



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Pharmacology/Toxicology Secondary Review
Division of Hematology Products Clinical Review
Office of Blood Research and Review

TO: The file

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STN BLA #: 125577/0

APPLICANT: Baxter Bioscience Corporation (Baxalta), Westlake Village, CA

PRODUCT: human, recombinant von Willebrand Factor (codenames BAX111 and rVWF; established name, vonicog alfa; proposed proprietary name VONVENDI™), for the prevention and treatment of spontaneous and trauma-induced bleeding episodes in patients diagnosed with von Willebrand Disease

SUBMISSION TYPE: original BLA submission

SUBMISSION DATE: December 19, 2014

REVIEW DATE: December 7, 2015

1. EXECUTIVE SUMMARY:

1.1 Introduction

Baxter Healthcare Corporation (Baxalta) has submitted an original biologics license application (BLA) to seek U.S. licensure for recombinant von Willebrand factor (rVWF), proprietary name VONVENDI™. VONVENDI is a recombinant DNA-derived von Willebrand factor, expressed in Chinese Hamster Ovary (CHO) cells. Von Willebrand factor (VWF) is a large multimeric glycoprotein that is normally found in plasma, alpha-granules of platelets, and intracellular organelles known as Weibel-Palade bodies. Once the VWF is released to the blood stream and comes in contact with ADAMTS13 (a naturally occurring, proteolytic enzyme), it is cleaved to smaller sizes that are biologically active and function as cofactors in the coagulation cascade, thereby promoting hemostasis. In normal hemostasis, VWF acts 1) as an adhesive molecule, mediating both the intrinsic and extrinsic pathways of primary hemostasis, for example through increased platelet adhesion to damaged vascular sub-endothelial tissues like collagen, and promotion of platelet aggregation, and 2) by functioning as a carrier protein for coagulation factor VIII, and also protecting it from rapid proteolysis.

VONVENDI is indicated for on-demand treatment and control of bleeding episodes in adults diagnosed with congenital or acquired deficiencies of von Willebrand factor deficiency (i.e., von Willebrand disease; VWD). Patients with VWD do not undergo normal hemostasis, and require intervention with either plasma-derived VWF or plasma protein concentrates to abrogate bleeding. The safety and efficacy of VONVENDI was demonstrated during its experimental use during clinical trials, and its effectiveness and safety profile 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 mice, congenitally VWF-deficient dogs and pigs, and VWF-replete (i.e., wild-type) mice, rats, rabbits, dogs and (b) (4) monkeys. VONVENDI allows for the correction of the hemostatic abnormalities experienced by VWD patients by replacement of the missing cofactor, thereby allowing the intrinsic and extrinsic coagulation pathways to proceed in a normal manner, resulting in cessation of bleeding.

1.2 Brief Summary of Nonclinical Findings

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.

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 FeCl₃-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 FeCl₃-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 ($t_{1/2\beta}$) 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 $t_{1/2}$ 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 $t_{1/2}$ 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.

Reviewer comment: The language above was incorporated on November 17, 2017 into **Section 4, Nonclinical Data** of the Summary Basis of Regulatory Action document, to support the final approval of STN BLA #125577/000.

1.3 Recommendations

1.3.1 Approvability

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. Therefore, STN BLA #125577/000 is recommended for approval.

1.3.2 Additional Nonclinical Recommendations

There are no recommendations for additional pharmacology, toxicology or safety studies, and no recommendations for either Post-Marketing Requirements or Post-Marketing Commitments from the nonclinical discipline reviewers.

1.3.3 Labeling

The following FDA revisions to the language for the **Use in Special Populations (Section 8)** and **Nonclinical Toxicology (Section 13)** sections of the Applicant's proposed labeling for rVWF were communicated to Baxalta on Sep 17, 2015 and have been incorporated into the final revision of the VONVENDI™ package insert:

Section 8. USE IN SPECIFIC POPULATIONS

Applicant's language:

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with VONVENDI. It is not known whether VONVENDI can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. VONVENDI should be given to a pregnant woman only if clearly needed.

FDA Revisions (accepted by Baxalta):

8.1 Pregnancy

Risk Summary

There are no studies of VONVENDI use in pregnant women. The background risk of major birth defects and miscarriage in the indicated population is unknown; however, the background risk of major birth defects in the U.S. general population is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. Animal reproduction studies have not been conducted with VONVENDI. It is not known whether VONVENDI can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. VONVENDI should be given to a pregnant woman only if clearly needed.

***Justification:** As of June 30, 2015 and as outlined in the FDA "Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biologic Products – Content and Format", the Pregnancy Categories are no longer being used to describe the risk of product use during pregnancy. The revised language incorporates the new format and suggested 'boilerplate' language for this section, when there are no human or animal data available on which to base communication of potential risks.*

Applicant's Language

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VONVENDI is administered to a nursing woman.

FDA Revisions (accepted by Baxalta)**8.2 Lactation****Risk Summary**

There is no information regarding the presence of VONVENDI in human milk, its effects on the breastfed infant, or its effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VONVENDI and any potential adverse effects on the breastfed infant from VONVENDI or from the underlying maternal condition.

Justification: This is the current, 'boilerplate' language as suggested by the FDA guidance document, above.

Applicant's Language:**8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VONVENDI is administered to a nursing woman.

FDA Revisions (accepted by Baxalta):

Revised to Section 8.2, Lactation (above). Sent the following comment to the Applicant, as justification for deleting Section 8.3:

Justification: Under the 2014 FDA "Pregnancy and Lactation Labeling Rule" and in the guidance cited above, Section 8.3 of the labeling (Females and Males of Reproductive Potential) is only included in the labeling when there are specific requirements or recommendations for pregnancy testing and/or contraception and when human and/or animal data suggest drug effects on fertility.

Section 13. NONCLINICAL TOXICOLOGY**Applicant's Language:****13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In vitro and in vivo genotoxicity studies indicated no mutagenic potential for VONVENDI. Studies to assess the carcinogenic potential of VONVENDI have not been conducted. Animal studies on reproductive and developmental toxicity with VONVENDI have not been conducted.

FDA Revisions (accepted by Baxalta):**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In vitro and *in vivo* genotoxicity studies indicated no mutagenic potential for VONVENDI. Long-term animal studies to assess the carcinogenic potential of

VONVENDI have not been performed. Animal studies evaluating the reproductive and developmental toxicity of VONVENDI have not been conducted.

Justification: *Revised language to be consistent with FDA approved labeling for other recombinant coagulation factors.*

Applicant's Language:

13.2 Animal Toxicology and/or Pharmacology

Pharmacology

In vivo, VONVENDI administered with ADVATE [Antihemophilic Factor (Recombinant)] was more effective than plasma derived VWF in several mouse models of VWD due to high levels of ULM. An rVWF preparation with lower levels of multimers showed results between those of VONVENDI and plasma derived VWF. The results indicated that the efficacy of VONVENDI is influenced by the degree of multimerization of VWF, and that recombinant ADAMTS13 effectively balances the pharmacological effect of VONVENDI by cleaving the ultra-large multimers.

Safety pharmacology studies in rats, guinea pigs, rabbits and dogs revealed no increased anaphylactoid and thrombogenic potential of VONVENDI administered either alone or with ADVATE.

Toxicology

Single dose toxicity studies were conducted in ADAMTS13 knockout mice, (b) (4) mice, VWF deficient mice, rats, rabbits, and (b) (4) monkeys. Repeated dose toxicity studies were conducted in rats and (b) (4) monkeys. Signs of microthrombosis were observed in mice after a single dose, and mild regenerative hemolytic anemia, thrombocytopenia, and inflammatory lesions were observed in rats after repeated dosing. These findings are interpreted as species-specific exaggerated pharmacological effects due to the low susceptibility of human rVWF to proteolysis by rodent ADAMTS13. Proteolysis of ULM by endogenous ADAMTS13 was observed in rabbits and (b) (4) monkeys, and there were no signs of toxicity observed in these species.

FDA Revisions (accepted by Baxalta):

Deleted the entire Section 13.2, Animal Toxicology and/or Pharmacology (above).

Sent the following comment to the Applicant, as justification for deleting Section 13.2:

Justification: *As per the 2013 FDA guidance “Labeling for Human Prescription Drugs and Biological Products – Implementing the PLR Content and Format Requirements”, nonclinical pharmacology and toxicology data are not included in the labeling unless there are findings in the animal studies that were not seen in clinical trials and could affect patient management, e.g., dose adjustments, monitoring, etc. The data from the clinical trials are more robust, as well as more representative of the expected effects in the indicated population than the findings from the animal studies are.*

2. DRUG INFORMATION

CAS Registry Number: 109319-16-6

Generic Name: vonicog alfa (International non-proprietary name, INN; USAN)

Code Name: BAX111; rVWF

Chemical Name (IUPAC): vonicog alfa

Molecular Formula/Molecular Weight: (b) (4)
(monomeric form)

Structure: (from Module 3, Section 3.2.S.1.2 of the original BLA submission)

(b) (4)

Pharmacologic Class: coagulation factor, replacement

3. RELEVANT INDs, IDEs, PMAs, DMFs

BB IND #14287

BB IND #13657

STN BLA #125063/000 and relevant supplements (BLA for ADVATE[®], recombinant, human FVIII)

4. STUDIES SUBMITTED

A listing of the nonclinical studies reviewed in support of STN BLA #125577/0, including those reviewed by Drs. Evi Struble (IND #13657) and M. Keith Wyatt (IND #14287), and those reviewed by Dr. La’Nissa Brown-Baker for STN BLA #125063 are included as Appendix 1 to this review.

5. NONCLINICAL PHARMACOLOGY , PHARMACOKINETICS AND TOXICOLOGY STUDIES

All nonclinical in vitro and in vivo proof-of-concept (effectiveness) and primary pharmacology studies, safety pharmacology studies, animal pharmacokinetics and toxicokinetics, and toxicology studies with rVWF were reviewed by Dr. Evi Struble for IND #13657, or by Dr. Wyatt for IND #14287. Combination pharmacology or toxicity studies using rVWF together with ADVATE were reviewed by Drs. Struble, Wyatt and Brown-Baker. VONVENDI demonstrated the expected, pro-coagulant activity in genetically modified, VWF-deficient or ADAMTS13-deficient mice, and congenitally VWF-deficient dog and pig models. Reported toxicities included thrombosis in lung, heart and other major organs that occurred in both genetically modified VWF-deficient mice and (b) (4) wild-type mice, but not in the congenitally deficient dog or pig models, and not in VWF-replete rabbits, rats or (b) (4) monkeys at doses of VONVENDI 2.5 to up to 30-fold the clinical starting dose. Mechanistic toxicity studies revealed that the findings in mice were due to species-specificity of ADAMTS13, and the inability of the murine enzyme to cleave the ultra-large molecular weight multimers present in VONVENDI (human recombinant VWF). Copies of Dr. Struble’s and Dr. Wyatt’s original IND reviews are attached as Appendix 2 and Appendix 3, respectively, to this review.

6. GENETIC TOXICOLOGY

In vitro genetic toxicology studies (i.e., (b) (4) studies) and in vivo mouse micronucleus studies were reviewed by Dr. Evi Struble in the original review for IND #13657. All studies were negative for evidence of genotoxicity or mutagenicity, and the results are appropriately reported in the labeling.

7. CARCINOGENICITY

No long-term animal studies to evaluate carcinogenicity were conducted with rVWF. VONVENDI is a recombinant human protein, and as such was immunogenic in repeat-dose toxicology studies. Exposure (as defined by Area Under the Concentration-Time Curve, AUC_t) was minimal by 14 days of repeated dosing in both rats and (b) (4) monkeys; therefore, a carcinogenicity study with daily dosing of VONVENDI in rats or mice is not feasible to conduct. The lack of carcinogenicity data is appropriately addressed in the labeling, and justification for not conducting these studies is supported by the ICH S6 guidance document “*Nonclinical Safety Testing for Biotechnology-Derived Pharmaceuticals*”.

8. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

No animal studies were conducted to evaluate the reproductive or developmental toxicities with rVWF. In addition to VONVENDI being immunogenic in repeat-dose toxicology studies, rVWF contains high and ultra-high molecular weight multimeric forms of the protein and is not expected to cross the placenta. The lack of developmental and reproductive toxicity data is appropriately addressed in the labeling, and justification for not conducting these studies is supported by the ICH S6 guidance document “*Nonclinical Safety Testing for Biotechnology-Derived Pharmaceuticals*”.

9. SPECIAL TOXICOLOGY STUDIES

a. Mechanistic Toxicity

An in vitro study (Study #RD_VB_110702) was conducted using plasma from genetically modified, VWF-deficient mice, wild-type VWF-replete mice, and VWF-replete rats, rabbits, dogs, (b) (4) monkeys and human subjects. This study was reviewed in the original IND for IND #14287 by Dr. Wyatt, and showed that ADAMSTS13 from either VWF-deficient or wild-type mice failed to cleave VWF multimers to the lower molecular weight, active species. These data suggest that inability of murine ADAMSTS13 to effectively cleave the ultra-high molecular weight VWF multimers present in VONVENDI is likely responsible for the thrombosis effects that were seen only in the murine species, e.g. as an exaggerated pharmacologic effect of platelet binding to the ultra-high molecular weight multimers and initiation of coagulation via the extrinsic cascade. Dr. Wyatt’s review of these data is attached in his review of IND #14287; a full review of this mechanistic study by this reviewer will be provided as an addendum to this BLA review at a later date.

b. Impurities

A risk assessment of the detergent Polysorbate 80 ((b) (4)) which is used as (b) (4) in the manufacturing of VONVENDI as well as an excipient in the final drug formulation was provided by the Applicant. Additional evaluation of the safety of Polysorbate 80 was performed by this reviewer based on data published in the literature and in online databases. The

final amount of Polysorbate 80 in the finished drug product following reconstitution is 0.1 g/L (0.1 mg/mL), which is approximately 2- to 7-fold lower than that present in other FDA-approved biologic therapies administered as high volume, intravenous infusions (e.g., Erbitux[®], Rituxan[®]). A full review of the toxicologic risk assessment of Polysorbate 80 will be provided as an addendum to this review.

c. Safety of Extractable and Leachables

Data were provided by Baxalta in Module 3, Sections 3.2.S and 3.2.P to address the safety of potential extractable and leachable compounds that may be present in the drug substance and drug product, respectively. All extractions, safety and biocompatibility testing were performed in compliance with the (b) (4) standards, and the results for all studies were determined to pass the specific testing requirements. A full review of these studies, including the extractable and leachable components present in the container-closure system will be provided at a later date as an addendum to this review.

APPENDIX 1**A. LISTING OF NONCLINICAL STUDIES REVIEWED FOR THIS SUBMISSION****Pharmacology Studies***Primary Pharmacodynamic Studies*

1. Efficacy of rVWF in an arterial thrombosis model (FeCl₃-induced carotid occlusion model). Evaluation of one preclinical lot of rVWF alone and in combination with human rFVIII. Study # BA0107. Final report dated 7/3/2007.
2. Efficacy of rVWF in the tail-tip bleeding model in von-Willebrand-deficient mice: Evaluation of one preclinical lot of rVWF alone and in combination with human rFVIII. Study #BA0207. Final report dated 10/24/2007.
3. Influence of human rADAMTS13 on rVWF efficacy. Study #BA1207. Final report dated 11/27/2007.
4. Study to compare human recombinant von Willebrand factor with plasma-derived von Willebrand factor in von Willebrand factor-deficient dogs. Study #RD_VB_110703. Final report dated 12/20/2007.

Safety Pharmacology Studies

1. Study on the anaphylactoid potential of recombinant human von Willebrand factor (rVWF) alone and in combination with recombinant human Factor FVIII (rFVIII) on bronchospastic activity in guinea pigs. Study #PV1900605. Final report dated 8/31/2007.
2. Study on the anaphylactoid potential of rVWF: Blood pressure lowering in spontaneously hypertensive rats: Evaluation of preclinical lots alone and in combination with Advate. Study #PV2040705. Final report dated 8/31/2007.
3. Investigation of potential thrombogenicity of recombinant human von Willebrand factor (rVWF) alone and in combination with recombinant human Factor FVIII (rFVIII) in a rabbit stasis model. Study #PV2010701. Final report dated 11/27/2007.
4. Human recombinant von Willebrand factor (rVWF): Single-dose cardiovascular and respiratory safety pharmacology study in anesthetized dogs. Study #34572. Final report dated 12/19/2007.

Pharmacokinetic Studies*Absorption*

1. Pharmacokinetics of human rVWF compared with Haemate[®] P in von Willebrand factor-deficient mice: Evaluation of one preclinical lot of rVWF alone and in combination with human rFVIII. Study #PV1910605. Final report dated 7/3/2007.

2. Pharmacokinetics of human rVWF compared with Haemate® P in rats: Evaluation of one preclinical lot of recombinant human von Willebrand factor (rVWF) alone and in combination with recombinant human Factor VIII (rFVIII). Study #PV1910605. Final report dated 8/16/2007.
3. Study to compare human recombinant von Willebrand factor with plasma-derived von Willebrand factor in von Willebrand factor-deficient dogs. Study #RD_VB_110703. Final report dated 12/20/2007.
4. Human recombinant von Willebrand factor (rVWF) pharmacokinetic study by intravenous (bolus) administration to (b) (4) monkeys. Study #BAX0010. Final report dated 1/22/2008.
5. Analysis of plasma samples for pharmacokinetic evaluation of human rVWF alone and combined with human rFVII after single intravenous administration in (b) (4) monkeys. Study #DI07K001. Final report dated 8/29/2008.

Distribution

1. In vivo organ distribution of rVWF in a VWF deficient mouse model by use of (b) (4) -Study). Study (b) (4) . Non-GLP; final report dated August, 2007.

General Toxicology Studies

Single Dose Studies

1. Acute toxicity of human recombinant von Willebrand factor (rVWF) combined with human recombinant ADAMTS13 (rADAMTS13) after intravenous application in ADAMTS13-deficient mice. Study #AU0507W01. Final report dated 1/8/2008.
2. Acute toxicity of human recombinant von Willebrand factor (rVWF) alone or in combination with human recombinant Factor VIII (rFVIII) after intravenous application in VWF-deficient mice. Study #PV1930601. Final report dated 1/14/2008.
3. Acute toxicity of human recombinant von Willebrand factor (rVWF) alone or in combination with human recombinant Factor VIII (rFVIII) after intravenous application in ADAMTS13-deficient mice. Study #PV1940601. GLP; Final report dated 1/14/2008.
4. Acute toxicity of human recombinant von Willebrand factor (rVWF) alone or in combination with human recombinant Factor VIII (rFVIII) after intravenous application in (b) (4) mice. Study #PV1990701. GLP; Final report dated 1/14/2008.

5. Acute toxicity of human recombinant von Willebrand factor (rVWF) alone or in combination with human recombinant Factor VIII (rFVIII) after intravenous application in rats. Study #PV1950601. GLP; Final report dated 11/27/2007.
6. Human recombinant von Willebrand factor (rVWF) single dose toxicity study by intravenous administration to rabbits. Study #BAX0009. Final report dated 1/25/2008.
7. Analysis of plasma samples for toxicokinetic evaluation of human rVWF alone and combined with human rFVIII after single intravenous administration in rabbits. Study #PV2140708. Final report dated 10/15/2008.
8. Human recombinant von Willebrand factor (rVWF) single dose toxicity study by intravenous (bolus) administration to (b) (4) monkeys. Study #BAX0011. Final report dated 2/13/2008.
9. Analysis of plasma samples for toxicokinetic evaluation of human rVWF alone and combined with human rFVIII after single intravenous administration in (b) (4) monkeys. Study #DI08K001. Final report dated 9/8/2008.

Repeat-Dose Toxicity Studies

1. Human recombinant von Willebrand factor (rVWF): 14-day intravenous toxicity study in rats. Study #33981. Final report dated 1/3/2008.
2. Human recombinant von Willebrand factor (rVWF) by intravenous (bolus) administration to (b) (4) monkeys for 14 days followed by an 18 day recovery period. Study #EWA0015. Final report dated 6/3/2009.
3. Study to investigate human recombinant von Willebrand factor in von Willebrand factor-deficient pigs. Study #RD_VB_110704. Final report dated 12/20/2007.

Genotoxicity Studies

In vitro (b) (4)

1. "rVWF": (b) (4) test. Study #BAX22. Final study report dated 10/2/2007.

In vitro (b) (4)

1. Human recombinant von Willebrand factor (rVWF) in vitro (b) (4) test in human lymphocytes. Study #BAX0013. Final study report dated 5/27/2008.

In vivo Mouse (b) (4)

1. "rVWF": (b) (4) test in mice. Study #BAX24. Final study report dated 11/28/2007.

Special Toxicology Studies*Local Tolerability*

1. Investigation of local tolerance of recombinant human von Willebrand factor (rVWF) alone and in combination with recombinant human Factor VIII (rFVIII) in rabbits. Study #PV2000701. Final report dated 10/16/2007.

Immunogenicity

1. Comparative immunogenicity of recombinant and plasma-derived human von Willebrand factor in (b) (4) mice. Study #FS-IM00907. Final report dated 10/25/2007.
2. Experimental study report: Influence of co-administration of VWF and Advate on the immunogenicity of Advate in two conventional (b) (4) hemophilic mouse models and in the new (b) (4) hemophilic human F8 transgenic mouse. Study #IMM_R&D_017_11. Final report dated 8/31/2011.

Mechanistic Toxicity

1. Species-dependent variability of ADAMTS-13-mediated proteolysis of human rVWF. Study #RD_VB_110702. Final report dated December 18, 2007.

APPENDIX 2 – ORIGINAL IND REVIEW, IND #16357 (Evi Struble, PhD, reviewer)

APPENDIX 3 – ORIGINAL IND REVIEW, IND #14287 (M. Keith Wyatt PhD, reviewer)