



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology

VONVENDI, Recombinant von Willebrand Factor BLA 125577
Pharmacovigilance Plan Review Memorandum

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Office of Blood Research and Review (OBRR)

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Subject: Pharmacovigilance Plan Review Memorandum

Applicant: Baxter Healthcare Corporation

Product: VONVENDI, Von Willebrand Factor / Antihemophilic Factor
Complex (Recombinant); rVWF; vonicog alfa; Bax111

Proposed Indication: Prevention and treatment of bleeding episodes in adults (age 18 and
older) diagnosed with von Willebrand disease.

CBER received date: December 19, 2014

Action Due Date: December 18, 2015 (standard review)

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1. INTRODUCTION

1.1 Objectives and Scope

Office of Biostatistics and Epidemiology, Division of Epidemiology (OBE/DE) has completed a pharmacovigilance review of BLA 125577 seeking initial licensure of recombinant von Willebrand Factor (rVWF); proposed trade name VONVENDI. The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance, studies, or other pharmacovigilance activities, should the product be licensed. As part of a comprehensive safety evaluation, the pharmacovigilance plan (PVP) submitted by Baxter as part of the Risk Management Plan (RMP) with supporting background clinical trial information from the BLA is hereby reviewed. Currently VONVENDI is not licensed in any country and there is no postlicensure safety data.

This memo will use recombinant von Willebrand Factor (rVWF) and VONVENDI interchangeably.

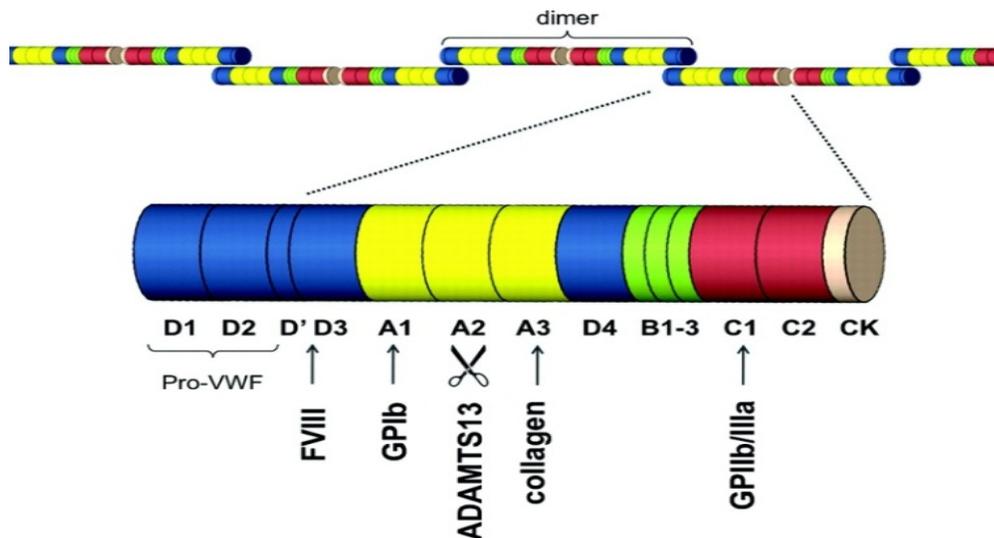
1.2 Background on endogenous VWF and Product Description of VONVENDI (rVWF)

Endogenous VWF

Von Willebrand Factor (VWF) is a large multimeric glycoprotein normally found in plasma, encoded by VWF gene on chromosome 12 (depicted in Figure 1 below) and synthesized by megakaryocytes and endothelial cells. VWF plays a dual role in hemostasis: (i) VWF is the carrier molecule for Factor VIII (FVIII) and stabilizes FVIII through formation of a non-covalent VWF-FVIII complex which increases the half-life of FVIII fivefold; (ii) VWF functions as a bridging protein for platelet adhesion/aggregation at sites of vascular injury. Therefore, a decrease in VWF also leads to a decrease in FVIII. Depending on the severity of bleeding, treatment of VWD may require co-administration of both VWF and FVIII. (On the other hand, Hemophilia A patients have decreased levels of factor VIII and normal levels of VWF.)

Figure 1: The von Willebrand Factor multimer

Source: Kleinschnitz et al. Stroke. 2012 Feb;43(2):599-606



Metalloproteinase ADAMTS13 plays an important role in the regulation of VWF for normal hemostasis, by mediating the cleavage and proteolysis of VWF. Of note, studies have shown that a deficiency of ADAMTS13 is associated with an increased incidence of thrombotic thrombocytopenic purpura (TTP). Animal studies have also demonstrated formation of vascular thrombi in ADAMTS13-/- mice.¹

VONVENDI (recombinant VWF)

Deficiency of VWF causes Von Willebrand Disease. Currently only plasma-derived VWF is available and if approved, **VONVENDI will be the first recombinant VWF** (pharmacologic class: recombinant coagulation factor). As per Baxter it will be “the only high purity VWF product.”

VONVENDI (rVWF) (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. Proteins

present in the final container product other than rVWF are trace quantities of mouse immunoglobulin (IgG, from the immunoaffinity purification), host cell (i.e., CHO) protein, rFurin (used to further process rVWF), (b) (4).

¹ Rick et al. Biology and normal function of von Willebrand factor. Accessed UpToDate, July 29, 2015: http://www.uptodate.com/contents/biology-and-normal-function-of-von-willebrand-factor?source=search_result&search=von+willebrand+disease&selectedTitle=4%7E150

1 Page determined to be not releasable: b(4)

Reviewer Comment: (b) (4)

Dosage form: Lyophilized powder in single-use vials containing dosage strengths 650 or 1300 IU/vial; requires reconstitution with sterile water.

Route of administration: intravenous

Dosing Regimen: 40-60 IU/kg for minor bleeding, 50-80 IU/kg for major bleeding, with ADVATE with first dose if FVIII activity less than 40%

Baxter's proposed Indication: "Prevention and treatment of bleeding episodes in adults (age 18 and older) diagnosed with von Willebrand disease. Limitation of Use: VONVENDI is not indicated for prevention of excessive bleeding during and after surgery."

Reviewer Comment: VONVENDI is not indicated for prophylaxis at this time, and to avoid confusion between "prevention" and prophylaxis, FDA has proposed the following language: "on-demand treatment and control of bleeding episodes in adults (age 18 and older) diagnosed with von Willebrand disease." VONVENDI is also not indicated for surgery at this time. Baxter has planned clinical studies to (b) (4). Furthermore, VONVENDI is not indicated for treatment of hemophilia A, though Baxter submits data from an early phase trial in hemophilia A patients.

1.3 Disease to be treated: Von Willebrand Disease^{2, 3, 4}

Deficiency of VWF causes Von Willebrand Disease (VWD), the most frequent inherited bleeding disorder, affecting approximately 1% of the population (inheritance may be autosomal dominant or recessive; congenital or acquired). The deficiency of VWF may be quantitative or qualitative (functional) and VWD patients experience mild to severe clinical symptoms, depending on the type of genetic mutation. VWD is further classified as Type 1, 2 or 3, as described in the Table 1 below. Though VWD is the most common inherited bleeding disorder, the majority of VWD patients have mild disease.

Reviewer Comment: The proposed indication for VONVENDI includes all types of inherited VWD (types 1, 2 and 3). Baxter does not mention use in acquired VWD.

Table 1: Types of von Willebrand Disease

	% VWD	Type of deficiency	Clinical manifestations
VWD Type 1	70%	quantitative	Mostly mild clinical symptoms

² Rick et al. Treatment of von Willebrand disease. Accessed UpToDate, July 29, 2015: http://www.uptodate.com/contents/treatment-of-von-willebrand-disease?source=see_link

³ Rick et al. Clinical presentation and diagnosis of von Willebrand disease. Accessed UpToDate, July 29, 2015: http://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-von-willebrand-disease?source=see_link

⁴ Lillicrap D. Translational medicine advances in von Willebrand disease. J Thromb Haemost. 2013 Jun;11 Suppl 1:75-83.

VWD Type 2 (subtypes 2A, 2B, 2M, 2N)	25 – 30%	qualitative (functional)	Moderate bleeding diathesis, mostly affecting mucosal tissues
VWD Type 3	1 – 5%	quantitative (near absence of VWF; consequently low FVIII)	Severe hemorrhagic symptoms: bleeding in mucosal tissues, muscle and joints.

Choice of therapy for VWD is based on the individual patient’s clinical manifestations. Some of the current treatment options for VWD are desmopressin (DDAVP), replacement therapy with plasma derived VWF concentrates, antifibrinolytic agents, and topical therapy with thrombin or fibrin sealants. Available replacement therapy options are limited to plasma FVIII concentrates that also contain VWF, such as Humate P, Alphanate, Wilate and Koate-DVI.

Reviewer Comment: Of available plasma derived concentrates, some products like Humate-P, Wilate, Alphanate have a fixed ratio of VWF:FVIII and are indicated for VWD, while others contain only trace amounts of VWF and are indicated for hemophilia A (and may be used off-label for VWD patients). Plasma derived VWF and FVIII concentrates vary in the ratio of VWF:FVIII content depending on the source plasma and the manufacturing process, which could lead to excess FVIII doses in VWD patients. The known safety concerns of plasma derived products indicated for VWD (as per the labels for these products) include:

- development of neutralizing antibodies (inhibitors)
- thromboembolic events
- hypersensitivity reactions including anaphylaxis
- transfusion transmitted infections

Of note, unlike plasma-derived products, recombinant VWF (VONVENDI) is manufactured in the absence of animal or human plasma proteins, thus minimizing risk of transmission of blood-borne pathogens. The safety clinical trial data for VONVENDI includes assessment of the risks of thromboembolic events, hypersensitivity reactions and development of inhibitor antibodies to VWF. There may be a theoretical concern that recombinant products may be more immunogenic than plasma derived products.

1.4 Regulatory History

IND 13657

- Orphan Designation was granted on Nov 23, 2010 (#103222).
Of note, orphan designation was also granted by the European Commission.

Original BLA 125577 submission

- Pediatric Research Equity Act (PREA) was triggered since rVWF is a new active ingredient. Baxter submitted a pediatric study plan and requested deferral under Amendment 76 of the IND 13657. Since rVWF has Orphan drug designation, PREA is waived.
- Breakthrough designation was denied.

- ADD: December 18, 2015 (standard 12 month review)

2. MATERIALS REVIEWED

Table 2: Materials reviewed for Pharmacovigilance review of VONVENDI

Documents	Source
Pharmacovigilance Plan, Version 1.0, dated November 19, 2014	BLA 125577, Module 1.16 ⁵
Clinical Overview	BLA 125577, Module 2.5
Summary of Clinical Safety	BLA 125577, Module 2.7.4
Summary of Clinical Efficacy	BLA 125577, Module 2.7.3
120-day safety update	BLA 125577, eCTD sequence# 0004
Integrated Summary of Safety	BLA 125577, Module 5.3.5.3
Discipline reviews and discussion	CBER BLA review team

3. CLINICAL STUDIES

Three clinical trials of VONVENDI have been completed, and a total of 78 subjects have received VONVENDI. Efficacy of VONVENDI is supported by the single pivotal Phase 3 clinical trial 071001. Additional supportive early phase studies are included in Table 3 below.

Table 3: Design of completed clinical studies with VONVENDI

(Source: table and associated footnotes from BLA 125577, Module 2.5)

Study number /Report	Study type	Subject population	Subjects exposed to rVWF	Doses administered (IU/kg VWF:RCo)
070701 Full CSR	Phase 1 PK and tolerability	Adults with severeVWD ^a	31 ^b	2, 7.5, 20, 50
071001 Full CSR	Phase 3 Safety, Efficacy, PK	Adults with VWD ^b	37	50, 80
071104 Full CSR	Phase 1 (supportive) PK and tolerability	Adults with Hemophilia A	12	10, 50

^a Severe Type 1 VWD or Type 2A VWD (VWF:RCo \leq 10% and FVIII:C <20%), or Type 3 VWD (\leq 3 IU/dL VWF:Ag).

^b One subject in cohort 4A was randomized to receive rVWF:rFVIII for the first infusion, however the subject was actually administered pdVWF combined with rFVIII and subsequently did not receive any rVWF.

^c Type 1 VWD (VWF:RCo<20IU/dL), Type 2 VWD or Type 3 VWD (VWF:Ag<3IU/dL).

⁵ Baxter BLA 125577, Risk Management Plan, module 1.16.

(b) (4)

Efficacy and safety of VONVENDI is supported by the single pivotal phase 3 clinical trial 071001, summarized in Table 4.

Table 4: Phase 3 clinical trial 071001

Study title (Study 071001) A phase 3 clinical study to determine the pharmacokinetics, safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in subjects diagnosed with von Willebrand disease		
Study design Phase 3, prospective, multicenter, open-label, two part study Part A: PK assessments and/or treatment of bleeding episodes (BEs) Arm 1: PK50 with treatment of BEs Arm 2: PK50 only Arm 3: PK80 with treatment of BEs Arm 4: Treatment of BEs Part B: continue on-demand treatment for BEs for additional 6 months		
Study population 37 VWD patients; inclusion criteria: VWD type 1, 2A, 2B, 2N, 2M, Type 3		
Study duration: total 12 months (6 months in Part A; 6 months in Part B)		
Intervention: VONVENDI (rVWF) with or without ADVATE (rFVIII)		
Primary Endpoint (Efficacy) Number of subjects with a <u>treatment success</u> for treated BEs (according to a rating scale of excellent – good – moderate – none based on scale below).		
Efficacy Rating Scale		
Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	Major Bleeding Events
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF containing coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation	<1.5x infusions greater than estimated required to control that bleeding episode No additional VWF containing coagulation
Moderate (=3)	3 or more infusions greater than estimated used to control that bleeding event No additional VWF containing coagulation	≥1.5x more infusions greater than estimated used to control that bleeding event No additional VWF containing coagulation
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF containing coagulation factor containing product required

Secondary Endpoints

Efficacy: number of treated BEs with an efficacy rating of ‘excellent’ or ‘good’; number of infusions and number of units of rVWF:rFVIII and/or rVWF per bleeding episode

Safety: Development of neutralizing and total binding anti-VWF antibodies; development of neutralizing antibodies to FVIII; development of antibodies to CHO proteins, mouse IgG or rFurin; occurrence of thrombotic events; other treatment related AEs

[There were other additional pharmacokinetic and exploratory endpoints.]

Efficacy Results⁶

100% of subjects receiving VONVENDI met the criterion of a treatment success (median efficacy rating of <2.5).

192/192 bleeding episodes treated with VONVENDI in 22/37 VWD subjects [type 3 (N = 17), type 2A (N = 4), type 2N (N = 1)] met the criterion for successful treatment; and all bleeds were controlled with VONVENDI or VONVENDI in combination with ADVATE with an efficacy rating of excellent (96.9%) or good (3.1%). 157/192 (81.8%) BEs required only a single infusion of VONVENDI (alone or in combination with ADVATE) to control the bleed. The median dose of VONVENDI per BE (with or without ADVATE) was 48.2 IU per kg.

4. CLINICAL TRIAL SAFETY DATA

4.1 Clinical Safety Database

Pooled data from 3 clinical studies comprise the safety dataset on VONVENDI:

- Phase 1 study 070701; N = 32 subjects with VWD (type 3, severe type 1, type 2A)
- Phase 1 study 071104; N = 12 subjects with severe hemophilia A
- Phase 3 study 071001; N = 37 subjects with VWD (type 1, 2A, 2B, 2N, 2M, Type 3)

Reviewer comment: Of note, phase 1 study 071104 (N = 12 subjects) was conducted in hemophilia A patients and thus differs from the patient population (VWD) for the proposed indication for VONVENDI in this BLA. Lower doses of VONVENDI were administered in the early phase clinical trials investigating PK and tolerability; the doses administered in the phase 1 clinical trials (protocols 070701 and 071104) varied widely from 2 to 50 IU/kg. Thus, safety assessment from the clinical safety data from the early phase clinical trials is limited by lower doses administered. In the single pivotal phase 3 trial (protocol 071001), 50 to 80 IU/kg dose was administered, in alignment with the recommended proposed dose of 40-80 IU/kg.

Safety was assessed in terms of (i) adverse events (AEs), (ii) immunogenicity, and (iii) thrombogenicity. Metrics included: neutralizing and total binding antibodies to rVWF; neutralizing antibodies to rFVIII; antibodies to CHO proteins, murine IgG or rFurin; coagulation assessments; signs of thrombosis or thromboembolic complications; viral serology (hepatitis A, B, or C; human immunodeficiency virus 1 or 2; parvovirus B19). An independent data monitoring committee assessed the safety dataset.

⁶ Summarized from Clinical Review and BLA module 2.7.3 Summary of Clinical Efficacy.

Integrated Safety Analysis in VWD: pooled data from phase 1 study 070701 and phase 3 study 071001.

The pooled analysis set includes a total of 66 unique subjects from studies 070701 and 071001 (1 subject in study 070701 received plasma derived VWF instead of VONVENDI and was not included in the integrated safety analysis dataset; 2 subjects were treated with VONVENDI in both studies), with a total of 355 infusions. The median age at screening was 36 years (range: 18 – 64y) and subjects were distributed evenly by gender. There were no gender-specific differences in the occurrence of AEs. Fifty-six (85%) of subjects were diagnosed with VWD type 3; 4 subjects with VWD type 1; 5 subjects with VWD 2A and 1 subject with VWD type 2N.

Reviewer comment: We note that majority of subjects in the clinical trial had severe type 3 VWD (N = 56 subjects); while in the general population, the majority of VWD patients have type 1 VWD and mild disease. This is appropriate, since in clinical practice, DDAVP, which is used to elevate levels of endogenous VWF, is commonly used for management of mild type 1 disease. Replacement therapy (such as VONVENDI, should it be approved, or other plasma derived concentrates) is used for management of more severe VWD. However, different therapeutic strategies (non-replacement therapy and replacement therapy) to control bleeding in VWD are not mutually exclusive, and patients may simultaneously receive multimodal treatment, depending on the clinical setting.

Adverse Events

AE verbatim terms were coded in Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and by preferred term. Adverse events were categorized according to: seriousness (serious and non-serious), severity (mild, moderate, and severe), and causal relationship determined by the investigator (not related, unlikely related, possibly related and probably related) to infusion.

Reviewer comment: The definition of serious AE is not clearly described; it is unclear if Baxter is following regulatory definition of seriousness of AE as per 21 CFR 600.80.

Table 5 summarizes adverse events. No subject died on study. A total of 175 AEs were reported in 44/66 (66.7%) subjects during or after treatment with at least one infusion of VONVENDI: 10 serious and 165 non-serious. The rate of AEs by infusion was 23.4% (83/355 infusions).

Reviewer comment: Note that VONVENDI was administered with or without ADVATE in clinical trials, and ADVATE may be a co-suspect in assessment of AEs for VONVENDI. The Integrated Summary of Safety (ISS, module 5.3.5.3) discusses the clinical safety data for VONVENDI and states that “no distinction was made in this analysis between exposure to rVWF alone vs. administered with rFVIII.”

Table 5: Overall Summary of Adverse Events in all subjects treated with VONVENDI
(pooled studies 070701 and 071001)

[Source: Table 10, CSR 070701 Section 12.3.1.1; CSR 071001 Section 12.3.1.1]

	N=66 (%)
Subjects with ≥1 AE	44 (66.7%)

Subjects with treatment-related non-serious AEs	8 (12.1%)
Subjects with ≥ 1 SAE	8 (12.1%)
Subjects with treatment-related SAEs	1 (1.5%)
Deaths	0 (0%)
Subjects discontinued from the study due to an AE	1 (1.5%)

Abbreviations: AE=adverse event; SAE=serious adverse event (during or after infusion with rVWF or rVWF rFVIII)

Source: [Table 10, CSR 070701 Section 12.3.1.1](#); [CSR 071001 Section 12.3.1.1](#)

Table 6: Overview of Adverse Events that occurred during or after VONVENDI Infusion and relatedness to treatment (pooled studies 070701 and 071001)

[Source: 2.7.4 Summary of Clinical Safety]

Seriousness of AE	Severity	Relationship to VONVENDI	# AEs	By Subject N= 66 (%)	By Infusion N= 355 (%)
Serious	Mild	Unrelated	2	1 (1.5)	1 (0.3)
		Related	0	0 (0.0)	0 (0.0)
	Moderate	Unrelated	1	1 (1.5)	1 (0.3)
		Related	2	1 (1.5)	1 (0.3)
	Severe	Unrelated	5	5 (7.6)	5 (1.4)
		Related	0	0 (0.0)	0 (0.0)
	Total	Unrelated	8	7 (10.6)	7 (2.0)
		Related	2	1 (1.5)	1 (0.3)
		Total	10	8 (12.1)	8 (2.3)
Non-Serious	Mild	Unrelated	103	22 (33.3)	49 (13.8)
		Related	12	7 (10.6)	9 (2.5)
	Moderate	Unrelated	48	18 (27.3)	29 (8.2)
		Related	2	1 (1.5)	1 (0.3)
	Severe	Unrelated	0	0 (0.0)	0 (0.0)
		Related	0	0 (0.0)	0 (0.0)
	Total	Unrelated	151	40 (60.6)	78 (22.0)
		Related	14	8 (12.1)	10 (2.8)
		Total	165	43 (65.2)	81 (22.8)
Total	Total	Total	175	44 (66.7)	83 (23.4)

As per Baxter: In study 070701 subjects in cohort 4 were also treated with pdVWF/FVIII. Adverse events that occurred after infusion of pdVWF/FVIII are not included in the table above.

If a single subject experiences multiple AEs categorized under the same causality assessment, this subject is shown only once at its most serious severity.

Number of IP infusions associated with an AE divided by the total number of IP infusions multiplied by 100. If an infusion is associated with multiple AEs categorized under the same causality assessment, this infusion is shown only once at its most serious severity.

Serious AEs

Eight (8/66; 12.1%) subjects experienced 10 serious AEs (further summarized in the table below) and the overall serious AE frequency by infusion is 2.3% (8/355). There were no severe allergic or anaphylactic reactions in any subject.

Table 7. Summary of Serious AEs in VWD patients (pooled studies 070701 and 071001)
[Source: 2.7.4 Summary of Clinical Safety]

Study	(b) (6)	SAE (Preferred Term)	Relatedness
070701	(b) (6)	Dental caries	Not related
071001	(b) (6)	Osteomyelitis	Not related
071001	(b) (6)	Constipation	Not related
071001	(b) (6)	Uterine polyp	Not related
071001	(b) (6)	Spontaneous abortion	Not related
071001	(b) (6)	Gastrointestinal hemorrhage	Not related
071001	(b) (6)	Mesenteric hematoma	Not related
071001	(b) (6)	Hemorrhoids	Not related
071001	(b) (6)	Chest discomfort	Possibly Related
071001	(b) (6)	Increased heart rate	Possibly Related

Reviewer comment: There was a low incidence of serious AEs with VONVENDI in these two clinical trials. While this finding is reassuring, the data should be interpreted with caution due to the small sample size. The majority (8 serious AEs in 7 subjects) were considered unrelated to VONVENDI. Some PTs likely represent confounding by indication, e.g., bleeding, which is not surprising in individuals with an underlying bleeding diathesis. Furthermore, taken together, these PTs do not suggest a clinical pattern or cluster.

Of the 10 serious AEs, only 2 AEs in 1 subject (b) (6) were considered possibly related to treatment. Subject (b) (6) was a 36 year-old male who experienced “chest discomfort” and increased heart rate during infusion with VONVENDI in combination with ADVATE. The subject received standard treatment with oxygen and symptoms improved within 10 minutes and fully recovered after 3 hours without sequelae. This subject withdrew from the study due to this serious AE.

Reviewer comment: Transfusion reactions including hypersensitivity reactions with symptoms such as tachycardia and chest discomfort can occur after infusion of biologic products. The PT “chest discomfort” is non-specific and of unclear etiology in this case; it may refer to chest pain, palpitations or breathing difficulties – all of which may occur after infusion of blood products. Moreover, chest discomfort and tachycardia are probably related to each other and likely represent a single post-infusion experience. It is important to note that the symptoms were self-limited/transient and improved within 10 minutes without sequelae; fully resolved within 3h. There was no evidence that these symptoms

⁷ Full Clinical Study Report 071001, Appendix 16.2.7, p8 (BLA module 5.3.5.2 Adverse Event Listings)

were associated with any kind of thrombotic event. The symptoms may also be due to VONVENDI and/or ADVATE. Chest discomfort /pain is listed in the Package Insert of ADVATE.

Non-serious AEs

The majority of AEs were non-serious: 165 AEs in 43/66 subjects and most of these were mild (115 AEs in 29 subjects). The 3 most common non-serious AEs (occurring in >5% of subjects) included headache (10.6%), laceration (6%) and contusion (6%).

Reviewer comment: Note limitations of small sample size in the interpretation of the “most common” AEs occurring in >5% i.e. AEs were isolated events. The majority of non-serious AEs (N = 151) were assessed as unrelated to treatment. Above mentioned AEs, laceration and contusion, were unrelated to treatment.

Treatment related AEs and temporal association

The following PTs were assessed as treatment-related by investigators: platelet disorder, tachycardia, increased heart rate, nausea, chest discomfort, infusion site paresthesia, electrocardiogram T wave inversion, dizziness, dysgeusia (distorted sense of taste), psychomotor hyperactivity, tremor, pruritus, and hot flush. Temporal association with VONVENDI infusion (defined as during or within 24 hours after infusion) was observed for 47/175 (27%) of the overall number of AEs; the most common temporally associated AEs (i.e. occurring in >3% of subjects) were vertigo, vomiting, infusion site paresthesia, headache, dizziness, and generalized pruritus.

Reviewer comment: The AEs that were considered possibly related to treatment and those that were temporally associated with VWF do not suggest any safety signals, but again we note small sample size.

Immunogenicity

Subjects exposed for the first time to VONVENDI and/or ADVATE were to be screened after 4-6 weeks post-infusion. If, at any time during the course of the study, a subject's bleeding episode did not adequately respond to VONVENDI therapy, he/she was to be evaluated for the presence of inhibitory and total binding anti-VWF antibodies. None of the subjects treated in studies 070701 or 071001 developed neutralizing antibodies against rVWF or rFVIII. In study 070701, 29 subjects had negative results for specific binding antibodies against rVWF throughout the study; 2 subjects (subject (b) (6) and (b) (6)) had high *pre-infusion* titers for binding anti-VWF antibodies of 1:1280 at screening that was confirmed for specificity. In study 071001, all 37 subjects had negative results for specific binding antibodies against rVWF throughout the study. All subjects tested negative for specific binding antibodies against CHO cell proteins, rFurin or murine IgG throughout the study; and there was no *de novo* development or treatment related increase of specific binding antibodies against impurities.

Reviewer comment: In study 070701, positive titers for specific binding antibodies against VWF were identified in 2 subjects prior to their first exposure to VONVENDI. These subjects did not have inhibitor antibodies to VWF (before treatment with VONVENDI) and did not develop inhibitor antibodies to rVWF post-treatment with VONVENDI. There were no reports of changes in either subject's^s medical

condition, including no change in the therapeutic requirements for the treatment of bleeding episodes. We agree with Baxter’s assessment that “no *de novo* development or treatment related increase of specific binding antibodies against rVWF was observed” during clinical trials. However, while this is reassuring, the data should be interpreted with caution due to the small sample size of the clinical safety dataset. The risk for VWD patients to develop neutralizing or binding antibodies against VONVENDI or potential impurities present in the product will be further assessed in the postmarketing setting, should the product be licensed. “Danger signals” elicited in patients under certain conditions – infection, bleeding episode, surgery, recent vaccination, inflammatory cytokines – have been postulated to play a role in the mechanisms leading to immunogenicity of FVIII products^{8, 9} It is unknown if similar mechanisms exist leading to immunogenicity of VWF.

Thrombogenicity

There is a potential risk for thrombotic and thromboembolic events with VONVENDI treatment, especially in individuals with known risk factors for thrombosis, such as low ADAMTS13 levels (endogenous ADAMTS13 mediates cleavage of VWF). Excess levels of VWF and/or FVIII may also be risk factors for thrombosis. During clinical development, *in vivo* levels of cleavage of rVWF by ADAMTS13 was demonstrated in VWD patients, with the rapid appearance of proteolysed products 15 minutes after VONVENDI infusion. In the clinical studies, none of the subjects had abnormally low baseline levels of ADAMTS13, and no thrombotic events were observed in the clinical trials.

Reviewer comment: While this result is reassuring, the data should be interpreted with caution due to the small sample size of the clinical safety dataset.

4.2 120-day Safety Update

In the 4-month (120-day) Safety Update for VONVENDI, Baxter states “*There is no new safety information learned about the drug that may reasonably affect draft labeling.*” Baxter describes an emergency IND 16288 (submitted 23 January 2015):

65 year-old male with Type 2A VWD with a history of urothelial cell carcinoma, presented with hematuria and experienced severe allergic reactions to both Humate and Alphanate, and was treated with rVWF from 11DEC14 – 13JAN15, under an emergency IND. Post-study, in 27 February 2015, subsequent to esophagogastroduodenoscopy (EGD), he experienced a serious AE of gastrointestinal (GI) bleed that resolved; this was assessed as unrelated to VONVENDI by the investigator. EGD showed “non-bleeding varices and portal gastropathy (thought to be the likely source of bleeding).”

Reviewer comment: The GI bleed occurred 6 weeks after initial rVWF infusion and was likely associated with EGD procedure and pre-existing varices. We agree that this AE is likely unrelated to VONVENDI.

⁸ Miller et al. Danger signal-dependent activation of human dendritic cells by plasma-derived factor VIII products. *Thromb Haemost.* 2015 Jul 28;114(2):268-76.

⁹ Pfistershammer et al. Recombinant factor VIII and factor VIII-von Willebrand factor complex do not present danger signals for human dendritic cells. *Thromb Haemost.* 2006 Sep;96(3):309-16.

5. PHARMACOVIGILANCE PLAN¹⁰

5.1 Pharmacovigilance Plan: Overview of the important risks and proposed actions

Baxter proposes routine pharmacovigilance (PV) and labeling. Routine PV includes 15-day expedited reports for serious, unlabeled (unexpected) AEs and quarterly periodic safety reports for the first three years following licensure (annual submissions thereafter). Additionally, two phase 3 clinical studies are planned (b) (4)) and will collect additional safety data.

Table 8: Overview of the important identified and potential risks and proposed PV actions

Safety Concerns	Baxter Proposed Actions
Important Identified Risk: Hypersensitivity reactions	<ul style="list-style-type: none"> ▪ Routine PV and labeling ▪ Collect safety data to add to the clinical safety dataset for VONVENDI from postmarketing studies (efficacy studies: (b) (4))
Important Potential Risks: <ol style="list-style-type: none"> 1. Inhibitor formation 2. Thromboembolic events 	
Important Missing Information: <ol style="list-style-type: none"> 1. Insufficient clinical data in children under 18 years of age 2. Insufficient clinical data on use in pregnancy and lactation 3. Insufficient clinical data on use in patients 65 years of age and older 	Routine PV and labeling

5.2 Safety Concerns

1. Hypersensitivity reactions: Important Identified Risk

A spectrum of hypersensitivity reactions from mild rash to life-threatening anaphylaxis may occur with this class of biological blood products. VONVENDI is contraindicated in patients with known anaphylactic reactions to the active substance, mouse or hamster proteins, or constituents of the product.

Data: No severe hypersensitivity or anaphylactic reactions were reported in any subject during the 3 completed clinical studies with VONVENDI. Possible hypersensitivity symptoms, including nausea (n=3), chest discomfort (n=1) and pruritus generalized (n=2) were reported in clinical studies.

PV Actions

- Passive surveillance of spontaneous AE reports, medical literature.
- Labeled in in Package Insert (PI) sections: Contraindications, Warnings and Precautions, Clinical Trials Experience, Nonclinical Toxicology and Patient Counseling Information.

¹⁰ Baxter BLA 125577, Risk Management Plan, module 1.16.

(b) (4)

- Additional safety data will be collected from postmarketing clinical trials (efficacy studies: (b) (4))

Reviewer comment: Though there were no severe allergic/anaphylactic reactions from clinical trial data, mild signs/symptoms that may be associated with hypersensitivity reactions were observed. In addition, it is important to note that VWD patients who develop antibodies against VWF are at risk for these types of reactions following repeated exposure. Hypersensitivity has been reported with plasma derived VWF. Based on the small size of VONVENDI trials and their limited duration, the risk of allergic/anaphylactic reactions with VONVENDI cannot be excluded. However, we agree with Baxter that the “potential risk is considered to be low, though some possible hypersensitivity symptoms (e.g. nausea, chest discomfort, pruritus generalized) have been reported in clinical studies.” At this time, routine PV and labeling are adequate.

2. Inhibitor formation: Important Potential Risk

Development of inhibitor antibodies is a potential risk of VONVENDI treatment. Depending on the level of inhibitor present, clinical manifestation may vary from non-serious asymptomatic lack of response to treatment to potentially serious life-threatening hemorrhage. Patients may need to be evaluated by inhibitor assays for the development of neutralizing antibodies. Additionally, in patients with high levels of inhibitors to VWF or FVIII, recombinant VWF may not be effective due to neutralizing antibodies, and may lead to severe adverse reactions. Of note, inhibitor antibodies may occur concomitantly with anaphylactic reactions, and patients who develop an anaphylactic reaction should also be evaluated for inhibitors.

Data: None of the subjects treated in studies 070701 or 071001 (VONVENDI treatment for VWD patients) developed neutralizing antibodies against VONVENDI or FVIII after treatment with VONVENDI. However, in study 070701, 2/31 subjects had a high pre-infusion titer for binding anti-VWF antibodies of 1:1280 at screening. There were no treatment-related increase in antibody titers against VWF exposure and for both subjects the investigators did not report any changes in medical condition. All 37 evaluated subjects in study 071001 showed negative results for specific binding antibodies against rVWF. In study 071104 (VONVENDI treatment in hemophilia A patients), no subject had neutralizing antibodies against FVIII or rVWF and all 12 subjects showed negative results for specific binding antibodies against rVWF.

From this data, Baxter considers VWD patients to be a low-risk for develop neutralizing or binding antibodies against rVWF. Also, potential impurities present in rVWF are considered to be low.

PV Actions:

- Passive surveillance of spontaneous AE reports, medical literature.
- Labeled in Package Insert sections: Dosage and Administration, Warnings and Precautions (Sections 5.3 and 5.4 describe potential development of VWF and/or FVIII inhibitors and use of appropriate inhibitor assays); Patient Counseling Information.
- Additional safety data will be collected from postmarketing clinical trials (efficacy studies: (b) (4))

Reviewer comment: Clinical trial data demonstrates low risk of inhibitor formation, although the studies were small. At this time, routine PV and labeling are adequate.

3. Thromboembolic events: Important Potential Risk

Thromboembolic reactions such as disseminated intravascular coagulation (DIC), venous thrombosis, pulmonary embolism, myocardial infarction, and stroke can occur, particularly in patients with known risk factors for thrombosis, including low ADAMTS13 levels, and concomitant overuse of FVIII.

Data: No thrombotic or thromboembolic events occurred in any subject enrolled in clinical studies with rVWF, although the studies were small.

PV Actions:

- Passive surveillance of spontaneous AE reports, medical literature.
- Labeled in in Package Insert section: Warnings and Precautions.
- Additional safety data will be collected from postmarketing clinical trials (efficacy studies: (b) (4)

Reviewer comment: At this time, routine PV and labeling are adequate. Note that the risk of thrombotic and thromboembolic events with use of VONVENDI in combination with FVIII is described in the PI as follows: “Monitor plasma levels of factor VIII activity in patients requiring frequent doses of VONVENDI with ADVATE. An excessive rise in factor VIII levels can increase the risk for thromboembolic events.”

4. Missing information on pediatric and geriatric patients, and pregnant/lactating women are labeled in the PI (Use in Special Populations). Missing information on pregnant women (Pregnancy Category C: animal reproduction studies have not been conducted and no data on whether rVWF can cause fetal harm or affect reproductive capacity) is also labeled in the PI under sections: Use in Special Populations and Nonclinical Toxicology.

Reviewer comment: Of note, VONVENDI is designated an orphan drug and is exempt from PREA; however Baxter has submitted a pediatric study plan. At this time, routine PV and labeling are adequate.

5.3 Postmarketing Clinical Trials

Baxter has two planned phase 3 clinical trials; the protocols of these studies were submitted under IND 13657.

- (b) (4)

(b) (4)

Reviewer comment: At this time, the available data do not suggest a safety concern that would necessitate a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. The two planned postmarketing clinical trials (studies (b) (4)) are designed to (b) (4) of VONVENDI, and they will collect additional safety data and add to the clinical safety dataset for VONVENDI.

6. OBE/DE ASSESSMENT AND RECOMMENDATIONS

6.1 Conclusion

If approved by FDA, VONVENDI will be the first recombinant VWF for the prevention and treatment of bleeding episodes in VWD patients 18-64 years of age. Depending on the clinical setting, the treatment of VWD may involve the co-administration of VONVENDI and ADVATE; the first dose of VONVENDI is to be co-administered with ADVATE in a 1.3:1 ratio if FVIII baseline levels are below 40% or if FVIII levels are unknown. Excess VWF and/or FVIII may be risk factors for thromboembolic events. No safety signal was identified from clinical trial data; specifically there were no reports of thromboembolic events or treatment-related development of neutralizing antibodies against VONVENDI or neutralizing antibodies against ADVATE. AEs were mostly non-serious and generally mild. There were no confirmed seroconversions for any blood-borne viruses.

In the pivotal phase 3 clinical trial (study 071001), 192/192 bleeding episodes treated with VONVENDI in 22/37 VWD subjects met the criterion for successful treatment; and all bleeds were controlled with VONVENDI or VONVENDI in combination with ADVATE with an efficacy rating of excellent (96.9%) or good (3.1%).

Recombinant VWF has several potential advantages over currently available plasma derived VWF:

- Purity: intact/uncleaved high molecular weight and ultra large multimers (active form of VWF) since it is not exposed to protease ADAMTS13 during production
- Minimal risk of transmission of blood-borne pathogens. As per Baxter, “in contrast to plasma-derived coagulation factors, no therapeutic protein produced by a recombinant cell line has ever resulted in virus transmission; which is primarily due to the ability to control the recombinant cell line manufacturing environment.”

- Recombinant technology overcomes the limitations of supply of plasma derived VWF concentrates

In conclusion, clinical trial data demonstrate a positive benefit/risk ratio for use of VONVENDI. However, while these results are reassuring, the data should be interpreted with caution due to the small sample size of the clinical safety dataset and a single phase 3 efficacy study with limited follow-up. The risk for VWD patients to develop neutralizing antibodies against VONVENDI or potential impurities present in the product may be further assessed during VONVENDI use in the postmarketing setting, should the product be licensed, as well as from other clinical studies using VONVENDI.

6.2 OBE/DE Recommendations

At this time OBE/DE has determined that routine pharmacovigilance as per Baxter's proposed Pharmacovigilance Plan, Version 1.0, dated November 19, 2014, is satisfactory. The available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. The two planned postmarketing (b) (4) clinical trials (b) (4) will collect additional safety data and add to the clinical safety dataset for VONVENDI.