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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**GUIDELINE ON THE CLINICAL INVESTIGATION OF HUMAN PLASMA DERIVED  
VON WILLEBRAND FACTOR PRODUCTS  
(CPMP/BPWG/220/02)**

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**\* Note:**

**This second consultation was specifically on Section 3 of the Guideline and the related Summary Table because of a revision of the recommendations for modified von Willebrand factor products.**

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## 1. INTRODUCTION

Von Willebrand factor (VWF) is a large multimeric glycoprotein with three biological functions: it serves as a carrier for the pro-coagulant factor VIII and protects it from in vivo proteolysis, it mediates platelet adhesion to sub-endothelium of the damaged blood vessel and it also mediates platelet aggregation among each other. VWF circulates in blood as a series of multimers ranging in size from 500 to 20000 kDa. Only the largest multimers of VWF are active in platelet adhesion, while all multimers are apparently functional for FVIII binding.

VWF is synthesised by endothelial cells and megakaryocytes. The VWF gene is located on the short arm of chromosome 12. The gene encodes pre-pro-VWF consisting of a pre-peptide, a large 741 amino acid pro-peptide (which is cleaved off during intracellular processing) and the mature subunit of 2050 amino acids (VWF monomer). Each subunit or VWF monomer contains binding regions for FVIII coagulant activity (FVIII:C), for collagen and for platelet glycoproteins GPIb and GPIIb/IIIa. Dimers are formed by the creation of inter-subunit disulphide bonds at the C-terminal ends. Multimerisation takes place in the Golgi apparatus by formation of inter-subunit N-terminal disulphide bonds at the amino-terminal end. VWF is stored in the Weibel-Palade bodies in endothelial cells and in  $\alpha$ -granules in platelets. Regulation of the physiological release of VWF from these sites is not fully understood. While a physiological (constitutive) secretion of VWF dominates in the healthy subject, acute-phase inducers, including pro-inflammatory cytokines, are known to promote acute release of VWF from stores.

### Prevalence and classification of von Willebrand disease

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, affecting both males and females. Population screening indicates that mildly deficient heterozygous persons with few or no symptoms are extremely common, representing approximately 1% of otherwise healthy persons. VWD is clinically a heterogeneous group of disease variants, each being characterised by distinct quantitative or qualitative abnormalities in VWF, which are caused by widely heterogeneous mutations in the various domains of the VWF gene<sup>1</sup>.

In 1994 the Subcommittee on von Willebrand factor of the Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) endorsed a revised classification of VWD<sup>2</sup> :

- Type 1 VWD refers to a partial quantitative deficiency in VWF, which is qualitatively normal. Type 1 VWD is the most common form of VWD accounting for 70-80% of the patients.
- Type 2 VWD refers to qualitative deficiency of VWF, which is functionally abnormal. Type 2 VWD accounts for approximately 20% of the patients. Based upon the major mechanism by which the VWF function is impaired four major subcategories (2A, 2B, 2M, 2N) are recognised: Type 2A VWD refers to qualitative variants with decreased platelet-dependent function that is associated with the absence of high molecular weight (HMW) VWF multimers. Type 2B VWD refers to qualitative variants with increased affinity for platelet GPIb that spontaneously bind VWF. In type 2M variants, the platelet dependent function is decreased but this is not caused by the absence of HMW VWF multimers. Finally, type 2N VWD refers to qualitative variants with markedly decreased affinity of VWF for factor VIII. Several other Type 2 variants have been described.
- Type 3 VWD accounts for 1-3% of cases of VWD. These patients have virtually complete deficiency of VWF in plasma and platelets and factor VIII:C levels are decreased to below 4% of normal.

### Treatment of patients with von Willebrand disease

Most patients with VWD have only mild symptoms and only require treatment in case of surgery or severe trauma. Desmopressin acetate (DDAVP) is often the treatment of choice for mild to moderate

<sup>1</sup> Sadler JE et al. Impact, Diagnosis and treatment of von Willebrand disease. *Thromb Haemost.* 2000; 84: 160-174.

<sup>2</sup> Sadler JE. A revised classification of von Willebrand disease. *Thromb. Haemost.* 1994; 71: 520-525.

type 1 VWD. DDAVP causes release of VWF from the endothelial cells resulting in an increased level of VWF and factor VIII:C in plasma. DDAVP may also be effective in the treatment of some patients with type 2A VWD, whereas it is not effective in type 3 VWD. In patients with type 2B VWD, DDAVP is considered contraindicated by most experts because of in vivo enhancement of platelet aggregation, risk of thrombosis, and exacerbation of pre-existing thrombocytopenia. The newly diagnosed patient with VWD, except for patients with type 2B and type 3 VWD, should be tested for his/her response to DDAVP.

Patients who do not respond adequately to DDAVP, patients who display significant side effects to DDAVP and patients in whom DDAVP is contraindicated, are potential candidates for replacement therapy with a product containing VWF (20 to 30% of patients with VWD) to control bleeding. In addition, if repeated infusions of DDAVP are given, tachyphylaxis may develop in initially responsive patients, requiring VWF replacement therapy when adequate haemostasis has to be maintained for longer periods of time. Furthermore in cases of severe bleedings, major and/or repeated surgery VWF-substitution in addition to DDAVP therapy is required.

Purified, viral inactivated, plasma derived VWF/FVIII products are most frequently used nowadays for VWF replacement therapy. The quantity of the ristocetin cofactor activity (VWF:RCo) in comparison to the factor VIII:C content varies by product<sup>3 4</sup>. In addition, a purified plasma derived VWF product, almost depleted of FVIII, has been developed. In the future recombinant VWF products might become available. Highly purified FVIII concentrates (monoclonal antibody purified and recombinant) should not be used to treat VWD because of their lack of VWF.

## Data requirements

Clinical trial data, addressing efficacy and safety, are required in an application for marketing authorisation. The present Guideline summarises the clinical trials required for authorisation with respect to human plasma derived VWF products. These data are required for:

- products for which an application for a marketing authorisation is to be submitted, referred to as 'new products' in the text and
- authorised products where a significant change in the manufacturing process has been made referred to as 'modified products' in the text.

The clinical trials described in this Guideline should be performed according to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

According to good clinical practice all patients entered into clinical trials should be vaccinated against hepatitis A and B (unless protective antibodies are present resulting from a previously experienced infection), and evidence of immunisation should be present at baseline.

### 1.1 Efficacy

Assessment of the efficacy of a VWF containing product requires clinical trials performed in patients with more severe types of VWD, who are potential candidates for replacement therapy. Because of the concerted action of VWF together with FVIII, efficacy assessment of a VWF concentrate requires *ex vivo* biochemistry data relevant to primary haemostasis and coagulation in VWD as well as clinical bleeding endpoints. Depending on the patient's clinical situation, adequate amounts of FVIII may need to be injected along with the VWF product. Because VWF products may contain quite varying amounts of FVIII there is a need for documenting pharmacokinetic data on VWF as well as on FVIII along with clinical efficacy in various clinical situations.

In clinically evaluating VWF products for the treatment of patients with VWD, the initial trial typically examines the pharmacokinetics of the principal active factor, VWF, but also of FVIII. Appropriate pharmacokinetic data (incremental recovery, half-life, area under the curve (AUC), mean residence time (MRT) and clearance) are the most important (surrogate) endpoints for efficacy of a

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<sup>3</sup> Mannucci PM. How I treat patients with von Willebrand disease. *Blood* 2001; 97: 1915-1919.

<sup>4</sup> Menache D and Aronson DL. New treatments of von Willebrand disease: Plasma derived von Willebrand factor concentrates. *Thromb. Haemost.* 1997; 78: 566-570.

new VWF product. The International Society on Thrombosis and Haemostasis (ISTH) also provides guidance on pharmacokinetic studies. It is useful to consult this guidance for advice when designing studies.

## **1.2 Safety**

Safety aspects of VWF products include viral safety, safety with regard to TSE, immunogenicity to the active product and all components and other adverse events. For products containing FVIII:C in addition to VWF, thrombogenicity should also be considered a safety issue.

### **1.2.1 Adverse events**

All adverse events occurring in relationship with any use of the new product should be recorded and reported.

### **1.2.2 Viral safety**

Manufacturers of plasma products such as vWF products are obliged to optimise viral safety by selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective steps for the inactivation/removal of viruses in manufacturing processes.

The above-mentioned procedures are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses.

These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and parvovirus B19. The safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies.

The applicant is still required to provide all available data gathered on patients with the product in clinical trials. Investigators should continue using their normal clinical practice of monitoring patients. The applicant should demonstrate that there are systems in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation.

For products with an entirely novel manufacturing process other principles may apply. These applications should be discussed with the Regulatory Authorities prior to submission.

### **1.2.3 Immunogenicity**

The occurrence of antibodies against VWF is a rare complication of VWD replacement therapy. The risk of inhibitor development appears to be limited to patients with type 3 VWD. It has been estimated, based on two relatively large surveys, that allo-antibodies to VWF develop in 7.5% and 9.5% of patients with type 3 VWD<sup>5</sup>. This complication is strictly associated with the presence of large or complete VWF gene deletions or other gene mutations that lead to the synthesis of a truncated protein or no protein at all.

Inhibitor risk may be associated with commencing or changing treatment or where the antigenicity of the product has been altered due to changes in the manufacturing process. Previously treated patients would be the most suitable candidates to test the product-related immunogenicity of a modified VWF product.

### **1.2.4 Thrombogenicity**

Treatment with VWF products that also contain FVIII could be associated with thrombosis as high levels of exogenous plus endogenous FVIII:C may be achieved. The infusion of VWF into patients with VWD causes a normalisation in survival of endogenous FVIII, leading to a rise of the endogenous FVIII:C levels. Moreover, in patients with Type 2A and 2B VWD, baseline endogenous FVIII:C levels are often not significantly decreased.

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<sup>5</sup> Mannuci PM, Federici AB. Alloantibodies to von Willebrand factor in von Willebrand disease. In: Aledort LM, Hoyer LW, Reisner JM, White GC II, eds. Inhibitors to coagulation factor in the 1990s. New York, NY: Plenum Press; 1995:87-92.

## 2. PRODUCTS FOR WHICH AN APPLICATION FOR A MARKETING AUTHORISATION IS TO BE SUBMITTED: 'NEW PRODUCTS'

### 2.1 Clinical trials with new human plasma derived VWF products

#### 2.1.1 Pharmacokinetics

A pharmacokinetic trial should be performed in at least 12 subjects suffering from severe VWD defined here as baseline VWF:RCo < 15-20%. At least<sup>6</sup> 6 out of 12 patients should be suffering from hereditary type 3 VWD for separate analysis. The remaining patients can be diagnosed with severe type 1 or 2A VWD. Patients should be at least 12 years of age. They should not have received an infusion of DDAVP or of a VWF containing product for at least five days prior to participation in the trial. The study should be performed in patients without inhibitors to FVIII and VWF, who are not actively bleeding.

The pharmacokinetic trial should include measurements of VWF as well as FVIII. The following parameters should be recorded: incremental recovery, *in vivo* half-life, area under the curve (AUC), C<sub>max</sub>, t<sub>max</sub>, clearance and mean residence time (MRT). Analysis of these parameters should be performed in a centralised laboratory specialised in coagulation.

Samples for determination of VWF:RCo, VWF:Ag<sup>7</sup>, VWF:CB<sup>8</sup>, and FVIII:C should be taken before infusion of 80 VWF:RCo IU/kg of the product and at 15 minutes, 1, 3, 6, 12, 24, 30, and 48 and 72 hours after the infusion. At least three different lots should be employed in the trial.

Incremental recovery is determined using the peak level recorded within 3 hours after the infusion and reported as [IU/ml]/[IU/kg]. Note: in case of a VWF product almost depleted of FVIII, any incremental recovery of FVIII is not expected. However, in all instances FVIII:C should be monitored after the infusion of the VWF product because the FVIII:C level will rise as a result of endogenous secretion. The samples from all type 3 patients obtained before 15 minutes and 6 hours after the infusion should be used to investigate the multimer distribution of the VWF by multimeric sizing analysis using low- and high resolution electrophoresis gels (preferably 1% and > 2% gels). These analyses should be performed in a centralised laboratory specialised in VWD phenotyping.

It is anticipated that some deviation from the recommendation may occur in clinical practice. For this reason, it is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Patients taking part in the pharmacokinetic trial should continue treatment with the same product to monitor clinical efficacy. Type 3 VWD patients should be re-tested for the same pharmacokinetic parameters after at least 6 months using the same dose as in the first investigation. The reason behind the repeat pharmacokinetic study is to re-test pharmacokinetic parameters and compare them with the initial results. Type 3 VWD patients are selected for the repeat pharmacokinetic study as they are most likely to develop allo-antibodies, although it is recognised that the incidence of inhibitor development, even in these patients, is limited.

#### 2.1.2 Efficacy

Clinical efficacy of the VWF product should be evaluated in at least 20 patients, suffering from severe VWD (for definition of severe VWD please refer to 2.1.1) including preferably all the patients who participated in the pharmacokinetic trial. All patients should be at least 12 years of age. During an observation period of at least 12 months any event (spontaneous bleeding, trauma, surgery, labour) should be documented in detail.

Surgery is a common event requiring treatment in a patient suffering from VWD. At least 15 surgical procedures, 10 of which are considered major, should be available for assessment of efficacy. In patients undergoing surgical procedures, response of the VWF product will be determined by the

<sup>6</sup> Due to the rareness of hereditary type 3 vWD (prevalence between 0.55 to 6.0 per million) applicants might encounter difficulties to enrol 6 patients with type 3 vWD. In this case the competent authority should be contacted.

<sup>7</sup> VWF:Ag: von Willebrand factor antigen

<sup>8</sup> VWF:CB: von Willebrand factor collagen binding

physician, including efficacy of haemostasis, loss of blood, and requirements for transfusion. In addition, at least 10 bleeding episodes with at least 5 major mucosal bleeding episodes should be documented. Response should be assessed as ‘none’, ‘moderate’, ‘good’ or ‘excellent’ by the physician for those patients who receive treatment with the product for major bleeds. In the remaining cases clinical efficacy after administration should be assessed from the clinical response as reported by the patients.

If prophylaxis is claimed, a minimum of 5 patients with type 3 VWD should be followed for a year for the absence of spontaneous bleeding episodes or obvious reduction of the number of haemorrhagic manifestations.

Clinical efficacy should also be assessed by calculating the consumption of vWF and FVIII (administered as part of the VWF product or administered as a separate infusion in case of a VWF product depleted of FVIII), expressed as the number of infusions as well as IU/kg per event (on-demand and surgery), or IU/kg per month or year, in case of prophylactic use.

### **2.1.3 Safety**

Clinical safety will be assessed in all patients receiving the VWF product:

- in patients included in the pharmacokinetic trial: blood pressure, heart rate, temperature, respiratory rate and adverse events
- in all patients participating in the efficacy/safety trial: adverse events.

All adverse events should be recorded and reported in accordance with the ICH guideline “structure and content of clinical study reports” (CPMP/ICH/137/95E3)

### **Immunogenicity testing**

There is no standardisation for anti-VWF antibody testing. Therefore the detection and measurement of inhibiting antibodies to VWF should be performed at a centralised laboratory. The assay applied to detect inhibitors should be described and justified.

Before entering the pharmacokinetic study or the subsequent efficacy/safety trial, all patients should be tested for inhibitors to VWF and FVIII. All patients should be re-tested every three months until the end of the observation period of 1 year. Patients should always be tested if they are suspected of having developed inhibitors (reduced *in vivo* recovery, poor clinical response).

For all patients who develop inhibitors a full clinical report should be provided including clinical relevance, the cumulative incidence and the number of exposure days. The titre of the antibody should be reported and the method used should be specified.

Blood samples of patients who are suspected of inhibitors or who have developed inhibitors should be stored at -70°C for possible future inhibitor and DNA testing.

### **Viral safety**

Compliance with CHMP recommendations with regard to viral safety under 1.2.2 is necessary for all plasma derived products and is verified by information supplied in Part II of the dossier.

A pre-treatment sample from each patient included in the clinical trials should be stored at -70°C for possible future testing.

### **Thrombogenicity testing**

This is relevant for products containing FVIII in addition to VWF and especially for products with a ratio of FVIII/VWF  $\geq 1.0$  in situations of repeated administration as high FVIII:C levels can be reached. Clinical evaluation of thrombosis should be performed by safe objective means in all patients undergoing surgical procedures.

### **2.1.4. Treatment of children**

Since children may respond differently compared to adults, an open multi-centre efficacy trial should include at least 8 children with VWD under the age of six years suffering from severe VWD defined as VWF:RCo < 15-20%, regardless of prior treatment. Three of these should be suffering from hereditary type 3 VWD. Initially PK-data should be collected in accordance with the requirements in

adults. For the children with type 3 VWD, a recovery study should be performed after 6 months. The physician's assessment of response in the treatment of any major bleeds or surgery should be reported. The VWF consumption (expressed as the number of infusions as well as IU/kg per event (on-demand and surgery), or IU/kg per month or year, in case of prophylactic use should be monitored as well as the consumption of FVIII, administered as part of the VWF product or administered as a separate infusion in case of a VWF product depleted of FVIII. Before entering the trial, all patients should be tested for inhibitors to VWF and FVIII. All patients should be re-tested every three months until the end of the observation period of 1 year. Patients should always be tested if they are suspected of having developed inhibitors (reduced *in vivo* recovery, poor clinical response).

The trial should not be started until interim data of 1 year of exposure are available in 10 patients older than 12 years, who are included in the efficacy trial. The study should continue until the patients have been treated for one year. For all patients who develop inhibitors a full clinical report should be provided including clinical relevance, the cumulative incidence and the number of exposure days in relation to development of inhibitors. The titre of the inhibitor should be reported as well as the method used.

Plasma samples from patients who are suspected of inhibitors should be stored at -70°C for possible future inhibitor and DNA testing.

It should be ensured that this study should at least be at the stage of patient recruitment at the time of marketing authorisation submission. General requirements specified in EU legislation on paediatric medicines should be taken into account.

The final report of this study may be submitted after a marketing authorisation is granted. The number of children treated should be reflected in the SPC. Until such a study has been carried out, the SPC should include a statement that there is no data from a clinical study to characterise the response to use of the product in children less than 6 years of age.

#### **2.1.5. Post-marketing study.**

To ensure consistency in the long-term between data from the clinical studies and from routine use, a post-marketing study should be undertaken and a protocol submitted with the dossier. The results of the efficacy/safety trial should be taken into account in the design of this study.

### **3. CHANGE IN THE MANUFACTURING PROCESS OF AUTHORISED PRODUCTS: 'MODIFIED PRODUCTS'**

#### **3.1 Introduction**

Changes in the manufacturing procedures may lead to significant changes in the product and may thereby alter the structure of the coagulation factor and its activity. The effects of changes in the manufacturing process (e.g. viral inactivation steps or purification procedures) on the biological characteristics and activity of the product should be investigated. If significant impact on the activity of the coagulation factor cannot be excluded, data on pharmacokinetics, efficacy and safety should also be provided with the application. (See also EMEA/CHMP/3097/02 "Guideline on comparability of medicinal products containing biotechnology derived proteins as active substance, non-clinical and clinical issues".)

Historically, two outbreaks of FVIII inhibitor development occurred in the early 1990's in previously tolerant haemophilia A patients who had been treated for a number of years. Inhibitor formation in these cases took place following exposure to a plasma derived FVIII product subjected to a modified virus inactivation method. Therefore, alteration of the VWF molecules by any change in the manufacturing process, should be monitored for appearance of neoantigenicity of the product.

#### **3.2 Clinical trials with modified plasma derived VWF products**

##### **3.2.1. Pharmacokinetics**

Evidence should be provided to demonstrate that the change in the manufacturing process has not affected the pharmacokinetics of the product.



A comparative cross-over pharmacokinetic trial should be performed in at least 12 subjects suffering from severe VWD defined here as baseline VWF:RCo < 15-20 % . At least 6<sup>9</sup> out of 12 patients should be suffering from hereditary type 3 VWD for separate analysis. The remaining patients can be diagnosed with severe type 1 or 2A VWD. Patients should be at least 12 years of age. They should not have received an infusion of DDAVP or of a VWF containing product for at least 5 days prior to participation in the trial. The study should be performed in patients without inhibitors to FVIII:C and VWF, who are not actively bleeding.

The pharmacokinetic trial should include measurement of VWF as well as FVIII. The following parameters should be recorded: incremental recovery, *in vivo* half-life, area under the curve (AUC), C<sub>max</sub>, t<sub>max</sub>, clearance and mean residence time (MRT). Analysis of these parameters should be performed in a centralised laboratory specialised in coagulation.

Samples for determination of VWF:RCo, VWF:Ag, VWF:CB, and FVIII:C should be taken before infusion of 80 VWF:RCo IU/kg of the product and at 15 minutes, 1, 3, 6, 12, 24, 30, 48 and 72 hours after the infusion. At least three different lots should be employed in the trial.

Incremental recovery is determined using the peak level recorded within 3 hours after the infusion and reported as [IU/ml]/[IU/kg]. Note: in case of a VWF product almost depleted of factor VIII, any incremental recovery of FVIII is not expected. However, in all instances FVIII:C should be monitored after the infusion of the VWF product because the FVIII:C level will rise as a result of endogenous secretion. The samples obtained before, 15 minutes and 6 hours after the infusion should be used to investigate the multimer distribution of the VWF, by multimeric sizing analysis using low- and high resolution electrophoresis gels (preferably 1% and > 2% gels). These analyses should be performed in a centralised laboratory specialised in VWD phenotyping.

It is anticipated that some deviation from the recommendation may occur in clinical practice. For this reason, it is very important to record the exact time post-infusion at which the actual samples were collected and to use these precise values in the analysis.

Patients taking part in the pharmacokinetic trial should continue treatment with the modified product to monitor clinical efficacy and safety and especially immunogenicity (see 3.2.2. and 3.2.3). The type 3 VWD patients should be re-tested for the same pharmacokinetic parameters after at least 6 months using the same dose as in the first investigation. The reason behind the repeat pharmacokinetic study is to re-test pharmacokinetic parameters and compare them with the initial results. Type 3 VWD patients are selected for the repeat pharmacokinetic study as they are most likely to develop allo-antibodies, although it is recognised that the risk of inhibitor development, even in these patients, is limited.

### 3.2.2 Efficacy

Clinical efficacy of the VWF product should be evaluated in at least 20 patients, suffering from severe VWD (for definition of severe VWD please refer to 2.1.1) including preferably all the patients who participated in the pharmacokinetic trial. All patients should be at least 12 years of age. During an observation period of at least 12 months any event (spontaneous bleeding, trauma, surgery, labour) should be documented in detail.

Should any of the patients participating in the clinical trials undergo surgical procedures, response will be determined by the physician, including efficacy of haemostasis, loss of blood, requirement for transfusion and, for products containing FVIII, clinical evaluation of thrombosis by safe objective means. In patients with known risk factors for thrombosis caution should be exercised and antithrombotic measures should be considered.

Response should be assessed as 'none', 'moderate', 'good' or 'excellent' by the physician for those patients who receive treatment with the product for major bleeds. In the remaining cases clinical efficacy after administration should be assessed from the clinical response as reported by the patients.

If prophylaxis is claimed, a minimum of 5 patients with type 3 VWD should be followed for a year for

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<sup>9</sup> Due to the rareness of hereditary type 3 vWD (prevalence between 0.55 to 6.0 per million) applicants might encounter difficulties to enrol 6 patients with type 3 vWD. In this case the competent authority should be contacted.

the absence of spontaneous bleeding episodes or obvious reduction of the number of haemorrhagic manifestations.

Clinical efficacy should also be assessed by calculating the consumption of VWF and FVIII (administered as part of the VWF product or administered as a separate infusion in case of a VWF product depleted of FVIII), expressed as the number of infusions as well as IU/kg per event (on-demand and surgery), or IU/kg per month or year, in case of prophylactic use.

### **3.2.3. Safety**

Please refer to requirements for new human plasma-derived VWF products. (See 2.1.3)

### **3.2.4. Post-marketing study**

See 2.1.5

**SUMMARY TABLES**

**Clinical trials with plasma-derived von Willebrand factor products: new products**

<b>TRIAL, SUBJECTS</b>	<b>INVESTIGATION</b>	<b>PARAMETERS</b>
12 patients with severe VWD (baseline VWF:RCo <15-20 %; F VIII <20%) without inhibitors and not actively bleeding, including at least 6 type 3 VWD <sup>1)</sup> . Age >12 years. Retesting of type 3 VWD patients after at least 6 months.	1. Pharmacokinetics  2. Safety	VWF:RCo, VWF:Ag, VWF:CB and FVIII:C: Incremental recovery, half-life, AUC, clearance and mean residence time. Multimeric sizing analysis. Note: for VWF products depleted of FVIII:C, incremental recovery of FVIII:C cannot be determined. However, FVIII:C levels should still be monitored.  Blood pressure, heart rate, temperature, respiratory rate and adverse events.
20 patients suffering from severe VWD, including preferably all patients from the PK study. Age >12 years.  Followed for 1 year.	1. Clinical efficacy  2. Immunogenicity  3. Safety	Response documented in all bleeding episodes. VWF and FVIII consumption <sup>2)</sup>  Inhibitor titre <sup>3)</sup>  Adverse events.
At least 15 surgical procedures (10 major)	1. Clinical efficacy  2. Safety	Efficacy of haemostasis, loss of blood and requirement for transfusion. VWF and FVIII consumption <sup>1)</sup>  Adverse events. Thrombogenicity (for products containing FVIII).
At least 10 bleeding episodes (5 major mucosal)	1. Clinical efficacy  2. Safety	Response documented in all bleeding episodes. VWF and FVIII consumption <sup>2)</sup>  Adverse events.
If prophylaxis claimed:  A minimum of 5 type 3 VWD patients followed for 1 year.	1. Efficacy  2. Immunogenicity  3. Safety	Obvious reduction or absence of spontaneous bleedings. VWF and FVIII consumption <sup>2)</sup>  Inhibitor titre <sup>3)</sup>  Adverse events.
Open multicentre trial in 8 children (<6 years) to be started after results of 1 year of exposure in 10 patients >12 years have become available.  Continue until 1 year of treatment.	1. Pharmacokinetics 2. Clinical efficacy  3. Immunogenicity  4. Safety	Similar to adults. Recovery study in type3 VWD patients after 6 months. Physician's assessment of response in treatment of major bleeds and surgery. VWF and FVIII consumption <sup>2)</sup>  Inhibitor titre <sup>3)</sup>  Adverse events.
Post-marketing study	1. Clinical efficacy 2. Immunogenicity 3. Safety	Protocol should be provided.

1) Due to the rareness of hereditary type 3 vWD (prevalence between 0.55 to 6.0 per million) applicants might encounter difficulties to enrol 6 patients with type 3 vWD. In this case the competent authority should be contacted.

2) VWF and FVIII consumption: number of infusions, IU/kg per event (on-demand and surgery), or IU/kg per month or year, in case of prophylactic use.

3) Inhibitor titre: at baseline, every 3 months until the end of the observation period of 1 year, and also if there is any suspicion of inhibitor development.

### Clinical trials with plasma derived von Willebrand factor products: modified products

TRIAL, SUBJECTS	INVESTIGATION	PARAMETERS
<p>Cross-over 12 patients with severe VWD (baseline VWF:RCo &lt;15-20 %; FVIII &lt;20%) without inhibitors and not actively bleeding, including at least 6 type 3 VWD<sup>1)</sup>. Age &gt;12 years.</p> <p>Retesting of type 3 VWD patients after at least 6 months.</p>	<p>1. Pharmacokinetics</p> <p>2. Safety</p>	<p>Comparative study: VWF:RCo, VWF:Ag, VWF:CB and FVIII:C: Incremental recovery, half-life, AUC, clearance and mean residence time.</p> <p>Multimeric sizing analysis.</p> <p>Note: for VWF products depleted of FVIII:C, incremental recovery of FVIII:C cannot be determined. However, FVIII:C levels should still be monitored.</p> <p>Blood pressure, heart rate, temperature, respiratory rate and adverse events.</p>
<p>20 patients suffering from severe VWD, including preferably all patients from the PK study. Age &gt;12 years.</p> <p>Followed for 1 year</p>	<p>1. Clinical efficacy</p> <p>2. Immunogenicity</p> <p>3. Safety</p>	<p>Response documented in all bleeding episodes. VWF and FVIII consumption <sup>2)</sup></p> <p>Inhibitor titre <sup>3)</sup></p> <p>Adverse events.</p>
<p>Any patients undergoing surgical procedures.</p>	<p>1. Clinical efficacy</p> <p>2. Safety</p>	<p>Efficacy of haemostasis, loss of blood and requirement for transfusion. VWF and FVIII consumption <sup>2)</sup></p> <p>Adverse events. Thrombogenicity (for products containing FVIII).</p>
<p>If prophylaxis claimed:</p> <p>A minimum of 5 type 3 VWD patients followed for 1 year.</p>	<p>1. Efficacy</p> <p>2. Immunogenicity</p> <p>3. Safety</p>	<p>Obvious reduction or absence of spontaneous bleedings. VWF and FVIII consumption <sup>2)</sup></p> <p>Inhibitor titre <sup>3)</sup></p> <p>Adverse events.</p>
<p>Post-marketing study</p>	<p>1. Clinical efficacy</p> <p>2. Immunogenicity</p> <p>3. Safety</p>	<p>Protocol should be provided.</p>

1) Due to the rareness of hereditary type 3 vWD (prevalence between 0.55 to 6.0 per million) applicants might encounter difficulties to enrol 6 patients with type 3 vWD. In this case the competent authority should be contacted.

2) VWF and FVIII consumption: number of infusions, IU/kg per event (on-demand and surgery), or IU/kg per month or year, in case of prophylactic use

3) Inhibitor titre: at baseline, every 3 months until the end of the observation period of 1 year, and also if there is any suspicion of inhibitor development.