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<b>Committee Chair</b>	Chava Kimchi-Sarfaty, PhD
<b>Clinical Reviewer(s)</b>	Victor Baum, MD
<b>Project Manager</b>	Cherie Ward-Peralta, MS
<b>Priority Review</b>	No
<b>Reviewer Name(s)</b>	Shuya (Joshua) Lu, PhD
<b>Review Completion Date / Stamped Date</b>	
<b>Supervisory Concurrence</b>	Renee Rees, PhD
	Boguang Zhen, PhD
	Estelle Russek-Cohen, PhD
<b>Applicant</b>	Baxter Healthcare Corporation
<b>Established Name</b>	BAX 111
<b>(Proposed) Trade Name</b>	VONVENDI [von Willebrand Factor (Recombinant)]
<b>Pharmacologic Class</b>	
<b>Formulation(s), including Adjuvants, etc</b>	
<b>Dosage Form(s) and Route(s) of Administration</b>	Lyophilized powder in single-use vials containing nominally 650 or 1300 international units VWF:RCo.
<b>Dosing Regimen</b>	40 to 80 IU/kg
<b>Indication(s) and Intended Population(s)</b>	On-demand treatment and control of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand disease (VWD)

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## GLOSSARY

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AESI	Adverse Events of Special Interest
BE	Bleeding Episode
BLA	Biologics License Application
CHO	Chinese Hamster Ovary
CI	Confidence Interval
EDR	Electronic Document Room
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVIII	Factor VIII
FVIII:C	coagulation FVIII activity
GEE	General Estimating Equation
GI	Gastrointestinal
HMW	high molecular weight
HRQoL	Health-related Quality of Life
IgG	immunoglobulin G
IP	Investigational Product
LOCF	Last Observation Carried Forward
pdVWF	plasma-derived VWF
PK	Pharmacokinetics
PP	Per Protocol
rVWF	recombinant von Willebrand Factor
VWD	von Willebrand disease
VWF	von Willebrand Factor
VWF:RC <sub>o</sub>	von Willebrand factor: Ristocetin cofactor activity

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### 1. EXECUTIVE SUMMARY

This Biologics License Application (BLA) for recombinant von Willebrand Factor (rVWF) is for the proposed indication of on-demand treatment and control of bleeding episodes (BEs) in adults (age 18 years and older) diagnosed with von Willebrand disease (VWD).

The primary evidence is based on the pivotal study 071001: A phase 3, multicenter, open-label clinical study to determine the pharmacokinetics (PK), safety, and efficacy of rVWF:rFVIII and rVWF in the on-demand treatment and control of bleeding episodes in subjects diagnosed with severe type 3 and severe non-type 3 VWD. The primary efficacy endpoint is the number of subjects with a treatment success for treated bleeding episodes. A treatment success was defined as a mean efficacy rating score of < 2.5 (please refer to

Table 2 on page 12) taking into account all bleeding episodes in a subject treated with rVWF (with or without ADVATE) during the study period.

The proportion of subjects with treatment success was 100% (18/18) for bleeds where the assessments were made prospectively and excluding Gastrointestinal (GI) bleeds. The exact Clopper-Pearson 90% confidence interval (CI) is 84.7% to 100% and these results achieve the pre-specified success criteria of the lower limit of the 90% CI, 65%. The 95% CI is 81.5% to 100% and the lower limit is above 65% as well.

The safety evaluation revealed that no subjects developed inhibitory or total binding anti-VWF antibodies. This reviewer confirmed that the primary efficacy endpoint analysis provides adequate statistical evidence to support the claims proposed in this BLA.

No statistical issue was found during the review of this application.

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

Qualitative and/or quantitative deficiencies of von Willebrand Factor (VWF) lead to a highly variable bleeding diathesis known as VWD, the most common of the hereditary coagulation factor deficiencies. VWF is a large multimeric glycoprotein with a molecular weight that varies from 500 to 20,000 kDa. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis, which leads to fibrin clot formation.

The current biochemical-based classification distinguishes disorders arising from partial quantitative (type 1), qualitative (type 2), or virtually complete (type 3) deficiencies of VWF. Up to 70% of VWD patients are diagnosed with type 1 VWD, which may also be associated with minor functional defects in the molecule. In general, patients with type 1 VWD display mild clinical symptoms. Approximately 20 to 30% of VWD patients are diagnosed with type 2 VWD. Type 2 VWD is further divided into 4 subtypes (A, B, N, and M), reflecting distinct classes of functional abnormalities. These defects result in abnormal functional and/or multimeric distribution patterns that facilitate their diagnosis. All VWD patients, particularly those with type 2 or type 3 VWD, are at an increased risk for life-threatening bleeding episodes.

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

Prior to the introduction of low-purity coagulation factor concentrates, VWD was treated with cryoprecipitate. Some coagulation factor concentrates have been employed in clinical practice for more than 25 years. Prospective clinical data on plasma-derived VWF (pdVWF) coagulation factor concentrates were published in recent years, serving as the basis for the European Medicines Agency (EMA) guidelines on the clinical investigation of pdVWF products.

Many VWD patients are currently treated with pdVWF/FVIII concentrates, which were initially developed for the treatment of hemophilia A. These pdVWF/FVIII concentrates contain a variable ratio of VWF/FVIII (ranging from 0.6 to over 2.4) and also lack, to a varying extent, high molecular weight- (HMW-) VWF multimers normally found in human plasma. The dosing strategy for pdVWF/FVIII concentrates, either based on FVIII or VWF, may lead to undesirably high plasma levels of coagulation FVIII activity (FVIII:C) or von Willebrand factor: Ristocetin cofactor activity (VWF:RCo). The relationship between FVIII:C levels and an increased risk of venous thrombosis may be notable.

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

Currently human recombinant VWF is not authorized anywhere in the world. Recombinant VWF is designated as an orphan product for the on-demand treatment and control of bleeding episodes in patients with severe VWD both in the US and Europe: both the U.S. Food and Drug Administration (FDA) and the European Commission granted orphan designation in November 2010 (Commission Decision of 26 November 2010 – EU/3/10/814).

The rVWF protein is expressed in Chinese Hamster Ovary (CHO) cells that also express the licensed rFVIII product, ADVATE, a FVIII product approved by FDA on December 14, 2011, so (b) (4) .

The cumulative clinical data from three clinical trials (Phase 3 efficacy and safety study 071001, Phase 1 PK and tolerability study 070701 in VWD, and a supportive Phase PK and safety study 071104 in hemophilia A) were considered by the FDA to be sufficient to submit a BLA to support licensure of rVWF for the on-demand treatment and control of bleeding episodes in adult VWD patients (CRMTS # 9386; May 30, 2014). FDA has previously agreed that data supporting the safety and efficacy of rVWF in the perioperative management of bleeding obtained in the Phase 3b study can be submitted post-approval (CRMTS # 5570; April 24, 2006).

## **3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

### **3.1 Submission Quality and Completeness**

The submission is adequately organized for conducting a complete statistical review of the primary efficacy endpoint without unreasonable difficulty.

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

##### 4.1 Chemistry, Manufacturing, and Controls

During the review of this submission, this reviewer received a consult question from the CMC chair regarding the applicant's specifications for the various tests of the drug substance and product. The applicant used the K factor correction for the process capability of specification setting, and the CMC reviewer requested verification that the method is appropriate. After reviewing the CMC documents, this statistical reviewer confirmed that the K factor correction is appropriate for this CMC submission.

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

All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

##### 5.1 Review Strategy

There are three clinical studies (IND 13657) in this submission: completed Phase 3 study 071001 and two completed Phase 1 studies, 070701 and 071104. For a summary of each study refer to Section 5.3. Study 071001 is the pivotal study and study 071104 is a supportive study to provide information about the PK and tolerability of the product. Only study 071001 is reviewed in this memo.

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

Documents and datasets for the original BLA were reviewed.

BLA	125577/0	
	Module 1.14	Label
	Module 2.7	Clinical summary
	Module 5.2	Tabular listing of all clinical studies
	Module 5.3.5.2	Clinical study reports 071001: Study Report Body, Protocol, Statistical Analysis Plan
	Module 5.3.5.2	Data files adsl.xpt, adhemeff.xpt, adce.xpt
	125577/27	
	Module 1.11	Information Amendment

### 5.3 Table of Studies/Clinical Trials

The following clinical studies, summarized in Table 1, are included in the submission.

Table 1 Summary of clinical studies in the BLA

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
<b>Pivotal Study</b>							
Efficacy	071001	Hemostatic efficacy for treatment of bleeding episodes, safety, PK of rVWF alone and with rFVIII (ADVATE), repeated PK	Phase 3, uncontrolled	PK: 50 or 80 IU/kg VWF:RCo rVWF alone, iv admixture with ADVATE or placebo, intravenous, bolus  <u>Bleed treatment:</u> 40-60 IU/kg VWF:RCo (up to 80 IU/kg for major BEs), with ADVATE for initial infusion; with or without ADVATE for subsequent infusions.	37	VWD	Single dose PK, repeat PK, bleed treatment
<b>Supportive Study</b>							
PK and tolerability	071104	Evaluate whether rVWF extends half-life of ADVATE in hemophilia A patients	Phase 1, uncontrolled, proof of concept	50 IU/kg ADVATE alone and with rVWF at 10 and 50 IU/kg VWF:RCo, intravenous, bolus	12	Severe hemophilia A	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
<b>Other Studies</b>							
PK and tolerability	070701	- Evaluate immediate tolerability and safety - Define PK	Phase 1, dose-escalating (four dose cohorts), including one controlled, randomized cross-over cohort	rVWF in an iv admixture with rFVIII (ADVATE) at a 1.3 ± 0.2:1 ratio, intravenous, bolus, 2 U/kg, 7.5 IU/kg, 20 IU/kg, 50 IU/kg VWF:RCo	32	Severe VWD	Single dose
PK, PD, in vitro, human biomaterials	PD_VB_061404_R	Investigate the functional properties and hemostatic efficacy of ULM containing rVWF in human VWF deficient blood in comparison with a pdVWF concentrate and a rVWF fraction lacking ULM	In vitro	rVWF, rVWF fraction lacking ULM, Haemate-P	11	Blood samples from 8 patients with severe VWF and 3 healthy volunteers	No treatment
In vitro	Kragh et al., 2014	Collaborative in vitro pharmacodynamic to investigate the dependency of aggregate formation on ULM in solution and on rVWF coated surface at shear rates of 20.000 s <sup>-1</sup> and above.	In vitro	rVWF, rVWF lacking ULM	Not applicable	Healthy volunteers	No treatment

Source: Original BLA 125577 submission, section 5.2.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study 071001

#### 6.1.1 Objectives (Primary, Secondary, etc.)

The objectives of this study are:

- To compare the PK parameters of rVWF alone or concomitantly with rFVIII in subjects with type 3 VWD
- To examine the PK parameters of rVWF in subjects with severe VWD
- To evaluate the hemostatic efficacy, safety, and tolerability of rVWF:rFVIII and rVWF alone in subjects with VWD receiving the investigational product (IP) for the on-demand treatment of bleeding episodes
- To evaluate tolerability and safety of rVWF including the development of inhibitory and total binding anti-VWF antibodies and clinically significant changes in laboratory parameters following drug administration
- To assess changes in health-related quality of life (HRQoL)

#### 6.1.2 Design Overview

This is a phase 3, multicenter, open-label clinical study to assess the PK, safety and efficacy of rVWF:rFVIII and rVWF in the on-demand treatment of bleeding events in adult subjects with severe VWD. To better control the subject's FVIII levels and to treat the BEs effectively the instructions provided were to administer the first dose of rVWF with Advate (the licensed rFVIII) at a ratio of 1.3:1 ± 0.2 and the subsequent doses of rVWF were to be administered alone, as long as therapeutic FVIII levels were maintained. The study consisted of two parts (Part A and Part B).

##### Part A

Part A consisted of PK assessments (PK50 or PK80) and/or a treatment period of 6 months for bleeding episodes.

Subjects were enrolled into one of four arms, per discussion with the study investigator:

**Arm 1: PK 50 with treatment of bleeding episodes:** subjects were randomized in a 1:1 ratio to one of two treatment groups to receive either an infusion of 50 IU/kg rVWF:RCo rVWF and 38.5 IU/kg rFVIII (Advate), or an infusion of 50 IU/kg rVWF:RCo rVWF and placebo. After a washout period of 18 ± 10 days, subjects in each dose group crossed-over to receive the alternative infusion, either 50 IU/kg rVWF:RCo rVWF and placebo or 50 IU/kg rVWF:RCo rVWF and 38.5 IU/kg rFVIII (Advate). With each infusion, PK was assessed. After initial exposure to rVWF, subjects received on demand treatment of bleeding episodes for 6 months. (Minimum of 7 subjects with type 3 VWD.)

**Arm 2: PK 50 only:** subjects were randomized in a 1:1 ratio to one of two treatment groups to initially receive either an infusion of 50 IU/kg rVWF:RCo VWF and 38.5

IU/kg rFVIII (Advate), or an infusion of 50 IU/kg rVWF:RCo VWF and placebo. After a washout period of 18±10 days, subjects in each group crossed-over to receive the alternative infusion, either 50 IU/kg rVWF:RCo VWF and placebo or 50 IU/kg rVWF:RCo VWF and 38.5 IU/kg rFVIII (Advate). PK was assessed with each IP infusion. There was no on demand treatment for bleeding episodes so subjects either exited the study after the second dose of IP or opted to undergo new informed consent for on demand treatment of bleeding episodes at home and then were considered part of Arm 1. (Minimum of 7 subjects with type 3 VWD.)

**Arm 3: PK 80 with treatment of bleeding episodes:** subjects received an infusion of 80 IU/kg rVWF:RCo rVWF followed by 6 months of on demand treatment for bleeding episodes and then received another infusion of 80 IU/kg rVWF:RCo rVWF PK was assessed with each of the two study IP infusions. (Minimum of 12 subjects with severe VWD, as defined.)

**Arm 4: Treatment of bleeding episodes only:** subjects received IP treatment for bleeding episodes on demand only (no PK assessments) for 6 months. (Approximately seven subjects independent of VWD subtype.)

#### Part B

Part B was an open label follow-up period of 6 months in which at least 32 of the subjects who participated in the treatment of bleeding episodes in Part A (Arm 1, Arm 3, Arm 4, and subjects in Arm 2 that opted for treatment for bleeding episodes before their End of Study Visit), were treated with rVWF for a total study duration (Part A and Part B) of 12 months. That is, in Part B, subjects receiving IP treatment for bleeding episodes in Part A, continued treatment for 6 additional months for a total of 12 months.

#### 6.1.3 Population

Subjects must have met all of the following criteria to be eligible for inclusion in the study:

1. The subject was diagnosed with:
  - Type 1 (VWF:RCo < 20 IU/dL) or,
  - Type 2A (VWF:RCo < 20 IU/dL), Type 2B (as diagnosed by genotype), Type 2N (FVIII:C < 10% and historically documented genetics), Type 2M or,
  - Type 3 (VWF:Ag ≤ 3 IU/dL) or,
  - Severe VWD with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding
2. The subjects, who participated for the treatment for bleeding episodes, had a minimum of 1 documented bleeds (medical history) requiring VWF coagulation factor replacement therapy during the previous 12 months prior to enrollment.
3. The subject had a Karnofsky score ≥ 60.
4. The subject was at least 18 and not older than 65 years of age at enrollment.
5. If female of childbearing potential, the subject presented with a negative pregnancy test.

6. The subject agreed to employ adequate birth control measures for the duration of the study.
7. Subject was willing and able to comply with the requirements of the protocol.

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

##### Pharmacokinetic Assessments:

Pharmacokinetic assessments were performed after the following infusions:

- Subjects participating in Part A Arms 1 and 2 received two infusions: one infusion of 50 IU/kg rVWF:RCo rVWF and 38.5 IU/kg rFVIII (Advate), and one infusion of 50 IU/kg rVWF:RCo rVWF with physiologic saline (placebo), with a washout period of 18±10 days between infusions.
- Subjects participating in the Part A Arm 3 received an initial infusion of 80 IU/kg rVWF:RCo rVWF, and had 6 month of on-demand treatment, and 6 months later another infusion of 80 IU/kg rVWF:RCo rVWF.

Administration of IP for the purpose of PK assessments always occurred in the clinic.

##### Treatment of Bleeding Episodes:

The estimated number of infusions required for treatment of different types of bleeding episodes at various anatomical locations were determined and individualized by the investigator. The subject verified treatment regimen with the investigator prior to starting treatment. Administration of IP could be either in clinic or at home.

An initial dose of 40-60 IU/kg VWF:RCo (+ 30-45 IU rFVIII/kg), was infused to treat bleeding episodes in Parts A and B. In cases of major bleeding episodes, a dose of up to 80 IU/kg could be infused. Subsequent doses, if necessary, was administered to maintain VWF:RCo and FVIII levels for as long as deemed necessary by the investigator. Additional doses of rFVIII were administered with the rVWF product if plasma FVIII levels fell below 30 IU/dL during the treatment period.

#### 6.1.6 Sites and Centers

Participation was from 30 study centers from 16 countries world-wide.

#### 6.1.7 Surveillance/Monitoring

The study monitor was responsible for ensuring and verifying that each study site conducted the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator permitted the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement.

#### 6.1.8 Endpoints and Criteria for Study Success

##### Primary Endpoint

The primary efficacy endpoint is the proportion of subjects with treatment success for treated bleeding episodes. Treatment success was defined as the extent of control of

bleeding episodes and assessed as a mean efficacy rating score of < 2.5 (please refer to Table 2 on page 12) for a subject’s IP-treated bleeding episodes during the study period. If a subject experienced only one IP-treated bleeding episode, the value of the single bleed was used. The following scores (defined in Table 2) were used by the investigator to assess the extent of control of the bleeding episodes.

Table 2 Efficacy Rating Scale for Treatment of Bleeding Episodes

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

Source: Original BLA 125577; Clinical study protocol for study 071001 Amendment 3, p.74.

The study success criterion was an overall level of significance (one-sided) less than 0.05 for testing the null hypothesis of the primary endpoint.

### Secondary Endpoint(s)

Two secondary efficacy endpoints were included in this study.

1. The number of treated bleeding episodes with an efficacy rating of ‘excellent’ or ‘good’
2. The number of infusions and number of units of rVWF:rFVIII and/or rVWF per bleeding episode

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

#### Determination of Sample Size:

For the primary endpoint, the null hypothesis of the proportion of subjects with a treatment success of  $\leq 0.65$  ( $H_0: p \leq 0.65$ ) versus an alternative hypothesis of  $> 0.65$  ( $H_A: p > 0.65$ ) was tested at the one-sided 5% level of significance. The proportion of subjects with treatment success under the alternative hypothesis is expected to be approximately 0.90. If 20 subjects were treated the study provides 86% power to reject the null hypothesis.

To assess the first secondary efficacy endpoint, the null hypothesis of the proportion of excellent/good efficacy ratings for all IP-treated bleeding episodes of  $\leq 0.6$  ( $H_0: p \leq 0.6$ ) versus an alternative hypothesis of  $> 0.6$  ( $H_A: p > 0.6$ ) was tested at the one-sided 5% level of significance. The proportion of excellent/good treatment outcomes for all IP-treated bleeding episodes under the alternative hypothesis is expected to be approximately 0.85. If 30 independent bleeding episodes are treated the study provides  $> 90\%$  power to reject the above null hypothesis.

#### Analysis Populations:

The following safety and efficacy populations were defined for analyses:

#### **Safety Analysis Set**

The Safety Analysis Set was comprised of all subjects who received any amount of IP: rVWF:rFVIII or rVWF alone.

#### **Efficacy Analysis Sets**

- **Full Analysis Set**

The Full Analysis Set (FAS) was comprised of all subjects with at least one available efficacy rating scale assessment for an IP-treated bleeding episode.

Within the FAS, there were three different analysis sub-groups for the efficacy analysis and the definitions are described in Table 3. Note that sub-group 3 is the entire FAS.

Table 3 Efficacy Analysis Sub-groups within FAS

Group Number	Timing of investigator's initial estimate of the number of infusions required to treat a blood was made	Gastrointestinal (GI) Bleeds
1	Prospectively	Excluded
2	Prospectively	Included
3	Prospectively or Retrospectively	Included

Source: Original BLA 125577; Clinical Study Report of 071001, p.123 and p.124.

- **Per Protocol Analysis Set**

The Per Protocol (PP) analysis set was comprised of all subjects with available efficacy rating scale assessments for IP-treated bleeds. Only subjects who met all study entry criteria and who had no major protocol violations that might impact efficacy assessments for IP-treated bleeding episodes been included in the PP analysis set.

The primary efficacy analysis was pre-specified to be based on FAS sub-group 1. As supportive analyses, the same analysis was also carried out on FAS sub-group 3 and the PP.

The secondary efficacy analysis was performed on various FAS sub-groups. For the first secondary endpoint, analyses were performed on FAS sub-groups 1 and 3, while sub-groups 2 and 3 were used for the second secondary endpoint.

Primary Efficacy Endpoint Analysis:

The following hypothesis was tested on a (pre-specified) 5% one-sided level using a one-sided exact test for single proportions:

- Null hypothesis  $H_0$ :  $p \leq 0.65$
- Alternative hypothesis  $H_A$ :  $p > 0.65$

$p$  = proportion of subjects with a treatment success

Point estimates and corresponding two-sided Clopper-Pearson exact confidence intervals (CIs) at the 90% confidence level were calculated.

Secondary Efficacy Endpoints Analysis:

The proportion (90% CI) of all IP-treated BEs with excellent or good treatment outcome was estimated within a general estimating equation (GEE) model framework. The model accounted for the repeated subject effect.

The following hypothesis was tested on a 5% one-sided level implicitly, by estimating the two-sided 90% CI of the rate of all IP-treated BEs with excellent or good treatment outcome within the GEE model:

- Null hypothesis  $H_0$ :  $p \leq 0.60$
- Alternative hypothesis  $H_A$ :  $p > 0.60$

$p$  = proportion of IP-treated BEs with excellent or good treatment outcome according to the efficacy rating scale.

In addition, BEs were considered independent, and point estimates and corresponding two-sided exact CIs according to Clopper-Pearson at the 90% confidence level were calculated.

Summary tables by treatment outcome according to the efficacy rating scale were provided for all IP-treated BEs in total, by type of bleeding (joint vs. GI vs. other), by cause of bleeding, by severity of bleeding, by VWD type, by dosing (premixed vs. sequential) and by batch.

Frequency tables were prepared for the number of infusions (rVWF:rFVIII and rVWF) required for the treatment of a bleeding episode. The median number of infusions per BE (and 90% CIs) were estimated. Similarly, rFVIII and rVWF units per BE were analyzed.

Interim Analysis:

No interim analysis was planned or conducted for this study.

Missing Data:

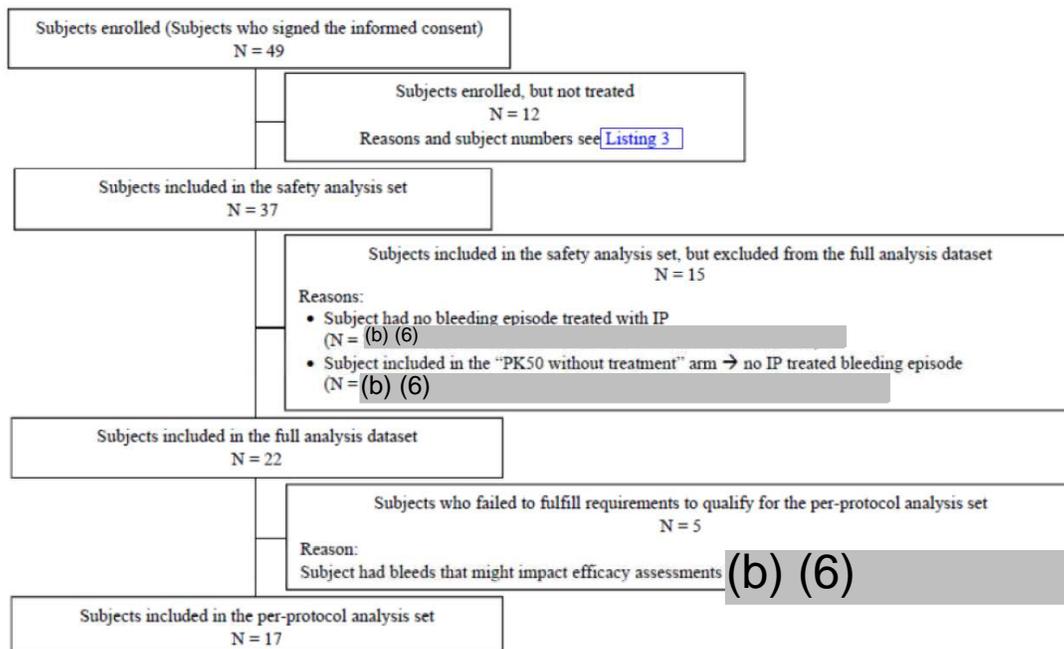
1. Missing efficacy rating scores as determined by the investigator were not replaced and thus were not considered in the calculation of the mean efficacy rating score.
2. If a subjective efficacy rating score was missing, the last available measurement was carried forward (LOCF approach).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The safety analysis set was comprised of 37 subjects, of whom 22 subjects were included in the full analysis set. Of these 22 subjects, 17 were included in the per protocol analysis population and five subjects were excluded because of one or more major protocol deviations that could have a potential impact on efficacy assessments, such as IP administration, or incorrect dose. Figure 1 shows an overview of the populations enrolled.

Figure 1 Overview of Enrolled Populations



Source: Original BLA 125577; Clinical Study Report, Table 4

Table 4 shows the analysis populations used for the final analysis.

**Table 4 Number of Subjects Included in the FAS Sub-groups**

Group Number	Timing of investigator's initial estimate of the number of infusions required to treat a blood was made	Gastrointestinal (GI) Bleeds	Subjects were included in the analysis
1	Prospectively	Excluded	18
2	Prospectively	Included	20
3	Prospectively or Retrospectively	Included	22

Source: Original BLA 125577; Clinical Study Report, p.123 and p.124.

#### 6.1.10.1.1 Demographics

The mean age ( $\pm$  SD) was  $33.9 \pm 12.6$  years in the FAS. Females comprised 54.5% (12/22) of the subjects, and the majority of the subjects (90.9%, 20/22) were white. The other baseline characteristics and demographics for the FAS are described in Table 5 and Table 6, respectively.

**Table 5 Baseline Characteristics (FAS)**

Parameter	Statistics	Overall	
Age at Screening [yrs.]	N	22	
	Mean	33.9	
	SD	12.6	
	Min	18	
	1st Quartile	25	
	Median	28	
	3rd Quartile	40	
	Max	64	
	Weight [kg]	N	22
		Mean	74.85
SD		16.31	
Min		50	
1st Quartile		62	
Median		73	
3rd Quartile		85	
Height [cm]	Max	105	
	N	22	
	Mean	168	
	SD	8.31	
	Min	155	
	1st Quartile	162	
	Median	167	
	3rd Quartile	174.5	
	Max	185	

Source: Original BLA 125577; Clinical Study Report, p.109

Table 6 Demographics (FAS)

Parameter	Category	N = 22 n (%)
Gender	Male	10 (45.5)
	Female	12 (54.5)
Race	White	20 (90.9)
	Black or African American	0 (0.0)
	Asian	2 (9.1)
	American Indian or Alaska Native	0 (0.0)
	Native Hawaiian or other Pacific Islander	0 (0.0)
Ethnicity	Hispanic or Latino	2 (9.1)
	Not Hispanic or Latino	20 (90.9)

Source: Original BLA 125577; Clinical Study Report, p.114

#### 6.1.10.1.2 Medical Characterization of the Enrolled Population

For VWD type, the majority of subjects (17/22 [77.3%]) had type 3 VWD, four (18.2%) subjects had type 2A VWD, and one (4.5%) subject had type 2N VWD.

#### 6.1.10.1.3 Subject Disposition

A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (Arm 1 and Arm 2 only), 37 subjects were treated with IP (all study arms) and 30 subjects completed the study.

A total of 19 subjects discontinued from the study. Twelve subjects discontinued prior to treatment (six subjects were screen failures, three subjects withdrew consent, one subject started a dental procedure after enrollment, one subject was withdrawn by the physician, and one signed for the PK50 arm after the arm was closed). Seven subjects discontinued after treatment started. Among these seven subjects, four subjects withdrew consent, one subject became pregnant, one subject withdrew due to an AE, and one subject had been treated with an immunomodulatory drug within 30 days prior to enrollment and was included in the PK80 arm but was withdrawn prior to the PK2 infusion.

Table 7 shows the disposition of this study.

Table 7 Subject Disposition

Category	PK50+ Treatment (Arm 1) N (%)	PK50 (Arm 2) N (%)	PK80+ Treatment (Arm 3) N (%)	Treatment Only (Arm 4) N (%)	No Arm Assigned N (%)	Overall N (%)
Enrolled subjects (i.e. subjects who signed the informed consent)	9 (100)	9 (100)	16 (100)	6 (100)	9 (100)	49 (100)
Subjects randomized	9 (100)	9 (100)	NA	NA	NA	18 (36.7)
Subjects treated with IP	8 (88.9)	8 (88.9)	15 (93.8)	6 (100)	NA	37 (75.5)
Subjects enrolled but discontinued study	5 (55.6)	1 (11.1)	3 (18.8)	1 (16.7)	9 (100)	19 (38.8)
Subjects completed study	4 (44.4)	8 (88.9)	13 (81.3)	5 (83.3)	NA	30 (61.2)

Source: Original BLA 125577; Clinical Study Report, p.98

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

For the primary analysis population, all 18 subjects (100%) had “treatment success”. The Clopper-Pearson exact 90% CI was 84.7 to 100.0; therefore the success criterion was met since the lower limit of the 90% CI is greater than 65%. In addition, the 95% CI was 81.5 to 100.0. One bleeding episode for subject 540002 (start date: 2013-01-31, end date: 2013-02-16) did not have an efficacy rating score recorded. For this bleeding episode, rVWF:rFVIII was received for the first and second infusions, but HAEMATE P was used for the third infusion due to logistical reasons. Therefore, this bleeding episode was excluded from the statistical analyses. Except this bleeding episode, all other bleeding episodes (n=126) had an efficacy score rating.

The treatment success proportion for FAS sub-group 3 was 100% (22/22) and the 90% CI was 87.3 to 100. The treatment success rate for the PP analysis set was 100% (17/17) with a Clopper- Pearson exact 90% CI of 83.8 to 100.0. Both these analyses support the primary efficacy analysis.

#### *Reviewer Comments:*

*(1)The final analysis sample size is 18 subjects which is smaller than the planned number (20 subjects), but the result still meets the pre-specified criterion.*

*(2)This reviewer re-calculated the mean efficacy score for subject (b) (6) using a worst case scenario for the missing efficacy rating score. A score of 4 was imputed, resulting in a revised mean score of 2, which is still <2.5. Therefore, the conclusion of the primary efficacy analysis is not affected by the missing efficacy rating score.*

*(3)The lower limit of 95% CI was 81.5% and it is also greater than the pre-specified success criterion of 65%.*

#### 6.1.11.2 Analyses of Secondary Endpoints

Because the proportion of treatment success for all IP-treated bleeding episodes was 100%, the planned GEE model did not fit. Therefore, the applicant calculated the 90% CIs using only the Clopper-Pearson method with the BEs treated as independent events.

For FAS sub-group 1, the proportion of IP-treated BEs with an ‘excellent’ or ‘good’ efficacy rating was 100% (126/126) and the Clopper-Pearson exact 90% CI was 97.7 to 100. For FAS sub-group 3, the percentage of hemostatic efficacy with ‘excellent’ was 96.9% (186/192) and 3.1% (6/192) with ‘good’.

Table 8 shows an overview of hemostatic efficacy by bleeding severity and number of infusions required to treat a bleeding episode for the FAS sub-group 3 analysis population.

Table 8 Number of Infusions by Severity of BEs for FAS Subgroup 3

Number of infusions per bleed	Minor n (%) n=122	Moderate n (%) n=61	Major/Severe n (%) n=7
1	113 (92.6%)	41 (67.2%)	1 (14.3%)
2	8 (6.6%)	13 (21.3%)	4 (57.1%)
3	1 (0.8%)	6 (9.8%)	2 (28.6%)
4	0	1 (1.6%)	0

Source: Original BLA 125577; Clinical Study Report, p.134

For minor BEs in the FAS sub-group 3, the median cumulative dose to treat a bleeding episode was 43.3 (range, 25.2 to 158.2) IU/kg. For moderate BEs, the median cumulative dose was 52.7 (range, 23.8 to 184.9) IU/kg. For major/severe BEs, the median cumulative dose was 100.0 (range, 57.5 to 135.0) IU/kg.

*Reviewer Comment:*

- (1) This reviewer confirmed that the above results for the secondary efficacy endpoints analyses are correct.
- (2) The applicant's assumption that the BEs are independent events for calculating the Clopper-Pearson CIs is an acceptable approximation. With the high efficacy ratings (100% excellent or good in both the FAS sub-groups 1 and 3), the number of BEs per subject and the type of BE does not appear to influence the efficacy rating of an individual BE. For the FAS sub-group 1, the median number of BEs per subject is 5.5 (range, 1 to 35) and for the FAS sub-group 3, the median is 4 (range, 1 to 35).

6.1.11.3 Subpopulation Analyses

Since the success rate for the primary efficacy endpoint was 100%, no differences were observed for any age, race and sex subgroup.

6.1.11.4 Dropouts and/or Discontinuations

Of the seven subjects who received IP but discontinued early, three had at least one BE and were included in the FAS, two of which were included in FAS sub-group 1. The pre-specified primary efficacy analysis did not take into account the length of time subjects participated in the study.

No statistical techniques were used to identify and exclude any observations as outliers from the analyses.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No subjects died during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Seven subjects experienced a total of nine SAEs during or after IP infusion. Out of these nine SAEs, seven SAEs which were judged by the investigator as unrelated to IP

(osteomyelitis, constipation, uterine polyp, spontaneous abortion, GI hemorrhage, mesenteric hematoma, hemorrhoids), and one subject (b) (6) in Arm 1 experienced two related SAEs (one chest discomfort and one increased heart rate) that were considered by the investigator as related to rVWF.

Eight SAEs had resolved prior to the end of the study. One unrelated SAE in subject (b) (6) was ongoing at the time of study completion.

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

No subjects developed inhibitory, total binding anti-VWF antibodies, anti-VWF neutralizing, binding antibodies, anti-FVIII neutralizing antibodies, against rFurin, Chinese hamster ovary (CHO) proteins, or mouse immunoglobulin G (IgG).

One subject (b) (6) in Arm 3 tested positive for a binding antibody to Murine IgG prior to first IP treatment, but had a negative titer after the first IP infusion and until the end of Part B of the study.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

There is no major statistical issue in this BLA submission. The submission includes the final analysis of the pivotal study 071001, a phase 3, multicenter, open-label study. The primary efficacy endpoint is the number of subjects with treatment success for treated bleeding episodes. The proportion of subjects (n=18) with treatment success was 100% (Clopper-Pearson exact 90% CI is 81.5 to 100.0) for bleeds where the assessments were made prospectively and excluding GI bleeds. The results achieve the pre-specified success criteria since the lower limit of the 90% CI exceeds 65%. The 95% CI is 81.5% to 100% and the lower limit is above 65% as well.

The study did have a high dropout rate. Of the 49 subjects enrolled, 37 subjects were treated with IP, and 30 subjects completed the study. The study planned for 20 subjects in the primary efficacy analysis, and only 18 subjects were included (22 subjects had at least one bleeding episode).

The safety evaluation revealed that no subjects developed inhibitory or total binding anti-VWF antibodies.

### 10.2 Conclusions and Recommendations

In this BLA submission, the primary efficacy endpoint of the pivotal study was the proportion of subjects with treatment success, where the assessments were made prospectively and excluded GI bleeds. The results indicated that the lower bound of the 90% CI was higher than the pre-specified criterion. No safety concerns were noted. Therefore, adequate statistical evidence supports the proposed indication of on-demand treatment and control of bleeding episodes in adults (age 18 years and older) diagnosed with VWD).

\*\*\*\*\*  
IMPORTANT - DO NOT CHANGE ANYTHING BELOW THIS SECTION!  
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