safe and well tolerated
PK results	rhVWF was comparable to plasma-derived VWF/FVIII concentrate for VWF:RCo, with a tendency of a longer t1/2 and showed a sustained stabilisation of endogenous FVIII	FVIII levels increased substantially after rhVWF alone, indicating that rhVWF induces a sustained increase in endogenous FVIII activity	Within 60 minutes postinfusion of a 50 IU/kg rhVWF dose, median concentrations of VWF:RCo, VWF:Ac, VWF:Ag, and VWF:CB reached peak levels and gradually declined over a period of 72 hours postinfusion

Ag = antigen; CB = collagen binding assay; PK = pharmacokinetics; RCo = ristocetin co-factor activity; rFVIII = recombinant FVIII; $t_{1/2}$ = half-life
Bleeds for which efficacy assessments were made prospectively and excluding gastrointestinal bleeds (126 bleeds in 18 subjects)

Chronically debilitating and/or life-threatening nature

The applicant discusses the different bleeding complications in affected patients including: Joint haemorrhages with development of arthropathy; Frequent epistaxis in children, leading to severe anaemia ;Frequent mucous membrane, muscle, central nervous system or GI bleeding; Severe menorrhagia and Postpartum haemorrhages.

It can be acknowledged that in children with von Willebrand's disease, the most frequent presenting symptoms are bruising and epistaxis, while in adults the most common symptoms are hematomas, menorrhagia, and bleeding from minor wounds. Health-related quality of life for patients with von Willebrand's disease is lower than for the general population is strongly associated with the bleeding phenotype (Wee et al, J Thromb Haemost. 2010 Jul;8(7):1492-9).

Number of people affected or at risk

The applicant performes a literature search and argues that references for countries of the European Union are in line with this statement as an estimated prevalence of VWD of 0.05 to 2.74 cases per 10 000 inhabitants . Population based studies (that challenge the threshold and may not be clinically relevant) are rejected by the applicant who focuses only on referral based studies. It is stated that from a clinical standpoint, the aim of diagnosing VWD should be to offer advice to the patient and treatment for his/her bleeding symptoms. The highest figure of 2.74 stems form a Report of the World Federation of Haemophilia for Ireland.

This is indeed an issue that may be further discussed. On the basis of population studies, the prevalence of von Willebrand's disease is 0.6 to 1.3%, but not not all persons with low von Willebrand factor levels have clinically relevant bleeding symptoms. On the basis of referrals to specialized centers, the estimated prevalence of von Willebrand's disease is approximately 1 case per 10,000 persons. Literature suggests that while the diagnosis is based on a cut-off level for von Willebrand factor of 30 IU per deciliter, the principles of care specify a cutoff level of 40 IU per deciliter. In daily practice, clinicians do not always follow these guidelines, especially since the official classification of the International Society on Thrombosis and Haemostasis (ISTH) does not specify cutoff values (Leegbeek and Eikenboom, N Engl J Med. 2016 Nov 24;375(21):2067-2080.) Persons with a bleeding tendency who have VWF levels between 30 and 50 IU per deciliter (the lower limit of the normal range) are classified as having "low VWF" or "possible type 1 disease" but are not classified as having definitive VWD.

The sponsor may therefore be invited to clarify what the proposed cut-off point is and provide a sensitivity analysis to ensure that the statutory threshold is respected.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

In the European Union, desmopressin and plasma derived FVIII/VWF concentrates are authorised for the orphan indication. The sponsor provides a list of authorised products (in the October 17 report) and refers to the National Hemophilia Foundation guidelines and the United Kingdom Haemophilia Centre Doctor's Organisation recommendations.

Treatment of von Willebrand's disease is based on normalizing von Willebrand factor and factor VIII levels in case of bleeding or before an intervention. The following table recapitulates treatment and is reproduced from Leegbeek and Eikenboom, N Engl J Med. 2016 Nov 24;375(21):2067-2080.

Table 2.

Disease Type	Treatment	Alternative or Additional Treatment
Low VWF†	Desmopressin, administered intravenously (0.3 μg per kilogram of body weight), intranasally (total dose, 300 μg [150 μg per nostril]; in patients with body weight <50 kg, only one dose of 150 μg), or subcutaneously (0.3 μg per kilogram)	Alternative or additional treatment: tranexamic acid (1 g, 3 or 4 times daily)
Type 1	Desmopressin, at same doses as above	Additional treatment: tranexamic acid, at same dose as above
Type 2	Desmopressin, at same doses as above, or VWF–factor VIII or VWF concentrate‡	Additional treatment: tranexamic acid, at same dose as above
Type 3	VWF–factor VIII or VWF concentrate	Additional treatment: tranexamic acid, at same dose as above

* VWF denotes von Willebrand factor.
† Patients presenting with bleeding symptoms and VWF levels between 30 and 50 IU per deciliter (the lower limit of the normal range) are classified as having low VWF but not von Willebrand's disease.
‡ Desmopressin is contraindicated in patients with type 2B disease.

Significant benefit

The sponsor is focusing the discussion versus platelet derived concentrates, as they are targeting a severely affected population not eligible for desmopressin. In their discussion versus pdVWF, the reduced number of needed injections is put forward as the basis for significant benefit. The Applicant sought protocol assistance prior to the Phase 3 clinical study (EMEA/H/SA/1378/2/2011/PA/III) and it was then stated that a single arm, uncontrolled study will probably not be sufficient to demonstrate significant benefit compared with other methods of treatment. The sponsor considered however that such a study would not be feasible, for reasons of heterogeneity of population and choice of comparators.

Significant benefit is thus argued on the basis of indirect comparisons. These arguments are outlined below (in italics), followed by comments on the sponsor's position. In particular it is argued that the proposed product compared to plasma derived concentrates:

- *Requires fewer infusions/treatment days to control bleeding (median of 1 infusion, maximum of 4 in Study 071001; for pdVWF, maximum infusions ranged from 12 to 46). It is expected that this will lead to fewer hospitalisations, fewer blood transfusions and a better quality-of-life;*

As regards this first point, the sponsor performs an indirect comparison of the study 071001with the results of three literature studies for plasma derived concentrates (Gill. Haemophilia. 2003;9:688-695, Borel-Derlon J Thromb Haemost. 2007;5:1115 1124, Berntorp . Haemophilia. 2009;15:122-130). The applicant analyses the number of infusions reported in these studies as per severity of bleeding and other variables adjusted using statistical modelling. They provide the following table of results for the Poisson model, while other models are also used and are in line with the one below.

Table 3. Summary of Indirect Comparisons of Mean or Median Number of Infusions Required per Bleed Based on Poisson Model. Adopted from the sponsor;s maintenance report (p55/166)

		Comparison of rhVWF vs. pdVWF		
Explanatory variables adjusted	**Levels[a]**	**Humate-P (Gill et al, 2003)**	**Wilfactin (Borel-Derlon et al, 2007)**	**Wilate (Berntorp et al, 2009)**
Severity of bleeds	Mild	1 vs. 1 [med]	n.a.	n.a.
	Moderate	1 vs. 2 [med]	n.a.	n.a.
	Severe	2 vs. 4 [med]	n.a.	n.a.
Daily dose[a]	(IU/dL)	1 vs. 2 [med]	1 vs. 3 [med]	1.2 vs. 1.9 [mean]
VWD type	2	n.a.	n.a.	1.1 vs. 4.0 [mean]
	2A	1 vs. 2.5 [med]	n.a.	n.a.
	3	1 vs. 1 [med]	n.a.	1.3 vs. 1.8 [mean]
Bleeding site	Gastrointestinal	n.a.	1 vs. 5 [med]	1.3 vs. 4.2 [mean]
	Genital tract	n.a.	1 vs. 9 [med]	n.a.
	Joints	n.a.	n.a.	1.3 vs. 1.7 [mean]
	Musculoskeletal	n.a.	1 vs. 4 [med]	n.a.
	Nasopharyngeal	n.a.	1 vs. 2 [med]	n.a.
	Oral	n.a.	1 vs. 1 [med]	1.1 vs. 1.8 [mean]
Age	(Years)	1 vs. 2 [med]	1 vs. 3 [med]	1.3 vs. 1.9 [mean]
Baseline VWF:RCo[a]	(IU/dL)	n.a.	1 vs. 3 [med]	1.1 vs. 1.9 [mean]
Severity of bleeds and daily dose[a]	Mild	1 vs. 1 [med]	n.a.	n.a.
	Moderate	1 vs. 2 [med]	n.a.	n.a.
	Severe	4 vs. 4 [med]	n.a.	n.a.
VWD type and daily dose[a]	2	n.a.	n.a.	1.1 vs. 4.0 [mean]
	2A	1 vs. 2.5 [med]	n.a.	n.a.
	3	1 vs. 1 [med]	n.a.	1.2 vs. 1.8 [mean]
Bleeding site and daily dose[a]	Gastrointestinal	n.a.	1 vs. 5 [med]	1.2 vs. 4.2 [mean]
	Genital tract	n.a.	1 vs. 9 [med]	n.a.
	Joints	n.a.	n.a.	1.2 vs. 1.7 [mean]
	Musculoskeletal	n.a.	1 vs. 4 [med]	n.a.
	Nasopharyngeal	n.a.	1 vs. 2 [med]	n.a.
	Oral	n.a.	1 vs. 1 [med]	1.0 vs. 1.8 [mean]
VWD type and age[a]	2	n.a.	n.a.	1.1 vs. 4.0 [mean]
	2A	n.a.	n.a.	n.a.
	3	n.a.	n.a.	1.3 vs. 1.8 [mean]
VWD type, age and daily dose[a]	2	n.a.	n.a.	1.1 vs. 4.0 [mean]
	2A	n.a.	n.a.	n.a.
	3	n.a.	n.a.	1.2 vs. 1.8 [mean]
Baseline VWF:RCo and VWD type[a]	2	n.a.	n.a.	1.0 vs. 4.0 [mean]
	2A	n.a.	n.a.	n.a.
	3	n.a.	n.a.	1.2 vs. 1.8 [mean]
Baseline VWF:RCo, daily dose and VWD type[a]	2	n.a.	n.a.	1.0 vs. 4.0 [mean]
	2A	n.a.	n.a.	n.a.
	3	n.a.	n.a.	1.1 vs. 1.8 [mean]

a) Mean = comparison of means; med = comparison of medians; n.a. = comparison could not be made (no information available in published paper)

b) For continuous variables, comparisons of point estimates are made at the reported mean or median for the pdVWF

What is absent from the sponsor's exercise is how the improved (fewer) number of injections may be linked to a clinically relevant advantage such as improved efficacy or a major contribution to patient care (e.g. PRO improvement such as quality of life). The sponsor reports improvements in quality-of-life after treatment with rhVWF in the Phase 3 VWD-on demand study but a comparison with other products on this aspect is not present. This aspect of potential translation to meaningfull effects is now entirely missing and the sponsor may be requested to provide the missing data to justify significant benefit.

- *Does not contain FVIII; thus, FVIII supplementation can be individualised and VWF can be dosed to the optimal levels*;

This second point is not discussed on the basis of any clinical comparisons on the effects of FVIII presence in the concentrates, direct or direct, and may not be considered at this point in time. A clinically relevant advantage or a major contribution to patient care has to be documented for the maintenance procedure based on clinical observations.

- *Has demonstrated efficacy in difficult-to-treat bleed types. For some of these patients, pdVWF is ineffective resulting in months of treatment without controlling the bleeding;*

This point is supported by a case report by Racquel et al, (Blood Coagul Fibrinolysis. 2017 Oct;28(7):570-575). The authors report successful on-demand and prophylactic use of rVWF for the management of gastrointestinal bleeding and menstrual bleeding in a patient with type 2A VWD and a 5-month history of inadequate response to Humate-P. The authors hypothesize that the presence of ultra large multimers in the recombinant product may have contributed to the successful outcome in this patient. It is however of note that the patient had compliance issues and the starting of recombinant VWF coincided with the placement of a permanent catheter. This may have confounded the observations, and indeed when the PICC was removed the patient was noncompliant and stopped infusing rVWF as well; 2 weeks after the PICC removal, the patient attended hospital with gastrointestinal bleeding requiring a PRBC transfusion (Blood Coagul Fibrinolysis. 2017 Oct;28(7):570-575)

- *Carries no risk of transmission of adventitious agents and other blood borne pathogens;*

This argument cannot be accepted in the absence of documented and serious infections by blood borne pathogens in the course of administration of plasma derived concentrates in VWD patients. In one of the available products (Wilate) asymptomatic ParvoB19 seroconversion has been observed in clinical trials (Wilate product monograph, october2011). The sponsor also notes the development erythema multiforme after B19 infection in one patient with a plasma derived product, but B19 has not been reported to be associated with serious clinical consequences when transmitted by factor concentrates (Manucci et al, Blood. 2002 Jan 15;99(2):450-6). An asymptomatic prion transmission in a haemophilic patient treated with FVIII is also discussed but this is out of the context of the specific comparators and specific indication.

- *In particular for severe disease, it is argued that that there are currently no treatment options for patients who are refractory to pdVWF in GI bleeds or for patients who are allergic to pdVWF*.

Two case reports are put forward for this claim, the first of which has been already commented above. In the second case report, a patient with type 2A VWD who was allergic to pdVWF (Humate P and Alpanate) was successfully treated with rVWD. The patient was a 65 year-old male who was

hospitalised with haematuria due to a kidney mass. He was treated with rhVWF on demand and then as prophylaxis and underwent a major surgery with satisfactory bleeding control according to the treating physician. This is a relevant argument that could benefit from: a) a description of the extent of allergy issues in terms of population size that cannot be treated and b) a discussion of the other safety aspects (including a quantification of the thromboembolic risks)of the proposed recombinant product versus the plasma derived counterparts.

- *The presence of ULMs provide a scientific rationale for the rhVWF product to be more effective than pdVWF products*

This argument may not be considered in the absence of a demonstration of improved efficacy, which is as noted above is missing. The applicant notes that Phase 3 studies treatment success and an overall haemostatic efficacy rating of "excellent" or "good" were 100%, while in the on-demand study most bleeds resolved after 1 infusion of rhVWF:rFVIII or rhVWF (81.8%), and none required more than 4 infusions. Such observations have to be compared to the effects of other available products in comparable settings to justify significant benefit. The discussion falls sort of comparisons of clinically relevant outcomes.

- *A major contribution to patient care is also argued on the basis of improved supply as only one of the comparators is centrally authorised.*

In order to consider such an argument, the COMP would expect a documentation of a shortage of supply and the serious issues arising thereof, before entering into the discussion of how the central authorisation may impact on the situation.

In conclusion, the sponsor has not followed the PA recommendation for controlled studies and has not produces a comparison documenting improved efficacy, safety or a major contribution to patient care. At this point in time only theoretical benefits are put forward which are not acceptable for maintenance of orphan designation. The sponsor will be requested to elaborate on the issues described above.

4. COMP list of issues

Number of people affected

The sponsor is invited to clarify the diagnostic criteria used for the prevalence estimate, and justify the exclusion of "low VWF" or "possible type 1 disease"(Leegbeek and Eikenboom, N Engl J Med. 2016 Nov 24;375(21):2067-2080).

Significant benefit

In order to justify a clinically relevant advantage or a major contribution to patient care, versus plasma derived concentrates authorised of the proposed condition the sponsor in invited to:

- Document, in comparison to the authorised counterparts, how the claimed reduced number of injections results in improved efficacy, safety or major contribution to patient care
- Provide clinical data to document, compared to the authorised counterparts, any claims of improved efficacy.
- Provide clinical comparisons, to document any improved safety claims. In particular the population size that experiences allergic reactions to the plasma-derived products will be relevant towards this end.
- Provide a comparative discussion of patient reported outcomes to demonstrate a major contribution to patient care.

- Provide evidence to justify any serious problems with the supply of the authorised counterparts leading to patient harm in the EU, and how these problems will be addressed by the proposed product.