Summary Basis for Regulatory Action

Date: December 8, 2015

From: Chava Kimchi-Sarfaty, Chair of the Review Committee

BLA/ STN#: 1255770/0

Applicant Name: Baxalta US Inc. (formerly Baxter Healthcare Corporation)*

Date of Submission: December 19, 2014

PDUFA Goal Date: December 19, 2015

Proprietary Name/ Established Name: VONVENDI, von Willebrand factor (recombinant)

Indication: On-demand treatment and control of bleeding episodes in adults diagnosed with von Willebrand disease

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Dr. Jay Epstein, Director, Office of Blood Research and Review, CBER
□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Offices Signatory Authority: Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, CBER
□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

*The original submission was submitted under Baxter Healthcare Corporation, but the firm went through reorganization and in the September 28, 2015 amendment changed their name to Baxalta US Inc.

Discipline	Reviewer(s) Name
Clinical	Victor Baum & Mitchell Frost
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Statistics	Shuya (Joshua) Lu
CMC	Chava Kimchi-Sarfaty (Chairperson), Jie He & Zuben E. Sauna
Pharmacology/ Toxicology Review	Anne M. Pilaro
Labeling	Loan Nguyen, Iftekhar Mahmood, Zuben E. Sauna, Chava Kimchi-Sarfaty, Anne M. Pilaro, Victor Baum & Mitchell Frost
Bioresearch Monitoring Review	Colonious King
Establishment Inspection Report	Jie He (Lead Inspector), Zuben E. Sauna & Chava Kimchi-Sarfaty
Pharmacovigilance	Meghna Alimchandani, Christopher Jankosky
Quality Control tests and Method Validation	Lokesh Bhattacharyya, Grainne Tobin, Noel Baichoo, Tao Pan, Parmesh Dutt, Kouassi Ayikoe, Ritu Agarwal, Mark Levi, Hsiaoling Wang, Alfred Del Grosso & Hyesuk Kong
Lot Release Testing Plan	Karen Campbell
In-support Testing	Parmesh Dutt, Grainne Tobin, Ritu Agarwal & Hyesuk Kong
Advisory Committee	Waived

1. Introduction

Baxter Healthcare Corporation has submitted an original biologics license application (BLA) to seek U.S. licensure for recombinant von Willebrand factor (VWF). The firm has since undergone reorganization and the entity that is responsible for this BLA application is now named Baxalta US Inc. The proprietary name of the U.S. marketed product will be VONVENDI. VONVENDI is a lyophilized powder available in nominal dosage strengths of 650 or 1300 international units (IU) of recombinant von Willebrand factor (hereafter, rVWF) potency. The product is reconstituted with the provided sterile Water for Injection (WFI) for intravenous administration.
VONVENDI is indicated for on-demand treatment and control of bleeding episodes in adults diagnosed with von Willebrand disease (VWD).

2. Background

VWD is the most common inherited bleeding disorder in humans, with an incidence estimated to be from 1:100 to 1:1000 live births, divided equally among men and women. VWF corrects the hemostatic abnormalities experienced by VWD patients by: 1) acting as an adhesive molecule, mediating platelet adhesion to damaged vascular sub-endothelial tissues like collagen, and platelet aggregation; and 2) functioning as a carrier protein for factor VIII and protecting it from rapid clearance. VWD can be due to quantitative (types 1 and 3) or qualitative (type 2) abnormalities in VWF. The distribution of the various types is as follows: type 1 - approximately 70-80% of cases, type 2 - approximately 20% of cases, and type 3 - approximately 1-5% of cases. Mutations in the VWF gene can result in these distinct VWD phenotypes because they can disrupt a complex biochemical process at several steps to impair the assembly, intracellular targeting, or secretion of VWF. Other mutations impair the survival of VWF in plasma or the function of specific ligand binding sites.

VWF is a large multimeric glycoprotein that is normally expressed in endothelial cells and megakaryocytes, stored in platelet alpha-granules and within the Weibel-Palade bodies of endothelial cells, and released into the plasma. The multimers of VWF range in molecular weight from 500 to > 20,000 kDa, and are composed of monomers with an apparent molecular weight of approximately 250 to 270 kDa. Mature VWF is proteolytically degraded by the von Willebrand factor-cleaving protease (VWFCP), a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). This process occurs under shear conditions in the plasma following secretion of VWF. ABO-blood type antigens are found on 15% of the N-glycans in VWF circulating in plasma. The rVWF and the VWF that is stored in platelets do not contain ABO blood type antigens.

The von Willebrand Ristocetin Cofactor [VWF:RCo] assay measures the ability of a patient's plasma to agglutinate platelets in the presence of the antibiotic Ristocetin. The rate of Ristocetin induced agglutination is related to the concentration and functional activity of the plasma VWF. This is the assay used to assign potency for VONVENDI.

rVWF is expressed in Chinese Hamster Ovary (CHO) cells that also express the licensed rFVIII product ADVATE. (b) (4) by a recombinant furin (rFurin), (b) (4), and concentrated to approximately 130 IU VWF: Ristocetin cofactor activity (VWF:RCo)/mL. Only trace quantities of rFVIII, murine immunoglobulin (IgG, from the immunoaffinity purification of (b) (4) VONVENDI), CHO protein, and rFurin are present in the final container product.

VONVENDI is not exposed to proteolysis by ADAMTS13 during the manufacturing process and therefore contains all sizes of multimers including the ultra-large non-proteolysed multimers, which are the most active multimers and are observed in the endogenous VWF immediately after secretion from the storage sites. In vitro studies have demonstrated that the presence of ultra-large multimers in high-shear flow conditions leads to rapid platelet-VWF conglomerate formation as well as platelet adhesion to, and platelet aggregation on collagen, which is found in vascular sub-endothelium. Under high flow conditions, ADAMTS13 limits platelet-VWF-conglomerate formation as well as aggregate formation on collagen.

Clinical trials that provided the evidence for the safety and efficacy of VONVENDI were conducted under IND 13657. To support licensure for the proposed indication, the clinical development program included a Phase 1 trial to evaluate the safety of VONVENDI co-administered with ADVATE, in subjects with hemophilia A; a Phase 1 PK trial in two type 1, and 29 type 3 subjects with VWD, to establish the dosing of VONVENDI for the treatment of bleeding episodes; and a Phase 3 trial in two type 1, five type 2A, one type 2N, and 29 type 3 patients with VWD to test the clinical efficacy and safety of VONVENDI in treating bleeding episodes. All trials enrolled only adult subjects, ages 18 to 64 years of age.

VONVENDI is not currently approved or marketed in any country.

This original BLA was reviewed under the PDUFA V program, which had a 12-month review schedule. The review milestones are listed in the table below:

Review Milestones

Milestone	*Date*
Received	December 19, 2014
Committee assignment	December 22, 2014
Filing date	February 13, 2015
Proprietary name review decision	March 26, 2015
Inspections	(b) (4)
FDA Form 483 issuance	(b) (4)
Mid-cycle communication	June 11, 2015
Late-cycle meeting	September 3, 2015
Advisory Committee	Waived
Action Due Date	December 19, 2015

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Description
VONVENDI is a sterile, non-pyrogenic, preservative-free, white or almost white, lyophilized powder reconstituted with WFI. After reconstitution of the lyophilized powder, all dosage strengths yield a clear, colorless solution and contain the excipients: tri-sodium citrate, glycine, mannitol, trehalose, and polysorbate 80. VONVENDI is available in single-use vials containing nominal VWF potencies of 650 or 1300 IU VWF VWF:RCo. Each VONVENDI vial is labeled with the actual rVWF potency. Sterile water for reconstitution and a Mix2Vial device are also provided. After reconstitution the product is administered intravenously.

Analytical Characterization
VWF is a blood glycoprotein that is initially synthesized as a 2813 amino acid pro-VWF molecule. The pre-pro-VWF is composed of a 22 amino acid signal peptide, a 741 amino acid pro-peptide and a 2050 amino acid mature VWF subunit. The pro-VWF is composed of four repeats (A-D), which contain functional domains that have been identified as interaction sites with factor VIII (FVIII), platelet glycoproteins GPIb and GPIIb/IIIa, collagen and heparin.

VWF has multiple post-translational modifications; it is composed of a series of high molecular weight multimers that range between approximately 500 kDa (VWF dimer) to >20,000 kDa. The monomer of VWF has an apparent molecular weight (by SDS-PAGE analysis) between 250 and 270 kDa. VONVENDI contains all the VWF multimers found in plasma in addition to ultra-large multimers which are usually only found in physiological VWF stored in the Weibel–Palade bodies of endothelial cells and in platelet α-granules.

Impurities

Adequate removal of product and process related impurities by the commercial manufacturing process was demonstrated during process development and process validation.

Residual amounts of the following product and process related impurities were characterized and monitored in (b) (4) drug product:

- Host cell related impurities: CHO Host Cell Protein (tested by (b) (4) host cell related proteins, (b) (4) and residual rFurin (tested by (b) (4)
- rFurin (characterized using an array of test attributes)
- Residual FVIII (tested by (b) (4)
- Murine monoclonal antibodies ((b) (4))
- (b) (4)
- Polysorbate-80

Drug Product Release Specification

Baxter used characterization data and risk assessment to propose the final drug product release specification presented below, based on (b) (4) rVWF lots. The release specifications in the table below are considered adequate to confirm product quality and manufacturing consistency.

Parameter	***Test Method***	***Acceptance Criteria***
VWF:RCo Activity	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	

(b) (4)	(b) (4)	
Sterility	(b) (4)	
Endotoxin	(b) (4)	
Appearance (lyophilized cake)	Visual	White to off-white friable powder
Appearance (reconstituted solution)	Visual	Clear, colorless solution, free from particles
Reconstitution Time	Time	(b) (4)
(b) (4)	(b) (4)	
Residual Moisture	(b) (4)	
(b) (4)	(b) (4)	
Particulate Matters	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
Citrate	(b) (4)	
Polysorbate-80	(b) (4)	
((b) (4)		
Glycine	(b) (4)	
Sodium	(b) (4)	
Mannitol	(b) (4)	
Trehalose	(b) (4)	

At each significant phase of pre-market development, product quality was linked to manufacturing control through a comparability program that integrated nonclinical animal studies and clinical trial experience with extensive analytical characterization.

Manufacturing Control

Process Description

(b) (4)

Critical Process Parameters and Their Control
The rVWF is manufactured and formulated in the absence of animal or human plasma proteins. Recombinant VWF protein is expressed in Chinese Hamster Ovary (CHO) cells that also express the licensed rFVIII product ADVATE. (b) (4) by rFurin, (b) (4) . The process was established using small scale batches in the development phase where process ranges were established. These acceptable ranges were adhered to in scale up which followed the one factor at a time (OFAT) paradigm. The process was thus brought to manufacturing scale (b) (4)

Baxter assessed the process at manufacturing scale for removal of product and process related impurities. Consistent removal of the impurities is demonstrated with data from (b) (4) Process Performance Qualification (PPQ) batches.

Process Validation
(b) (4) lots were validated for the manufacturing process. Since the modification of the process, using a (b) (4) drug substance lots and (b) (drug product lots were manufactured and their release specification attributes were reviewed and found acceptable. The drug product conformance lots are summarized in the tables below.

The following major Chemistry, Manufacturing and Controls product issues were discussed and resolved with Baxter during the review of the IND:

Establish similar kinetics of ADAMTS13 degradation to plasma-derived VWF (pVWF).
Initially, Baxter did not provide data that could demonstrate that rVWF multimers show the same pattern as plasma-derived VWF (pVWF). Consequently the Agency placed the application on clinical hold in May 2008 and requested that Baxter demonstrate that rVWF show the same sensitivity to ADAMTS13 cleavage as pVWF. In addition Baxter was requested to perform studies that could show a correlation between the changes in the multimeric structure of VWF molecules following ADAMTS13 cleavage to changes in VWF activity. Baxter performed additional studies and showed that the kinetics of ADAMTS13 degradation of rVWF are comparable to those of pVWF degradation. Additionally, Baxter correlated the changes in multimeric structure of rVWF molecules over time to changes in rVWF activity, such as ristocetin cofactor activity (VWF:RCo) and/or collagen binding (VWF:CB) activity.

Establish a test to detect host cell proteins (HCPs).
Baxter addressed the Agency's request to adequately detect and evaluate HCP impurities. Chinese Hamster Ovary (CHO) cells, used to produce rVWF, (b) (4) , can be the source of HCPs. Baxter added a (b) (4)

(b) (4) analysis to compare the amount of HCPs from the (b) (4) The results of the test are satisfactory.

Establishment of (b) (4) *, Mix2Vial, to clear sub-visible insoluble particles and test method for drug product appearance.*

Data from stability studies conducted by Baxter showed the presence of sub-visible insoluble particles in the final drug product which appear only during vigorous shaking of the product. These particles were shown to appear only under harsh conditions. Baxter validated a biophysical method (b) (4) which is now part of the release testing for rVWF Final Drug Product (FDP). (b) (4)

Additionally Baxter added the Mix2Vial (b) (4) which is included in the VONVENDI clinical kit. The family of Mix2Vial transfer devices are 510(k) cleared [510(k) # K031861] and CE marked. They are distributed by MEDIMOP Medical Products Ltd., a West Company. This (b) (4) will clear particles at point of care should they develop due to excessive shaking.

(b) (4)

Conformance lots manufacture

Origin of Final Drug Product Lots, 650 IU/vial

(b) (4)			

(b) (4)			

Origin of Final Drug Product Lots, 1300 IU/vial

(b) (4)			

Analytical Methods
Suitable analytical methods have been validated to support quality control throughout manufacture, final product release and stability monitoring. An acceptable reference standard qualification and maintenance program has been established.

Container/Closure System
The 650 IU/vial drug product presentation is filled into a 10 mL (b) (4) glass vial ((b) (4) closed with a 20 mm (b) (4) butyl rubber (b) (4) stopper (b) (4) and sealed with a 20.3 mm aluminum white flip-off crimp seal (b) (4) Baxter conducted the container closure integrity testing, using a (b) (4) test and all acceptance criteria were met.

The 1300 IU/vial drug product presentation is filled into a 30 mL (b) (4) glass vial (b) (4) closed with a 20 mm (b) (4) butyl rubber (b) (4) stopper (b) (4) and sealed with a 20.3 mm aluminum white flip-off crimp seal (b) (4) Baxter conducted the container closure integrity testing using a (b) (4) test method and all acceptance criteria were met.
The 5 mL sWFI reconstitution diluent is filled into a 6 mL (b) (4) glass vial (b) (4) closed with 20 mm (b) (4) chlorobutyl rubber stopper (b) (4) and sealed with 20 mm gray flip-off caps (b) (4) (b) (4) conducted the container closure integrity testing using a (b) (4) test method; all acceptance criteria were met.

The 10 mL sWFI reconstitution diluent is filled into a 10 mL (b) (4) glass vial (b) (4) closed with 20 mm (b) (4) bromobutyl rubber stopper and sealed with 20 mm light blue flip-off caps (b) (4) conducted the container closure integrity testing using the (b) (4) test method; all acceptance criteria were met.

Stability
The proposed shelf-life of VONVENDI drug product is (b) (4) months when stored at 5 °C and 30 °C, (b) (4) The proposed shelf-life of the drug substance is for (b) (4) The available stability data indicate no critical trends during the observed long-term storage period.

The available photostability data indicates that the product is not sensitive to light, but due to the large amount of disulfide bridges present in the mature form, the rVWF protein is considered to be susceptible to UV radiation in particular and therefore should be stored away from light.

Microbiological Test Qualifications
Baxter's bioburden, sterility, and bacterial endotoxin test using (b) (4) methods were qualified according to (b) (4) respectively, by demonstrating the rVWF matrix is suitable for these intended test methods.

Viral safety
All cell banks have been demonstrated to be free of infectious viruses. The manufacturing process does not use animal-derived raw materials. Additionally, the risk of BSE/TSE and adventitious viruses is minimized by the sourcing of the raw material and in the submitted documents of certification. (b) (4)

(b) (4) Additionally, no human- or animal derived proteins are used in the VONVENDI manufacturing process. The CHO cell line is grown and expanded in (b) (4) . These measures virtually eliminate the theoretical possibility that a potential viral contaminant could be introduced into the VONVENDI manufacturing process via the process auxiliaries and additives.

The viral safety profile for VONVENDI is considered acceptable. The results are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

b) CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-by-lot release by CBER is not required for VONVENDI because it is a well-characterized recombinant product. Thus, exemption of VONVENDI from CBER Lot Release is justified. CBER has performed in-support testing of commercial scale VONVENDI product lots of 650 IU and 1300 IU nominal potencies. Test results were deemed consistent with the proposed commercial release specifications.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of VONVENDI are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities for VONVENDI

Name/Address	***FEI Number***	***Duns Number***	***Inspection/ Waiver***	***Results/ Justification***
Drug Product Manufacturing, primary labeling and final packaging Baxter Healthcare Corporation 1700 Rancho Conejo Blvd. Thousand Oaks, CA 91320	1000519965	009471603	Waived	Team Biologics 2/19-28/2014 VAI
Drug Substance Manufacturing and release testing Baxter	(b) (4)			
Drug Substance Manufacturing Baxter	(b) (4)			
Drug Substance Warehousing and release testing Baxter	(b) (4)			
Drug Product Diluent Manufacturing	(b) (4)			

CBER conducted a pre-license inspection (PLI) of Baxter's (b) (4) , for QC release testing of VONVENDI. At the end of the inspection, CBER issued a Form FDA 483 with two observations. Deficiencies included inadequate SOPs and deviation management for QC tests. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

CBER conducted a pre-license inspection (PLI) of Baxter's (b) (4) for the purification processes and QC release testing of VONVENDI. At the end of the inspection, CBER issued a Form FDA 483 with four observations. Deficiencies included inadequate SOPs and deviation management for QC tests, inadequate autoclave validation and inadequate shipping validation for BDS. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

Team Biologics conducted a surveillance inspection of Baxter's Thousand Oaks, CA facility from February 19 -28, 2014. The inspection was classified as Voluntary Action Indicated (VAI). All Form 483 issues were resolved.

Team Biologics conducted a surveillance inspection of Baxter's (b) (4) . The inspection was classified as VAI. All Form 483 issues were resolved.

Team Biologics conducted a surveillance inspection of (b) (4) . The inspection was classified as VAI. All Form 483 issues were resolved.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

General Considerations

The safety and efficacy of VONVENDI were supported by a series of in vitro, in vivo and ex vivo studies in genetically modified, von Willebrand factor (VWF)-, ADAMTS13-, and factor VIII (FVIII)-deficient (i.e., VWF-knockout) mice, congenitally VWF-deficient dogs and pigs, and VWF-replete (i.e., wild-type) mice, rats, rabbits, dogs and (b) (4) monkeys. Risk assessments of the potential extractable and leachable compounds in the VONVENDI drug substance related to the production process, and in the final drug product related to the container closure system, as per the (b) (4) standards, were also provided for review.

a. Pharmacological/Toxicological Findings

Pharmacology

In vitro, mechanistic studies with VONVENDI using a model designed to evaluate the effects of the ultralarge VWF multimers on platelet function (i.e., aggregation and rolling) showed that coincubation of human platelets with increasing concentrations of rVWF containing the ultralarge multimers increased both the formation and size of rolling platelet aggregates both in solution, and on rVWF-coated surfaces under shear stress (i.e., conditions that approximate those in large vessels in vivo), as compared to incubation with comparator control VWF products or plasma. In the presence of VONVENDI, these aggregates were increased in size under elevated shear rates, demonstrating that VONVENDI is biologically active in mediating platelet function associated with hemostasis; however, these data also suggest that the risk of thrombosis may be elevated in vivo, due to the increased platelet aggregates induced by the ultralarge VWF multimers. Additional in vitro studies showed that the increased formation of rolling platelet aggregates in vitro was diminished in the presence of added, recombinant ADAMTS13 (rADAMTS13) and was not significantly different from that observed when platelets were incubated with an equivalent dose of human plasma-derived VWF (pdVWF), suggesting that excessive thrombosis should not occur in vivo in patients with VWD and normal levels of ADAMTS13 after dosing with VONVENDI.

Nonclinical studies to assess the primary pharmacologic activity of VONVENDI in hemostasis were conducted in vivo using congenitally VWF-deficient dogs, and mice that were genetically engineered to delete expression of the murine VWF gene (i.e., VWF-knockout) mice. In an $FeCl_3$-induced model of arterial thrombosis in VWF-knockout mice, treatment with rVWF with or without human recombinant FVIII (i.e., ADVATE) led to dose-dependent increases in stable thrombus formation, and decreases in time to occlusion at the injured carotid artery site. When VONVENDI was co-administered with rADAMTS13 to VWF-knockout mice with $FeCl_3$-injured blood vessels, induction of thrombosis in both the macro- and microvasculature was reported, and was comparable to that observed when groups of VWF-knockout mice were dosed with increasing doses of pdVWF. These data suggest that human rADAMTS13 cleaves VONVENDI to result in potency similar to physiologic and supra-physiologic levels of pdVWF in VWF-knockout mice.

The ability of VONVENDI to promote hemostasis in animal models of von Willebrand disease was evaluated in VWF-knockout mice using a tail-transection bleeding model, and in congenitally VWF-deficient dogs by measuring changes in bleeding time, activated partial thromboplastin time (APTT) and hematology profiles as an estimation of blood loss. VWF-knockout mice were injected with a single, intravenous dose of VONVENDI with or without ADVATE (ratio of rVWF:rFVIII = 1.3:1), human pdVWF, or the negative (buffer) control. Five minutes later, the tails were surgically transected and the time to hemostasis (TTH) and blood loss were evaluated for each animal. Time to hemostasis and mean blood loss were

significantly improved in VWF-knockout mice dosed by intravenous injection with 10, 15, or 20 times the initial clinical dose of VONVENDI together - with the corresponding dose of ADVATE, as compared to the VWF-knockout mice injected with the buffer control. By contrast, there were no differences in TTH or blood loss between the negative control group and the VWF-knockout mice injected with any dose level of rVWF alone, or with human pdVWF at a dose equivalent to the highest VONVENDI dose tested. No clinical signs of toxicity secondary to thrombosis were reported in these studies; however, these study designs did not include necropsy or histopathology of major organ systems.

In a combined pharmacodynamics, pharmacokinetics and safety pharmacology proof-of-concept study in congenitally VWF-deficient dogs, one dog each was injected intravenously with an equivalent dose of human pdVWF or VONVENDI, at approximately 2.5-fold greater than the initial recommended clinical dose. Saline bleeding time (SBT; i.e., time to cessation of bleeding after a surgical nick in the ear and application of saline wash), plasma VWF levels and limited cardiovascular safety endpoints (heart rate, blood pressure) were measured at various time points up to 24 h after dosing. The animal dosed with human pdVWF showed mild but measurable blood loss as evidenced by decreases in erythrocyte parameters, increased APTT and prolonged SBT, as compared to the VWF-deficient dog dosed with VONVENDI. Additionally, the positive effects of VONVENDI on hemostasis in the treated dog were maintained for approximately 4 hours after dosing, which corresponded with plasma levels of VWF that were within the normal range (as measured by both (b) (4)/VWF:Ag and VWF:Riscocetin assays).

The pharmacokinetics profile of VWF showed an approximate 3-fold increase in exposure (Area Under the Concentration/Time Curve, AUC_{0-t}), a 3-fold decrease in clearance (CL), and an approximate 2-fold increase in both mean residence time (MRT) and elimination half-life ($t½_{\beta}$) in the VONVENDI-treated dog, as compared to the values obtained for each of these parameters in the dog dosed with the human pdVWF. A 35% decrease in platelet counts from baseline was reported 15 minutes after dosing with VONVENDI and subsequent surgical incision; however, this finding is expected due to the pharmacologic activity of VWF in promoting platelet aggregation at the wound site, and platelet counts for this dog returned to normal for the remainder of the study. There were no adverse changes in blood pressure or heart rate reported for either dog after dosing with VONVENDI or human pdVWF as compared to baseline levels, and all clinical chemistry parameters were within the normal range for the duration of the study. These data, together with the data from the arterial thrombosis models and tail bleeding models in the VWF-knockout mice were used to establish the clinical dose of 40 IU VONVENDI/kg body weight as a starting dose for use in clinical trials in patients with VWD.

Safety Pharmacology

Safety pharmacology studies to evaluate the effects of VONVENDI were performed in congenitally VWF-deficient dogs, and in VWF-replete, spontaneously hypertensive rats, guinea pigs, rabbits, and (b) (4) dogs. There were no reported adverse effects of VONVENDI on respiratory rate, blood pressure, heart rate or ECG in either VWF-replete (b) (4) dogs or VWF-deficient dogs following dosing with 2.5 times the clinical starting dose. In the spontaneously hypertensive rats, there was a greater than 30% decrease in mean arterial pressure in 17% of the rats within the first 10 minutes after an initial intravenous injection of VONVENDI at a 6-fold higher dose than the labeled clinical starting dose, which did not recur following injection with a second dose. Guinea pigs dosed with 6-fold higher doses of VONVENDI than the labeled clinical dose showed no effects on respiratory parameters (e.g., respiratory rate, pulmonary pressure); however, following a second dose of rVWF 25% of the animals demonstrated a 30% or greater increase in pulmonary inflation pressure within the first 10 minutes after repeated exposure to VONVENDI. Lastly, using the Wessler model there was no evidence of in vivo thrombogenicity in VWF-replete rabbits dosed with 20 to 30 times the labeled clinical starting dose of VONVENDI.

In summary, genetically modified, VWF-knockout mice dosed with VONVENDI and rFVIII showed the expected pharmacologic, pro-coagulant activity, whereas equivalent doses of rVWF alone or human pdVWF were inactive in these models. The lack of biologic activity of VONVENDI in the VWF-knockout mice is likely due to differences in species-specificity of both the murine ADAMTS13 for cleavage of the UHMWM in human rVWF, and decreased affinity of murine platelets for either human recombinant or pdVWF. These differences were not evident in other test animal species used in further pharmacology, safety pharmacology or toxicity testing. Blood loss, saline bleeding time and aPTT were normalized in a congenitally VWF-deficient dog treated with a single intravenous dose of 2.5 times the clinical starting dose of VONVENDI; by contrast, a second dog injected with an equivalent dose of human pdVWF showed mild but measurable blood loss, increased APTT and prolonged bleeding time compared to the VONVENDI treated dog. There were no apparent adverse, secondary pharmacology (safety pharmacology, thrombogenicity) effects in VWF-replete (b) (4) dogs or rabbits. Transient, although non-specific changes in mean arterial pressure and pulmonary inflation pressure were seen in a small number of VWF-replete, spontaneously hypertensive rats and guinea pigs, respectively. Mechanistic studies demonstrated that coincubation of human platelets with ADAMTS13 and VONVENDI resulted in in vitro platelet aggregation and rolling in a high shear stress model that was comparable to that achieved using an equivalent dose of pdVWF as a positive control. These data were used as proof-of-concept to demonstrate the biologic activity of VONVENDI, and to select an anticipated effective starting dose and support the rationale for its entry into clinical trials in patients with VWD.

Nonclinical Pharmacokinetics

Nonclinical pharmacokinetics (PK) studies with VONVENDI administered either alone or with rFVIII (ADVATE) at a ratio of rVWF:rFVIII = 1.3:1 IU/kg/dose were performed in VWF-replete rats and (b) (4) monkeys, and in VWF-knockout mice and congenitally VWF-deficient dogs. Serum rVWF assays were measured using both an (b) (4) assay specific for the human VWF protein and a VWF:Ristocetin cofactor assay. Serum FVIII levels were measured using an (b) (4) assay for FVIII:Ag, and using the (b) (4) assay. In vivo organ distribution of rVWF was measured using (b) (4) -labeled rVWF and (b) (4) in a VWF-knockout mouse model. Toxicokinetics evaluations were also incorporated in all pivotal single- and repeat-dose toxicity studies, to confirm exposure of the animals to VONVENDI, and to rFVIII where applicable.

Increases in VWF maximal plasma concentration (C_{max}) and exposure (AUC_{0-t}), as measured by either assay methodology were reported in VWF-knockout mice and VWF-deficient dogs, and in VWF-replete rats and (b) (4) monkeys following a single, intravenous dose of VONVENDI approximately 2.5- to 3-fold greater than the labeled clinical starting dose, as compared to baseline VWF levels. There was no evidence of accumulation or anti-VWF antibody development (i.e., immunogenicity) in these single dose studies. The values for C_{max} and AUC_{0-t} for rVWF in the VONVENDI-treated animals were approximately 3-fold higher than those achieved in the mice or dogs dosed with an equivalent dose of human pdVWF. Volume of distribution was approximately equivalent to the vascular space, and t½ ranged from approximately 2 hours in the rat and VWF-knockout mouse models, to 13 h in the VWF-deficient dogs. Co-administration of rFVIII together with VONVENDI did not affect the C_{max}, AUC_{0-t}, or CL of VONVENDI. Toxicokinetic evaluations in VWF-knockout mice and in VWF-replete mice, rats, rabbits and (b) (4) monkeys showed similar PK profiles following a single dose of VONVENDI of 2.5 to 50 times the clinical labeled dose; however, in these studies CL decreased and t½ increased with increasing doses of VONVENDI, suggesting that the mechanism by which rVWF is cleared from the circulation is saturable. The toxicokinetic profiles from repeat-dose administration toxicity studies also showed non-linear profiles; in these studies, accumulation of VONVENDI was shown between study day 1 and day 8; however, the majority of animals developed a rapid anti-VWF antibody response by study day 14, and exposures were markedly decreased by completion of dosing at study day 28.

Toxicology

Single dose toxicity studies with VONVENDI were conducted in VWF-knockout mice, ADAMSTS13-knockout mice, FVIII-knockout mice, and in wild-type (VWF-replete) mice, rats, rabbits and (b) (4) monkeys with or without the administration of ADVATE (ratio of rVWF:rFVIII = 1.3:1) or human, rADAMSTS-13. Toxicities, including thrombosis and/or microthrombi in the highly perfused organs (e.g., lungs, brain, heart, kidneys) were reported in both the wild-type and VWF-knockout mice, and in ADAMSTS13-knockout mice after a

single dose of approximately 6- to 100-fold greater than the labeled clinical dose of VONVENDI. Necrosis, secondary to thrombosis was also present in hearts from ADAMTS13-knockout mice following dosing with VONVENDI at 50-fold greater than the recommended clinical starting dose. Similar toxicities were also reported, and were not increased in either frequency or severity, in animals that received single doses of both VONVENDI (6- to 100-fold greater than the clinical dose) and rFVIII at the 1.3:1 IU/kg/dose ratio. Mechanistic toxicity studies revealed that murine ADAMTS13 is not capable of cleaving the ultra-large HMW VWF multimers present in VONVENDI, suggesting that the increased thrombosis and microthrombi in the VWF-knockout, ADAMTS13-knockout, and wild-type mice were secondary to the pharmacodynamic effects of the multimeric VWF on platelet aggregation. In ADAMTS13-knockout mice, which have circulating HMW multimers of murine VWF, dosing with physiologic levels of human rADAMTS13 did not decrease the thrombosis in the major organ systems, implying that the thrombosis, microthrombosis and necrosis reported in mice is a species-specific effect due to lack of cleavage of the ultra-large multimers of VWF in VONVENDI. By contrast, there were no remarkable toxicities reported in wild-type rats, rabbits, or (b) (4) monkeys following a single intravenous injection of VONVENDI at doses up to 30 times greater than the labeled clinical starting dose of 40 IU/kg, suggesting that the species-specificity of ADAMTS13 for VONVENDI is restricted to mice.

In repeat-dose toxicity studies, there were no remarkable findings in (b) (4) monkeys or in a single VWF-deficient pig dosed for up to 14 days with 1 to 2.5 times the recommended clinical dose level of VONVENDI, either alone or in combination with ADVATE at the dosing ratio of 1.3:1 IU/kg/dose. However, hematology findings including mild regenerative anemia, thrombocytopenia and microscopic findings of inflammatory lesions in the heart, liver, and salivary gland were present in (b) (4) rats dosed for 14 days with VONVENDI at 3 times the clinical starting dose level, with or without co-administration of ADVATE. All findings in the (b) (4) rats were reversible following a 15-day recovery period.

The International Conference on Harmonization (ICH) standard battery of in vitro and in vivo genotoxicity studies was conducted with VONVENDI as per the ICH S2(R2) guidance, and no mutagenesis was detected. No animal studies were conducted to evaluate the effects of VONVENDI on carcinogenesis, impairment of fertility, or reproductive and developmental toxicity, and as per the ICH S6(R1) guidance for biotechnology-derived products, therefore these studies are not required to support approval. Because VONVENDI is a human recombinant protein, anti-VWF antibodies to VONVENDI developed in rats and (b) (4) monkeys following 2 weeks of repeated, daily dosing with VONVENDI, which both accelerated its clearance and decreased or eliminated its exposure. Therefore, additional long-term, chronic toxicity testing or carcinogenicity studies (2-year, repeated daily dosing) with VONVENDI are not feasible. The lack of nonclinical carcinogenicity, fertility, and reproductive and developmental toxicity studies is appropriately addressed in the labeling for VONVENDI.

b. Nonclinical Conclusion

The results from the nonclinical development program with rVWF suggest that the safety profile of VONVENDI is adequate to support its use for on-demand treatment and control of bleeding in adults diagnosed with von Willebrand disease.

5. Clinical Pharmacology

Study #1: Recombinant von Willebrand Factor/Recombinant factor VIII Complex (rVWF:rFVIII): A Phase 1 study evaluating the pharmacokinetics, safety, and tolerability in severe von Willebrand disease (Study 070701). This was a multicenter, controlled, randomized, single-blind prospective phase 1 dose escalation study. The study consisted of 4 sequentially enrolled cohorts (there were 3 subjects in cohort 1, 5 subjects each in cohorts 2 and 3, 22 subjects in cohort 4A and 3 subjects in cohort 4B) who received a single IV infusion of rVWF:rFVIII as follows:

Cohort	Dose and IP	Subject diagnosis
Cohort 1	rVWF:rFVIII with 2 IU/kg VWF:RCo	Type 3 VWD
Cohort 2	rVWF:rFVIII with 7.5 IU/kg VWF:RCo	Type 3 VWD
Cohort 3	rVWF:rFVIII with 20 IU/kg VWF:RCo	Type 3 VWD
Cohort 4A	rVWF:rFVIII and pdVWF/FVIII with 50 IU/kg VWF:RCo, in random order	Type 3 VWD
Cohort 4B	rVWF:rFVIII and pdVWF/FVIII with 50 IU/kg VWF:RCo, in random order	Severe type 1VWD

The subjects were between 18 to 60 years of age and had hereditary type 3 VWD or severe type 1 VWD. Blood samples for PK study were taken at 15, 30, and 60 minutes after drug infusion, and at 3, 6, 9, 12, 24, 28, 32, 48, 72, and 96 hours. Pharmacokinetic parameters of Von Willebrand factor:Ristocetin cofactor activity (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB), and rFVIII:C were estimated by non-compartmental analysis. The PK of 2 IU/kg rVWF:rFVIII could not be estimated because the VWF levels were below the detection limit for the majority of PK time points. The PK parameters of 7.5, 20, and 50 IU/kg of VWF:RCo, VWF:AG, VWF:CB, and FVIIIC following rVWF/FVIII administration are summarized in Tables 1-3 of the Clinical Pharmacology section.

Table 1: Pharmacokinetic parameters (mean ± sd) **following 7.5 IU/kg rVWF/FVIII dose**

Parameters	***VWF:RCO***	***VWF:AG***	***VWF:CB***	***FVIII:C***
AUC (U*hr/dL)	254 ± 82	429 ± 104	443 ± 165	1950 ± 965
CL (mL/hr/kg)	3.3 ± 1.1	1.9 ± 0.4	2.0 ± 0.9	0.5 ± 0.2

Parameters	***VWF:RCO***	***VWF:AG***	***VWF:CB***	***FVIII:C***
Half-life (hrs)	7.5 ± 1.2	28.2 ± 5.8	23.1 ± 7.7	21.9 ± 2.5
IR (U/dL)/U/kg)	2.2 ± 0.3	2 ± 0.3	2.1 ± 0.6	6.9 ± 3.9

CL = clearance; IR = in-vivo recovery

Table 2: Pharmacokinetic parameters (mean ± sd) **following 20 IU/kg rVWF/FVIII dose**

Parameters	***VWF:RCO***	***VWF:AG***	***VWF:CB***	***FVIII:C***
AUC (U*hr/dL)	591 ± 181	838 ± 341	922 ± 293	2959 ± 740
CL (mL/hr/kg)	3.7 ± 1.4	2.8 ± 1.2	2.4 ± 0.8	0.7 ± 0.2
Half-life (hrs)	23.6 ± 24.7	26.1 ± 8.3	15.7 ± 5.4	20.4 ± 5.2
IR (U/dL)/U/kg)	1.5 ± 0.3	1.6 ± 0.5	2.1 ± 0.7	2.8 ± 0.6

Table 3: Pharmacokinetic parameters (mean ± sd) **following 50 IU/kg rVWF/FVIII dose**

Parameters	***VWF:RCO***	***VWF:AG***	***VWF:CB***	***FVIII:C***
AUC (U*hr/dL)	1541 ± 554	2245 ± 683	2998 ± 965	5376 ± 2380
CL (mL/hr/kg)	3.8 ± 2.8	2.8 ± 2.9	2.1 ± 2.0	1.6 ± 2.7
Half-life (hrs)	19.3 ± 11.0	25.3 ± 6.3	24.4 ± 14.6	24.3 ± 6.5
IR (U/dL)/U/kg)	1.7 ± 0.6	1.7 ± 0.5	2.7 ± 0.8	2.1 ± 0.8

The PK of rVWF:rFVIII in terms of its moieties differ from each other. The PK of rVWF/FVIII for VWF:RCo was linear between 20 and 50 IU/kg dose. The half-life of rVWF:rFVIII was longer (approximately 1.5-fold) than pdVWF and the clearance of rVWF:rFVIII was slower (approximately 1.3-fold) than pdVWF. rVWF:rFVIII and pdVWF are not pharmacokinetically equivalent (90% confidence interval for VWF:RCo ranged from 1.02-1.56).

Study #2: 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 VWD (Study 071001). This was a phase 3, multicenter study to assess the PK, safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes (BEs) in adult subjects with type 3 and severe type 1 VWD.

A total of 16 subjects in Arm 1 or Arm 2 included in the PK study (PK50 subjects), were randomized to receive an initial PK infusion of either 50 IU/kg VWF:RCo rVWF co-infused with 38.5 IU/kg rFVIII, or 50 IU/kg VWF:RCo rVWF co-infused with saline (placebo). These subjects then crossed over to the alternative treatment for the second infusion and PK assessment. A total of 15 subjects in Arm 3 included in the PK study (PK80 subjects) underwent PK assessment after an initial infusion of 80 IU/kg VWF:RCo rVWF, and

underwent a second PK assessment after an infusion of 80 IU/kg VWF:RCo rVWF after 6 months of treatment of BEs. Blood samples for PK study were taken at 15, 30, and 60 minutes after drug infusion, and at 3, 6, 9, 12, 24, 28, 32, 48, 72, and 96 hours. Pharmacokinetic parameters of VWF:RCo, VWF:Ag, VWF:CB and FVIII:C levels were estimated by non-compartmental analysis.

Pharmacokinetics of 50 IU/kg dose (crossover):
VWF Ristocetin Cofactor Activity (VWF:RCo): Mean VWF:RCo half-life (19.6 vs 21.9 hours) and clearance (0.033 vs 0.029 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

VWF Collagen Binding (VWF:CB): Mean VWF:CB half-life (19.2 vs 19.7 hours) and clearance (0.014 vs 0.013 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

VWF Antigen (VWF:Ag): Mean VWF:Ag half-life (22.7 vs 25.1 hours) and clearance (0.016 vs 0.015 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

Factor VIII:C: Mean factor VIII:C half-life (32.3 vs 31.2 hours) and clearance (0.008 vs 0.009 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

Overall, the crossover study of 50 IU/kg dose of rVWF alone and co-infused with rFVIII indicated that the half-life and clearance remained similar for VWF:RCo, VWF:AG, VWF:CB and FVIII:C.

Pharmacokinetics of 80 IU/kg dose: The PK parameters (clearance and half-life) of VWF:RCo, VWF:AG, VWF:CB and FVIII:C following 50 and 80 IU/kg of rVWF:rFVIII were similar. The PK parameters of aforementioned moieties following single and repeat dosing (after 6 months of treatment) of 80 IU/kg were comparable.

Conclusions:

- The PK of rVWF/FVIII for VWF:RCo was linear between 20 and 50 IU/kg dose.
- The half-life of rVWF:rFVIII was longer (approximately 1.5-fold) than pdVWF and the clearance of rVWF:rFVIII was slower (approximately 1.3-fold) than pdVWF.
- rVWF:rFVIII and pdVWF are not pharmacokinetically equivalent (90% confidence interval for VWF:RCo ranged from 1.02-1.56).
- The PK of rVWF alone and co-infused with rFVIII. were comparable.
- The PK parameters of VWF:RCo, VWF:Ag, VWF:CB and FVIII:C following 50 and 80 IU/kg of rVWF:rFVIII were similar. The PK parameters of aforementioned moieties following single and repeat dosing (after 6 months of treatment) of 80 IU/kg were comparable.
- The impact of age on the PK of rVWF:rFVIII was not evaluated.

6. Clinical/ Statistical

a) Clinical Program

Summary of Clinical Trials

Clinical trials for VONVENDI were conducted under IND 13657. Data from three clinical trials (070701, 071104, and 071001) were submitted to support the safety and efficacy of VONVENDI for the proposed indication of on-demand treatment and control of bleeding episodes (BE). All three trials evaluated the PK and safety of VONVENDI, and one (071001) evaluated efficacy.

Low levels of VWF can be associated with inadequate hemostatic levels of factor VIII (FVIII); therefore, co-administration of ADVATE (rFVIII]) with the first dose of VONVENDI was used in some clinical trials, and was used with the first dose of VONVENDI for the efficacy trial 071001. Subjects could enroll in both trials 070701 and 071001. Two subjects received VONVENDI as part of both trials. Sixty-six unique subjects with VWD were exposed to VONVENDI in these trials.

The clinical trials submitted to support the safety and efficacy of VONVENDI are summarized in Table 1 of the Clinical/ Statistical section.

Table 1: Clinical Trials

Trial ID (Type)	***Trial Design***	***Objective***	***Subjects[a]***	***Regimen[c]***	***Treatment Duration***
070701 (PK, safety, tolerability)	Randomized, controlled, single-blind, prospective, multicenter, dose escalation phase 1, PK	1) To establish the dosing of VONVENDI for the treatment of BE for use in trial 071001 2) To evaluate safety and tolerability of VONVENDI	Adults ≥ 18 years old; types 1 (severe) and 3 VWD 51 enrolled; 32 treated; 31 received correct drug[b]; **30** completed Escalating dose (cohorts 1-3): 9 subjects Crossover (cohorts 4A and 4B): 23 subjects; 3 discontinued	5 cohorts: 1-3) ADVATE + 2, 7.5, or 20 IU/kg VONVENDI 4A) Type 3 VWD: 50 IU/kg VONVENDI + ADVATE, or + plasma-derived - VWF/FVIII[d], crossover in random order N=20 4B) As in 4A, severe type1 VWD N=3	Single dose Duration: 30 day (cohorts 1-3) 40 day (cohort 4A and 4B)
071104 (PK, tolerability, supportive)	Open-label, multicenter, phase 1, PK	1) To assess the PK of co-infusion of VONVENDI and ADVATE in patients with severe hemophilia A 2) To assess the safety of co-admin. of VONVENDI and ADVATE	Adults ≥ 18 years old; severe hemophilia A 17 enrolled; 12 treated; **11** completed	ADVATE alone or with 10 or 50 IU/kg VONVENDI	3 PK analyses: 1)ADVATE alone 2) ADVATE + 10 IU/kg VONVENDI 3) ADVATE + 50 IU/kg VONVENDI

Trial ID (Type)	*Trial Design*	*Objective*	*Subjects*[a]	*Regimen*[c]	*Treatment Duration*
071001 (PK, Efficacy, Safety)	Open label, multicenter, phase 3 PK, on-demand treatment	1) To evaluate the PK of VONVENDI 2) To evaluate the clinical efficacy and safety of VONVENDI in treating BE	Adults ≥ 18 years old; types 1, 2 and 3 VWD 49 enrolled; 37 treated; **30** completed	Part A) Arm 1: PK + on-demand treatment Arm 2: PK only Arm 3: PK + on-demand treatment Arm 4: On-demand treatment only Part B) Continued on-demand treatment for arms 1, 3, 4	Part A - Arms 1-4; 6 months Part B – Arms 1, 3, 4 - additional 6 months

IU, international units; ADVATE, Baxter recombinant factor VIII product; VWD, von Willebrand disease

[a] Two subjects received VONVENDI in both trials 070701 and 071001.

[b] One subject received plasma-derived VWF in error

[c] Six subjects in cohorts 1-3 also participated in cohort 4A

[d] Containing the same dose of VWF

Demographics of the study population

A total of 78 subjects were exposed to VONVENDI during clinical development. The pooled results of the two larger trials (070701 and 071001) included 66 unique subjects with VWD with the following demographics:

- Median age was 36.0 years (range:18 to 64 years)
- Male to female ratio was 50:50
- 91% of subjects were white and 9% were Asian
- VWD types:
    - 85% type 3 disease (n=56)
    - 6% type 1 (n=4)
    - 8% type 2A (n=5)
    - 2% had type 2N (n=1)
    - No subjects with type 2B or type 2M VWD

Supportive trial 071104 comprised 12 adult male subjects with a history of severe hemophilia A.

Eleven subjects were discontinued from the trial after treatment, including two subjects who were discontinued as a result of adverse events (AEs).

- Subject 071001-(b) (6), a 36 year old male withdrew from trial 071001 due to the development of two possibly associated SAEs, chest discomfort and heart rate increase during an infusion of VONVENDI and ADVATE for a recurrent ankle bleed. This was specified by the subject as chest discomfort and not chest pain. He had received multiple prior doses and these symptoms developed after only approximately 1/10 the planned dose. EKG and troponin were normal. VWF:RCo activity was low at 4 (lower limit of normal 50) and FVIII level ((b) (4) assay) was 41.1 (lower limit of normal 51).These symptoms resolved spontaneously. He was observed overnight and there were no sequelae. Overall this was not suggestive of a thromboembolic cardiac event, but possibly considered to be a hypersensitivity reaction to VONVENDI or ADVATE.

- Subject 071104(b) (6), a 25 year old male had a negative anti-FVIII neutralizing antibody titer at screening. The subject received ADVATE for a BE prior to the first PK infusion. Subsequently, the subject received the first and second PK infusions but was withdrawn from the trial by the investigator prior to administration of the third PK infusion, after results of a sample drawn prior to the first PK infusion were received from the central laboratory, and showed development of a positive ((b) (4)) anti-FVIII neutralizing antibody titer. Antibody levels did not increase in this subject after further ADVATE exposure during the two PK infusions.

Efficacy Analysis

The primary efficacy endpoint was the number of subjects with treatment success for control of BEs. Treatment success was defined as a mean efficacy rating score of <2.5 for all BEs in a subject treated with VONVENDI (with or without ADVATE) during the trial period.

The efficacy rating was assessed using a 4 point rating scale comparing the prospectively estimated number of infusions needed to treat the bleeding episodes as assessed by the investigator to the actual number of infusions administered. The definitions for each of the 4 point rating scales are summarized in Table 2 of the Clinical/ Statistical section:

Table 2: Efficacy Rating Scale[a]

Rating	*Minor And Moderate Bleeding Events*	*Major Bleeding Events*
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that BE No additional VWF coagulation factor containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF coagulation factor containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF coagulation factor containing product required	<1.5x infusions greater than estimated required to control that bleeding episode No additional VWF coagulation factor containing product required
Moderate (=3)	3 or more infusions greater than estimated used to control that bleeding event No additional VWF coagulation factor containing product required	≥1.5x more infusions greater than estimated used to control that bleeding event No additional VWF coagulation factor containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF coagulation factor containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF coagulation factor containing product required

Source: Recombinant von Willebrand Factor; rVWF; vonicog alfa; Bax111 2.5 Clinical Overview, 2014 Nov 20, Table 5, page 24 of 61.

[a]The efficacy rating scale was agreed upon through a Type B meeting with FDA and is based on the scale employed by Lillicrap et al. (2002)[1] for the assessment of the efficacy of a plasma-derived Antihemophilic Factor/von Willebrand Factor Complex in a restricted use program in Canada.

Secondary efficacy measures were the number of treated BEs with an efficacy rating of 'excellent' or 'good,' the number of infusions and number of units of VONVENDI, administered with or without ADVATE, per BE.

Table 3 shows the recommended dosing of VONVENDI for BEs in clinical trial 071001. The recommended dosing was based on the results from nonclinical studies using VONVENDI, as well as on the recommended dosage for the treatment of acute BEs with plasma-derived VWF.

[1] Lillicrap D, Poon MC, Walker I et al. Efficacy and safety of the factor VIII/von Willebrand factor concentrate, haemate-P/humate-P: Ristocetin cofactor unit dosing in patients with von Willebrand disease. Thromb.Haemost. 2002;87:224-230.

Table 3: Dosing Recommendations for the Treatment of BEs in Trial #071001

Classification of VWD	***Hemorrhage***	***Dosage (IU VWF:RCO/KG Body Weight)***
Type 1 • severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g. readily managed epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g. severe or refractory epistaxis, menorrhagia, gastrointestinal (GI) bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment

Modified from rVWF Full Clinical Study Report 071001, 2014 OCT 23, page 37 of 704.

There were a total of 193[2] BEs that occurred in 22 subjects (17 subjects with type 3 VWD, four with type 2A VWD and one with type 2N VWD) in the efficacy trial 071001. There were 122 (63.2%) minor BEs, 62 (32.1%) moderate BEs, 7(3.6%) major/severe BEs, and 2 (1.0%) recorded as unknown. The majority of BEs[3] were mucosal (107), followed by joint bleeds (59). There were 6 gastrointestinal (GI) BEs, and 37 BEs that occurred in other locations (e.g., superficial, body cavity, soft tissue and muscle). Of the 193 BEs, 166 (86.0%) were spontaneous, 26 (13.5%) were traumatic, and 1 (0.5%) BE was of unknown cause.

The results of the primary efficacy outcome measure showed treatment success for all 192 BEs treated with VONVENDI, for a rate of 100% (95% CI: 84.6 to 100.0).

In terms of the secondary efficacy outcome measures, for a total of 192 BEs, the efficacy rating was ‘excellent’ (186/192 [96.9%]) or ‘good’ (6/192 [3.1%]); (combined 90% CI: 98.5 to

[2] For BE 1, subject (b) (6) received HAEMATE P for the third infusion due to logistical reasons. Therefore, this BE is excluded from the reported efficacy parameters, i.e., the efficacy results are based on a total of 192 BEs.
[3] One BE can occur in multiple sites

100.0). Table 4 of the Clinical/ Statistical section shows an overview of the treated BEs rated 'excellent' or 'good', with a breakdown by VWD type, severity, location, and cause.

Table 4: Overview of Treated BEs rated 'Excellent' or 'Good'

Category	***Subcategory***	***Excellent***		***Good***	
VWD Type	Type 3	97.7%	(171/175)	2.3%	(4/175)
	Type 2A	87.5%	(14/16)	12.5%	(2/16)
	Type 2N	100%	(1/1)	–	
	Type 1	–		–	
Bleed Severity	Minor	97.5%	(119/122)	2.5%	(3/122)
	Moderate	96.7%	(59/61)	3.3%	(2/61)
	Major/Severe	85.7%	(6/7)	14.3%	(1/7)
	Unknown	100%	(2/2)	–	
Bleed Location	Joint	96.6%	(57/59)	3.4%	(2/59)
	GI	83.3%	(5/6)	16.7%	(1/6)
	Mucosal	97.2%	(103/106)	2.8%	(3/106)
	"Other"	97.3%	(36/37)	2.7%	(1/37)
Bleed Cause	Spontaneous	97.0%	(160/165)	3.0%	(5/165)
	Traumatic	100%	(26/26)	–	
	Unknown	–		100%	(1/1)

Adapted from Recombinant von Willebrand Factor; rVWF; vonicog alfa; Bax111 2.5 Clinical Overview, 2014 Nov 20, Table 6, page 28 of 61.

The median number of infusions for treatment of BEs was 1.0 (90% CI, 1.0 to 1.0). The number of VONVENDI or VONVENDI plus ADVATE infusions required for treatment of BEs ranged from one to four as follows:

- 157/192 (81.8%) of BEs required a single infusion
- 25/192 (13.0%) BEs required 2 infusions:
    - 13 BEs in the joints (5 minor, 6 moderate and 2 major/severe)
    - 9 BEs in the genital tract (3 minor, 6 moderate)
    - 2 BEs in the GI tract (1 minor, 1 major/severe)
    - 1 minor BE in the nasopharyngeal tract)
- 9/192 (4.7%) BEs in 5 subjects (5 BEs in a single subject and 4 BEs in 4 others) required 3 infusions:
    - 4 BEs in the genital tract (1 minor, 2 moderate and 1 major/severe)
    - 3 BEs in the joints (2 moderate, 1 major/severe)
    - 1 moderate BE in the genital tract/oral cavity

- 1 moderate BE in the oral cavity
- A single BE required 4 infusions (1 moderate BE in genital tract/oral cavity)

Table 5 of the Clinical/ Statistical section summarizes these data.

Table 5: Number of Infusions by Severity of BEs

Number Of Infusions Per Bleed	***SEVERITY OF BLEEDING EPISODES***				
	Minor n (%) n=122	**Moderate n (%) n=61**	**Major/Severe n (%) n=7**	**Unknown n (%) n=2**	**All n (%) n=192**
1	113 (92.6%)	41 (67.2%)	1 (14.3%)	2 (100%)	157 (81.8%)
2	8 (6.6%)	13 (21.3%)	4 (57.1%)	0 (0.0)	25 (13.0)
3	1 (0.8%)	6 (9.8%)	2 (28.6%)	0 (0.0)	9 (4.7%)
4	0 (0.0)	1 (1.6%)	0 (0.0)	0 (0.0)	1 (0.5%)

Adapted from Recombinant von Willebrand Factor; rVWF; vonicog alfa; Bax111 2.5 Clinical Overview, 2014 Nov 20, Table 7, page 29 of 61.

It was required per protocol to use VONVENDI:ADVATE for the initial infusion to treat a BE. For subsequent infusions, the protocol required the additional use of ADVATE only as needed based on FVIII levels. An initial dose of VONVENDI:ADVATE was used to treat 182/192 (94.8%) of BEs. VONVENDI:ADVATE was also used subsequently in 14/35 (40%) of second infusions and 2/10 (20%) of third infusions. VONVENDI alone was used for the single fourth infusion.

The mean and median doses [IU/kg] of VONVENDI and ADVATE administered during the trial for the first infusions and of VONVENDI for subsequent infusions are shown in Tables 6, 7 and 8 of the Clinical/ Statistical section. Doses administered were within the range of, and thereby supportive of the labeled dose.

Table 6: Dose [IU/kg] of VONVENDI/ADVATE for the 1st Infusion

Analyte	***Number of BES***	***Mean ± Standard Deviation***	***Median***	***90% CI for Median***	***MIN, MAX***
VONVENDI	164	45.5 ±8.36	45.6	43.0 to 47.5	23.8, 63.0
ADVATE	166	35.9 ±13.90	33.6	32.4 to 36.8	16.6, 129.3

Source: Recombinant von Willebrand Factor [rVWF; vonicog alfa; BAX111], 1.11.3 Clinical Information Amendment, Table 1, page 2 of 4.
Number of Subjects: 20
Number of Infusions: 164
For BE 1, subject (b) (6) received HAEMATE P for the third infusion due to logistical reasons. This bleeding is therefore excluded from the table above.
Subject (b) (6) had 18 BEs and received IP treatment with unknown lot number. Therefore actual dose could not be calculated.

Table 7: VONVENDI Dose [IU/kg] for BEs Treated with VONVENDI Alone in the 2nd, 3rd and 4th Infusions

Analyte	*Number of BES*	*Mean ± Standard Deviation*	*Median*	*90% CI for Median*	*MIN, MAX*
VONVENDI	24	57.9 ±27.59	52.7	42.4 to 55.7	26.4, 132.0

Source: Recombinant von Willebrand Factor [rVWF; vonicog alfa; BAX111], 1.11.3 Clinical Information Amendment, Table 2, page 3 of 4.
Number of Subjects: 10
Number of Infusions: 30
For BE 1, subject (b) (6) received HAEMATE P for the third infusion due to logistical reasons. This bleeding is therefore excluded from the table above.

Table 8: VONVENDI Dose [IU/kg] for BEs Treated with VONVENDI/ADVATE or VONVENDI Alone in the 2nd, 3rd and 4th Infusions

Analyte	*Number of BES*	*Mean ± Standard Deviation*	*Median*	*90% CI for Median*	*MIN, MAX*
VONVENDI	34	58.8 ±28.71	48.7	46.5 to 55.7	6.2, 132.0

Source: Recombinant von Willebrand Factor [rVWF; vonicog alfa; BAX111], 1.11.3 Clinical Information Amendment, Table 3, page 4 of 4.
Number of Subjects: 14
Number of Infusions: 45
For BE 1, subject (b) (6) received HAEMATE P for the third infusion due to logistical reasons. This bleeding is therefore excluded from the table above.
Subject (b) (6) had 1 BE treated with more than one infusion (i.e., BE #10 with 2 infusions with unknown lot numbers). Therefore actual dose could not be calculated and the 2nd infusion is excluded from the table above.

b) Pediatric Study and PREA Requirements

VONVENDI was granted orphan-drug designation for the treatment of VWD on November 23, 2010 and therefore is exempt from PREA requirements. No clinical studies included pediatric subjects; however, Baxter has submitted a pediatric study plan.

c) Other Special Populations
No trial included pregnant or lactating subjects, or those ≥65 years of age.

d) Overall Comparability Assessment

- *Not applicable*

e) Bioresearch Monitoring
The Bioresearch Monitoring inspection of two clinical investigators did not reveal any issues that impacted the integrity of the submitted data.

7. Safety

The following safety endpoints were used to assess VONVENDI:

- Evaluation of the occurrence of AEs. AEs were assessed as mild, moderate or severe, serious or non-serious, and expected or unexpected using definitions predefined in the protocols. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA v. 16.1).
- The development of neutralizing antibodies to VONVENDI and/or ADVATE
- The development of binding antibodies to VONVENDI
- The development of antibodies against rFurin, Chinese hamster ovarian cell proteins and murine Immunoglobulin G (IgG)
- Viral safety
- Clinical hematology and clinical chemistry
- Physical assessments and vital signs

Safety data were pooled from trials 070701 and 071001, but not from 071104 as there were no AEs reported from trial 071104, and additionally, trial 071104 was done in subjects with hemophilia A. A total of 175 AEs occurred in 44 of 66 unique subjects during or after treatment with VONVENDI. There were 10 Serious Adverse Events (SAEs) in eight subjects. These are summarized in Table 9.

Table 9: Serious Adverse Events

System Organ Class ***Preferred Term***	***Number of Subjects (%)***
Gastrointestinal Disorders	
Dental caries	1 (1.5%)
Constipation	1 (1.5%)
Gastrointestinal hemorrhage	1 (1.5%)
Hemorrhoids[a]	1 (1.5%)

System Organ Class *Preferred Term*	*Number of Subjects (%)*
Mesenteric hematoma[a]	1 (1.5%)
General Disorders and Administration Site Conditions	
Chest discomfort[b]	1 (1.5%)
Infections and infestations	
Osteomyelitis	1 (1.5%)
Investigations	
Heart rate increase[b]	1 (1.5%)
Pregnancy, puerperium and perinatal conditions	
Abortion spontaneous	1 (1.5%)
Reproductive system and breast disorders	
Uterine polyps	1 (1.5%)

[a] Occurred in the same subject

[b] Occurred simultaneously in one subject

- Subject 071001-(b) (6) 36 year old male with chest discomfort and heart rate increase was treated with oxygen and the symptoms resolved without sequelae; however the subject was withdrawn from the trial. The chest discomfort and heart rate increase SAEs were assessed by the applicant as possibly related to VONVENDI:ADVATE, however, the subject had received multiple prior doses and these symptoms developed after only approximately 1/10 the planned dose. In addition, EKG and troponin were normal, and therefore this was not considered to be related to a cardiac thromboembolic event related to VONVENDI, and was possibly considered to be a hypersensitivity reaction.

- Subject 071001-(b) (6) was a 41 year old female taking oral contraceptives. Two days after receiving VONVENDI, ADVATE and tranexamic acid for an oral bleed, she reported a positive pregnancy test (5 weeks after her last menstrual period). Two weeks later she had a spontaneous abortion. She was discharged from the hospital the following day. Confounding factors were maternal age and the contraindication for tranexamic acid, when taking hormonal contraceptives (an independent risk of thromboembolism). There was no evidence that this event was a thromboembolic event related to VONVENDI.

All other SAEs were assessed as unrelated to VONVENDI. No new safety concerns were identified during the review of the safety data from the clinical trials.

Immunogenicity

Neutralizing antibodies:

- No subject in trials 070701 or 071001 developed neutralizing antibodies against VWF or FVIII. An analysis at 6 months in study 071001 after a second PK infusion confirmed the absence of inhibitors after repeat doses of VONVENDI. One subject in study 071104 had a positive anti-FVIII inhibitor titer prior to treatment. The titer did not change after receiving two infusions of ADVATE.

Binding antibodies:

- Against VONVENDI: Two subjects in trial 070701 had a high titer prior to the first exposure to VONVENDI. There were no increases in titer with exposure to VONVENDI, and there were no reported changes in medical condition following exposure to Vonvendi. There was no binding antibody formation in any subject in study 070701. No subjects in studies 071104 and 071001 developed binding antibodies to VONVENDI.
- Against impurities: There were no antibodies detected against rFurin, Chinese Hamster Ovary cell proteins or murine IgG in any subject at any time during the three trials.

Viral Safety

No subject had confirmed seroconversion to HIV, hepatitis A, B or C virus, or parvovirus B19 at any time during the three trials.

Clinical Laboratory Evaluations

There were no clinically relevant changes in laboratory values considered to be related to VONVENDI by either the applicant or the clinical reviewer.

Physical Assessments and Vital Signs

The clinical reviewer found no concerns regarding trends in vital signs observed after infusions of VONVENDI.

AEs of special interest

- Thrombotic events (including TTP [thrombotic thrombocytopenic purpura]-like syndrome):

  Two subjects had adverse events that could have potentially represented thrombotic phenomena. Subject (b) (6) developed chest discomfort and tachycardia. Review of the clinical course did not suggest a thromboembolic event. Subject (b) (6), had a spontaneous abortion. Review of the clinical data did not suggest a thrombotic event. Thus no thrombotic events were observed in any subject.

- Hypersensitivity: No severe allergic or anaphylactic events were observed.

Overall Clinical Assessment/Conclusions

VONVENDI demonstrated adequate efficacy with an acceptable safety profile in adult patients with VWD. The clinical reviewer recommends approval for the indications of on-demand treatment and control of bleeding episodes in adults diagnosed with VWD.

8. Advisory Committee Meeting

The Division of Hematology Research and Review and the Division of Hematology Clinical Review in the Office of Blood Research and Review reviewed the information in this application and determined that referral to the Blood Products Advisory Committee prior to product approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

VONVENDI is a (b) (4) To remove a known source of viral contamination, Baxter has eliminated animal derived raw materials from the manufacturing process. (b) (4)

The purification of rVWF starts with the (b) (4) These steps remove impurities and pathogens satisfactorily. In addition, products manufactured by recombinant DNA technology are generally considered to present a minimal risk of carrying adventitious agents. Maturation of rVWF occurs by (b) (4)

Evaluation of the safety data in rVWF clinical studies did not reveal any issues which are unexpected in this class of products. Major potential complications associated with pdVWF include the development of inhibitors (inhibitory anti- drug antibodies) to VWF, and a risk of thrombogenicity due to the inclusion of FVIII. As VONVENDI is a recombinant product generated in CHO cells, this product contains only trace amounts of FVIII. VONVENDI is degraded in vivo in a comparable manner to pdVWF. The study design to evaluate the efficacy of VONVENDI was adequate and well controlled and the results of the study did not raise any

concerns related to its safety or efficacy. No inhibitors to FIX, FVIII or CHO proteins were detected and no events of thrombosis were reported.

Review of the information submitted in the BLA for VONVENDI did not raise any controversial issues or pose unanswered scientific questions which would have benefited from advisory committee discussion and recommendations.

9. Other Relevant Regulatory Issues

The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences. There were no other relevant regulatory issues.

10. Labeling

a) Proprietary Name

The proposed proprietary name for the product, VONVENDI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) for misbranding and safety concerns, and was recommended to be acceptable on March 3, 1015. VONVENDI was found acceptable as the proprietary name for the product by CBER on March 26, 2015.

b) Conclusions of APLB and Committee Review of Draft Package Insert and Other Labeling

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) and carton/vial labels were reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. CBER comments and recommendations regarding the product labeling and carton/vial labels were initially conveyed to Baxalta on June 3, 2015, and negotiated throughout the months of September 2015 to December 2015.

Final versions of the product labeling and labels submitted to the BLA on December 7, 2015 were considered acceptable. A copy of the prescribing information is attached.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The CBER review committee recommends approval of this BLA. The manufacturing process for VONVENDI was found validated and adequately controlled. Clinical efficacy and safety data for VONVENDI support a favorable benefit/risk determination for the proposed indication of on-demand treatment and control of bleeding episodes in adults with VWD.

b) Risk/ Benefit Assessment

VWD is the most common of the hereditary coagulation deficiencies, caused by quantitative or qualitative deficiencies in VWF. VWF mediates the adhesion of platelets to sites of vascular

injury and is also a carrier protein for FVIII. Patients with VWD have qualitative or quantitative abnormalities in VWF and are at risk for developing acute bleeding episodes, particularly mucocutaneous bleeding. Current approved VWF preparations are plasma-derived and contain variable amounts of FVIII. VONVENDI is the first recombinant VWF.

Benefits

The efficacy of VONVENDI has been established for the indication of on-demand treatment and control of BEs using data from the phase 3 clinical trial 071001. Twenty-two subjects met all per protocol requirements encompassing 192 BEs. Using a pre-specified efficacy criterion, treatment was successful in all 192 (100%) BE. Treatment response was deemed excellent in 186/192 (97%) and good in 6/192 (3%) BE. Data from trial 071001 demonstrate that the proposed dosing for the treatment of acute BE is effective. Thus VONVENDI, which contains only residual amounts of FVIII and an increased proportion of the hemostatically active ultra-large multimers, adds a recombinant alternative to the treatment regimen of patients with VWD.

Risks

Potential safety concerns for VONVENDI include hypersensitivity reactions, the development of neutralizing antibodies to VWF or to FVIII, and thromboembolic events. Hypersensitivity reactions have been reported with plasma-derived VWF concentrates and may manifest as anaphylactic or allergic reactions. There were no severe allergic or anaphylactic reactions reported during the clinical trials. One 36 year old male subject experienced an SAE of chest discomfort that was possibly considered to be a hypersensitivity reaction; however, this subject's chest discomfort occurred on the fifth exposure to VONVENDI and the infusion included ADVATE. The development of this SAE after multiple exposures and in combination with ADVATE makes it less likely to be attributable to a hypersensitivity reaction to VONVENDI. Therefore, based on the clinical data, the risk of severe hypersensitivity reactions cannot be excluded, but the potential risk is considered to be low.

The development of neutralizing antibodies to VWF, FVIII, or CHO cells was not reported in any subject during treatment with VONVENDI, with or without ADVATE, in the three clinical trials. However, the development of neutralizing antibodies to VWF or to FVIII can occur and if expected plasma activity is not attained, testing for the development of neutralizing antibodies should be performed.

There is a theoretical increased risk for thromboembolic events with the use of VONVENDI because it contains a higher proportion of the hemostatically active ultra-large multimers than is normally present in plasma. The potential thrombogenicity of these ultra-large multimers is of greatest concern immediately following infusion of VONVENDI because, as reported in the PK analyses, the median percentage of ultra-large multimers increases from 0% pre-infusion to 30% within 15 minutes post-infusion. This immediate rise in ultra-large multimers is followed by a decline to approximately half the 15 minute post-infusion concentration by 24 hours post-

infusion due to degradation by endogenous ADAMTS13, and near-baseline levels were reported in all subjects by 96 hours post-infusion. The theoretical increased risk for thromboembolic events is partially allayed by the reported nonclinical and clinical data.

Nonclinical data from single dose and repeat-dose toxicity studies support the thrombogenic safety of VONVENDI within the labeled dose range. There were no thrombotic toxicities reported in VWF-replete rats, rabbits, or (b) (4) monkeys following a single intravenous injection of VONVENDI at doses up to 30 times greater than the labeled clinical starting dose. Similarly, there were no reports of thrombosis from repeat-dose toxicity studies in (b) (4) monkeys or in a single VWF-deficient pig dosed with 2.5 times the labeled clinical starting dose, either alone or in combination with ADVATE, for up to 14 days.

No thromboembolic events were reported in the clinical trials. There were two reported SAEs (chest discomfort and spontaneous abortion) which have the potential to be linked to a thromboembolic etiology. However, the 36 year old male subject with chest discomfort and tachycardia was documented to specifically have discomfort and not chest pain, the electrocardiogram and serum troponin levels were normal, and the symptoms resolved spontaneously, without sequelae, during overnight observation. The 41 year old female subject who experienced a spontaneous abortion had confounding factors of advanced maternal age and concomitant medications that included unspecified combined oral contraceptives and tranexamic acid. Advanced maternal age predisposes to a higher rate of early pregnancy loss and the administration of tranexamic acid is contraindicated when hormonal contraceptives are being used due to an increased thrombotic risk. Although there is no data to definitively determine whether these two SAEs were related to a thromboembolic etiology, given the clinical narratives, it is unlikely in the subject with chest discomfort, and the confounding factors associated with the spontaneous abortion make it less likely to be attributable to the use of VONVENDI.

Overall Benefit/Risk Profile

The safety of VONVENDI was demonstrated in the 69 subjects exposed to VONVENDI in trials 070701 and 071001, and in an additional 37 subjects with hemophilia A, who received VONVENDI in trial 071104. The overall benefit/risk profile of VONVENDI is favorable. The phase 3 clinical trial demonstrated efficacy of VONVENDI for its labeled indication. VONVENDI would be the first recombinant VWF approved in the U.S.

c) Recommendation for Postmarketing Risk Management Activities

At this time, the available clinical trial safety data do not suggest a safety concern that would require a Risk Evaluation and Mitigation Strategy (REMS) to ensure that benefits of VONVENDI outweigh its risks.

d) Recommendation for Postmarketing Activities

At this time, routine pharmacovigilance and labeling are adequate to monitor the safety of VONVENDI use in the postmarketing period. Routine pharmacovigilance includes AE reporting in accordance with 21 CFR 600.80: 15-day expedited reports for serious unlabeled AEs and quarterly periodic safety reports for 3 years (annual thereafter). The available clinical trial safety data do not suggest a safety concern that would necessitate a postmarketing study as a commitment (PMC) or a requirement (PMR) that is specifically designed to evaluate safety as a primary endpoint.