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Application Type	Efficacy Supplement
STN	125251/139
CBER Received Date	October 8, 2014
PDUFA Goal Date	August 8, 2015
Division / Office	DHCR /OBRR
Priority Review	No
Reviewer Name(s)	Laurence Landow
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Established Name	von Willebrand Factor/Coagulation Factor VIII Complex (Human)
(Proposed) Trade Name	Wilate
Pharmacologic Class	Coagulation Factor
Formulation(s), including Adjuvants, etc	Sterile Water for Injection, diluent; Glycine, (b) (4); Sucrose, (b) (4) Sodium Chloride, (b) (4); Sodium Citrate, (b) (4); von Willebrand Factor, active; Coagulation Factor VIII, active; Total Protein, (b) (4)
Dosage Form(s) and Route(s) of Administration	Powder for solution, Intravenous injection
Dosing Regimen	Loading Dose and Maintenance Dose(s)
Indication(s) and Intended Population(s)	Prevention of excessive bleeding during and after surgery in VWD patients
Orphan Designated (Yes/No)	No

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GLOSSARY

ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BW	Body weight
BUN	Blood urea nitrogen
CRF	Case report form
DDAVP	Desmopressin acetate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDMC	Independent Data Monitoring Committee
IVR	In vivo recovery
LDH	Lactate dehydrogenase
RCT	Randomized controlled study
SAE	Serious adverse event
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:Ag	von Willebrand factor antigen
VWF:CB	von Willebrand factor collagen-bound
VWF:RCo	von Willebrand factor ristocetin cofactor
VRS	Verbal Rating Scale

1. Executive Summary

Wilate® [von Willebrand Factor/Coagulation Factor VIII Complex (Human)1] was approved in 2009 for prophylaxis and treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD), as well as in patients with mild or moderate VWD in whom use of desmospressin (DDAVP) is known or suspected to be ineffective or contraindicated. .

This efficacy supplement is for perioperative use of Wilate to reduce bleeding in adult and pediatric patients with VWD undergoing surgery. Evidence to support this indication is derived from three prospective, multinational, multicenter, uncontrolled, open-label studies: a pivotal IND study (WIL-24) initiated post-licensure, and two supportive non-IND studies (WIL-14 and TMAE-104) completed pre-licensure (WIL-14 is being submitted for the first time whereas TMAE-104 was included as part of the original BLA in 2006). A new pediatric assessment also has been submitted that aggregates safety and efficacy information from the pediatric surgery cohort enrolled in these three studies. Wilate has been granted orphan designation for the treatment of VWD except for surgical and/or invasive procedures in patients with VWD in whom DDAVP is either ineffective or contraindicated. Under the Pediatric Research Equity Act (PREA), the pediatric assessment portion of this submission was presented before the Pediatric Review Committee (PeRC).

— Pivotal Study WIL-24

WIL-24 was a prospective, multicenter, open-label, uncontrolled phase 3 study that comprised a Safety Population of 41 subjects (39 individuals) undergoing major or minor surgery. Eleven adult subjects were prematurely terminated due to Screening failure (N=9) or premature withdrawal (N=2), one at sponsor request for slow site enrollment and another at subject request. The remaining 30 subjects (28 individuals, 25 adults and 3 adolescents) included 2 adults who underwent additional procedures and were assigned different ID numbers. Most procedures were orthopedic or dental; obstetric/gynecological, gastrointestinal, ENT, and ophthalmologic procedures comprised the remainder. Of the 21 VWD Type 3 subjects, 17 underwent major surgery and 4 underwent minor surgery.

Past Medical History was remarkable for bleeding episodes that were of mild (N=6) or moderate (N=22) intensity and occurred approximately every month. Demographic characteristics included a median age of 36 years with females (N=21) outnumbering males 2:1. The population was predominantly Caucasian (N=18) and Asian (N=11), with a noticeable underrepresentation of Black/African American (N=1) and Hispanics (N=0). Most subjects (N=21) had Type 3 disease (complete absence of von Willebrand factor, VWF); the remainder were Type 1 (partial quantitative VWF deficiency, N=7) or Type 2 (partial qualitative VWF deficiency, N=2).

Approximately 1-2 hours prior to incision, a loading dose of product was infused, followed by 2 (or more) maintenance infusions every 12 hours as needed to control hemostasis. Dose titration was based on the type of surgery (major, minor, gastrointestinal procedures) and expected blood loss. The size of the loading dose was based on in vivo recovery (IVR) for VWF:RCo, VWF:Ag and FVIII:C calculated at a central laboratory from blood samples collected at the Screening/Baseline visit following administration of a 60 IU VWF:RCo/kg BW (labeled potency) dose. Results were

[1] Referred to hereafter as Wilate

reported as (IU/dL)/(IU/kg). The IVR value for VWF:RCo was used to determine the recommended loading and maintenance doses and communicated to the study site prior to the start of the procedure.

Hemostatic efficacy, the primary endpoint of the study, was assessed by the surgeon at the conclusion of surgery, and by the investigator-hematologist at 24 hours following completion of the final maintenance dose, using a prospectively defined 4-point scoring system (excellent, good, moderate, none) in which "success" was defined as a rating of excellent or good. All outcomes were adjudicated *post hoc* by an independent Data Monitoring Committee (IDMC). In situations where the IDMC's assessment differed from that of the surgeon and/or investigator-hematologist, the IDMC assessment took priority.

The study was terminated prematurely after a planned interim analysis found that the success rate (29/30 procedures rated excellent or good) exceeded the prespecified stopping threshold of ≥25/30 successful procedures (only one procedure, lumbar laminectomy in a VWD Type 1 Caucasian male adult, was judged as a failure). Successful outcomes were reported in 89% of males and 100% of females; 94% of Caucasians, 100% of Asians and 100% of Blacks; and 100% of subjects aged 12-17 years, 96% of subjects aged 18-65, and 100% of subjects aged >65 years.

Two subjects experienced serious adverse events (SAE): vaginal hemorrhage in an adult and erosive gastritis in an adolescent; another adult experienced a severe intensity nonserious wound infection adverse event (AE). These events were assessed by this reviewer as unrelated to Wilate according to temporal and/or mechanistic criteria. Mild-moderate intensity AEs (n=118), most commonly procedural pain, nausea and vomiting, and assessed as unlikely related or not related, were reported in 29 subjects (70.7%). Attribution of almost all AEs as unrelated or probably unrelated is reasonable given the limitations inherent in an uncontrolled study. Five subjects experienced mild-moderate intensity AEs probably related to Wilate®: anxiety, chest discomfort, hypersensitivity, hypertension and hypotension. The incidence of AEs was similar when stratified by demographic factors (sex, race, age) as follows: male (N=9): 67%, female (N=21): 72%; Caucasian (N=18):79%, Asian (N=11): 69% and Black (N=1): 0%; and age 12-17 years (N=3): 67%, 18-65 years (N=25): 74%, and >65 years (N=2): 50%, respectively. No evidence was found of VWF inhibitors, accumulation of coagulation factors over time, iatrogenic thromboembolism or treatment-emergent viral infection.

— Supportive Studies WIL-14 and TMAE-104

WIL-14 was a prospective, multicenter, open-label, uncontrolled study in children (N=15) <6 years of age. The primary objective was to assess hemostatic efficacy of the product when administered either for (a) spontaneous/post-traumatic bleeding (N=8) or (b) surgical prophylaxis (N=7). Children in the surgical prophylaxis subgroup were aged 0 to <2 (N=3) and 2 to <6 (N=4) years, and underwent 9 procedures (major: n=3; minor: n=6). Hemostatic efficacy was rated as excellent or good in 100% of cases.

TMAE-104 was a prospective, multicenter, open-label, uncontrolled study in adult and pediatric subjects undergoing surgery. The primary objective was to assess plasma levels of FVIII:C, VWF:Ag, VWF:CB and VWF:RCo as surrogate markers of efficacy (clinical efficacy was a secondary endpoint). Children in the surgical prophylaxis subgroup were aged 6 to <12 years (N=3). Hemostatic efficacy was rated as excellent or good in 100% of cases.

— Pediatric Assessment

The pediatric assessment comprised aggregate data from the pediatric surgical cohorts enrolled in WIL-24 (N=3), WIL-14 (N=7), and TMAE-104 (N=3), representing subjects aged 12 to <16, 0 to <2 and 2 to <6, and 6 to <12 years of age, respectively. Hemostatic efficacy was rated as excellent or good in 100% of cases. A total of 6 subjects experienced 19 unrelated SAEs.

In conclusion, the strength of pivotal study WIL-24 — enrollment of a high proportion of VWD subjects with Type 3 (severe) disease undergoing major surgery, strong evidence of hemostatic efficacy, and validation of a dosing schedule capable of normalizing VWF and FVIII levels without triggering serious safety concerns — outweighs the limitations inherent in a small, unblinded, uncontrolled study; data from the pediatric assessment, although limited, lend additional support to this conclusion.

I recommend approval of this supplement and revision of the draft Package Insert (PI).

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

VWD is the most common inherited hemorrhagic disorder, affecting 1% of the population with equal frequency among men and women (although women are more often symptomatic because of physiological events related to menstruation, pregnancy, and birth). The disease arises from a congenital quantitative (Types 1 and 3) or qualitative (Type 2) deficiency in von Willebrand factor (VWF).

VWF promotes hemostasis in two ways. First, it acts as a “bridging molecule” between adjacent platelets at sites of vascular injury to facilitate platelet adhesion and aggregation. Second, it acts as a “stabilizer” to maintain normal FVIII levels. Since patients with VWD frequently have low endogenous FVIII levels, treatment often involves co-administration of FVIII and VWF.

Three types of inherited VWD are recognized and classified in accordance with the following criteria:

1) Type 1: partial quantitative deficiency of VWF (70-80% of VWD patients)
2) Type 2: partial qualitative deficiency of VWF in sub-categories (20%)
    (a) 2A (decreased platelet-dependent function with loss of high MW multimers)
    (b) 2B (increased affinity for platelet glycoprotein 1b)
    (c) 2M (decreased platelet dependent function not associated with loss of high MW multimers)
    (d) 2N (decreased affinity for FVIII)
3) Type 3: complete absence of VWF (1-3%)

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

Humate-P, Alphanate, and DDAVP are currently licensed specifically for treatment of bleeding in VWD patients. Only Humate-P is indicated in patients undergoing major surgery or in those with severe disease (Type 3).

2.3 Safety and Efficacy of Pharmacologically Related Products

The following excerpts are from the PIs of products specifically approved for VWD:

<u>Humate-P</u>

- Efficacy: indicated for VWD: in adults and pediatric patients in the (1) treatment of spontaneous and trauma-induced bleeding episodes, and (2) prevention of excessive bleeding during and after surgery. Applies to patients with severe VWD as well as patients with mild to moderate VWD where the use of desmospressin is known or suspected to be inadequate.

- Safety: most common adverse reactions observed by >5% of subjects after receiving Humate-P are allergic-anaphylactic reactions (e.g., urticaria, chest tightness, rash, pruritus, edema) and, in patients undergoing surgery, postoperative wound and injection-site bleeding, and epistaxis.

Alphanate

- Efficacy: indicated for surgical and/or invasive procedures in adult and pediatric patients with VWD in whom DDAVP is either ineffective or contraindicated. **Not indicated for patients with severe VWD (Type 3) undergoing major surgery**.

- Safety: most frequent AEs reported with Alphanate in > 5% of subjects are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

DDAVP

- Efficacy: indicated for patients with mild to moderate (but not severe) classic VWD (Type I) with Factor VIII levels greater than 5%. **Not effective in patients with Type 3 VWD and contraindicated in Type 2B VWD patients**. Can also be contraindicated for other clinical reasons or can be associated with significant side effects.

- Safety: most frequent AEs reported with DDAVP are transient headache, nausea, mild abdominal cramps, vulval pain, local erythema, swelling or burning pain, and facial flushing.

2.4 Previous Human Experience with the Product (Including Foreign Experience)
Since the start of clinical development, Octapharma has completed 14 clinical studies. Cumulatively, 265 individual subjects have been exposed: 110 subjects with hemophilia A and 155 subjects with VWD. Between 8-FEB-2005 (International Birth Date) and 30-SEP-2014, approximately [redacted] of Wilate were sold worldwide, corresponding to [redacted] exposure days assuming a mean daily dose of 1,500 IU.

Included in the original 2006 BLA submission were data from four prospective, open-label, uncontrolled, non-IND clinical studies, each of which included a small subgroup of subjects (denoted by "N") undergoing one or more surgical procedures (denoted by "n"): TMAE-104 (N=41; n=22), TMAE-105 (N=14; n=2), TMAE-106 (N=14; n=8), TMAE-109 (N=16; n=2). Request for the surgical prophylaxis indication was denied at the time of BLA approval because the aggregate surgical cohort data failed to meet the success criterion used for other VWD products (i.e., Humate-P, Alphanate) approved for surgical prophylaxis, i.e., lower bound of the 95% confidence interval (CI) ≥70%.[2]

2 The success rate for hemostatic efficacy in the subpopulation (N=34) receiving Wilate for surgical prophylaxis (33 minor and 26 major procedures) in the original BLA submission was 74.6% (point-estimate), but the lower bound of the 95% confidence interval was only 61.6%.

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

4-DEC-2009

Approval of Wilate for treatment of spontaneous or trauma-induced bleeding episodes in patients with severe VWD as well as patients with mild or moderate VWD in whom the use of DDAVP is known or suspected to be ineffective or contraindicated.

Reviewer's Comments

Apart from failure to attain the prespecified statistical criterion for success (lower bound of the 95% CI ≥0.7), FDA found additional reasons for denying the surgical prophylaxis indication at time of licensure:

(a) The 4-point Verbal Rating Score (VRS) used by investigators in the non-IND studies was ambiguous and poorly defined

(b) The sponsor's classification of major vs. minor surgery was unacceptable in 8/59 cases

(c) 5/28 of the procedures classified as major surgery used a continuous Wilate infusion for hemostasis with bolus injection for the remaining subjects that "…rendered [the data] unevaluable [for single dose IV injection]" (BLA clinical review memo).

26-MAY 2010

WIL-24 protocol submitted for the surgical prophylaxis indication.

14-MAR-2011

Protocol amendment submitted.

- Sample size: increased from 40 to 41 to provide a power of ≥85%, provided the true percentage of outcomes classified as excellent or good was ≥90%.
- Primary endpoint: overall efficacy (success or failure) to be derived from the surgeon's assessment of intra-operative hemostatic efficacy and the investigator's assessment of post-operative hemostatic efficacy. IDMC adjudication of the data was added to the protocol.
- Interim Analysis: an interim analysis was introduced after 30 procedures to test for early success with $\alpha = 0.005$. The study would be terminated early and success claimed if the 99.5% CI for the overall success rate excluded and was >0.70 (equivalent to ≥29 successes out of the 30 procedures; page 50 of 1472, WIL-24 protocol). If success was not demonstrated after 30 procedures, the study was to continue to include a total of 41 procedures and the final analysis was to use $\alpha = 0.045$, success being defined if the 95.5% CI for the overall success rate excluded and was >0.70. Seven or more failures would make it impossible to reach the criteria for success.
- Dosing: clarification that baseline IVR for VWF:RCo would be used to calculate the recommended loading and maintenance dosing:

17-OCT-2012

Protocol amendment submitted.

- Study population: addition of VWD Type 1 and Type 2 subjects (in addition to Type 3) and inclusion of both major and minor surgeries. At least 10 of the enrolled subjects were to have VWD Type 3. The Per Protocol population

definition was changed to reflect the addition of VWD Type 1 and Type 2 subjects to the study.

- Primary endpoint: ultimate adjudication of success or failure was redefined as follows: in situations where differences existed between assessments made by the surgeon and/or investigator and the IDMC, the IDMC's assessment would take priority.
- Statistical analysis: the null and alternative primary hypotheses were changed to H_0: p_0 <0.6 versus Ha: p_0 ≥0.6.
- Interim Analysis: the **interim analysis was amended** to indicate the study would be terminated early and success claimed if the 98.75% CI for the overall success rate excluded and was **>0.60** (equivalent to 25 or more successes out of the 30 procedures). If the study were to continue to include a total of 41 procedures, the final analysis would use α = 0.0375, success being defined if the 96.25% CI for the overall success rate excluded and was >0.60. Nine or more failures in the study would make it impossible to reach the criteria for success.

Reviewer's Comment

Protocol Amendment 5 (dated 10-DEC-2012) amended the null and alternative hypothesis from H_0: p_0 <0.7 versus Ha: p_0 ≥0.7 to H_0: p_0 <0.6 versus Ha: p_0 ≥0.6. According to the previous clinical reviewer of this supplement, the rationale for changing the lower boundary was in response to slow enrollment (email received 2-MAR-2015 from Stephanie Omokaro, MD clinical reviewer, DHCR, OBRR).

8-OCT-2014

- DCC receipt date of efficacy supplement 139.

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. All subjects in the Safety Population were accounted for.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Major protocol violations (N=6) were reported in the Safety population, but none was reported in the Intention to Treat (ITT) population (N=30). Minor protocol violations, such as failure to collect a protocol-specified blood sample, failure to capture a vital sign(s), or infusion of Wilate outside the dosing window, were common in 29/30 (96.7%) ITT subjects (Table 14.1.2.2, Final Study Report).

Complete, signed copies of Investigator CVs were included in the submission.

According to an IR received from Octapharma after submission of the Supplement,

- All Independent Ethics Committees involved in the study complied with requirements set forth in 21 CFR 312.3.
- Subjects did not receive incentives to participate in the study. Reimbursement for time or travel expenses was made on a site or country specific basis.
- Investigators received ICH-GCP training during the investigator meetings and investigator responsibilities also were discussed during the site initiation visits. Three investigator meetings took place in total: 1st Investigator Meeting (New Delhi, India): April 2011; 2nd Investigator Meeting (Barcelona, Spain): November

2011; 3rd Investigator Meeting (Miami, FL): February 2012. In addition all investigators and site personnel involved in clinical research underwent GCP training on a continuous basis according to their IRB requirements.

3.3 Financial Disclosures

Covered clinical study (name and/or number): WIL-24		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 25		
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		
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)): N/A 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 ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) ____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

There were no significant CMC issues for this supplement.

4.2 Assay Validation

There was no issue related to assay validation for this supplement. .

4.3 Nonclinical Pharmacology/Toxicology

There were no significant nonclinical pharmacology/toxicology issues for this supplement.

4.4 Clinical Pharmacology
The applicant submitted two clinical pharmacology studies in patients with VWD only in the context of safety (Studies WIL-12 and WIL-21). No clinical pharmacology studies with Wilate in surgery have been performed.

4.4.1 Mechanism of Action
VWF and FVIII are normal constituents of human plasma. VWF mediates the binding between platelets and damaged subendothelium; it also is involved in the transport and stabilization of FVIII. In VWD patients, reduction in VWF concentration results in a correspondingly low FVIII activity and abnormal platelet function, thereby resulting in excessive bleeding. Plasma-derived VWF reverses these effects by promoting platelet adhesion to vascular subendothelium at the site of vascular damage and correcting the associated impairment in FVIII activity.

4.4.2 Human Pharmacodynamics (PD)
PD studies in surgery settings were superseded by clinical studies in pediatric subjects undergoing surgery.

4.4.3 Human Pharmacokinetics (PK)
The PK of Wilate and Humate-P was assessed in two prospective, randomized, controlled open-label, 2-arm cross-over safety studies that enrolled subjects with inherited VWD (Wilate PK has not been studied in a surgery setting). When administered in approximately equal doses, there was no appreciable difference in the mean terminal half-lives for VWD Type 3 and Type 1 subjects (12 vs. 13 hours for the VWF:RCo assay). For VWD Type 2 subjects, mean terminal half-lives were longer [18 h (range: 5 to 32 h) vs. 28 h (range: 6 to 76 h), but the difference did not reach statistical significance. No significant differences were observed in recovery or in C_{max} and AUC.

These results are acceptable.

4.5 Statistical
The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance
The review of the Pharmacovigilance Plan and available safety data has identified no substantive issues.

Postmarketing Experience
In the reporting interval 8-OCT-2013 to 7-OCT-2014,

(a) No new areas of concern related to the use of Wilate in its licensed indications were identified
(b) No actions relating to Wilate were taken by regulatory authorities or by the marketing authorization holder

As of 7 OCT 2014, a total of 23 serious Individual Case Safety Reports (ICSRs) from clinical studies using Wilate had been received by Octapharma from worldwide sources (see Table 1).

The surveillance period from 12 Mar 2012 to 12 Mar 2015 has been reviewed by the Division of Epidemiology/Office of Biostatistics and Epidemiology (DE/OBE). DE/OBE

has not identified any new safety concerns. DE/OBE plans continued routine surveillance for Wilate.

Table 1: Summary of SAEs from Completed Studies using Wilate in VWD Subjects up to 7 OCT 2014

System Organ Class Preferred Term	Not Related Events	Related Events
Gastrointestinal Disorders	13	
Hemorrhage	4	
Hematemesis	1	
Melena	7	
Immune System Disorders	1	
Transplant rejection	1	
Infections and infestations	2	
Catheter sepsis	1	
Hepatitis A	1	
Injury, Poisoning and Procedural Complications	2	
Investigations		1
Parvovirus B19 Serology Positive		1
Musculoskeletal and Connective Tissue Disorders	1	
Torticollis	1	
Renal and Urinary Disorders	2	
Hematuria	2	
Respiratory, Thoracic and Mediastinal Disorders	1	
Epistaxis	1	
Vascular Disorders	1	
Hemorrhage	1	

Source: Periodic Safety Update Report for 8 OCT 2013 to 7 OCT 2014

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

5.1 Review Strategy

The draft PI was reviewed first. This was followed by review of final study reports not submitted previously; final study reports for non-IND studies submitted to the original BLA and corresponding clinical review memos; responses to information requests seeking clarification of information in the submission; and financial disclosure forms.

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

- Draft PI
- 4-DEC-2009 Wilate approval letter
- Final study reports for WIL-24 and WIL-14
- Pediatric assessment
- Original BLA clinical review memos as well as summaries of clinical safety and efficacy data reviewed previously by the Medical Officer for the original BLA
- Latest available Periodic Safety Update Report (8-OCT-2013 to 7-OCT-2014)
- Information submitted by the applicant in response to IRs: number of subjects in WIL-24 aged 12-17 years stratified by major and minor surgery; post-marketing data reports; size of surgical vs. nonsurgical safety population for each clinical study
- Risk Management Plan
- List of IEC/ IRBs and CVs of investigators
- Financial disclosure forms
- PIs for Humate-P, Alphanate, DDAVP

5.3 Table of Studies/Clinical Studies

Supplement 139 included the following documents (see Table 2):

a. Final study report for WIL-24, the pivotal phase 3 IND clinical study, designed to investigate efficacy and safety in adult and adolescent subjects undergoing surgery.
b. Final study report for WIL-14, a non-IND phase 2 study in children aged 0 to <6 years designed to assess efficacy and safety.
c. Pediatric assessment comprising aggregated efficacy and safety data from pediatric subjects enrolled in WIL-24, WIL-14, and TMAE-104 (NB: TMAE-104 enrolled adults as well as children undergoing surgery).

Table 2: Study Population and Outcomes in Subjects Undergoing Surgery

Study	No. of Procedures (major, minor) (Sample Size) Gender Age Range	Efficacy Rating	No. (%) of Subjects with SAEs (No. of SAEs)
IND STUDY			
WIL-24	30 procedures (21 major, 9 minor) (28 subjects) 9 M, 21 F 12-74 years	Excellent or Good in 97% of procedures as assessed by an IDMC	2 (7) 2
NON-IND STUDIES			
WIL-14	9 procedures (3 major, 6 minor) (7 subjects) 4 M, 3 F 1.8−5.2 years	Excellent or Good in 100% of procedures as assessed by Investigator and subject's parents	3 (43) 4
TMAE-104	10 procedures (10 minor) (3 subjects) 6-12 years	Excellent or Good in 100% of procedures as assessed by Investigator and subject's parents	2 (66) 13

Source: Table 25, WIL-24 Final Study Report; Appendix Table 2.7.3.1, Clinical Efficacy Summary; Appendix Table 2.7.4.2, Clinical Safety Summary; Table 5, Information Request 17-DEC-2014; Synopses of Individual Studies

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL STUDIES

6.1 Pivotal Study WIL-24

6.1.1 Objectives

— Primary

Hemostatic efficacy of Wilate in preventing excessive intra- and post-operative bleeding in subjects with VWD who require a VWF product and are about to undergo a surgical procedure

— Secondary

a. To evaluate the intra- and post-operative surgical hemostatic efficacy of Wilate in preventing excessive bleeding in pediatric and adult patients with VWD who require a VWF product and undergo a surgical procedure.
b. To assess the safety of Wilate used in VWD patients who undergo surgical procedures.
c. To document the capability of Wilate to normalize the coagulation defect in VWD as demonstrated by an increase of the plasma activity of VWF, ristocetin cofactor (VWF:RCo), and FVIII:C.
d. To analyze the actual dosage and duration of treatment in surgical procedures.

6.1.2 Design Overview

WIL-24 was a prospective, open-label, uncontrolled, multi-center, phase 3 clinical study. Each subject could undergo multiple independent surgeries, in which case they were counted as separate surgical events. Subjects participated for 30 days starting from the day of surgery or until discharge, whichever came last. The protocol stipulated that the study would be terminated prematurely if it met a prespecified efficacy criterion at interim analysis.

Reviewer Comment

WIL-24 provided strong evidence of hemostatic efficacy and minimal safety concerns. In retrospect, the study's credibility could have been strengthened even more a priori had the applicant:

a) Enrolled more subjects (although admittedly, the Humate-P pivotal study for surgical prophylaxis in VWD patients was similarly sized: N=35).
b) Attached greater importance to enrolling more African-American and Hispanic subjects.
c) Minimized potential bias by using a double-blind, randomized, controlled design, e.g., comparing Wilate vs. Humate-P.
d) Appointed an Adjudication Committee to determine, in a blinded manner, whether reported outcomes were accurate and free of bias so that individual events and risk-benefit assessment were not determined by the same body, i.e., IDMC.

6.1.3 Population

— Inclusion Criteria

1. Male or female subjects > 6 years of age
2. Diagnosed with congenital VWD (any type) where VWF:RCo is <40% at Screening or the subject has a diagnosis of VWD Type 1, 2 or 3 and a history of VWF:RCo <40% documented in their medical notes at enrollment
3. Requires therapy with a VWF product to treat any potential surgical procedure

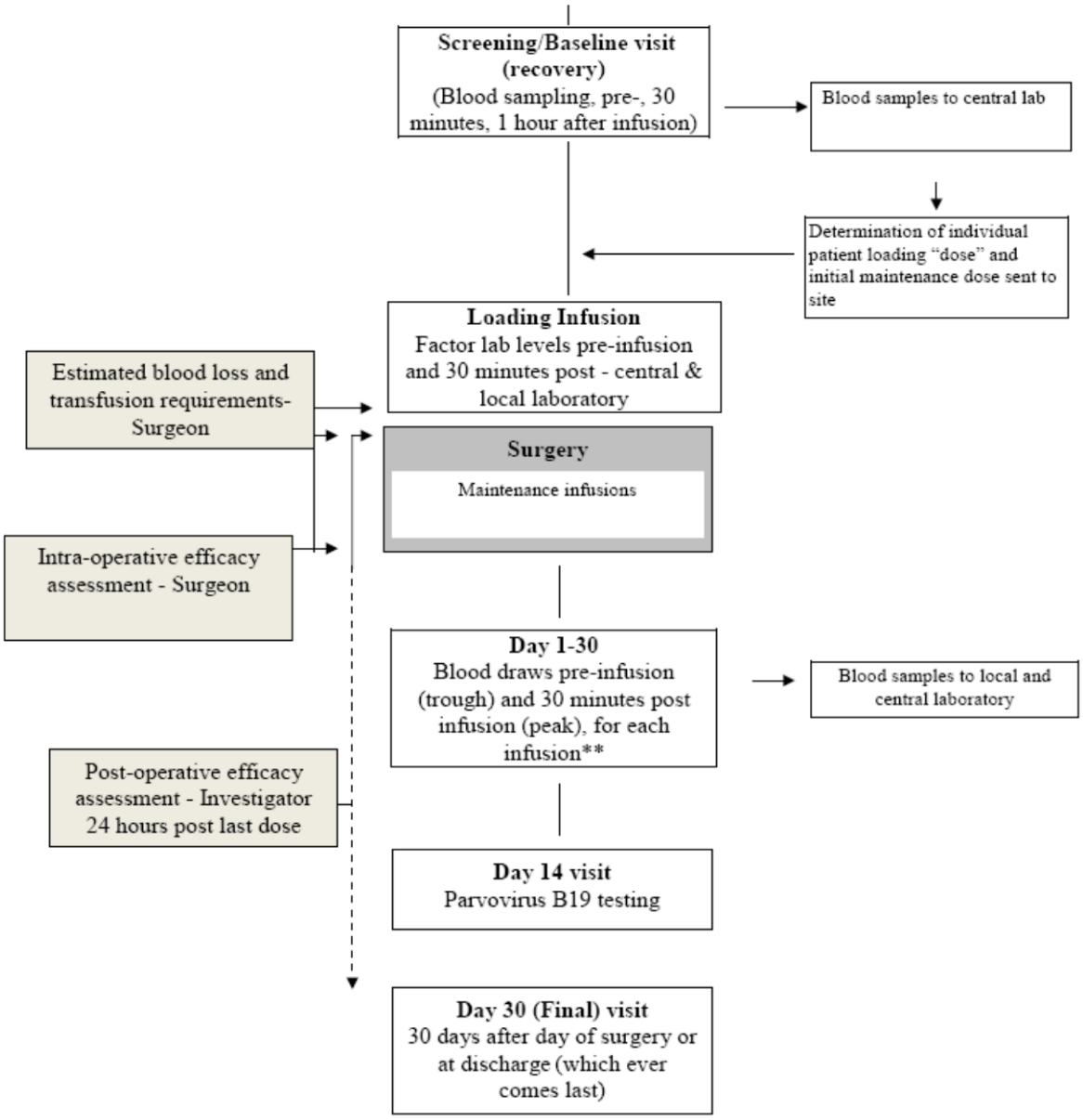
4. Negative for anti-human immunodeficiency virus (HIV); if positive, viral load <200 particles/µL or <400,000 copies/mL and CD4+ count >200/µL
5. The subject and/or their legally acceptable representative understands the nature of the Study, gives written informed consent to participate in the Study and is willing and able to comply with the protocol

— Exclusion Criteria

1. Known coagulation disorder other than congenital VWD
2. Any VWF-containing product administered within 3 days prior to the Screening visit
3. Any subject for whom it is planned to infuse the investigational product via continuous infusion
4. Known history of, or suspected to have, VWF or FVIII inhibitors
5. Emergency surgery or any surgery with a degree of urgency not permitting completion of baseline assessment required by the Study protocol
6. Suffering an acute or chronic medical condition, other than VWD, which may in the opinion of the investigator affect the conduct of the Study
7. Active hepatic disease (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels >5 times the upper limit of normal)
8. Known or suspected hypersensitivity or previous evidence of severe side effects to Wilate or other VWF/FVIII concentrates
9. Receiving immune-modulating drugs (other than anti-retroviral chemotherapy) such as α-interferon, prednisone (equivalent to >10 mg/day), or similar drugs at Study start
10. Pregnant women within the first 20 weeks of gestation
11. Evidence or a history (within the previous 12 months) of abuse of any drug substance, licit or illicit
12. Participation in another interventional clinical Study currently or during the past 4 weeks

6.1.4 Study Treatments or Agents Mandated by the Protocol

The following procedures were performed on each subject prior to product administration. See the schematic, below.



** In case of 2 or more doses per day, peak and trough levels should be obtained at least once per treatment day. For major surgeries, at least 2 maintenance doses should be given in the first 24 hours.

Figure 1: Study schematic
Source: 090-CSP Wilate 24-06 protocol_2012 12 10

1. IVR Investigations

IVR for VWF:RCo, VWF:Ag and FVIII:C in all subjects was calculated at the central laboratory from blood samples collected at the Screening/Baseline visit. For the Baseline recovery investigation, a dose of 60 IU VWF:RCo/kg body weight (BW) (labeled potency) was administered.[3] Results were reported as (IU/dL)/(IU/kg). The IVR value for VWF:RCo was used to determine the recommended loading and maintenance doses and communicated to the study site prior to the start of the procedure. IVRs also were calculated for VWF:RCo, VWF:Ag and FVIII:C based on the samples obtained prior and 30 minutes post-infusion for all loading and maintenance doses.

For calculation of recovery, the actual potency of Wilate as tested at the central laboratory was used. The following formula was applied:

$$Recovery = (C_{max}-C_{base})*BW/dose$$

2. Anti-VWF Antibodies and VWF Inhibitor Testing

Samples for anti-VWF antibody testing were collected at Screening/Baseline before IVR dose administration and at the Final visit. Anti-VWF antibodies were assessed by (b) (4) and if detected, two confirmatory tests were performed.

A sample that was found to be positive on more than one anti-VWF test was also checked for its ability to neutralize activity of VWF:RCo and/or VWF:CB (inhibitor tests) using the Bethesda assay.[4] This testing was performed in the central laboratory and, as this was not a standard laboratory assay, the results were considered exploratory. If the sample contained >0.10 IU/mL of VWF:RCo activity, an assay by Mannucci was used to increase reliability of the result.[5]

Subjects received a loading dose within 3 hours of the start of surgery at a dose corresponding to the dose defined as the IVR-derived dose that would achieve a VWF:RCo peak level of 100% for major surgery and 50% for minor surgery.

[3] The IVR doses administered based on actual potencies ranged from 44.1 to 81.1 IU/kg VWF:RCo. Mean incremental IVRs were 1.73 ± 0.43 (IU/dL)/(IU/kg) (VWF:RCo), 2.09 ± 0.51 (IU/dL)/(IU/kg) (VWF:Ag) and 1.95 ± 0.47 (IU/dL)/(IU/kg) (FVIII:C, measured by chromogenic [CS] assay). IVR values were generally as expected. The exceptions were 3 subjects who had IVR values (based on VWF:RCo) of 1.0 [IU/dL]/[IU/kg], who also had very low BW and body mass index.

[4] The Bethesda assay involves two control samples, one that estimates the contribution of normal plasma and one that measures the contribution from the subject's plasma. The combined activity of the two controls gives the "expected: value and a sample with a mixture of subject and normal plasma gives the "observed" value. The cut-off for positivity is a (expected-observed/expected) ratio of >0.25.

[5] The Mannucci assay is a modification of the Bethesda assay that involves two control samples, one that estimates the contribution of the normal plasma and one that measures the contribution from the patient plasma. The combined activity of the two controls gives the 'expected' value and a sample with a mixture of patient and normal plasma gives the 'observed value. The cut-off for positivity is a (expected-observed/expected) ratio of >0.25.

Dose titration was based on the type of surgery and expected blood loss for three types of surgical procedures:

- Major surgery
  - Loading dose: 40–60 VWF:RCo IU/kg to achieve peak plasma VWF:RCo level of 100%
  - Maintenance dose: 20–40 VWF:RCo IU/kg every 12–24 hours or half of the loading dose. Trough levels of VWF:RCo were to be maintained at >50% for at least 6 days. At least two maintenance doses were to be administered within the first 24 hours after the start of the surgery.
- Minor surgery
  - Loading dose: 30–60 VWF:RCo IU/kg to achieve peak plasma VWF:RCo level of 50%
  - Maintenance dose: 20–40 VWF:RCo IU/kg every 12–24 hours or half of the loading dose. Trough levels of VWF:RCo were to be maintained at >30% for at least 2 days.
- Gastrointestinal (GI) surgery
  - Increased dosing and shorter intervals of treatment allowed as necessary.

6.1.5 Directions for Use

Initial loading and subsequent maintenance doses were administered by bolus intravenous infusion at a rate not to exceed 2−4 mL/minute (as tolerated by the subject).

6.1.6 Sites and Centers

A total of 25 centers participated: United States (9 centers); India (3 centers); Turkey (2 centers); Poland (2 centers); Italy (3 centers); South Africa (1 center); Bulgaria (1 center); Romania (3 centers); and Oman (1 center).

6.1.7 Surveillance/Monitoring

Subjects were monitored throughout the study. At each (scheduled or unscheduled) study visit, AEs were documented by the investigator on specific pages of the case report form (CRF). Any AE or SAE occurring during the study was noted in detail on the appropriate pages of the CRF. If a subject reported several signs or symptoms representing a single syndrome or diagnosis, the latter was recorded. The investigator graded the severity (mild, moderate, or severe) and seriousness (serious or non-serious) of all safety events as well as causality according to pre-defined criteria in the study protocol. The sponsor was responsible for assessing the expectedness of each adverse drug reaction (ADR) (expected or unexpected). In the event of clinically relevant abnormal laboratory findings, the tests were repeated and followed up until they returned to normal and/or an adequate explanation was available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of study medication were not considered as AEs when observed at a later stage, unless they represented an exacerbation in intensity or frequency (worsening). The responsible investigator was accountable for providing detailed information concerning any abnormalities and the nature of, and reasons for, any necessary action(s) as well as any other observations or comments that were useful for the interpretation and understanding of the patients' AEs or SAEs.

The following parameters were regularly monitored by hospital staff throughout the study: vital signs, safety laboratory assessments (hematology including platelet count;

total bilirubin; AST, ALT, BUN, serum creatinine, and LDH), AE and immunogenicity. See the Monitoring Schedule, below.

Table 3: Monitoring Schedule

	Screening/Baseline			Surgery Visit			Day 1–30**		Day 14 (±2 days)	Day 30 (±1 week)
	Pre-infusion (≤3 h)*	Post-infusion (30±5 min)	Post-infusion (60±10 min)	Pre-infusion (≤3 h)	Post-infusion (30±5 min)	End of surgery	Pre-infusion (≤30 min)	Post-infusion (30±5 min)		
Hematology (RBCC, WBCC, HB, HCT, PC)	X			X		X				X
Chemistry (BILI, ALT, AST, BUN, CREA, LDH)	X			X		X				X
Anti-HIV / PCR	X									
CD4+	X									
VWF:RCo	X	X	X	X	X		X	X		
VWF:Ag	X	X	X	X	X		X	X		
FVIII:C level	X	X	X	X	X		X	X		
VWF inhibitors	X									X
Anti-HCV	X									X
Parvovirus B19	X								X	
Retained plasma sample	X	X	X	X	X		X	X		X
Retained serum sample	X									X

* ≤30 min before the infusion for coagulation parameters.
** In case of 2 or more doses per day, peak and trough levels were to be obtained at least once per treatment day.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; BUN = blood urea nitrogen; CREA = serum creatinine; FVIII:C = Factor VIII coagulant activity; HB = hemoglobin; HCT = hematocrit; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; PC = platelet count; PCR = polymerase chain reaction; RBCC = red blood cell count; WBCC = white blood cell count; VWF = von Willebrand Factor; VWF:Ag = von Willebrand factor antigen; VWF:RCo = von Willebrand factor ristocetin cofactor.

Source: 090-CSP Wilate 24-02 FINAL 22Aug2014

After the IDMC had reviewed data from the first 10 subjects, they requested investigators to explicitly collect data on post-operative bleeding and oozing, rather than just providing the assessment as excellent, good, moderate, or none without further explanation (page 66/1472, Final Study Report). A new page was implemented into the CRF for this purpose. This information was collected prospectively via CRFs for the subsequent 20 subjects.

Reviewer's Comment
Since the investigators' postoperative assessment was excellent or good for the first 10 subjects, it can reasonably be assumed that post-operative bleeding/oozing was not higher than expected (as per definition of efficacy using the prespecified assessment scale; see Section 6.1.8).

6.1.8 Endpoints and Criteria for Study Success

— Primary Endpoint: hemostatic efficacy of Wilate in the treatment of VWD subjects undergoing a surgical procedure

At the end of surgery and again at 24 hours after the last postoperative infusion of Wilate, hemostatic efficacy was assessed independently by the surgeon and investigator-hematologist, respectively, using a prospectively defined, 4-point scoring system of excellent, good, moderate, or none. See Tables 4 and 5, below.

Table 4: Hemostatic Efficacy Assessment by Surgeon at End of Surgery (after last suture)*

Efficacy Grade	Definition
Excellent	Intra-operative blood loss and transfusion requirements were lower than or equal to the average expected ones for the type of procedure performed in a subject with normal hemostasis and of the same sex, age, and stature.
Good	Intra-operative blood loss and transfusion requirements were higher than the average expected but lower or equal to the maximal expected blood loss and transfusion requirements for the type of procedure in a subject with normal hemostasis.
Moderate	Intra-operative blood loss and transfusion requirements were higher than maximal expected for the type of procedure performed in a subject with normal hemostasis, but hemostasis was controlled
None	Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.

* For all ratings (excellent, good, moderate and none), unexpected blood loss due to surgical complications was not taken into consideration when assessing intra-operative efficacy. These included 1. Direct injury of a vessel (artery or vein); 2. Vessel injury not adequately responding to routine surgical procedures achieving hemostasis; 3. Accidental injury of parenchymous tissue (e.g., liver, lung).
Source: Table 7, 090-CSP Wilate 24-02 FINAL 22Aug2014

Table 5: Hemostatic Efficacy Assessment by Investigator at 24 Hours Following the Last Wilate Infusion

Efficacy Grade	Definition
Excellent	Absence of post-operative bleeding and oozing that was both: (1) not due to complications of surgery; and (2) beyond that expected for a normal operative subject as anticipated for the type of procedure
Good	Absence of post-operative bleeding and oozing that was both: (1) not due to complications of surgery; and (2) beyond that expected for a normal operative subject as anticipated for the type of procedure but required increased dosing with Wilate or additional infusions, not originally anticipated for the type of procedure.
Moderate	Some post-operative bleeding and oozing that was both: (1) not due to complications of surgery and (2) beyond that expected for a normal operative subject. The control of post-operative bleeding required increased dosing with Wilate or additional infusions, not originally anticipated for the type of procedure.
None	Extensive uncontrolled post-operative bleeding and oozing that was both: (1) not due to complications of surgery; and (2) beyond that expected for a normal operative subject. The control of post-operative bleeding required use of an alternate VWF:RCo/FVIII concentrate.

Source: Table 8, 090-CSP Wilate 24-02 FINAL 22Aug2014

The IDMC conducted an independent adjudication of all hemostatic efficacy results ("secondary adjudication"). Bleeding during either the intraoperative or postoperative period (but not both, which would be rated a failure) was classified into one of the categories marked "primary adjudication" but final determination made by the IDMC ("secondary adjudication"), i.e., the IDMC's assessment, not that of the surgeon or investigator, was used in cases where the assessment of the surgeon/investigator differed from that of the IDMC's.[6] See Table 6, below.

6 The IDMC membership comprised

Table 6: Intra-Operative and Post-Operative Assessment of Hemostatic Efficacy

Intra-operative assessment	Post-operative assessment			
	Excellent	**Good**	**Moderate**	**None**
Excellent	Success	Success	Success	**Primary adjudication**
Good	Success	Success	**Primary adjudication**	Failure
Moderate	Success	**Primary adjudication**	Failure	Failure
None	**Primary adjudication**	Failure	Failure	Failure

Source: Table 9, 090-CSP Wilate 24-02 FINAL 22Aug2014

— Secondary Endpoints (Objectives)[7]

1. Evaluation of intra- and post-operative surgical hemostatic efficacy of Wilate in preventing excessive bleeding in pediatric and adult patients with VWD who require a VWF product and undergo a surgical procedure.

   Prior to surgery, the surgeon provided written estimates of the following:
   - Volume (mL) of average expected blood loss for the planned surgical procedure, as it would be expected for the same procedure in a patient with normal hemostasis, of the same sex, age, and stature
   - Volume (mL) of maximal expected blood loss for the planned surgical procedure as it would be expected for the same procedure in a patient with normal hemostasis, of the same sex, age, and stature
   - Volume (mL) of average expected whole/packed blood transfusion requirements for the planned surgical procedure as it would be expected for the same procedure in a patient with normal hemostasis, of the same sex, age, and stature.
   - Volume (mL) of maximal expected whole/packed blood transfusion requirements for the planned surgical procedure as it would be expected for the same procedure in a patient with normal hemostasis, of the same sex, age, and stature.

   Following the surgery, actual blood loss was recorded by the surgical team.

2. Safety of Wilate when used in VWD patients who undergo surgical procedures.
   - In addition to monitoring for AEs, blood samples were collected for (a) HIV markers (viral load and CD4+); (b) FVIII:C, VWF:RCo, VWF:Ag; (c) VWF inhibitors; and (d) viral safety (HCV, Parvovirus B19) at prespecified study times.

   - Ability of Wilate to normalize the coagulation defect in VWD as demonstrated by an increase of the plasma activity of VWF ristocetin cofactor VWF:RCo)

[7] A search for the term “Secondary Endpoint” in the WIL-24 final study report was unsuccessful. Secondary Endpoints cited in this review are paraphrased as “Secondary Objectives.

and FVIII:C. See Section 6.1.11.2 for further discussion of secondary objectives/endpoints.

3. Analysis of actual dosage and duration of treatment in surgical procedures.
   - Number of Exposure Days
   - Load + maintenance cumulative dose, IU/kg/procedure
   - Preoperative loading dose, IU/kg/infusion
   - Maintenance dose, IU/kg/infusion

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary analysis focused on the overall proportion of surgical procedures rated excellent or good as per the composite assessment algorithm. The proportion of surgeries with successful treatment was calculated and the following null and alternative primary hypotheses tested:

$$H_0: p_0 < 0.6 \text{ versus } Ha: p_0 \geq 0.6$$

where p_0 represents the overall proportion of successfully treated surgical episodes.

An interim analysis was planned after completion of 30 procedures, using a two-sided 98.75% (Clopper-Pearson) CI constructed around the estimate of p0. If early success was not demonstrated at the interim analysis, a two-sided 96.25 % CI was to be used at the end of the study. The treatment with Wilate could be claimed as effective if the lower limit of the confidence interval was ≥0.6 at either analysis.

•

6.1.10 Study Population and Disposition

Study WIL-24 comprised a Safety Population of 41 subjects (39 individuals) and an ITT Population of 30 subjects (28 individuals). Two subjects were enrolled twice for different procedures and counted separately.[8]

All prematurely terminated subjects (N=11) were adults and included 9 Screening failures[9] and 2 premature withdrawals, one at sponsor request and another at subject request.[10] All but 2 centers enrolled no more than 2 subjects: Center 11 enrolled 9 subjects and Center 81 enrolled 4 subjects. See Table 7, below.

[8] Subject [redacted] (VWD Type 3) underwent left knee arthroplasty (major surgery) on 18-Oct-2012. The same subject underwent right knee arthroplasty (major surgery) on 22-May-2013 as subject [redacted]. The second subject (VWD Type 1) underwent tooth extractions (minor surgery) on 03-Sep-2013 and 15-Oct-2013, entering the Study as subject [redacted] and [redacted], respectively.

[9] Subject [redacted] (U.S.), [redacted] and [redacted] (India) [redacted] (Italy) [redacted] and [redacted] (South Africa), [redacted], [redacted] (Romania), and [redacted] (Oman) were Screening failures.

[10] Subject [redacted] (U.S.) prematurely withdrew consent following a hypersensitivity event; subject [redacted] (Italy) was prematurely withdrawn when the Study was terminated by the sponsor.

Table 7: Subject Withdrawals (N=11)

Study	Center No. (Country)	Subject No. (sex, age)	Reasons for Withdrawal
WIL-24	3 (U.S.)	(b) (6) (F, 57)	Withdrew consent
	9 (U.S.)	(F, 60)	Did not meet inclusion criteria
	11 (India)	(F, 22)	Did not undergo planned surgery as per sponsor decision
		(F, 26)	High FVIII and VWF:RCo levels
	50 (Italy)	(F, 83)	Protocol violation
		(M, 76)	Study terminated by sponsor
	60 (South Africa)	(F, 29)	Screening failure
		(M, 37)	Screening failure
	80 (Romania)	(M, 27)	Surgery postponed indefinitely
		(F, 23)	Met exclusion criteria; surgery no longer needed
	90 (Oman)	(F, 38)	Screening failure; not possible to provide appropriate dosing recommendations

*Screening failure. These subjects did not have surgery during the study but were included in the safety population as they had a recovery assessment at Screening.
Source: Appendix, Table 2.7.4.3, Clinical Safety Summary

6.1.10.1 Populations Enrolled/Analyzed

- Safety population (N=41): subjects exposed to any amount of product.
- ITT population (=30): subjects in the Safety population in whom data were collected post-treatment with Wilate.
- Per-Protocol (PP) population (N=30): subjects in the ITT population who completed the study without major protocol violations, which were defined as follows:
  - Violation of the following inclusion or exclusion criteria
    - Present or past VWF or FVIII inhibitor activity
    - Any other coagulation disorder besides VWD
  - Significant non-compliance with the protocol, for example non-completion of the surgeon's efficacy determination
  - Dosing or treatment errors, e.g., several unexplained and significant deviations from the recommended dose regimen
  - Procedures where another VWF concentrate was used because of logistical or accidental reasons other than rescue

Reviewer's Comment
Note that the ITT and PP populations were identical.

6.1.10.1.1 Demographics
The demographic composition of the Safety population was heavily represented by female Caucasian adults with Type 3 disease, two Black/African-American subjects (both from Oman) and no Hispanic subjects. See Table 8 below.

Table 8: Demographics: Safety Population (N=41)

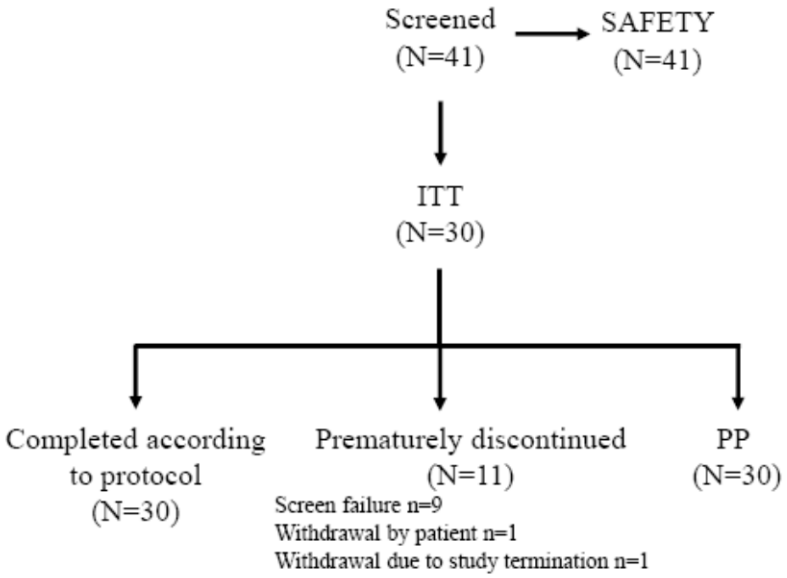
Parameter		Number	Percent
Age	>16	38	93
	12-16	3	7
Sex	Male	12	29
	Female	29	71
Race	White	24	59
	Asian	13	32
	African-American/Black	2	5
	Omani	2	5
	Hispanic	0	0
VWD Type	1	10	24
	2	7	17
	3	24	59

Source: Listing 16.2.4.1, 090-CSP Wilate 24-02 FINAL 22Aug2014

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The Safety population consisted of Caucasian (N=21), Asian (N=8) and Black (N=1,from Oman) individuals with long standing VWD (median: 18.8 years). A positive family history (FH) for VWD was elicited in 17 subjects, a negative FH in 17, and an unknown FH in 4 (data missing: 3 subjects). VWF inhibitor activity was negative in 38 subjects (data missing: 3 subjects). At Screening, 1 subject was receiving prophylaxis, 25 were receiving on-demand treatment, and 12 were not on any treatment. The median number of annual bleeding episodes was 12.

6.1.10.1.3 Subject Disposition



N = number of procedures; ITT = intention-to-treat population; PP = per-protocol population.

Figure 2: Subject disposition

Twenty-eight individual subjects underwent 30 surgical procedures. Subject [redacted] (VWD Type 3) underwent left knee arthropathy (major surgery) on 18-Oct-2012. The same subject underwent right knee arthropathy (major surgery) on 22-May-2013 as Subject [redacted]. The second subject (VWD Type 1) underwent tooth extractions (minor surgeries) on 03-Sep-2013 and 15-Oct-2013, entering the study as Subject [redacted] and [redacted], respectively.

Most procedures were orthopedic or dental; obstetric/gynecological, gastrointestinal, ENT, and ophthalmologic procedures comprised the remainder. Of the 21 VWD Type 3 subjects, 17 underwent major surgery and 4 underwent minor surgery. See Table 9 below.

Table 9: Surgical Procedures per Body System by Type of Surgery (ITT Population, N=30)

Body System	Minor Surgery N (%)	Major Surgery N (%)	All Surgeries N (%)
Dental	5 (55)	2 (10)	7 (23)
Orthopedic	2 (22)	8 (38)	10 (33)
Gastrointestinal	0	4 (19)	4 (13)
Ophthalmologic	1 (11)	0	1 (3)
Obstetric/gynecologic	0	5 (24)	5 (17)
ENT	1 (11)	2 (10)	3 (10)

Source: Table 14, 090-CSP Wilate 24-02 FINAL 22Aug2014

6.1.11 Efficacy Analyses

Efficacy was measured using a 4-point VRS that was based on number of bleeding episodes, amount of product required (consumption of Wilate), and number of exposures necessary to stop bleeding episodes or achieve hemostasis after surgery. See Section 6.1.8.

6.1.11.1 Analyses of Primary Endpoint(s)

Primary Endpoint: hemostatic efficacy in the ITT population was 96.7% (rate of success: 0.967; CI 0.784 to 1.000). Treatment was successful in 100% of minor surgeries and 95.2% of major surgeries (1 failure, subject [redacted]; see below). Hemostatic efficacy was 100% of surgeries in VWD Type 3 and Type 2 subjects, and 85.7% in Type 1 subjects (1 failure, same subject). See Table 10 below.

Table 10: Success Rate by Surgery Severity (upper panel) and VWD Type (lower panel)

Efficacy	Minor (n=9)		Major (n=21)		All Procedures (n=30)	
	n (%)	98.75% CI	n (%)	98.75% CI	n (%)	98.75% CI
Success	9 (100)	0.569, 1.000	20 (95.2)	0.704, 1.000	29 (96.7)	0.784, 1.000
Failure	0		1 (4.8)		1 (3.3)	

Efficacy	VWD Type 1 (7)		VWD Type 2 (n=2)		VWD Type 3 (n=21)	
	n (%)	98.75% CI	n (%)	98.75% CI	n (%)	98.75% CI
Success	6 (85.7)	0.328, 0.999	2 (100)	0.079, 1.000	21 (100)	0.785, 1.000
Failure	1 (14.3)		0		0	

n=number of surgical procedures

Source: Tables 16 and 17, 090-CSP Wilate 24-02 FINAL 22Aug2014

Subject [redacted] was considered a treatment failure. Intra-operative hemostatic efficacy of Wilate for this subject was rated as moderate by both the surgeon and the IDMC, and the post-operative hemostatic efficacy was rated good and moderate by the investigator and the IDMC, respectively, which resulted in a derived overall assessment of failed hemostatic efficacy. This subject had VWD Type 1 and underwent left lumbar spine H-5 laminectomy (major surgery) on 20-Jun-2013. He experienced slightly greater blood loss (25 mL) than the expected maximum (20 mL), which was due to diffuse ooze of blood from muscle soft tissue during surgery. He did not receive any transfusion or additional VWF/FVIII concentrate treatment for this oozing but was treated with 500 U of thrombin and 1 g of absorbable gelatin sponge. The post-operative bleeding and oozing was more than expected in a patient with normal hemostasis. Although the investigator later noted that this was due to a complication, the IDMC rated the event as moderate since the nature of the complication was not noted at the time. Postoperatively, the patient developed a 4 cm bruising and induration associated with the lumbar incision.

Successful outcomes stratified by demographic factors for sex, race and age were males 89% and females 100%; Caucasians 94%, Asian 100%, and Black 100%; and age 12-17 years 100%; 18-65 96%, and >65 years 100%, respectively.

The revised Statistical Analysis Plan (protocol amendment 5, dated 10-DEC-2012) prespecified that the study would be terminated early if the lower bound of a 2-sided 98.75% CI for success was > 0.60 (equivalent to 25 or more successes out of the 30 procedures). Since there were 29 successes and the CI was >0.60 at the interim analysis, the study was prematurely terminated for success.

6.1.11.2 Analyses of Secondary Endpoints

1. **Secondary Endpoint #1**: evaluation of the intra- and post-operative surgical hemostatic efficacy of Wilate in preventing excessive bleeding in pediatric and adult patients with VWD who require a VWF product and undergo a surgical procedure.

   Blood loss during all procedures, except those in subjects [redacted] (treatment failure) and (b) (6) (treatment success but experienced slightly greater postoperative oozing than expected in a healthy individual), was lower than the maximal expected (mean difference -294.9 ± 502.2 mL); this was most pronounced in subjects with Type 3 subjects (-372.4 ± 572.1 mL).

   Intra-operative transfusion was expected in 5 subjects but required in only 2.

   - Subject (b) (6) underwent a delivery via caesarian section and received one platelet transfusion (250 mL) intra-operatively for thrombocytopenia. She also received 6 platelet transfusions pre-operatively and 3 platelet transfusions postoperatively. As she had a history of thrombocytopenia, these transfusions were planned. Her intra-operative treatment efficacy was judged as excellent by the surgeon and good by the IDMC and overall treatment was successful.

   - Subject [redacted] underwent abdominal hysterectomy with bilateral salpingo-oophorectomy. She received one transfusion (350 mL) of rejuvenated packed RBCs intraoperatively as adjuvant for surgery, which was planned pre-operatively. Her overall treatment was judged as successful.

Post-operative transfusion (unplanned) was required in 3 subjects.

- Subject [redacted] developed anemia (8.9 mg/dL) shortly after surgery. She had a blood loss of 1200 mL (maximal expected) during the surgical procedure due to an iatrogenic complication (uterine artery injury). She received an unplanned RBC transfusion. Her post-operative treatment efficacy was judged as good by the investigator and excellent by the IDMC and the overall treatment was successful.

- Subject [redacted] underwent normal vaginal delivery with low forceps and received 350 mL of packed RBCs due to a drop in hemoglobin. Her post-operative treatment efficacy was judged as moderate by the IDMC (but excellent by the investigator). Overall treatment was successful.

- Subject [redacted] underwent debrider-assisted endoscopic adenoidectomy with tonsillectomy and received 4 red blood cell transfusions for a drop in hemoglobin starting on 21-Jan-2012, with the last infusion on 07-Feb-2012; transfusion volumes ranged from 230 mL to 340 mL. She had a history of iron deficiency anemia. Her post-operative treatment efficacy was judged as good by the investigator and excellent by the IDMC.

An overview of expected and actual blood loss and transfusion requirements is provided in Table 11.

Table 11: Blood Loss: Maximal Expected, Actual and Difference

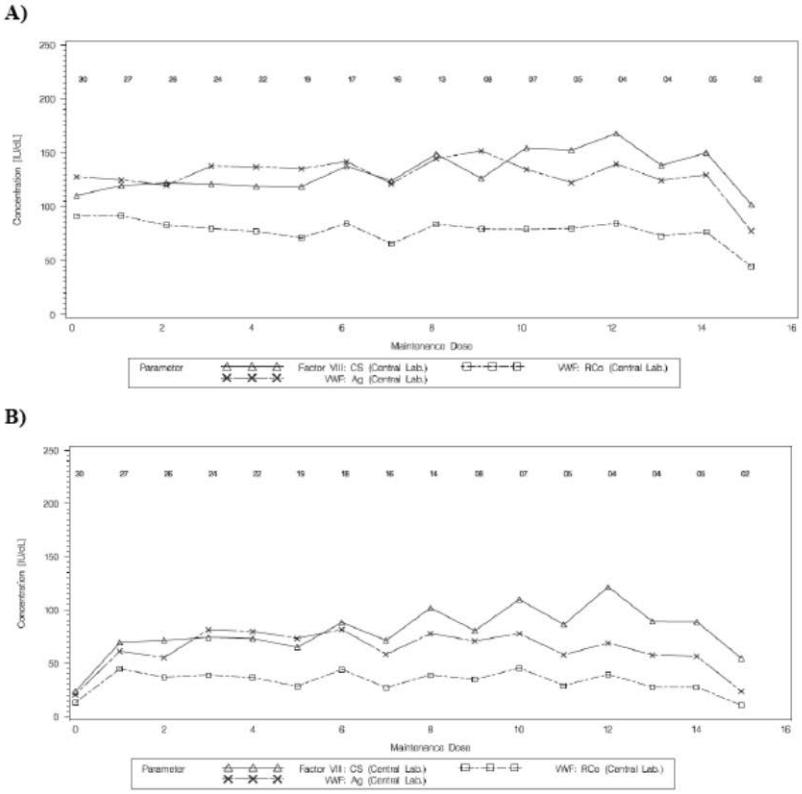
	Mean ± SD Median (Range)		
	Major	**Minor**	**All Surgeries**
Volume of Blood Loss (mL)			
Maximal expected	600.5 ± 622.1 500.0 (20-2000)	74.6 ± 72.4 50.0 (1-200)	484.7 ± 585.6 200.0 (1-2000)
Actual	261.2 ± 307.6 100.0 (0-1200)	23.2 ± 20.9 15.0 (1-50)	189.8 ± 278.7 50.0 (0-1200)
Difference between maximal expected and actual	-399.3 ± 571.4 -100.0 (-1900 - -20	-51± 52.5 -30.0 (-150 - 0)	-294.9 ±502.2 -100 (-1900 - -20)
Transfusions (mL)			
Units of packed cells, maximal expected	N=5 390.0 ± 204.3 350.0 (150.0-600.0)	-	N=5 390.0 ± 204.3 350.0 (150.0-600.0)
Units of whole blood, maximal expected	N=5 1190 ± 1140 800 (0-2400)	-	N=5 1190 ± 1140 800 (0-2400)
Actual, units of whole blood and platelets	N=2 287.5 ± 88.4 287.5 (225.0-350.0)	-	N=2 287.5 ± 88.4 287.5 (225.0-350.0)

Source: Table 20, 090-CSP Wilate 24-02 FINAL 22Aug2014

2. **Secondary Endpoint #2**: safety of Wilate used in VWD patients who undergo surgical procedures**.**
   - Three clinical events unrelated to Wilate were reported: 2 bleeding SAEs and 1 non-serious wound infection AE of severe intensity. No cases of VWF inhibitors were reported, although one subject had a non-inhibitory anti-VWF antibody. No cases of coagulation factor accumulation over time or thromboembolic events were reported. See Section 6.1.11.2

3. **Secondary Endpoint #3**: capability of Wilate to normalize the coagulation defect in VWD as demonstrated by an increase of the plasma activity of von Willebrand factor ristocetin cofactor (VWF:RCo) and FVIII:C.

   Normalization of the coagulation defect in VWD was demonstrated by an increase of the plasma activity of VWF:RCo and FVIII:C. FVIII:C and VWF:RCo plasma levels were monitored throughout the treatment period with the goal of not exceeding a maximum level of 250% FVIII:C and of maintaining a trough level of 50% VWF:RCo for major surgery and 30% for minor surgery. Figure 1, below, reproduced from the supplement, shows that average VWF and FVIII:C plasma concentrations remained stable during maintenance dose administrations. No accumulation of FVIII:C was observed over time and no thromboembolic events were observed. See Figure 3, below.



* Only the maintenance infusions with values available for more than one patient are shown.
0 = pre-surgery loading dose.
Numbers at the top of each figure represent the number of patients at that particular time point.
FVIII:CS = FVIII coagulant activity as measured by the chromogenic assay; IU = international units; N = number of surgeries; SD = standard deviation; VWF:Ag = von Willebrand factor antigen; VWF:RCo = von Willebrand factor ristocetin cofactor.

Figure 3: Mean course of peak (A) and trough (B) values by maintenance dose for VWF and FVIII:C concentrations (IU/dL)
Source: Figure 1, 090-CSP Wilate 24-02 FINAL 22Aug2014

Reviewer's Comment:
While not directly affecting clinical outcome, several issues related to FVIII activity levels merit additional comment.

1. *Not all values were captured per protocol.*
    a. *Subject [redacted] and Subject [redacted] received 17 and 22 maintenance doses, respectively, but only single values for some of these infusions were available. As a result, coagulation factor values for more than one subject are available only up to maintenance infusion 15. Because no minor surgery was treated for more than 5 days and only a few major surgeries were treated for more than 8 days, variability increases in the peak and trough levels after that time point.*
2. *Several outliers with implausibly low values from the central lab were reported.*
    a. *All values for Subject [redacted] and Subject [redacted] as well as maintenance infusions 3 and 4 for Subject [redacted] and maintenance infusions 1 and 2 for Subject [redacted] were deemed potentially invalid by the central laboratory due to poor sample quality. The results obtained by the central laboratory for these subjects do not correlate with the local laboratory results,*

which are in most cases significantly higher, suggesting that the central lab results are inaccurate.

3. *FVIII:C values >250 IU/dL (central laboratory) during maintenance infusions were reported in 7 subjects. These plasma levels correlated with higher dosing and some of them were adjusted by decreasing the dose. No accumulation of FVIII over time was observed in any subject.*

4. **Secondary Endpoint #4**: analysis of the actual dosage and duration of treatment in surgical procedures.

— Dosage

Note: one loading dose of Wilate per procedure was administered for the majority of procedures (26/30, 86.7%). Two loading doses per procedure were administered for 3 procedures (10.0%) and 3 loading doses were administered for one procedure (3.3%). These additional loading doses were due to delays in the start of surgery.

Loading Dose: the total per infusion was 51.4 IU/kg (mean), with major surgeries requiring a 54.7 IU/kg compared with 41.9 IU/kg for minor surgeries per loading infusion.

Maintenance Dose: the total per infusion was 28.5 IU/kg (mean), with major surgeries requiring 29.6 IU/kg compared with 21.6 IU/kg for minor surgeries per maintenance infusion. Cumulative loading and maintenance doses overall (293.1 IU/kg/procedure) were 3-fold higher for major surgery (368.9 IU/kg/procedure) than for minor surgery (116.2 IU/kg/procedure). When stratified by VWD severity, Type 2 subjects required the *highest* total loading dose (mean: 61.5 IU/kg/infusion), with Type 3 requiring slightly less (51.5 IU/kg/infusion) and Type 1 still less (45.4 IU/kg/infusion). Cumulative loading and maintenance doses were highest in Type 3 (330.7 IU/kg/procedure), followed by Type 2 (275.9 IU/kg/procedure) and Type 1 (185.3 IU/kg/procedure).

— Duration of Treatment

The average exposure was 7 days, with major surgery requiring slightly more (8 days) and minor surgery slightly less (4 days) than the median. VWD Type 3 subjects required the longest number of exposure days (median: 8). Subjects with Type 3 disease also received the highest mean cumulative loading and maintenance dose. See Table 12 and Table 13, below.

Reviewer's Comment

Larger loading doses were needed in Type 2 subjects (N=2) than in Type 3 subjects (N=21) possibly due to random variation associated with small sample sizes.

Table 12: Summary of Wilate Dosages per Infusion Administered by Type of Surgery (ITT Population, N=30)

Parameter	Mean ± SD Median (Range)		
	Major	**Minor**	**Total**
Number of Exposure Days	9.0 ± 3.5 8.0 (4-17)	4.7 ± 2.4 4.0 (3-10)	7.7 ± 3.8 7.0 (3-17)
Load + maintenance cumulative dose, IU/kg/procedure	N=21 368.9 ± 139.8 360.0 (147-700)	N=9 116.2 ± 32.3 127.5 (66-163)	N=30 293.1 ± 166.3 270.6 (66-700)
Preoperative loading dose, IU/kg/infusion*	N=26 54.7 ± 10.1 55.5 (36-69)	N=9 41.9 ± 15.0 37.5 (27-77)	N=35 51.4 ± 12.6 52.1 (27-77)
Maintenance dose, IU/kg/infusion	N=214 29.6 ± 9.3 30.0 (8-63)	N=31 21.6± 6.4 20.6 (14-38)	N=245 28.5 ± 9.3 28.5 (8-63)

*Three subjects received 2 loading doses and one subject received 2 loading doses.
Source: Table 21, 090-CSP Wilate 24-02 FINAL 22Aug2014

Table 13: Summary of Wilate Dosages per Infusion Administered by VWD Type (ITT population, N=30)

Parameter	Mean ± SD Median (Range)		
	VWD Type 1	**VWD Type 2**	**VWD Type 3**
Number of Exposure Days	4.9 ± 2.7 4.0 (3-10)	6.0 ± 4.2 6.0 (3-9)	8.8 ± 3.6 8.0 (4-17)
Load + maintenance cumulative dose, IU/kg/procedure	N=7 185.3 ± 150.2 138.9 (66-475)	N=2 275.9 ±191.7 275.9 (140-411)	N=21 330.7 ± 160.9 340.4 (107-700)
Preoperative loading dose, IU/kg/infusion*	N=7 45.4 ±12.7 46.3 (27-59)	N=4 61.5 ±11.8 58.6 (52-77)	N=24 51.5 ±12.1 49.7 (31-69)
Maintenance dose, IU/kg/infusion	N=34 28.8 ± 13.3 25.9 (14-63)	N=10 30.6 ±12.0 26.0 (8-52)	N=201 28.4 ±8.4 28.5 (13-60)

N=number of subjects
*Three subjects received 2 loading doses and one subject received 2 loading doses.
Source: Table 22, 090-CSP Wilate 24-02 FINAL 22Aug2014

6.1.11.3 Efficacy in Pediatric (Adolescent) Subjects
Hemostatic efficacy was 100% in the three adolescent subjects enrolled in WIL-24.

6.1.11.4 Dropouts and/or Discontinuations
Two subjects who experienced an AE discontinued from the study. Subject [redacted] experienced moderate hypersensitivity that led to discontinuation during the pre-surgery loading infusion, which was stopped early. Subject [redacted] experienced chest discomfort, dizziness and feeling hot, which led to withdrawal of study drug during maintenance dose 8 after major surgery.

6.1.12 Safety Analysis

- No deaths were reported
- Two bleeding SAEs and 1 wound infection AE of severe intensity (all unrelated to Wilate) were reported
- AE incidence stratified by demographic factors for sex, race and age were as follows:
  - Male 67% and female 72%
  - Caucasian 79%, Asian 69% and Black 0%
  - Age 12-17 years 67%, 18-65 years 74%, and >65 years 50%, respectively
- Mild-moderate intensity AEs (n=118) (unlikely related or not related to Wilate), most commonly procedural pain, nausea and vomiting, were reported in 29 subjects (70.7%)
- Mild-moderate intensity AEs ("probably related" to Wilate) necessitating medical intervention within 24 hours in three of the five subjects:
  - Subject [redacted]: hypersensitivity-anxiety (midazolam; subject withdrew from study)
  - Subject [redacted]: chest discomfort
  - Subject [redacted]: hypersensitivity-chest discomfort, feeling hot, dizziness (brief pause of loading dose, followed by completion of study)
  - Subject [redacted]: hypertension
  - Subject [redacted]: hypotension (bolus infusion of normal saline)

See Tables 14 and Table 15 below.

Table 14: Number of Subjects in the Safety Population (N=41) Experiencing Adverse Events

Classification	All Subjects (%)
Adverse event	29 (70.7)
Serious adverse event	2 (4.9)
Related adverse events	5 (12.2)
Severe intensity adverse event	1 (2.4)
Adverse event leading to discontinuation of Wilate	2 (4.9)
Adverse event leading to death	0

Source: Table 25, Final Study Report; Table 14.3.1.1.1 and 14.3.1.1.2)

Table 15: Number of Subjects in the Safety Population (N=41) Experiencing ≥2 Adverse Events

Primary System Organ Class **Preferred Term**	**No. of Subjects (%)**
Any SOC	29 (71%)
Injury, poisoning and procedural complications	13 (32%)
Procedural pain	8 (20%)
Gastrointestinal disorders	10 (24%)
Nausea	6 (15%)
Vomiting	6 (15%)
Constipation	2 (5%)
Hematemesis	2 (5%)
General disorders and administrative site conditions	10 (24%)
Pain	4 (10%)
Pyrexia	4 (10%)
Infections and infestations	8 (20%)
Viral upper respiratory tract infection	2 (5%)
Wound infection	2 (5%)
Investigations	7 (17%)
Hemoglobin decreased	4 (10%)
Nervous system disorder	6 (15%)
Dizziness	2 (5%)
Headache	2 (5%)
Musculoskeletal and connective tissue disorders	4 (10%)
Back pain	2 (5%)
Vascular disorders	4 (10%)
Hypertension	4 (10%)
Reproductive system and breast disorders	3 (7%)
Menorrhagia	2 (5%)
Immune system disorder	2 (5%)
Hypersensitivity	2 (5%)

Source: Table 26,090-CSP Wilate 24-02 FINAL 22Aug2014

6.1.12.3 Deaths

No deaths were reported in any Wilate surgical clinical study.

6.1.12.4 Nonfatal SAEs

Two WIL-24 subjects, a 30 year old Asian female [redacted] and a 15 year old Asian female [redacted], experienced bleeding SAEs lasting 15 minutes and 5 days, respectively. Both events were unrelated to Wilate.

Reviewer's Comment

The two bleeding SAEs were almost certainly unrelated to Wilate exposure based on the elapsed time from last maintenance treatment to onset of event, as both subjects had been discharged from hospital in stable condition: vaginal hemorrhage in Subject [redacted] occurred 11 days after her last treatment; hematemesis (erosive gastritis) in Subject [redacted] occurred 9 days after her last treatment. A causal association between Wilate and wound infection is unlikely given postmarketing safety data. Attribution of almost all AEs as unrelated or probably unrelated is reasonable given the limitations inherent in an uncontrolled study.

6.1.12.5 Adverse Events of Special Interest (AESI)

The Warnings and Precautions section of PIs from other VWD products lists events that can be classified as AESI: infection; thromboembolism/elevated levels of VWF and FVIII:C activities; hypersensitivity reactions; and inhibitor formation. Review of the WIL-24 safety database found no cases of transmitted infectious pathogens (subject [redacted] experienced a wound infection of severe intensity considered unrelated to the product), thromboembolic events/accumulation of VWF or FVIII:C, or VWF inhibitors at Screening or on Day 30. See 6.1.12.6 for a discussion of AESI.

6.1.12.6 Clinical Test Results

— Hematology

Six subjects [redacted] experienced anemia of mild-moderate intensity following bleeding. Five of these subjects received a RBC transfusion.

— Chemistry

No clinically significant abnormal values for chemistry parameters or CD4+ T cell tests were reported.

— Transmission of Infectious Pathogens

Parvovirus B19: 39 subjects were tested for anti-Parvovirus B19 antibodies at Screening (the two subjects enrolled twice were only tested once). Parvovirus B19 IgG antibody levels were above the Limit of Quantification (LQ) (<0.9) in 31 individuals and below LQ in 8. Parvovirus B19 IgM antibody was not detected in any subject. Those subjects who tested positive for Parvovirus B19 IgG antibody at Screening were not required to be retested at a later date, although some had the test performed regardless. Those subjects who did not have a surgical procedure (11 subjects) were not retested at a later date. All subjects who underwent a surgical procedure and who were negative at Screening also had negative Parvovirus B19 DNA levels at Day 14.

HCV: 39 subjects (N=39) were tested for anti-HCV antibodies at Screening (2 subjects who enrolled twice were only tested once); 14 were positive and 1 was equivocal/weakly positive at this time point. All 30 subjects who underwent surgery were re-tested at Day 30, and 15 subjects (14 positive and one equivocal subject who was weakly positive in the confirmatory testing at Screening) were found also to be positive at Day 30. None of the subjects negative at Screening was positive at Day 30.

HIV: 36 subjects had HIV testing at Screening (results were not reported for 4 subjects who were screen failures, and one subject who enrolled twice only had HIV Screening once). All were HIV negative, except subject [redacted], who had a very low viral load (<37 c.v./mL) and CD4+ T cells in the normal range (778 cells/µL). All subjects who underwent a surgical procedure met the inclusion criterion for HIV results.

Reviewer's Comment

Since both components of Wilate are derived from human plasma, a potential safety concern is risk of transmission of infectious pathogens. Of particular interest is risk of transmission of Parvovirus B19. In trials conducted prior to licensure, no study subjects were found to have evidence of seroconversion for several screened viruses including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis A virus (HAV). In the most recent Periodic Safety Update Report (PSUR), no virus transmission with respect to these four viruses was observed in any clinical trial.

Evidence of Parvovirus B19 seroconversion in study subjects was noted, however, in several trials conducted pre-licensure: 4 reports each from TMAE-104 and WIL-14, and 1 report from TMAE-106.

The applicant cites recent studies which may explain the finding of seroconversion with Parvovirus B19 but not with other tested viruses. While heat inactivation results in total capsid disintegration for some viruses, this is not the case with Parvovirus B19. The heat inactivation process in the manufacture of Wilate results in the extrusion of Parvovirus B19 DNA and some proteins from the viral capsid, resulting in an empty but intact capsid. The free DNA, extruded proteins and intact but empty capsid may all be antigens that induce seroconversion to Parvovirus B19 in the absence of actual infection by live virus. In addition, given the prevalence of Parvovirus B19, community exposure may account for some cases of seroconversion. Octapharma reports that while some PCR testing of product received by study subjects who seroconverted was positive for Parvovirus B19, none of the batches tested exceeded the recommended limit for manufacturing pools of plasma derived products. In addition, positive values for Parvovirus B19 could have resulted from pre-licensure acquisition of plasma from fractionators other than U.S. FDA approved plasma donation centers, early in the development of Wilate. The applicant notes that as of March 2010, Wilate is derived from plasma collected at U.S. FDA approved plasma donation centers and all plasma is tested for viral markers in compliance with both EU and FDA guidances. In addition to conformance with current regulatory guidelines for plasma acquisition, Octapharma has incorporated various manufacturing steps into the production of Wilate to reduce the risk of viral transmission, e.g., viral inactivation by solvent detergent and dry heating treatments, testing for the presence of certain viruses, and [redacted] and chromatography to remove both prions and viruses. Inclusion of these steps in the manufacturing process reduces but does not eliminate the risk of transmission of infectious agents, and given that Parvovirus B19 infections may be serious in pregnant women and immunodeficient individuals, continued surveillance for transmission of Parvovirus B19 and other infectious pathogens is warranted. Continued routine surveillance is recommended (see the DE/OBE reviewer's memo).

— Immunogenicity

No subject tested positive for VWF inhibitors at Screening or on Day 30. Four subjects had confirmed anti-VWF antibodies at Screening (2 additional subjects tested positive initially but negative on confirmation) and were confirmed non-inhibitory. At Day 30, 6 subjects had confirmed anti-VWF antibodies. Subject [redacted] tested negative for non-inhibitory antibody at Screening, but was confirmed positive at Day 30; her FVIII:C, VWF:Ag and VWF:RCo did not appear to be affected during the study and overall hemostatic efficacy of Wilate for her surgery was rated as successful.

— Thromboembolism

No thromboembolic events were observed in the surgical prophylaxis studies.

Reviewer's Comment

Thrombotic events are a potential concern in the VWD surgical population because treatment may require multiple doses of Wilate, resulting in high plasma levels of both VWF and factor VIII. A recent literature review of thrombotic adverse events (AE) with factor concentrates used in the treatment of hemophilia and VWD found that thrombotic

AEs accounted for 1.9% of non-inhibitor-related AEs, with a higher prevalence and more reports of major thrombosis in VWD patients than in hemophiliacs.[11]

In clinical studies conducted prior to licensure, a single thromboembolic event was observed in study TMAE-104. This event was classified as being unrelated to Wilate by the investigator. In post-marketing surveillance, 3 reports of thromboembolic events were received: 2 cases of pulmonary embolism and 1 report of injection site thrombosis. Octapharma estimates that thromboembolic events are very rare, occurring with a frequency of 1 report per 95,849 exposure days. Continued routine surveillance is recommended (see the DE/OBE reviewer's memo).

— Hypersensitivity

Five hypersensitivity reactions deemed product-related were reported.

Reviewer's Comment

As with any plasma-derived product of human origin, allergic type hypersensitivity reactions may occur with Wilate. Hypersensitivity and allergic reactions have been observed with Wilate in clinical studies conducted prior to licensure as well as in the postmarketing setting. In October 2010, the sponsor voluntarily withdrew a batch of Wilate distributed to a single healthcare center in the UK due to three reports of allergic reactions in June of that year. The sponsor's analysis of all postmarketing data showed an increase in adverse events in 2010 and that the increase involved allergic or anaphylactoid reactions. This was thought to be due to an increase in sales as the percentage of batches resulting in adverse reactions per year did not increase significantly over time. Additionally, a rapid rate of infusion, rather than a product-specific problem, was thought to account for some of the allergic reactions reported. Nonetheless, the sponsor investigated the implicated lots and found no abnormalities in either the drug substance or the solvent used in these lots. A review of patient characteristics, storage and handling processes in reporting facilities and the sponsor's manufacturing processes also identified no abnormalities. The following year, the sponsor reported the number of allergic or anaphylactoid reactions had returned to expected levels. As a safety measure, Octapharma amended the product information leaflet insert to remind customers not to utilize higher infusion rates that they may have employed with previously used products. See the DE/OBE reviewer's memo recommending no additional safety measures other than routine surveillance.

— Development of Inhibitors to VWF

No subject developed inhibitors to VWF.

Reviewer's Comment

On occasion, patients with severe VWD have been reported to develop inhibitory antibodies to VWF. These antibodies may render replacement therapy ineffective and result in uncontrolled and potentially fatal bleeding. The applicant reports in the most recent pharmacovigilance plan that in the completed clinical studies, no inhibitors to VWF were observed and no reports of antibodies against VWF have been received. Continued routine surveillance is recommended (see the DE/OBE reviewer's memo).

[11] Coppola A *et al.* Thrombotic adverse events to coagulation factor concentrates for treatment of patients with haemophilia and von Willebrand disease: a systematic review of prospective studies. *Haemophilia* 2012:18; e173-87

6.1.12.7 Dropouts and/or Discontinuations
Two subjects discontinued due to AEs: Subject [redacted] (hypersensitivity) and Subject [redacted] (chest discomfort, feeling hot and dizziness).

6.1.13 Study Summary and Conclusions
Efficacy data from pivotal study WIL-24 showed a strong treatment effect in VWD subjects undergoing major and minor surgery. Major procedures commonly experienced by the target population, enrollment of a high proportion of Type 3 subjects, and normalization of VWF and FVIII levels with multiple infusions Wilate infusions support hemostatic efficacy. Data from a limited number of pediatric subjects (N=10) undergoing surgery lend additional support to this conclusion, although interpretation is somewhat limited by small sample size (a feature it shares with the pivotal study (N=35) for Humate-P), underrepresentation of minority subjects, an open-label/ uncontrolled study design, and failure to utilize a stand-alone Adjudication Committee to QC incoming data.

The safety of Wilate was assessed by monitoring AEs, vital signs, laboratory parameters and immunogenicity. Major risks reported with administration of plasma-derived products were rare (hypersensitivity) or not observed (thromboembolic disease, infectious disease transmission, inhibitors). AEs (n=118) were recorded in 29/41 patients (70.7%). Two serious AEs (vaginal hemorrhage and gastritis erosive) occurred post-operatively in 2 subjects. Both were unrelated to Wilate and resolved without sequelae. One severe wound infection AE resolved without sequelae and was not related to Wilate. A total of 8 mild-moderate intensity AEs in 5 subjects (2 cases of hypersensitivity in 1 subject; 1 case of hypersensitivity in another subject; chest discomfort, feeling hot and dizziness in a third subject; hypertension in a fourth subject; hypotension in a fifth subject) were probably related to study drug. Wilate's safety profile in the surgical setting supports a favorable benefit-risk profile.

6.2 Supportive Pediatric Studies: WIL-14 and TMAE-104
6.2.1 Overview of Efficacy
WIL-14 and TMAE-104 were small, single-arm, non-IND supportive studies that enrolled pediatric VWD subjects undergoing surgical procedures. Hemostatic efficacy was rated by the investigator and the subjects' parents as excellent or good in 100% of cases.

Evaluation of hemostatic efficacy in the applicant's Pediatric Assessment was based on studies, WIL-14, TMAE-104 and WIL-24, representing 0 to <2 years, 2 to <6 years, 6 to <12 years and 12 to <16 years, respectively. A 100% success rate was achieved for all subjects. Table 16 summarizes the key features of these studies.

The primary objective of WIL-14 was to assess prevention and/or treatment of bleeding episodes during surgery. Secondary objectives included IVR prior to major surgery (optional for minor surgery), immunogenicity, safety and tolerability, PK and IVR in subjects with VWD Type 3.

The primary objective of TMAE-104 was to assess plasma levels of FVIII:C, VWF:Ag, VWF:CB and VWF:RCo as surrogate markers of efficacy. Secondary objectives included PK, bleeding time, overall efficacy, safety and tolerability.

Table 16: Study Characteristics and Demographics of Pediatric Surgery Studies

Subgroup (Study)	No. of Subjects No. of Procedures (Major, Minor)	Study Design	No. of Centers Countries	VWD Type (N, %)
0 to <2 years (WIL-14)	3 5 (2, 3)	Open label, uncontrolled, multicenter	3 Germany Poland	Type 1: 1 (33) Type 2: 2 (66)
2 to <6 years (WIL-14)	4 4 (1, 3)	Open label, uncontrolled, multicenter	4 Germany Poland Czech Rep	Type 1: 1 (25) Type 2: 2 (50) Type 3: 1 (25)
6 to <12 years (TMAE-104)	3 10 (0, 10)	Open label, uncontrolled, multicenter	1 Poland	Type 3: 3 (100)
12 to <16 years (WIL-24)	3 3 (2, 1)	Open label, uncontrolled, multicenter	3 USA India	Type 2: 1 (33) Type 3: 2 (66)

N=number of subjects
Source: Table 1, Table 2 and Table 11, Pediatric Assessment

Reviewer's Comment
Caution is warranted when assessing hemostatic efficacy in children based on pooled efficacy data because of the following limitations.

a. *Assessment of efficacy in WIL-14 occurred after each infusion but after each procedure in WIL-24 and TMAE-104.*
b. *Assessment of efficacy in WIL-14 and TMAE-104 was based on responses from investigators and parents, whereas an IDMC adjudicated efficacy in WIL-24.*
c. *Route of administration varied in WIL-14, i.e., some subjects were administered Wilate by intermittent injection whereas others received the product by continuous infusion*
d. *According to the original BLA clinical reviewer, the 4-point VRS grading scale used in TMAE-104 was "ambiguous and poorly defined" (NB: the same scale was used in WIL-14), in contrast to the grading scale used in WIL-24.*

6.2.2 Overview of Safety

— WIL-14

All subjects (N=15) were <6 years of age; 7 underwent surgery and belonged to one of two cohorts: age 0 to <2 years (N=3) and age 2 to <6 (N=4; see below).

The following safety events were reported in the 0 to <2 year cohort:

- One catheter sepsis SAE and one head trauma SAE (Subject [redacted].
- Inhibitors of FVIII or VWF were not detected but antibodies to FVIII were detected in 2 subjects, one of whom tested positive before the first administration of Wilate (Subject [redacted] and one who tested negative at the start of the study (Subject [redacted]. Bethesda inhibitor assays were negative in all cases.
- No changes in vital signs or AEs were observed in routine clinical laboratory testing.
- Seroconversion

- Seroconversion for hepatitis A attributed to vaccination was observed in Subject [redacted]; no seroconversions occurred in the other 2 subjects.

The following safety events were reported in the 2 to <6 year cohort:

- Subject [redacted] experienced 2 hematemesis SAEs and Subject [redacted] experienced one torticollis SAE.
- Inhibitors of VWF or FVIII were not detected.
- No changes in vital signs or AEs were observed in routine clinical laboratory testing.
- Seroconversion
  - Seroconversion for hepatitis B at 6 months attributed by the investigator to vaccination was reported in Subject [redacted].
  - Seroconversion for anti-parvovirus B19 IgG possibly related to Wilate was reported in Subject [redacted] who seroconverted, followed by a negative polymerase chain reaction (PCR) test and a negative anti-parvovirus B19 IgG test. The last test for anti-parvovirus B19 IgG was again positive, while the PCRs remained negative.
  - Seroconversion for both anti-parvovirus B19 IgG and IgM judged as not related by the investigator was reported in Subject [redacted], who also tested positive for PCR. The IgM and IgG seroconversions as well as detection of parvovirus B19 DNA were consistent with a recently acquired infection. Detection of parvovirus B19 DNA in subsequent samples was consistent with a prolonged course of an active infection.

— TMAE-104

Subjects (N=41) ranged in age from 6 to <85 years. In the subpopulation aged 6 to <12 years (N=8), three subjects underwent surgery (all minor procedures).

The following safety events were reported.

- Subject [redacted] experienced 3 bleeding SAEs after tooth extraction, 5 hemarthrosis SAEs, 2 synovitis SAEs, and 2 device-related infection SAEs. Subject [redacted] experienced a parotitis SAE.
- Inhibitors to VWF were not specifically examined, although samples were taken to be tested in case of a suspicion of inhibitors and the tests were performed retrospectively. No subjects with suspected inhibitor development were reported.
- No changes in vital signs or AEs were observed in routine clinical laboratory testing.
- Seroconversion
  - All 3 subjects seroconverted with respect to anti-hepatitis A antibodies which was attributed to vaccination.

9. ADDITIONAL CLINICAL ISSUES

9.1.1 Human Reproduction and Pregnancy Data

Wilate is currently labeled as Pregnancy Category C. Animal reproduction studies have not been conducted with Wilate. It is also not known whether Wilate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

9.1.2 Use During Lactation
Wilate has not been studied in lactating women.

9.1.3 Pediatric Use and PREA Considerations
The applicant has submitted a clinical study database in which the four pediatric subpopulations are represented. Please see 6.1.11.3, 6.2.1, and 6.2.2. VWD has received Orphan Designation except for surgical prophylaxis. Clinical outcome data in children have been presented to the PeRC.

10. CONCLUSIONS
Wilate is effective in surgical prophylaxis of subjects with VWD, including those with severe VWD (Type 3). The evidence indicates a strong treatment effect in both adult and pediatric subjects and except for potential safety concerns associated with other members of this class, the product is not associated with excess risk.

No new safety concerns have been identified in the latest postmarketing surveillance report. DE/OBE is in agreement with the sponsor's plan for ongoing routine surveillance and completion of four postmarketing studies (WIL-15; WIL-20; WIL-25; ITI-01) to evaluate safety and efficacy. Currently available safety data do not substantiate a need for a postmarketing requirement study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS).

Approval of the surgical prophylaxis indication is recommended.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS
11.1 Risk-Benefit Considerations
Hemostatic efficacy data establish a substantial likelihood of net benefit in adults and children with VWD undergoing surgery.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	VWD arises from a congenital VWF deficiency and is classified as Type 1, Type 2 or Type 3 - Type 1: partial quantitative deficiency, 70-80% of patients; o Type 2: partial qualitative deficiency, 20%; o Type 3: complete deficiency - Humate-P (CSL Behring), Alphanate (Grifols Therapeutics), and DDAVP (Sanofi-Aventis) are licensed to treat bleeding in VWD patients undergoing surgery.	Type 3 VWD patients undergoing surgery are at especially increased risk of bleeding during and after surgery.
Unmet Medical Need	Of currently available therapy, only Humate-P is indicated for bleeding in patients with severe disease (Type 3).	An unmet medical need does not exist for VWD patients undergoing surgery
Clinical Benefit	An open-label, uncontrolled pivotal study in VWD adults and adolescents undergoing major and minor surgery was submitted; additional support was provided by two other open-label, uncontrolled studies in VWD subjects aged 0-12 years undergoing surgery. The primary endpoint, hemostatic efficacy (excellent or good outcomes), was found in 29/30 (97%) of procedures in the pivotal study and 22/22 (100%) of procedures in the supportive pediatric studies. Thromboembolism, infection, inhibitor formation, VWF and FVIII:C activity elevations were not observed.	Strong evidence indicates Wilate reduced surgical bleeding in adult and pediatric VWD subjects undergoing surgery.
Risks	The major risk observed was hypersensitivity (flushing, nausea/vomiting, hypotension).	Evidence indicates the risk of hypersensitivity is manageable.
Risk Management	Hypersensitivity symptoms were mild-moderate in severity and self-limiting.	If approved, routine measures, such as the package insert and the current pharmacovigilance plan would be adequate to manage the risk.

11.2 Risk-Benefit Summary and Assessment
The clinical benefit of Wilate for the surgical prophylaxis indication exceeds the risk.

11.4 Recommendations on Regulatory Actions
I recommend Approval.

11.5 Labeling Review and Recommendations
Recommended revisions to the draft labeling communicated to the applicant included greater use of command language, consistent terminology when describing the product, deletion of statements that refer to practice of medicine, integration of safety information from clinical studies in subjects undergoing surgery and those not undergoing surgery, implementation of the new format for Section 8 (Use in Specific Populations), i.e., 8.1 Pregnancy, 8.2 Lactation, 8.3 Pediatric Use, and 8.4 Geriatric Use.

I recommend Approval of labeling for the PI and carton.

11.6 Recommendations on Postmarketing Actions
The OBI reviewer's memo indicates that at this time, available safety data do not substantiate the need for a PMR study or a REMS.

Octapharma plans to conduct routine pharmacovigilance activities for inhibitor hypersensitivity reactions that include anaphylactic reactions; inhibitors against VWF; viral safety; thrombogenicity; safety in pregnant or breast feeding women; elderly patients; and patients with renal or severe hepatic impairment.

In addition, Octapharma has funded three pharmacovigilance studies:

- WIL-15: An observational study to evaluate the safety and efficacy of Wilate in patients with inherited VWD of any type.
- WIL-20: An observational prospective study to assess the clinical efficacy and tolerability of Wilate when used in VWD patients with acute bleeding, on regular prophylaxis or undergoing surgery.
- WIL-25: An observational study of the tolerability and efficacy of Wilate in routine clinical care when used at the discretion of the physician for management of acute bleeding, routine prophylaxis or the perioperative care of patients with VWD.

These studies may prove useful with regard to further evaluating both identified and potential safety concerns and should be listed on the approval letter as clinical postmarketing commitment studies with commitments from the sponsor to submit interim and final study reports to FDA at prespecified intervals.

*****Do Not Change Anything Below This Line*****