

| | |
|--|--|
| Application Type | Original Application |
| STN | 125577/0 |
| CBER Received Date | December 19, 2014 |
| PDUFA Goal Date | December 19, 2015 |
| Division / Office | DHRR /OBRR |
| Priority Review | No |
| Reviewer Name(s) | Victor C. Baum |
| Review Completion Date / Stamped Date | |
| Supervisory Concurrence | |
| | |
| Applicant | Baxter Healthcare Corporation |
| Established Name | von Willebrand Factor (Recombinant) |
| (Proposed) Trade Name | Vonvendi |
| Pharmacologic Class | Recombinant coagulation factor |
| Formulation(s), including Adjuvants, etc. | Intravenous |
| Dosage Form(s) and Route(s) of Administration | Lyophilized powder in single-use vials containing nominally 650 or 1300 international units for intravenous use |
| Dosing Regimen | 40-60 IU/kg for minor bleeding, 50-80 IU/kg for major bleeding, with Advate® (recombinant antihemophilic factor) with first dose if factor VIII activity less than 40% |
| Indication(s) and Intended Population(s) | Treatment and control of bleeding episodes in adults (diagnosed with von Willebrand disease) |
| Orphan Designated | Yes |

TABLE OF CONTENTS

| | |
|---|-----------|
| GLOSSARY | 1 |
| 1. EXECUTIVE SUMMARY | 1 |
| 1.1 Demographic Information: Subgroup Demographics and Analysis Summary | 2 |
| 2. CLINICAL AND REGULATORY BACKGROUND | 3 |
| 2.1 Disease or Health-Related Condition(s) Studied | 3 |
| 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) | 5 |
| 2.3 Safety and Efficacy of Pharmacologically Related Products | 5 |
| 2.4 Previous Human Experience with the Product (Including Foreign Experience) | 6 |
| 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission | 6 |
| 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES | 7 |
| 3.1 Submission Quality and Completeness | 7 |
| 3.2 Compliance With Good Clinical Practices And Submission Integrity | 7 |
| 3.3 Financial Disclosures | 7 |
| 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES | 10 |
| 4.1 Chemistry, Manufacturing, and Controls | 10 |
| 4.2 Assay Validation | 10 |
| 4.3 Nonclinical Pharmacology/Toxicology | 10 |
| 4.4 Clinical Pharmacology | 10 |
| 4.5 Statistical | 10 |
| 4.6 Pharmacovigilance | 11 |
| 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW ... | 11 |
| 5.1 Review Strategy | 11 |
| 5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review | 11 |
| 5.3 Table of Studies/Clinical Trials | 11 |
| 5.4 Consultations | 12 |
| 5.4.1 Advisory Committee Meeting | 12 |
| 5.4.2 External Consults/Collaborations | 12 |
| 5.5 Literature Reviewed | 12 |
| 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS | 13 |
| 6.1 Trial #1 | 13 |
| 6.2 Trial #2 | 20 |
| 6.3 Trial #3 | 28 |
| 7. INTEGRATED OVERVIEW OF EFFICACY | 33 |
| 7.1 Indication #1 | 33 |
| 8. INTEGRATED OVERVIEW OF SAFETY | 35 |
| 8.1 Safety Assessment Methods | 35 |
| 8.2 Safety Database | 35 |
| 8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials | 35 |
| 8.4 Safety Results | 35 |
| 8.5 Additional Safety Evaluations | 37 |
| 8.6 Safety Conclusions | 37 |
| 9. ADDITIONAL CLINICAL ISSUES | 37 |

| | |
|---|-----------|
| 9.1 Special Populations | 37 |
| 9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered | 38 |
| 10. CONCLUSIONS | 38 |
| 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS | 38 |
| 11.1 Risk-Benefit Considerations | 38 |
| 11.2 Risk-Benefit Summary and Assessment | 40 |
| 11.3 Discussion of Regulatory Options | 40 |
| 11.4 Recommendations on Regulatory Actions | 40 |
| 11.5 Labeling Review and Recommendations | 40 |
| 11.6 Recommendations on Postmarketing Actions | 40 |

GLOSSARY

| | |
|------------------|---|
| AE | adverse event |
| AUC | area under the curve (subscripted for referred time points) |
| BE | bleeding episode |
| CHO | Chinese hamster ovary [cells] |
| CI | confidence interval |
| CL | clearance |
| C _{max} | maximum plasma concentration |
| FVIII | factor VIII |
| FVIII:C | factor VIII activity |
| IgG | immunoglobulin G |
| IP | investigational product |
| IR | incremental recovery |
| IVR | in vivo recovery |
| MRT | mean residence time |
| pd | plasma-derived |
| rFVIII | recombinant factor VIII (ADVATE) |
| rVWF | recombinant von Willebrand factor (VONVENDI) |
| SAE | serious adverse event |
| T _{1/2} | half-life |
| TTP | thrombotic thrombocytopenic purpura |
| V _{ss} | volume of distribution at steady state |
| VWD | von Willebrand disease |
| VWF | von Willebrand factor |
| VWF:Ag | von Willebrand factor antigen |
| VWF:C | collagen binding activity of von Willebrand factor |
| VWF:CB | von Willebrand factor collagen binding |
| VWF:Rco | von Willebrand factor: Ristocetin cofactor activity |

1. EXECUTIVE SUMMARY

VONVENDI is a recombinant von Willebrand factor (VWF), proposed for the on-demand treatment and control of bleeding episodes in adults with von Willebrand disease (VWD) (reflects recently instituted FDA preferred language in coagulation factor labeling). The Baxter indicates that the purported advantages of VONVENDI (recombinant product) over the other licensed products (plasma-derived) include purity (i.e. does not contain any factor VIII (FVIII)), higher concentration of the largest, hemostatically active multimers (as the product has not been exposed to the relevant protease during the manufacturing process), and lack of exposure to known or currently unknown blood-borne pathogens. Although the large multimers can be associated with a thrombotic risk, VONVENDI undergoes degradation in vivo by the naturally occurring protease ADAMTS13 similar to endogenous VWF. Thus in vivo excessive large multimers will not accumulate, diminishing potential thrombotic risk. ADVATE, Baxter's recombinant FVIII (rFVIII), is to be co-administered with the first dose of VONVENDI if low FVIII levels are present. Because one function of VWF is to transport FVIII, low VWF levels can result in

secondary low FVIII levels. Since adequate FVIII levels are required for appropriate hemostasis, co-administration can be indicated for the first dose.

Safety and efficacy data from three clinical trials were submitted in support of this Biologics License Application (BLA) with the Baxter's proposed indication, "prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with VWD" (the proposed indication was adjusted to comport with recently instituted FDA preferred language in coagulation factor labeling as noted in the preceding paragraph). Study 071104 was a Phase 1 trial to evaluate the pharmacokinetic (PK) effects of co-administration of VONVENDI with ADVATE. Study 070701, also a Phase 1 trial, evaluated the PK, safety and tolerability of four different doses of VONVENDI in severe VWD. Study 071001, the pivotal Phase 3 trial, determined the PK, safety, and efficacy of VONVENDI, and VONVENDI plus ADVATE, in the treatment of bleeding episodes (BE) in subjects with VWD.

Two PK trials were submitted. Trial 071104 showed that the PK of FVIII is unchanged if administered alone or with two different doses of VONVENDI. Trial 070701 demonstrated that the PK profile for recombinant VWF (rVWF) is comparable to the other licensed products containing VWF with FVIII, and shows a sustained stabilization of endogenous FVIII with the administration of VONVENDI. Data in this trial also indicated PK dose linearity for the higher investigated doses. Overall, the data indicate that VONVENDI can be infused at doses comparable to those of currently licensed VWD products utilized for the treatment of VWD. The Phase 3 trial 071104 was the only trial designed to assess efficacy. One hundred percent (192/192) of BEs met the criteria for treatment success with one or more doses of VONVENDI, and 82% of BEs met the criteria for treatment success with a single dose.

There were no safety concerns in any of the three trials, and specifically, there were no reports of immunogenicity or of thrombosis.

VONVENDI was studied in adults >18 years of age. In these clinical trials 50% were male, 91% were white and 9% Asian. Although Baxter has submitted a pediatric trial plan, VONVENDI is designated as an orphan drug, and therefore is exempt from the Pediatric Research Equity Act (PREA) required assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients.

Recommendation:

Based on my review of the submitted data, VONVENDI appears safe and effective in patients with VWD for the claimed indication of prevention and treatment of bleeding episodes in adults (age 18 years and older). Approval is recommended.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic data from the two trials enrolling subjects with VWD (trials 070701 and 071001) included 50% male and 50% female subjects; 90.9% of subjects were White and 9.1% were Asian; 90.9% were not-Hispanic or Latino, and 9.1% were Hispanic or Latino. All subjects were adults 10 to 60 years of age.

2. Clinical and Regulatory Background

VWD is a disorder of hemostasis due to quantitative or qualitative abnormalities in VWF, and is associated with mucocutaneous bleeding and the risk of excessive surgical bleeding. The proposed indication for VONVENDI is for the “prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand disease.” The preferred language for this indication (proposed by FDA following submission of this BLA) is “on-demand treatment and control of bleeding episodes”.

VONVENDI is a high purity rVWF, expressed in the same Chinese Hamster Ovary (CHO) cell line that expresses the currently licensed rFVIII, ADVATE, also manufactured and marketed by Baxter. VWF normally occurs in the plasma as a multimeric protein; the largest multimers are the most hemostatically active. VONVENDI is prepared in vitro, therefore it is not exposed to ADAMTS13, the normally occurring proteolytic enzyme found in the body. Because VONVENDI is not cleaved by this enzyme, it includes a high fraction of the largest high molecular weight and ultra-large multimers, which are believed to have greater hemostatic activity than the smaller multimers. In the body, however, the product is degraded in a similar fashion to the natural protein. As a recombinant product, the transmission risk of known or unknown blood-borne pathogens is decreased compared to the plasma derived product. Additionally, VONVENDI is not contaminated by variable amounts of FVIII, as are the currently available VWF products. As one of the roles of VWF is to transport FVIII, low levels of VWF can be associated with secondary low levels of FVIII, which may require variable degrees of FVIII replacement to assure adequate hemostasis.

(b) (4)



VONVENDI has been granted orphan drug designation (designation #10-3222). Baxter applied for breakthrough therapy designation, but was denied (January, 2014). The rationale for denial included a decision that the data from the clinical development program was insufficient to demonstrate substantial improvement over existing therapies. FDA agreed, however, that the product is intended for treatment of a serious or life-threatening disease.

2.1 Disease or Health-Related Condition(s) Studied

VWF is a multimeric plasma glycoprotein, synthesized in endothelial cells and megakaryocytes, and is essential for primary hemostasis. Following modifications in the Golgi apparatus, up to 95% is expressed constitutively and the remainder is stored intracytoplasmically in endothelial cells. The largest multimers are biologically active while the smallest are not. Deficiency of VWF results in the clinical disease, VWD.

VWD is the most common inherited bleeding disorder in humans, with an incidence of approximately 1:1000 live births. It can involve quantitative (types 1 and 3) or qualitative (type 2) abnormalities in VWF: type 1 (approximately 70-80% of cases); type 2

(approximately 20% of cases); and type 3 (approximately 1-5% of cases) (see below for a description of the types of VWD).

VWF serves as the first link between platelets and injured blood vessels, and also serves as a carrier for plasma FVIII. As such, it both localizes FVIII to the platelet plug and serves to protect FVIII from overly rapid proteolysis, thereby helping to maintain plasma levels of FVIII. Thus, VWD can be associated with low levels of FVIII, and concurrent treatment with exogenous FVIII is sometimes required until FVIII levels are restored. The most common clinical manifestation of VWD is mucocutaneous bleeding.

As autosomal disorders, VWD is present equally in men and women. However, due to the burden of excessive mucocutaneous bleeding in menstruating women, the disorder is diagnosed more frequently in women (approximately 2:1), and clinical manifestations are typically not apparent in the first months of life. Rarely, VWD can be an acquired disease, associated with malignancy, autoimmune disease, cardiac valvular disease, and induced by some drugs. Acquired disease presents similarly to type 2A (see below).

The types of VWD are as follows:

- Type 1: Partial quantitative deficiency of normally functioning VWF with normal distribution of multimers. On some occasions the disease may be mild, making diagnosis difficult. There is significant phenotypic variability, and mild disease can, on occasion, ameliorate in the second or third decade of life.
- Type 2A: Selective loss of the largest VWF multimers, and defective platelet dependent VWF functions. Since the large multimers are hemostatically active and the smaller multimers are not, this results in symptomatic disease. One class of mutations causes defective intracellular transport of VWF, impairing the assembly, storage, and secretion of large multimers. The other renders the protein more susceptible to proteolysis in the plasma. The majority of type 2 patients have type 2A.
- Type 2B: Gain-of-function mutation in the platelet-binding domain, with increased affinity of VWF for platelets. This results in spontaneous binding of VWF to platelets, and clearance of both from the circulation. Thrombocytopenia and inadequate high multimer VWF levels ensue, causing symptomatic disease. The associated thrombocytopenia can be exacerbated by surgery, pregnancy, or desmopressin.
- Type 2M: Decreased platelet binding due to mutations that inactivate specific ligand binding sites. Multimer distribution is normal.
- Type 2N: Associated with mutations in the FVIII binding domain of VWF resulting in a mild hemophilia A-like disorder.
- Type 3: Least common variant but most severe, associated with an almost complete absence of VWF, due to a homozygous or compound heterozygous state. The absence of VWF results in a secondary deficiency of FVIII, (usually <10%). There can be spontaneous joint and soft tissue bleeding, and it is possible that some of these patients will develop alloantibodies to VWF with

replacement therapy (7.5-9.5%). Anaphylactic reactions to exogenous VWF can occur.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, three classes of agents are used for treatment of BE and perioperative management in patients with VWD. These are:

- Desmopressin (DDAVP, a vasopressin V₂ agonist): DDAVP induces secretion of VWF and FVIII from endothelium, and can increase VWF levels by 2-3 fold.
- Human plasma derived VWF/FVIII (pdVWF/FVIII) products: Alphanate, Humate-P and Wilate are the three pdVWF/FVIII products currently licensed in the United States (Humate-P is also called Haemate P or Hemate P in other countries). The ratios of VWF to FVIII vary considerably in these products. Wilate, for example, has a 1:1 concentration of VWF:FVIII, whereas Humate-P has an average ratio of 2.4:1.
- Antifibrinolytics (tranexamic acid and aminocaproic acid): These are used in a nonspecific fashion to minimize bleeding through antifibrinolysis (inhibiting conversion of plasminogen to plasmin), thus limiting clot dissolution.

2.3 Safety and Efficacy of Pharmacologically Related Products

Adverse reactions are rare with the use of pdVWF/FVIII concentrates, but are known to include allergic and anaphylactic symptoms, which can be associated with the development of inhibitors. Since these products contain both VWF and FVIII, and since the half-life of FVIII is longer than that of VWF, continued therapy with pdFVIII could result in excessive FVIII levels, which is a risk factor for thrombosis.¹ A very low incidence of thromboembolic (TE) events has been reported, particularly in the setting of associated predisposing risk factors. A 2002 survey on the occurrence of TE events in VWD patients treated with pdFVIII-VWF concentrates that included 52 hemophilia treatment centers showed an incidence of 7 TE event cases in 12,640 yearly treatments over 10 years (corresponding to 1 case per 1,806 treatment-years).² There is also a rare risk of accumulation of anti-A and anti-B blood group isoagglutinins with repetitive dosing.³ Finally there is the potential for known or currently unknown blood-borne pathogen transmission, since these products are prepared from large quantities of human plasma.

Response to DDAVP can vary by VWD type as follows:

- Approximately 80% of type 1 patients will respond to DDAVP, the most severe cases may not respond
- Some patients with types 2A or 2M will be unresponsive
- Types 2N and 3 patients are generally unresponsive
- Thrombocytopenia can worsen with added release of VWF in type 2B disease

1 Makris M, Colvin B, Gupta V, Shields ML, Smith MP. Venous thrombosis following the use of intermediate purity FVIII concentrate to treat patients with von Willebrand disease. *Thromb Haemost* 2002;88:387.

2 Mannucci PM. Venous thromboembolism in von Willebrand disease. *Thromb Haemost* 2002;88:378.

3 Girelli G. Hemolytic anemia and F.VIII concentrate. *Eur J Haematol* 1989;42:414.

Additionally, DDAVP can be associated with dilutional hyponatremia, particularly at the extremes of age, and patients can become refractory with repeated doses.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

VONVENDI (previously referred to as BAX 111) is not currently licensed in any country. However, the product is made in the same cell lines as Baxter's licensed rFVIII product, ADVATE.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Pre-IND:

- CRMTS # 5570, May, 2006; clinically relevant points included:
 - FDA recommended release of rVWF as a single component product, rather than one with rVWF alone for maintenance therapy, and one combined with rFVIII (ADVATE) for urgent (first dose) use.
 - FDA did not agree with Baxter's plan to conduct all three parts of their proposed trial in parallel and recommended Part 1 (PK and safety) trial be completed first. FDA indicated that due to the different multimeric profile between rVWF and pdVWF, additional monitoring to assess TTP-like scenario needed to be evaluated in the Phase 1 safety trial.
 - FDA agreed with the concept of comparing PK of rVWF-rFVIII to Humate-P.
 - Part 3 of the proposed trial could take place post-licensure (b) (4)
 - Pediatric studies could be conducted as post-marketing commitments.
 - FDA suggested Baxter considers a plan for implementation of patient education prior to licensure.

During IND development:

- CRMTS #7787: February, 2011: FDA requested follow up information on patients in the Phase 1 trial who developed non-inhibitory binding antibodies to rVWF.
- CRMTS 7787 (follow up): March, 2011: FDA allowed re-enrollment of subjects in the Phase 1 trial into the Phase 3 trial.
- CRMTS # 8953: July, 2013: Given the lower than expected event rate of severe bleeding in the cohort of type 3 disease patients, FDA allowed the extension of the observation period from 6 to 12 months, and required 6-12 major bleeds from 6-12 unique subjects.
- CRMTS # 9386: May, 2014: FDA agreed that data from the single Phase 3 trial could suffice for licensure application with supportive data from Baxter's two previous human trials (070701 and 071104), and agreed to accept pooling of safety data from all three studies.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The studies supporting this submission were conducted in compliance with good clinical practices, including informed consent, site-specific issues, and in accordance with acceptable ethical standards.

| Site Number | Study Site | Location | Enrolled Subjects | FDA Form 483 Issued | Classification |
|-------------|--|-----------|-------------------|---------------------|----------------|
| 02 | Blood Center of Wisconsin | Wisconsin | 4 | No | NAI |
| 06 | The Mary M Gooley Hemophilia Center and Rochester General Hospital | New York | 2 | No | NAI |

NAI = No Action Indicated

Sponsor-identified protocol deviations

Study 070701: 18 major protocol deviations in 15 subjects and 269 minor deviations in 42 subjects. Major deviations (as percent of subjects enrolled) were eligibility (8), investigational product (IP) administration (16), procedure not done (2), protocol schedule (4), other (6).

Study 071001: 820 total deviations in 39 subjects, 84 major deviations in 18 subjects. Most were visits/assessments done outside protocol defined window.

Study 071104: 48 deviations in 12 subjects, six were major and all six involved ADVATE administration: 1 – IP not premixed, 5- subjects provided IP previously provided to others or that subject.

3.3 Financial Disclosures

| | | |
|---|---|--|
| Covered clinical study (name and/or number):070701 Phase 1 PK and tolerability. Adults with VWD | | |
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from |

| | | |
|---|------------------------------|--|
| | | applicant) |
| Total number of investigators identified: 18 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p style="padding-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p style="padding-left: 40px;">Significant payments of other sorts: _____</p> <p style="padding-left: 40px;">Proprietary interest in the product tested held by investigator: _____</p> <p style="padding-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: _____</p> | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

| | | |
|--|---|---|
| Covered clinical study (name and/or number):071001 Phase 3 Safety, Efficacy, PK. Adults with VWD | | |
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: 30 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p style="padding-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> | | |

| | | |
|--|------------------------------|--|
| Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

| | | |
|---|---|--|
| Covered clinical study (name and/or number): 071104 Phase 1 (supportive) PK and tolerability, Adults with Hemophilia A | | |
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: 5 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u> | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

VONVENDI consists of human rVWF expressed in CHO cells that are also used to express the licensed rFVIII, ADVATE. (b) (4)
(b) (4) by the use of a recombinant furin, (b) (4)
concentrated to approximately 130 IU VWF: Ristocetin Cofactor (RCo) per mL. VONVENDI is formulated as a sterile, non-pyrogenic, white or off-white, lyophilized powder preparation for intravenous injection, and is stabilized with a mixture of sugars, salts, and amino acids. It is supplied in single-dose glass vials with a nominal dose of 650 or 1300 IU per vial. Each dose is reconstituted with sterile water in a supplied vial.

4.2 Assay Validation

Validations of the assays were submitted in section 4.2.2.1

4.3 Nonclinical Pharmacology/Toxicology

Multiple preclinical studies of rVWF and rVWF+FVIII were done evaluating PK, pharmacodynamics (PD), safety and toxicology in mouse, dog, rabbit, and (b) (4) monkey. These included a trial of rVWF alone or in combination with rFVIII in ADAMTS 13-deficient mice, compared to a pdVWF (Humate P). ADAMTS13-deficient mice were sensitive to treatment with rVWF; developing microvascular thromboses in multiple organs. These thromboses developed at doses of 500 IU per kg (VWF:RCo), and clinical signs developed at 2000 and 4000 IU per kg, with or without rFVIII.

4.4 Clinical Pharmacology

Evaluation of the clinical PK of VONVENDI was the secondary endpoint for studies 070701 (Trial #1) and 071001 (Trial #2). The PK of FVIII when co-administered with VONVENDI was the secondary endpoint of trial 071104 (Trial #3).

4.4.1 Mechanism of Action

VONVENDI contains the active substance rVWF. As such, it temporarily restores the inadequate levels found in VWD, allowing for adequate hemostasis. VWF mediates the adhesion of platelets to the sites of vascular injury at high shear rates, forming a platelet plug. In addition, VWF is a carrier protein for FVIII, and required for normal FVIII survival in the circulation. The binding half-life of exogenous FVIII with exogenous VWF is approximately 2 seconds.

4.4.2 Human PD

The dosing range of VONVENDI is similar to that of other VWF preparations.

4.4.3 Human PK

The half-life and degradation time course of VONVENDI is similar to that of pdVWF (refer to section 6.1.11.2). The PK profile for rVWF is comparable to pdVWF/FVIII concentrate for VWF activity (VWF:RCo), and shows a sustained stabilization of endogenous FVIII. Data also indicate dose linearity for the higher investigated doses.

4.5 Statistical

The statistical reviewer verified that the primary trial endpoint analyses cited by Baxter were supported by the submitted data.

4.6 Pharmacovigilance

Baxter performs pharmacovigilance via its Global Pharmacovigilance organization with personnel in place at the local (country) level. In addition to routine pharmacovigilance, Baxter is planning two additional clinical trials: (b) (4)

In addition to these two trials, Baxter is planning a deferred pediatric trial. This Phase 3 trial will enroll approximately 24 subjects equally divided among age groups <6 years, 6 to 12 years and >12 to 18 years with at least 8 eight children <6 years old. This trial is estimated to start in Q4 2016 and end by approximately Q4 2019

Reviewer comment: The protocols for these three proposed trials have not been submitted.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Documents in the BLA were reviewed, specifically the results of the three clinical trials. The single Phase 3 trial is pivotal. All three clinical trials are reviewed below.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following sections of the BLA were reviewed:

- 1.2 Cover Letter
- 1.3.3 Debarment Certification
- 1.3.4 Financial Disclosure
- 1.4.4 Cross Reference to Other Applications
- 1.6.3 Correspondence Regarding Meetings
- 1.9.2 Request for Deferral of Pediatric Studies
- 1.12.1 Pre-IND Meeting Correspondence
- 1.14.1.3 Draft Labeling Text
- 1.16 Risk Management Plans
- 2.2 Introduction
- 2.5 Clinical Overview
- 2.7 Clinical Summary
- 5. Clinical Study Reports

5.3 Table of Studies/Clinical Trials

Table 1
Summary of Clinical Studies

| Protocol # | Name | # Subjects | Randomization |
|------------|--|------------|---------------|
| 070701 | Recombinant von Willebrand factor /recombinant Factor VIII complex (rVWF:rFVIII): A Phase 1 study evaluating the pharmacokinetics (PK), safety and | 32 | Yes |

| | | | |
|--------|---|----|-----|
| | tolerability in severe von Willebrand disease (VWD) | | |
| 071001 | A Phase 3 clinical study to determine the pharmacokinetics, safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in subjects diagnosed with von Willebrand disease | 37 | Yes |
| 071104 | Co-Infusion of recombinant von Willebrand factor/recombinant Factor VIII (rVWF:rFVIII): A Phase 1 study evaluating the pharmacokinetics, safety and tolerability in severe hemophilia A | 12 | No |

5.4 Consultations

5.4.1 Advisory Committee Meeting

Referral to the Blood Products Advisory Committee was waived on the following bases:

- 1) The mechanisms of action and function of VONVENDI in blood coagulation are well studied and understood. rVWF has structural and functional characteristics similar to endogenous VWF. In vitro and in vivo biochemical and functional characterizations of rVWF have demonstrated that its hemostatic activities are comparable to those of licensed pdVWF products.
- 2) Evaluation of the safety data in rVWF clinical trials did not reveal any issues which are unexpected in this class of products.
- 3) VONVENDI, (b) (4) (b) (4)
- 4) The purification of rVWF starts with the (b) (4)
- 5) (b) (4) manufacturing process.
- 6) Review of the information submitted in the BLA for VONVENDI did not raise any controversial issues or pose unanswered scientific questions that may have benefited from advisory committee discussion and recommendations.

5.4.2 External Consults/Collaborations

There were no external consults/collaborations needed during this review.

5.5 Literature Reviewed

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study 070701 – Recombinant von Willebrand factor /recombinant Factor VIII complex (rVWF:rFVIII): A Phase 1 study evaluating the pharmacokinetics (PK), safety and tolerability in severe von Willebrand disease (VWD)

6.1.1 Objectives (Primary, Secondary, etc.)

Primary: The tolerability and safety after single dose injections of rVWF:rFVIII at 2, 7.5, 20 and 50 IU per kg VWF:RCo (Ristocetin cofactor activity) for up to 30 days after the last infusion.

Secondary:

PK assessment of VWF:RCo, VWF:Ag (antigen) and multimeric composition of VWF, assessed at standardized time points after single dose injections of rVWF:rFVIII and pdVWF/FVIII

PK assessment of FVIII:C (activity) at the same time points indicated for rVWF

6.1.2 Design Overview

Multicenter, controlled, randomized, single-blind prospective Phase 1 dose escalation clinical trial. Cohort 4 included a two-period randomized-controlled crossover with a licensed pdVWF/FVIII concentrate. The trial lasted 7 weeks for cohorts 1-3, and 9 weeks for cohort 4 (see below for cohort definitions). Cohorts 1-3 were unblinded. Cohort 4 was randomized and blinded.

6.1.3 Population

Subjects had type 3 or severe type 1 VWD (VWF:RCo \leq 10% and FVIII<20%), a history of \geq 25 days of exposure to VWF/FVIII factor concentrates, and were 18-60 years of age. Subjects had to have a Karnofsky score \geq 70 (cares for self; unable to carry on normal activity or to do active work at the least).

Exclusion criteria included: additional coagulation disorder (acquired or hereditary); ADAMTS13 deficiency (<10% activity); presence of VWF inhibitor; FVIII inhibitor \geq 0.4 BU (Nijmegen assay) or \geq 0.6 BU (Bethesda assay); taking immune modulatory drugs; and treated with drugs known to induce TTP.

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Cohort 1 (Type 3 disease, N=3): rVWF:rFVII - 2 IU per kg rVWF:RCo
- Cohort 2 (Type 3 disease, N=5): rVWF:rFVII - 7.5 IU per kg rVWF:RCo
- Cohort 3 (Type 3 disease, N=5): rVWF:rFVII - 20 IU per kg rVWF:RCo
- Cohort 4A (Type 3 disease, N=22): rVWF:rFVIII or pdVWF/FVIII - 50 IU/kg rVWF:RCo, in random order
- Cohort 4B (Severe type 1 disease, N=3): rVWF:rFVIII or pdVWF/FVIII - 50 IU/kg rVWF:RCo, in random order

The ratio of rVWF:rFVIII was 1.3:1.

6.1.5 Directions for Use

Single dose

6.1.6 Sites and Centers

This trial was conducted at 18 sites: United States (7), Canada (1), United Kingdom (4), Austria (1), Germany (2), Italy (3).

6.1.7 Surveillance/Monitoring

Subjects were observed in a hospital/clinical research center for the first 24 hours. Follow-up visits were at 4, 11, and 30 days post-infusion.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was tolerability and safety of rVWF:rVIII after single dose injections of 2, 7.5, 20, and 50 IU per kg VWF:RCo.

Secondary endpoints compared the following parameters assessed at standardized time points in each dose cohort: area under the curve (AUC); area under the moment curve; plasma half-life ($T_{1/2}$); clearance (CL); mean residence time; volume of distribution at steady state (V_{ss}); maximum plasma concentration (C_{max}); incremental recovery (IR) of VWF:RCo; VWF antigen; collagen binding activity (VWF:CB); and multimeric composition of the VWF. In cohort 4, the PK of rVWF:rFVIII and pdVWF:FVIII were compared.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Cohort 4: The sample size estimate was calculated using an equivalence test of means in a crossover design, using a level of statistical significance of 5%. The analysis was carried out by calculating a two-sided 90% confidence interval (CI) of the ratio of the geometric means of $AUC_{0-\infty}$ of the test and reference preparations. The margins of equivalence were set to 80% and 125%. The standard deviation (SD) of the difference in $\log(AUC_{0-\infty})$ in VWF:RCo within each subject in the range of 0.28 to 0.30 provided adequate power in the range of 81% to 88%, with a total sample size of 18 subjects

Primary analysis: The number of subjects who experienced serious adverse events (AE), and the number of serious AEs (SAE) were tabulated. Safety analyses were performed separately by dose (i.e. cohort) and IP (rVWF/rFVIII or comparator plasma-derived VWF/FVIII, given in random order) (in Cohort 4). Shift tables and the number of subjects with abnormal values at each measurement point per laboratory test per trial drug were created.

PK analyses: Descriptive statistics including: median; two-sided 90% CI for the median; mean; and standard deviation. The coefficient of variation and geometric mean were used to summarize VWF:RCo, VWF:Ag, VWF:CB and FVIII:C levels and VWF multimer composition over time.

IR of VWF:RCo, VWF:Ag, VWF:CB (collagen binding), and FVIII:C were determined by subject, and were summarized by median, mean, SD, coefficient of variation, and geometric mean.

PK parameters (AUC_{0-96h}), $AUC_{(0-\infty)}$, terminal half-life, mean residence time (MRT), CL, V_{ss} , C_{max} , T_{max} , IR, and plasma half-life (calculated from the biphasic log-linear

model) were summarized per trial product and dose by median and two-sided 90% CI for the median, mean, SD, coefficient of variation, and geometric mean.

To assess PK equivalence of rVWF:rFVIII and pdVWF/FVIII, the 90% CI for the difference of the mean logarithms of $AUC_{0-\infty}$ between the 2 trial groups was calculated. The error variance used to calculate this CI was obtained from an analysis of variance (ANOVA) model with fixed factors accounting for the following sources of variation: sequence, subject nested in sequence, period, and treatment. The antilogs of the confidence limits constituted the 90% CI for the ratio of the geometric means (antilog of the means of the log) between rVWF:rFVIII and pdVWF/FVIII.

To establish PK equivalence in $AUC_{0-\infty}$ with a type I error of 5% the calculated two-sided 90% CI had to be contained completely in the margins of equivalence defined as 80% to 125%.

Secondary analyses of PK equivalence of VWF:Ag, VWF:CB and FVIII:C levels were limited to Cohort 4A (type 3 VWD) as subjects in Cohort 4B (subjects with severe type 1 VWD) would be less suitable for such analyses.

6.1.10 Study Population and Disposition

Subjects were almost equally divided by gender and were almost all white (Table 2)

6.1.10.1 Populations Enrolled/Analyzed

The trial population included subjects with both type 1 and type 3 disease. There were no type 2 patients in this Phase 1 trial.

6.1.10.1.1 Demographics

**Table 2
Demographics
Cohort^a**

| Parameter | Category | 1 N=3 N (%) | 2 N=5 N (%) | 3 N=5 N (%) | 4A N=22 N (%) | 4B N=3 N (%) | Total N=32 N (%) |
|-----------|----------------------------|-------------------|-------------------|-------------------|---------------------|--------------------|------------------------|
| Gender | Male | 2 (66.7) | 3 (60.0) | 5 (100) | 11 (50) | 1 (33.3) | 17 (53.1) |
| | Female | 1 (33.3) | 2 (40.0) | 0 (0) | 11 (50.0) | 2 (66.7) | 15 (46.9) |
| Race | White | 3 (100) | 5 (100) | 4 (80) | 22 (100) | 3 (100) | 31 (96.9) |
| | Black or African American | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | Asian | 0 (0) | 0 (0) | 1 (20) | 0 (0) | 0 (0) | 1 (3.1) |
| | American Indian or Alaskan | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

| | | | | | | | |
|-----------|---|------------|-----------|-----------|--------------|------------|--------------|
| | Native | | | | | | |
| | Native Hawaiian or other Pacific Islander | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Ethnicity | Hispanic or Latino | 0 (0) | 2 (40) | 1 (20) | 3 (13.6) | 0 (0) | 4 (12.5) |
| | Non-Hispanic or Latino | 3 (100) | 3 (60) | 4 (80) | 19 (86.4) | 3 (100) | 28 (87.5) |

^a Each subject can occur in cohort 1, 2 or 3 and in cohort 4A.
Adapted from Original BLA 125577; Full Clinical Study Report 070701, p.73

Reviewer Comment: There are very limited data on racial disparities in VWF levels. In this trial almost all subjects were White and a large majority were non-Hispanic or Latino.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable.

6.1.10.1.3 Subject Disposition

Subject disposition is shown in Table 3

Table 3
Subject Disposition

| Cohort | Enrolled | Screened | Enrolled/Not treated | Treated | Withdrawn | Completed Study |
|--------|----------|----------|----------------------|---------|-----------|-----------------|
| 1-3 | 13 | 13 | 0 | 13 | 0 | 13 |
| 4A/4B | 26 | 26 | 1 | 25 | 3 | 22 |

Six subjects completed cohort 1, 2, or 3 and continued in cohort 4

Reasons for exclusion were:

- Cohorts 1-3
- Screening anti-VWF antibody titer elevated (N=1)
 - Major protocol violations (N=2)
 - In addition, Cohort 1 was excluded from the PK dataset

- Cohort 4A
- Physician decision not to treat (N=1)
 - Elevated baseline anti-VWF antibody (N=1)
 - Subject requested withdrawal (N=1)
 - Subject did not receive correct form of IP (N=1)

- Excluded from PK dataset (N=13; 4A=12, 4B=1)
- Major protocol deviation (N=11)
 - No weight adjusted dose (N=2)

- Discontinued before end-of-trial visit (N=2)
- Subject withdrew consent (N=1)

- Subject did not receive correct form of IP
Cohort 4B (N=1)
- Discontinue before end-of-trial visit, physician decision (N=1)

6.1.11 Efficacy Analyses

Efficacy was not assessed in this Phase 1 trial.

6.1.11.1 Analyses of Primary Endpoint(s)

Safety and tolerability were confirmed (see safety data below).

6.1.11.2 Analyses of Secondary Endpoints

Median $T_{1/2}$ at the 50 IU per kg dose was 16 hours for rVWF and 12.6 hours for pdVWF, however the 90% CI were similar. $T_{1/2}$ appeared shorter with the smaller doses, but subject numbers were limited. T_{max} was independent of rVWF dose (0.43, 0.56 and 0.7 hours for 7.5, 20 and 50 IU per kg) and the T_{max} for the 50 IU per kg rFVIII dose was similar to the T_{max} with pdVWF (0.58 hours). Median C_{max} (U per dL) was similar for rVWF (66, 90% CI 62-92) and pdVWF (79.5, 90% CI 66-110) for 50 IU per kg dosing, and lower for lower doses. CL (mL per kg per hour) was lower with rVWF at the 50 IU per kg dose [3.37 (90% CI 2.69-4.01) versus pdVWF (4.7 (90% CI 4.17-6.72))] and independent of rVWF dose. V_{ss} (mL per kg) was similar between rVWF and pdVWF (83.7 versus 91.3) and was dose independent.

$AUC_{0-\infty}$ was higher for rVWF than for pdVWF for VWF:RCo (1.26:1, 90% CI 1.02-1.56), VWF:CB (1.18, CI 0.87-1.59) and FVIII:C (1.36, 0.93-1.99). VWF:Ag was lower for rVWF:Ag than for pdVWF.

Reviewer Comment: The disparity in $AUC_{0-\infty}$ for VWF:Ag may be due to the fact that activity (VWF:RCo) is higher for the pdVWF, resulting in a smaller dose of rVWF:Ag, since dosing was based on activity (VWF:RCo and not protein amount, VWF:Ag).

VWF:Ag and VWF:CB generally followed a similar pattern to VWF:RCo.

Post-infusion, ultra-high molecular weight multimers seemed to disappear from the circulation comparable to that observed with pdVWF, implying normal degradation by ADAMTS13. The single subject (1/23) who did not manifest this also had pre-existing non-neutralizing antibody to VWF, which may have impacted the detection of subunit cleavage. Please refer to Figure 1 below reproduced from the submission.

Figure 1
Degradation of VWF Over Time

rVWF

(b) (4)

FVIII PK parameters were comparable between the two VWF preparations, given the different amount of FVIII infused. The observed rise in secondary FVIII, beyond the expected 4-5 half-lives lifespan of the infused product, suggests that an infusion of rVWF alone could maintain sufficient VWF and FVIII to treat a BE, once FVIII levels have reached a therapeutic threshold.

Reviewer Comment: This is explicit in the proposed labeling. If FVIII levels are found to be inadequate in a BE, the first dose can be an infusion of both rVWF and ADVATE with subsequent infusions of rVWF only, pending normalization of FVIII levels.

PK Conclusion: The PK profile for rVWF is comparable to pdVWF/FVIII concentrate for VWF:RCo, and shows a sustained stabilization of endogenous FVIII. Data also indicate dose linearity for the higher investigated doses (7.5, 20, and 50 IU VWF:RCo/kg). However, these conclusions are limited by the low number of subjects in cohort 2 and cohort 3.

Reviewer Comment: Overall, the data suggest that rVWF can be infused at doses comparable to those utilized for the treatment of VWD with a currently licensed pdVWF/FVIII concentrate.

6.1.11.3 Subpopulation Analyses

Given the small number of overall subjects there were no subpopulation analyses. There are no data on the use of the product in children or the elderly (>60 years of age).

6.1.11.4 Dropouts and/or Discontinuations

Actual blood sampling times rather than nominal (protocol-based) times were utilized in PK calculations, so a deviation from protocol-specified times was not a reason for exclusion. However, if sampling time was not known or when concentration could not be determined, these samples were eliminated from calculations.

See [6.1.10.1.3](#)

6.1.11.5 Exploratory and Post Hoc Analyses
Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety dataset comprised all subjects who received any amount of VONVENDI.

6.1.12.2 Overview of Adverse Events (AEs)

Three subjects developed *de novo* non-neutralizing antibody titers against VWF, all in cohort 4: two developed low titers of 1:20. In one it was undetectable at 30 days. One subject developed titers against VWF (1:640), and also against CHO cell protein (1:320) and Furin, (1:80), both used in the manufacturing process.

Three subjects had pre-existing non-neutralizing antibodies. Titers increased following exposure in two, and could not be measured or confirmed in the third. In one subject (cohort 4) the titer rose following exposure to pdVWF but not further with exposure to rVWF.

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

There were no nonfatal SAEs.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no reports of thrombosis or inhibitor formation.

6.1.12.6 Clinical Test Results

No patterns of clinically significant laboratory abnormalities were identified.

6.1.12.7 Dropouts and/or Discontinuations

Not applicable.

6.1.13 Study Summary and Conclusions

rVWF:rFVIII was safe and well tolerated in this first-in-human trial. None of the theoretical risks associated with VWF or FVIII treatment occurred, including thrombotic events, TTP-like syndromes, neutralizing inhibitor development against VWF or FVIII, or allergic-type hypersensitivity reactions.

Reviewer Comment: The presence of ultra-large molecular weight multimers suggests a potential increased risk of thrombogenicity. However, in addition to the absence of clinical evidence of thrombogenicity, ADAMTS13 mediated cleavage fragments appeared in plasma after infusion, suggesting normal proteolysis in vivo.

6.2 Trial #2

Study 071001 - A Phase 3 clinical trial to determine the PK, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of BE in subjects diagnosed with VWD

Reviewer comment: Pivotal trial

6.2.1 Objectives (Primary, Secondary, etc.)

The primary objective was the number of subjects with successful treatment of BE. Success was defined as a mean efficacy rating score of <2.5 for VONVENDI-treated BEs during the trial period. This rating scale compared the actual versus the estimated number of infusions that would have been expected to have been required. The ordinal efficacy rating scale is summarized in Table 4.

**Table 4
Efficacy Rating Scale**

| Efficacy Rating Scale | | |
|-----------------------|---|---|
| Rating | Efficacy Rating Criterion | |
| | Minor and Moderate Bleeding Events | Major Bleeding Events |
| Excellent (=1) | <ul style="list-style-type: none"> • Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode • No additional product containing VWF required | <ul style="list-style-type: none"> • Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode • No additional VWF containing coagulation factor containing product required |
| Good (=2) | <ul style="list-style-type: none"> • 1-2 infusions greater than estimated required to control that bleeding episode • No additional product containing VWF required | <ul style="list-style-type: none"> • <1.5x infusions greater than estimated required to control that bleeding episode • No additional VWF containing coagulation factor containing product required |

| | | |
|---------------|---|---|
| Moderate (=3) | <ul style="list-style-type: none"> • 3 or more infusions greater than estimated used to control that bleeding event • No additional product containing VWF required | <ul style="list-style-type: none"> • $\geq 1.5x$ more infusions greater than estimated used to control that bleeding event • No additional VWF containing coagulation factor containing product required |
| None (=4) | <ul style="list-style-type: none"> • Severe uncontrolled bleeding or intensity of bleeding not changed • No additional product containing VWF required | <ul style="list-style-type: none"> • Severe uncontrolled bleeding or intensity of bleeding not changed • Additional VWF containing coagulation factor containing product required |

Adapted from Original BLA 125577; Full Clinical Study Report 071001, p.43

Secondary outcome measures were:

- The number of treated BE with an efficiency rating of Excellent or Good
- The number of infusions and the number of units of rVWF:rFVIII, and/or rVWF per BE

Secondary PK outcome measures were:

- Area under the plasma concentration/time curve from time 0 to infinity ($AUC_{0-\infty}/Dose$); area under the plasma concentration/time curve from time 0 to 96 hours ($AUC_{0-96h}/Dose$); MRT; CL; IR, elimination Phase $T_{1/2}$; V_{ss} of VWF:RCo, VWF:Ag, VWF collagen-binding (VWF:CB), and FVIII:C
- In vivo recovery (IVR) of VWF:RCo, VWF:Ag and VWF:CB
- Comparison of intra-subject PK of VWF:RCo, VWF:CB and VWF:Ag at baseline and after 6 months in a subset of at least 20 subjects with severe VWD (minimum of 6 subjects with type 3 VWD)

6.2.2 Design Overview

This was a double-blind cross-over trial evaluating PK and efficacy. After the PK trial (Part A) subjects were allowed to enroll in a period of treatment of BE with the dose of product based on the disease type and the severity of the bleeding. rFVIII was given with the first dose.

6.2.3 Population

Patients with:

- Type 1 (VWF:RCo < 20 IU per dL)
- Type 2A (VWF:RCo < 20 IU per dL)
- Type 2B (diagnosed by genotype)
- Type 2N (FVIII:C < 10% and historically documented genetics)
- Type 2M
- Type 3: (VWF:Ag ≤ 3 IU per dL)

-Or – Severe VWD with a history of requiring substitution therapy with VWF concentrate to control bleeding

Karnofsky score $\geq 60\%$

To participate in part B (treatment of BE) subjects had to have had at least one documented bleed requiring VWF factor replacement within the previous 12 months.

Exclusion criteria included the presence of inhibitors to VWF or FVIII, or the presence of an additional coagulation disorder

6.2.4 Study Treatments or Agents Mandated by the Protocol

There were two trial periods, parts A (PK assessment) and B (treatment of BE), and four treatment arms:

The trial protocol is summarized in [Figure 2](#), below:

Arm 1: PK assessment (50 IU per kg VONVENDI with or without rFVIII in a crossover after an 18 day washout) plus on-demand 6 month treatment of BE

Arm 2: PK assessment only (50 IU per kg VONVENDI, with or without rFVIII in a crossover after an 18 day washout) without treatment of BE

Arm 3: PK assessment of 80 IU per kg VONVENDI plus on-demand six month treatment of BE, then another PK of 80 IU per kg followed by another six month treatment of BE

Arm 4: On-demand treatment for BE only

Treatment of BE:

Type 1 disease: *Minor bleeding*: VONVENDI 40-50 IU per kg (one or two doses)
Major bleeding: VONVENDI 50-75 IU per kg, then 40-60 IU per kg every 8-12 hours for three days to keep trough VWF:RCo >50%, then 40-60 IU per kg daily for up to seven days of treatment, with Advate rFVIII for the initial infusion in a ratio of 1.3 rVWF:1 Advate; without Advate for subsequent infusions.

Types 2 and 3 disease: *Minor bleeding*: VONVENDI 40-50 IU per kg (one or two doses)
Major bleeding: initial dose of VONVENDI 60-80 IU per kg then 40-60 IU per kg every 8-12 hours for three days to keep trough VWF:RCo>50%; then 40-60 IU per kg daily up to seven days of treatment, with Advate for initial infusion; without Advate for subsequent infusions.

Subjects receiving treatment for BE in part A were to be entered into part B to continue on-demand treatment for BE for a total of 12 months in the trial.

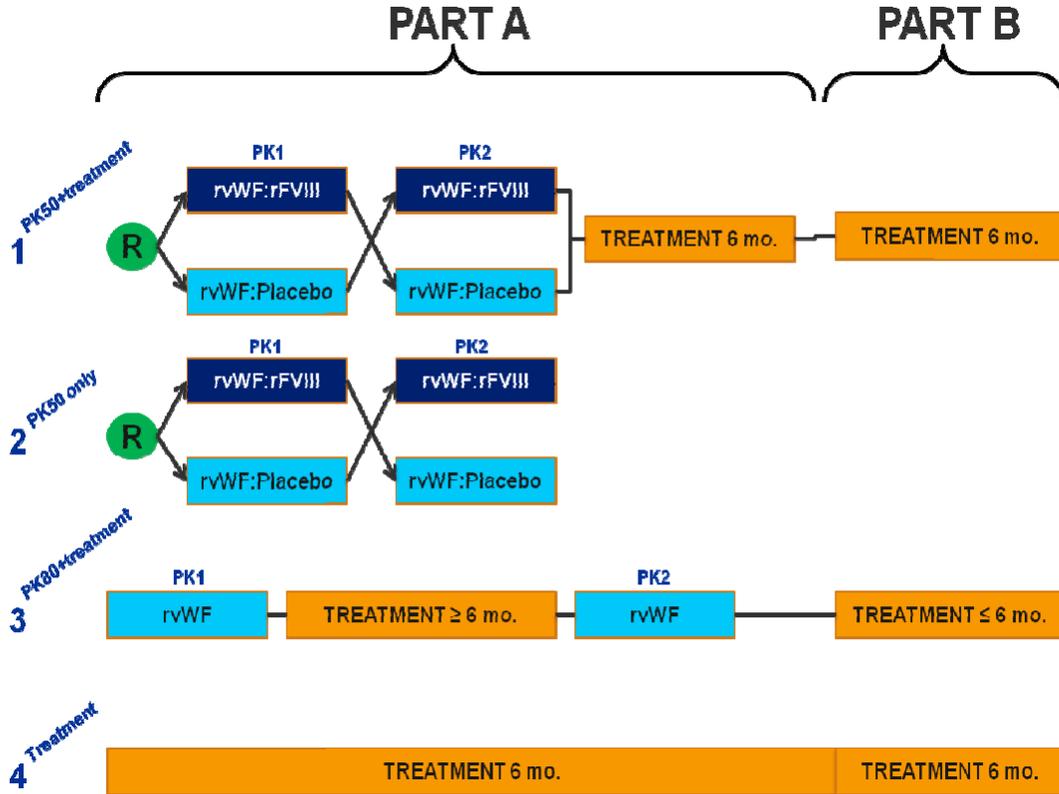
Arm 1: Minimum 7 subjects with type 3 VWD

Arm 2: Minimum 7 subjects with type 3 VWD

Arm 3: Minimum 12 subjects with severe VWD

Arm 4: Approximately 7 subjects independent of type

Figure 2 Study Protocol



Source: Original BLA 125577; Full Clinical Study Report 071001, p.111

6.2.5 Directions for Use

Single use

6.2.6 Sites and Centers

United States (11), Poland (8), Russia (5), United Kingdom (3), Italy (3), Bulgaria (3), Japan (3), Australia (3), Germany (2), Austria (1), Belgium (1), Netherlands (1), Spain (1), Sweden (1), India (1)

6.2.7 Surveillance/Monitoring

Subjects in arms 1, 3, and 4 were followed for 6 months. Patient maintained diaries to record VONVENDI/Advate infusions, details of BE, subjective hemostatic efficacy and AE.

6.2.8 Endpoints and Criteria for Study Success

See [6.2.1](#). There were no modifications during the trial.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Point estimates and CI were calculated considering all treated BEs. Two analyses were carried out: all BE and BE excluding gastrointestinal bleeds.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Subpopulations were defined as:

- A subset of at least 20 subjects with type 3 VWD with a minimum of 14 in the PK50 IU arm and 6 in the PK80 IU arm
- A subset of approximately three subjects with type 2 VWD but not more than 2 with type 2N
- Approximately 3 with type 1 VWD
- A minimum of 14 must be unique, i.e. did not participate in the Phase 1 trial (trial 070701)

6.2.10.1.1 Demographics

Subject demographics are displayed in Table 5, below. Males and females were both represented in approximately equal numbers. Most subjects were white with a smaller number of Asian subjects.

Table 5:
Combined Demographics for Studies 070701 and 071001

| Parameter | Category | 070701 ^a N=31 n (%) | 071001 N=37 n (%) | 070701 + 071001 ^b N=66 n (%) |
|-----------|---|--------------------------------------|-------------------------|---|
| Gender | Male | 17 (54.8) | 17 (45.9) | 33 (50.0) |
| | Female | 14 (45.2) | 20 (54.1) | 33 (50.0) |
| Race | White | 30 (96.8) | 32 (86.5) | 60 (90.9) |
| | Black or African American | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Asian | 1 (3.2) | 5 (13.5) | 6 (9.1) |
| | American Indian or Alaska Native | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Native Hawaiian or other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ethnicity | Hispanic or Latino | 4 (12.9) | 2 (5.4) | 6 (9.1) |
| | Not Hispanic or Latino | 27 (87.1) | 35 (94.6) | 60 (90.9) |
| vWD Type | 1 | 2 (6.5) | 2 (5.4) | 4 (6.1) |
| | 2A | 0 (0.0) | 5 (13.5) | 5 (7.6) |
| | 2B | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 2M | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 2N | 0 (0.0) | 1 (2.7) | 1 (1.5) |
| | 3 | 29 (93.5) | 29 (78.4) | 56 (84.8) |

^a For subjects who participated in cohort 1, 2, or 3 and cohort 4A, the values of the first cohort in which they were enrolled are taken.

^b For subjects who were treated with IP in both studies, the values of the first study are taken.

Source: Original BLA 125577; Integrated Summary of Safety, p.36

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
VWD type distribution is shown in Table 5.

6.2.10.1.3 Subject Disposition

A total of 49 subjects were enrolled (signed informed consent) and screened, 37 subjects were (all trial arms) and 30 subjects completed the trial.

Of the 19 discontinued subjects:

- 12 discontinued prior to treatment
- 7 discontinued after treatment began
 - 4 withdrew consent
 - 1 pregnancy
 - 1 AE (chest discomfort and tachycardia)
 - 1 deemed ineligible in retrospect

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

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

6.2.11.2 Analyses of Secondary Endpoints

Efficacy

192/192 (100%) of BE treated with rVWF:rFVIII (in 22/37 subjects – 17 type 3 VWD, 4 with type 2A VWD and 1 with type 2N VWD) met the criterion for successful treatment. All bleeds were controlled with rVWF or rVWF:rFVIII with an efficacy rating of excellent (96.9%) or good (3.1%). 157/192 (81.8%) required only a single infusion to control the bleed. The overall efficacy rating range was 1-4 (median 1.0). The median dose of rVWF per BE (with or without rFVIII) was 48.2 IU per kg (90% CI 43.9 to 50.2)

PK

Crossover results at 50 IU/kg VWF:RCo showed that the PK profile for rVWF VWF:RCo was independent of administration alone or with rFVIII ($T_{1/2}$: 19.4 hours for rVWF and 16.6 hours for rVWF:rFVIII; IR: 1.8 U/dL per IU/kg infused for both rVWF and rVWF:rFVIII; MRT: 26.7 hours for rVWF and 25.2 hours for rVWF:rFVIII). FVIII levels increased substantially with a median peak at 24 hours of 111.0 U/dL for rVWF:rFVIII and 86.0 U/dL after rVWF alone, indicating that rVWF induces a sustained increase in endogenous FVIII activity. The rVWF PK profile was comparable at 50 IU/kg and 80 IU/kg VWF:RCo, and repeated PK at 80 IU/kg VWF:RCo showed close agreement between pretreatment and end-of-trial results.

Reviewer Comment: All 10 BEs in 3 subjects treated with VWF alone (without rFVIII) for the initial infusion had an efficacy rating of Excellent, suggesting that an immediate rise in FVIII:C may not be necessary, or if the baseline FVIII:C level is sufficient to ensure hemostasis, rVWF can be administered without rFVIII. However, the sample size is too small to make this conclusion.

6.2.11.3 Subpopulation Analyses

There were no apparent endpoint differences among VWD types, or between male and female, or white and Asian subjects, in terms of treatment success (100% for all), hemostatic efficacy ratings, or infusions/number of units to treat a BE. However, most subjects were white (Table 5) and the remainder Asian, so limited variability precludes a

meaningful comparison by race. There were no unexpected gender-specific differences in the incidence of AEs.

There are no data on the use of the product in children or the elderly.

Table 6
Analysis by Subpopulation

| Category | Subcategory | Excellent | Good | Moderate | None |
|----------------|--------------|-----------------|--------------|----------|------|
| 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) | - | - |

Source: Original BLA 125577; Section 2.5, p.28

6.2.11.4 Dropouts and/or Discontinuations

There was only a single dropout for an AE for transient tachycardia and chest discomfort. Dropouts should not have affected the efficacy measure, successful treatment of individual BE.

6.2.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.2.12 Safety Analyses

6.2.12.1 Methods

There was an integrated safety analysis combining data from studies 070701 and 071001 [CRMTS # 9386]. AEs were actively solicited.

6.2.12.2 Overview of Adverse Events

- 175 AEs were reported in 44/66 subjects (66.7%) during or after 83/355 (23%) of infusions.
 - 117 mild, 53 moderate and 5 severe
- Nonserious AEs were reported in 43/66 subjects
- There were 10 SAEs in 8 subjects

- Eight SAEs in 7 subjects were unrelated to VONVENDI (dental caries, osteomyelitis, constipation, uterine polyp, spontaneous abortion, gastrointestinal hemorrhage, mesenteric hematoma and hemorrhoids)
- One subject developed chest discomfort and tachycardia during rVWF: rFVIII infusion. These were recorded by the investigator as 2 SAEs. The subject was withdrawn from the trial.
- Three nonserious AEs were observed in >5% of subjects: headache (10.6%), laceration (6%) and contusion (6%).
- No non-temporally related AEs occurred in >5% of subjects. Those occurring in >3% of subjects were vertigo, vomiting, infusion site paresthesia, headache, dizziness and generalized pruritus.

6.2.12.3 Deaths

There were no deaths in the trial.

6.2.12.4 Nonfatal Serious Adverse Events

See [6.2.12.2](#).

6.2.12.5 Adverse Events of Special Interest (AESI)

There were no reports of TE events. TE events have been observed with infusions of pdVWF. There was no treatment-related development of specific binding or neutralizing antibodies against rVWF or neutralizing antibodies against rFVIII.

Reviewer comment: There were no reports of TE events. There was no indication that the AE of chest pain/tachycardia was thrombotic in etiology. TE events have been observed with infusions of pdVWF. Similarly there were no laboratory parameters consistent with TTP.

6.2.12.6 Clinical Test Results

There were no laboratory data consistent with TTP. There was no antibody development to CHO cell protein, rFurin and murine IgG, components of the manufacturing process. No differences in rVWF proteolysis over time could be linked to subject differences in ADAMTS13 concentrations.

6.2.12.7 Dropouts and/or Discontinuations

There was a single subject who was removed from the trial for an AE (see [6.2.12.2](#)). This did not have an overall impact.

Nineteen subjects did not complete the trial (see [6.2.10.1.3](#)). This did not affect the efficacy analysis.

6.2.13 Study Summary and Conclusions

This trial showed a high degree of efficacy of the product (100%) with an acceptable safety profile.

6.3 Trial #3

Study 071104 - Co-infusion of recombinant von Willebrand Factor/recombinant Factor VIII (rVWF:rFVIII): a Phase 1 trial evaluating the PK, safety and tolerability in severe hemophilia A

6.3.1 Objectives (Primary, Secondary, etc.)

This preliminary trial is submitted in support of the Phase 3 trial. It evaluated whether the PK of FVIII changed when co-administered with two doses of rVWF, the first subclinical and the second in the range that is proposed to be used clinically. It included primary and secondary endpoints that assessed PK and safety.

6.3.2 Design Overview

This is a Phase 1, prospective, uncontrolled, non-randomized multicenter proof of concept trial assessing the safety of the addition of VONVENDI to rFVIII (Advate) in treating 12 subjects with hemophilia A. All subjects underwent 3 PK analyses: after rFVIII alone; after rFVIII plus 10 IU per kg rVWF; and after rFVIII plus 50 IU per kg rVWF.

6.3.3 Population

Subjects were previously treated (≥ 150 exposure days of FVIII) adults (18-60 years of age) who had severe hemophilia A (FVIII $<1\%$) of any ethnicity.

Important exclusion criteria included

- Coagulation disorder other than hemophilia A
- FVIII inhibitor at screening ≥ 0.4 BU (by (b) (4)) or ≥ 0.6 BU (by (b) (4))
- History of VWF inhibitor
- Average of one BE per week requiring factor replacement over the prior three months.

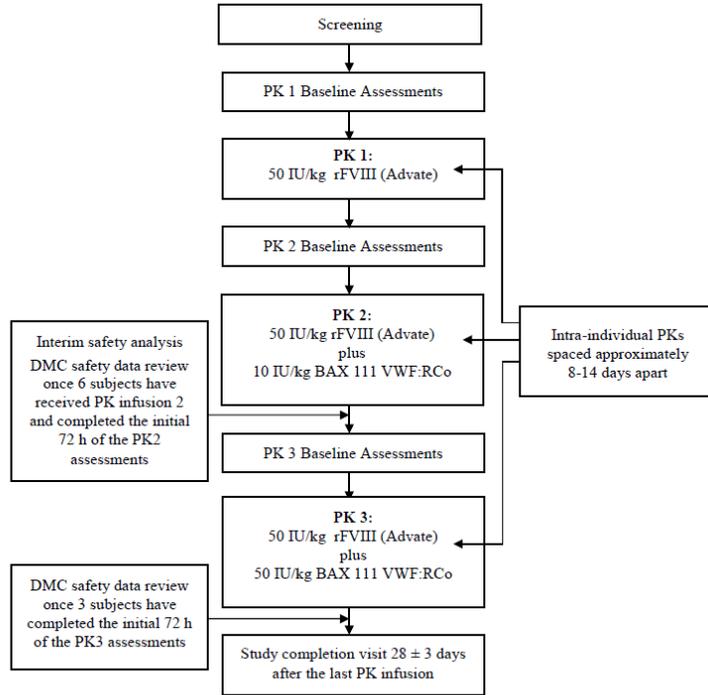
6.3.4 Study Treatments or Agents Mandated by the Protocol

All subjects received 3 PK infusions:

- 50 IU per kg rFVIII
- Premixed solution of 50 IU per kg rFVIII plus 10 IU per kg VONVENDI
- Premixed solution of 50 IU per kg rFVIII plus 50 IU per kg VONVENDI (once the safety and tolerability had been demonstrated in at least 6 subjects receiving the 10 IU rVWF dose.

PK analyses were performed at intervals of approximately 8-14 days. There was a washout period of 8 days after the prior rVWF infusion and 5 days since the last rFVIII or other hemostatic drug or factor.

Figure 3 Protocol Flowchart



Source: Original BLA 125577; Full Clinical Study Report 071104, p.19

6.3.5 Directions for Use

Single use

6.3.6 Sites and Centers

Subjects were accrued from 5 centers, three in the United States and one each in Bulgaria and Poland.

6.3.7 Surveillance/Monitoring

All infusions were done at a study site under the supervision of a physician. A termination visit occurred on approximately day 28 after the last infusion (see figure, above).

6.3.8 Endpoints and Criteria for Study Success

Primary Outcome

PK:
AUC_{0-∞}/Dose AUC_{0-120h}/Dose
MRT

- CL)
- T_{1/2} (elimination Phase half-life
- (Vss

Safety:

- Occurrence of treatment-related AEs

Secondary Outcomes

PK:

- In vivo recovery and incremental recovery of FVIII

Safety:

- Development of inhibitory antibodies to FVIII
- Development of antibodies to CHO proteins, mouse immunoglobulins and rFurin
- Occurrence of thrombotic events

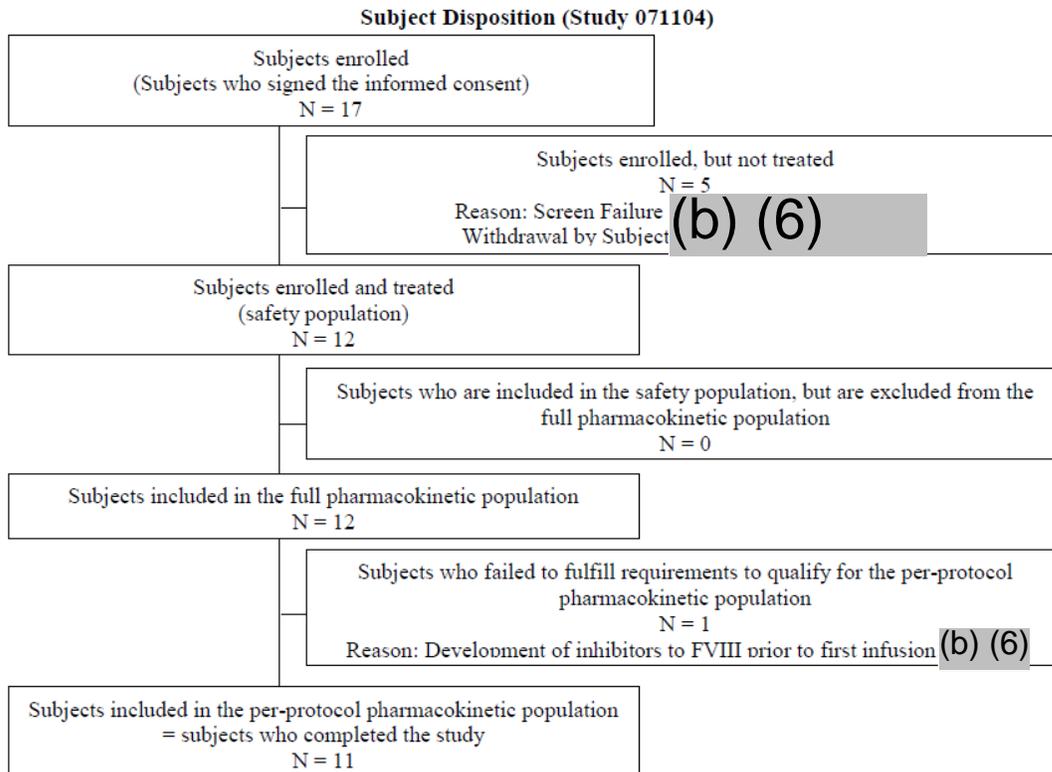
6.3.9 Statistical Considerations & Statistical Analysis Plan

This was an exploratory trial. The trial was unblinded and there was no placebo or comparator product. The sample size of 12 evaluable subjects was considered by Baxter to be sufficient to provide descriptive data and this reviewer concurs.

6.3.10 Study Population and Disposition

Subject disposition is shown in Table 7

Table 7



6.3.10.1 Populations Enrolled/Analyzed

The PK and safety analysis sets included all 12 subjects. The per protocol set included the 11 subjects who received VONVENDI.

6.3.10.1.1 Demographics

As the trial population had hemophilia A, all subjects were male (Table 8).

Table 8
Demographics and Baseline Characteristics - Categorical Data
(Study 071104: Safety Analysis Set)

| Parameter | Category | N=12 n (%) |
|-----------|------------------------|---------------|
| Gender | Male | 12 (100.0%) |
| Race | White | 11 (91.7%) |
| | Asian | 1 (8.3%) |
| Ethnicity | Not Hispanic or Latino | 12 (100.0%) |

Source: Original BLA 125577; Full Clinical Study Report 071104, p.19

Reviewer Comment: In this trial all subjects were male. Almost all were white and all were non-Hispanic or Latino. That could potentially affect the generalizability of the results. However, there is no mechanistic expectation of a gender or sex difference.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All subjects met the inclusion criteria without significant additional disease.

6.3.10.1.3 Subject Disposition

Seventeen subjects were enrolled and 11 completed the trial. Three were screen failures and two were withdrawn prior to receiving trial medication (one withdrew consent, one received an exclusionary medication). One additional subject developed FVIII inhibitors prior to the first infusion.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Data in the two tables below indicate that the PK for rVIII is unchanged when used alone or with two different doses of rVWF.

Table 9
PK Data with Co-infusion of rFVIII

| | AUC (0-120H) | AUC (0-∞) | MRT | CL | T1/2 | Vss |
|----------------------------|--------------|-----------|-------|-------|-------|------|
| rFVIII only | 1376 | 1410 | 15.17 | 0.035 | 12.05 | 0.54 |
| rFVIII + 10 IU per kg rVWF | 1396 | 1433 | 16.4 | 0.035 | 12.74 | 0.57 |
| rFVIII + 50 IU per kg rVWF | 1963 | 1994 | 18.06 | 0.025 | 13.74 | 0.46 |

Data are geometric means. FVIII was assayed by (b) (4).

Results were similar and only the (b) (4) assay is shown in this table although Sponsor reports (b) (4).

AUC = area under curve, MRT = mean residence time, CL = clearance, Vss = volume of distribution at steady state

Source: Data from original BLA 125577; Full Clinical Study Report 071104, Table 6

Reviewer Comment: PK data were similar to the two trials done in non-hemophilic subjects (070701 and 071001).

6.3.11.2 Analyses of Secondary Endpoints

Table 10
Secondary Endpoint PK Data with Co-infusion of rFVIII

| | Distributional T 1/2 | Cmax | Tmax | IR | IVR | | | | |
|----------------------------|----------------------|------|------|------|-----|--|--|--|--|
| rFVIII only | 7.69 | 105 | 0.44 | 2.12 | 211 | | | | |
| rFVIII + 10 IU per kg rVWF | 4.86 | 100 | 0.33 | 1.99 | 199 | | | | |
| rFVIII + 50 IU per kg rVWF | 7.63 | 115 | 0.34 | 2.29 | 229 | | | | |

Data are geometric means. FVIII was assayed by (b) (4)
Results were similar and only the (b) (4) assay is shown in this table although Sponsor report (b) (4)
Cmax = maximum concentration following infusion, Tmax = time to Cmax, IR = incremental recovery, IVR = in vitro recovery

Source: Original BLA 125577; Full Clinical Study Report 071104, Table 8

6.3.11.3 Subpopulation Analyses

There are no data on the efficacy of rVWF in children or the elderly (>56 years). There were no subgroup examinations or analyses. Due to the small number of subjects per site no cross-site comparison was performed.

6.3.11.4 Dropouts and/or Discontinuations

There was no difference seen in the data for the full PK analysis set and the per protocol analysis set, and results of the PK assessments of both data sets lead to the same conclusion. Only one subject discontinued the trial and was not included in the per protocol analysis set.

6.3.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.3.12 Safety Analyses

6.3.12.1 Methods

AEs were recorded by subjects in diaries.

6.3.12.2 Overview of Adverse Events

See 6.3.12.4

6.3.12.3 Deaths

There were no deaths in this trial.

6.3.12.4 Nonfatal Serious Adverse Events

There were no SAEs in this trial. Two SAEs, upper gastrointestinal bleeding and development of inhibitor to FVIII, were reported in a single subject prior to receiving any IP. There were five AEs reported, all considered by both Baxter and this reviewer to be mild.

6.3.12.5 Adverse Events of Special Interest (AESI)

No subjects developed neutralizing antibodies against FVIII or VWF, or antibodies to products involved in its preparation after exposure to VONVENDI (CHO cell protein, rFurin or murine IgG). One subject had a low anti-VWF titer prior to the trial (that could not be confirmed). It did not rise after treatment. There was no evidence of microvascular or grossly apparent thromboemboli. There was no viral seroconversion.

Reviewer comment: Subjects were selected who had a low likelihood of developing antibodies as they already had a significant exposure history to FVIII.

6.3.12.6 Clinical Test Results

No patterns of clinically significant laboratory abnormalities were identified.

6.3.12.7 Dropouts and/or Discontinuations

See 6.3.11.4

6.3.13 Study Summary and Conclusions

VONVENDI may slightly sustain rFVIII activity with a highest observed rFVIII half-life of 13.74 h after co-infusion of 50 IU/kg VONVENDI plus 50 IU/kg rVWF. An association between baseline VWF:Ag levels and increase of rFVIII half-life was found. In subjects with VWF:Ag levels below 100% the highest improvement in rFVIII circulating $t_{1/2}$ was observed.

Reviewer comment: Since one of the biologic functions of high molecular weight VWF is to carry and to stabilize FVIII from premature proteolysis, it might be theorized that rVWF, with its high fraction of large molecular weight multimers, would increase FVIII half-life. There was a slight an extension of FVIII terminal $t_{1/2}$ with the co-administration of VONVENDI and rFVIII, but this was insufficient to provide a rationale to significantly change infusion frequency. In clinical practice (in VWD patients, not hemophiliacs), rFVIII, if used, will only be given once, at the first dosing of rVWF. Those with the lowest baseline levels of VWF had the greatest improvement in rFVIII $t_{1/2}$.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Indicated for prevention and treatment of BE in adults (age 18 years and older) diagnosed with VWD.

7.1.1 Methods of Integration

Hemostatic efficacy was assessed in a single completed Phase 3 trial (Study 071001), see [6.2](#).

7.1.2 Demographics and Baseline Characteristics

See [Table 5](#)

Overall (Studies 070701 and 071001) the median age was 36 years (range 18 to 64). 85% had type 3 disease, 6% type 1, 8% type 2A and 2% type 2N. 50% were male, 91% white and 9% Asian. All subjects were tested and none had low baseline levels of ADAMTS13 (range 57-244%, normal range 50-160%).

7.1.3 Subject Disposition

See [6.2.10.1.3](#)

7.1.4 Analysis of Primary Endpoint(s)

100% of subjects receiving the VONVENDI met the criterion of a treatment success.

7.1.5 Analysis of Secondary Endpoint(s)

See [6.2.11.2](#)

7.1.6 Other Endpoints

7.1.7 Subpopulations

See [6.2.11.3](#)

7.1.8 Persistence of Efficacy

The onset of biological activity is essentially immediate and biological effects would not be expected to be prolonged beyond several $t_{1/2}$ (several days) following one or a few doses. Subjects were followed for up to 12 months during which they could have had treatment for several BE. No untoward events were noted. There was no evidence that efficacy declined after several doses. There was no antibody formation to VONVENDI over the course of the pivotal trial (12 months).

7.1.9 Product-Product Interactions

If baseline FVIII levels are low, the first dose of the VONVENDI would need to be given with FVIII (although studies are limited to Baxter's rFVIII). Study 071104 showed that the only interaction of rVWF and rFVIII was a slight prolongation of the $t_{1/2}$ of plasma FVIII, presumably as VWF protects FVIII from excessive proteolysis. While the $t_{1/2}$ was prolonged, the prolongation was inadequate to suggest that FVIII dosing, if needed, could be changed. In any event, FVIII levels in clinical practice would be measured, not assumed.

7.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7.1.11 Efficacy Conclusions

100% of subjects receiving VONVENDI met the criterion of a treatment success (median efficacy rating of <2.5), the primary endpoint. VONVENDI was also successful in meeting the secondary endpoints. 192/192 (100%) of bleeds treated with rVWF:rFVIII were controlled with rVWF:rFVIII or rVWF alone, and there was an efficacy rating of excellent (96.9%) or good (3.1%). 157/192 (81.8%) required only a single infusion to control the bleed. The overall efficacy rating range was 1-4 (median 1.0). The median dose of rVWF per bleeding episode (with or without rFVIII) was 48.2 IU per kg (90% CI 43.9 to 50.2)

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

AEs were actively solicited from subjects, in follow up examinations and by diary.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

All 81 subjects in the three trials were part of the safety pool.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Not applicable.

8.2.3 Categorization of Adverse Events

AE verbatim terms were coded in Medical Dictionary for Regulatory Activities (MeDRA). A single subject had two AEs that were probably related and would qualify as a single event (chest discomfort and tachycardia).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

All subjects from the two trials evaluating PK and efficacy/safety were combined. Subjects in both received the VONVENDI. Subjects in the supportive trial evaluating the interaction with FVIII were not included.

8.4 Safety Results

8.4.1 Deaths

There were no deaths in any of the three trials.

8.4.2 Nonfatal Serious Adverse Events

Ten nonfatal SAEs were reported in 8 subjects. Eight were considered not related (dental carries, osteomyelitis, constipation, uterine polyp, spontaneous abortion, gastrointestinal hemorrhage, mesenteric hematoma and hemorrhoids). Two, chest discomfort and tachycardia, in the same subject, (b) (6), were rated by Baxter as possibly related and this reviewer concurs.

This subject had previously received both pdVWF and rVWF arms of the PK trial. Eight days, 18 days and 27 days later he received single infusions of 51 mL for treatment of an ankle bleed. Two days later an infusion for a left ankle bleed was stopped after 6 mL due to chest discomfort and tachycardia. This was transient (improved within 10 minutes and fully recovered within three hours) and without sequelae; pulmonary embolus was not probable by any available data.

In trial 071104 (hemophilia patients) there were four AEs in three subjects: laceration, epistaxis, hypotension, tooth bleed. None of these was an SAE. All were unrelated and mild. Hypotension occurred in one subject after both treatments. The other AEs only occurred after the second or third treatment.

8.4.3 Study Dropouts/Discontinuations

Only one subject was removed from trial 070701 for reasons potentially attributable to the VONVENDI (nausea and variable p-selectin values). This patient withdrew consent after the first infusion but before the second. An AE was not provided by the investigator

as a reason for withdrawal. In the pivotal trial 071001, 19 subjects discontinued participation. Twelve discontinued participation prior to treatment. Of the seven who discontinued after treatment began four withdrew consent, there was one pregnancy, one was deemed ineligible in retrospect, and one developed an AE (chest discomfort and tachycardia).

8.4.4 Common Adverse Events

There were few AEs and they were distributed among broad areas. There was no common adverse outcome profile. Only three non-serious AEs were observed in >5% of subjects: headache (10.6%), laceration (6%) and contusion (6%), all of which are common events in this class of subjects. No temporally associated AEs occurred in >5% of subjects. Temporally related AEs occurring in >3% of subjects were vertigo, vomiting, infusion site paresthesia, headache and pruritis.

AEs that were assessed by investigators to be related to rVWF were platelet disorder, tachycardia, nausea, chest discomfort, infusion site paresthesia, electrocardiogram T wave inversion, increased heart rate, dizziness, dysgeusia, psychomotor hyperactivity, tremor, pruritus, and hot flush. Follow up evaluation by Baxter concluded that neither platelet disorder nor psychomotor hyperactivity was triggered by rVWF. Only pruritus occurred in more than one subject (3%)

Lacking an alternative cause, adverse drug reactions related to rVWF were determined to be tachycardia, nausea, chest discomfort, dizziness, dysgeusia, pruritus generalized, hot flush, hypertension, infusion site paresthesia, tremor and electrocardiogram T wave inversions. All of these occurred in a single infusion and in single subjects, with the exception of pruritis, which occurred in two infusions and two subjects.

Reviewer Comment: With one exception, all of these occurred in a single subject. Chest discomfort and tachycardia, both transient, occurred simultaneously in the same subject.

There was no apparent dose-dependency on the development of AEs.

8.4.5 Clinical Test Results

There were no AEs related to measures of hematology, clinical chemistry or viral serology

8.4.6 Systemic Adverse Events

None

8.4.7 Local Reactogenicity

None

8.4.8 Adverse Events of Special Interest

There was no evidence for the development of TTP. No subject developed neutralizing antibodies to FVIII or VWF after exposure to VONVENDI. A single subject had FVIII inhibitors prior to treatment. This subject received 50 IU per kg rVIII twice with no increase in titers (infusion 1: 1.4 BU per mL, infusion 2: 1.2 BU per mL, end of trial: 1.4 BU per mL. The subject did not receive the third dose and was removed from the trial.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

There was no apparent relationship between AEs and dose.

8.5.2 Time Dependency for Adverse Events

There was no time dependency for AEs.

8.5.3 Product-Demographic Interactions

The total population was small but there was no evidence of an age effect on either safety or efficacy, although elderly subjects were not studied.

8.5.4 Product-Disease Interactions

None

8.5.5 Product-Product Interactions

There was evidence that rVWF prolonged somewhat the half-life of endogenous FVIII. Given the physiologic function of VWF, and particularly of the largest multimers, this is not unexpected. However this prolongation was not so large as to affect dosing of rFVIII.

8.5.6 Human Carcinogenicity

There is no indication of carcinogenicity related to this product.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

None

8.5.8 Immunogenicity (Safety)

See [8.4.8](#)

8.5.9 Person-to-Person Transmission, Shedding

None

8.6 Safety Conclusions

VONVENDI was quite safe. AEs were generally mild and were most often unrelated.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data in pregnant women. The label will indicate that there are no human or animal data and that the product should be given to pregnant women only if clearly needed.

9.1.2 Use During Lactation

VONVENDI was not evaluated in lactating women. It is not known if the VONVENDI is excreted in human milk. The draft label notes that because of this, caution should be used when administered to nursing women.

9.1.3 Pediatric Use and PREA Considerations

No subjects <18 years of age were included in the clinical trials. As an orphan drug designated product, PREA was not triggered.

Baxter has submitted a Pediatric Study Plan. Baxter is proposing a Phase 3 prospective, multicenter, open-label trial to determine safety and efficacy in a pediatric population. There are proposed to be eight subjects >12 to 18 years of age, eight subjects 6 to 12 years of age and eight subjects < 6 years of age. The European Medicines Agency Guideline for the development of pdVWF products suggests enrolling at least eight children <6 years of age with severe VWD.⁴

9.1.4 Immunocompromised Patients

This product has not been specifically evaluated in immunocompromised patients. However, it is not an immunomodulatory agent and there is no reason to expect a different outcome in efficacy or safety in immunocompromised patients.

9.1.5 Geriatric Use

The product has not been studied in subjects >60 years of age. The draft label indicates that the product has not been studied in subjects >65 years of age

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None

10. CONCLUSIONS

rVWF (VONVENDI) is safe and effective. The in vitro recombinant manufacturing process may offer potential advantages over plasma-derived preparations, as does the absence of small or fixed amounts of FVIII and the higher proportion of the hemostatically active large multimers. VONVENDI undergoes normal in vivo proteolysis and there is no evidence that the increased proportion of high molecular weight multimers, compared to plasma-derived products, poses an increased thrombogenicity risk.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

⁴ EMA Guideline on the Role of Pharmacokinetics in the Development of Medicinal products in the Paediatric Population. EMEA/CHMP/EWP/147013/2004 Corrigendum 2006; 1-8.

Table 11 – Benefit-Risk Analysis

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|------------------------------|---|---|
| Analysis of Condition | <ul style="list-style-type: none"> VWD is an autosomally inherited congenital bleeding disorder affecting approximately 1% of otherwise healthy persons, although treatment is required in 1:10,000 people. VWD is due to qualitative or quantitative abnormalities in VWF. VWD can have clinical manifestations in all ages beyond infancy. | <ul style="list-style-type: none"> VWD can result in spontaneous or trauma-related mucocutaneous bleeding Menorrhagia can be severe Surgical bleeding can be severe Appropriate treatment can prevent significant morbidity |
| Unmet Medical Need | <ul style="list-style-type: none"> Advantage over desmopressin Potential advantage over plasma-derived VWF | <ul style="list-style-type: none"> Desmopressin is ineffective in type 3 and severe type 1 disease, has a variable response in types 2A and 2M, and is contraindicated in type 2B VWD. It may be contraindicated in patients with overt cardiovascular disease or in very young children. Dosing is typically required every 12-24 hours, but there is diminishing response with repeated doses. Hyponatremia is a risk at the extremes of age. Plasma derived VWF concentrates contain amounts of FVIII. Since VWD patients retain the ability to synthesize FVIII, and the half-life of FVIII is longer than that of VWF, continued infusions of VWF can result in excessive FVIII levels and present a risk of venous thrombosis. Plasma-derived products also carry the potential risk of transmitting blood-borne pathogens. |
| Clinical Benefit | <ul style="list-style-type: none"> By replacing the missing or inactive VWF, treatment would prevent morbidity and potentially mortality. One pivotal, open-label Phase 3a trial was submitted, which evaluated the safety and efficacy of rVWF:rFVIII and rVWF alone in the treatment of bleeding episodes in VWD patients. Subjects with types 1, 2 and 3 were included. | <ul style="list-style-type: none"> Treatment success was 100%. 82% of bleeds required only a single (weight-based) infusion. The median number of infusions was 1. |
| Risk | <ul style="list-style-type: none"> Potential risks include thrombogenicity and allergic reactions. There is the potential for the development of neutralizing antibodies. | <ul style="list-style-type: none"> There were no allergic reactions There was no evidence of thrombogenicity. There was no neutralizing antibody formation. There were no deaths. |
| Risk Management | <ul style="list-style-type: none"> Immunogenicity risk | <ul style="list-style-type: none"> In preclinical studies immunogenicity was similar to that of pdVWF No subjects developed binding or neutralizing antibodies against VWF No subjects developed binding or neutralizing antibodies against FVIII in patients treated with rVWF No subjects developed antibodies against potential impurities |

11.2 Risk-Benefit Summary and Assessment

Benefits:

The efficacy of VONVDENI has been established for the prevention and treatment of BE in adults diagnosed with VWD in clinical studies that enrolled 81 subjects and evaluated 192 BE. VONVENDI was uniformly effective. As a recombinant product, VONVENDI does not pose a risk of transmission of blood-borne pathogens. Unlike plasma-derived products, VONVENDI is free of FVIII.

Risks:

The formation of neutralizing antibodies was not observed in any trials. No TE events or hypersensitivity reactions were observed. Although none of these events was observed, the potential for developing these is discussed in the Warnings and Precautions section of the Package Insert.

Overall this product has an adequate clinical profile. It was shown to be effective in direct measures of control of bleeding and the safety profile was similarly acceptable. The risk/benefit profile of VONVENDI is favorable.

11.3 Discussion of Regulatory Options

Large prospective post-marketing surveillance studies that include the patient population at large and designed to actively monitor and evaluate the risk factors for inhibitor formation, hypersensitivity reactions and thrombotic risk are important for further characterization of these risks. The submitted Pharmacovigilance Plan is sufficient to address these important potential risks.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of this BLA. Efficacy and safety clinical data for VONVENDI were found adequate to make a favorable benefit/risk determination and to support approval for the proposed indication of:

Treatment and control of BE in adults diagnosed with VWD.

11.5 Labeling Review and Recommendations

The draft label will need to have the wording of the indication changed to agree with the current term: treatment and control of bleeding episodes.

11.6 Recommendations on Postmarketing Actions

Routine pharmacovigilance is appropriate. In addition Baxter has proposed three additional clinical trials (b) (4) and pediatric subjects) that will be considered clinical post-marketing commitments.