Application Type	BLA
STN	125251/139
CBER Received Date	08-Oct-2014
PDUFA Goal Date	08-Aug-2015
Division / Office	OBRR
Committee Chair	Laurence Landow
Clinical Reviewer(s)	Laurence Landow
Project Manager	Beth Walton
Priority Review	No
Reviewer Name(s)	Boris Zaslavsky
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renee Rees
	Boguang Zhen
Applicant	Octapharma Pharmazeutika Produktionsges.M.B.H.
Established Name	Von Willebrand Factor/Coagulation Factor VIII Complex (Human)
(Proposed) Trade Name	Wilate
Pharmacologic Class	A plasma-derived, stable, double virus inactivated, highly purified concentrate of freeze-dried active human blood coagulation factor VIII (FVIII) and von Willebrand factor
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Intravenous (infusion, continuous infusion).
Dosing Regimen	
Indication(s) and Intended Population(s)	Wilate has been approved in the US for the treatment of spontaneous and trauma-induced bleeding episodes in subjects with severe von Willebrand disease as well as subjects with mild or moderate von Willebrand disease in whom the use of desmopressin is known or suspected to be

	ineffective or contraindicated. The current supplement is seeking indication for the perioperative management of bleeding in von Willebrand disease subjects.

Table of Contents

Glossary

DDAVP	Desmopressin acetate
FVIII	Human blood coagulation factor VIII
HCV	Hepatitis C virus
IDMC	Independent data monitoring committee
IRB	Institutional Review Board
ITT	Intent to treat
IVR	In vivo recovery
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
TEAE	Treatment emergent adverse events
VRS	Verbal rating scale
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:RCo	von Willebrand factor activity measured via ristocetin cofactor

1. EXECUTIVE SUMMARY

Wilate is a plasma-derived, stable, double virus inactivated, highly purified concentrate of freeze-dried active human blood coagulation factor VIII (FVIII) and von Willebrand factor (VWF). The current supplement is seeking to expand Wilate's indication to the perioperative management of bleeding in von Willebrand disease patients. The pivotal surgical study WIL-24 has been completed after a planned interim analysis of 30 surgeries and the recommendation of the independent data monitoring committee (IDMC) to stop early because the pre-specified efficacy criteria for early stopping were met.

WIL-24 was a prospective, open-label, uncontrolled, multi-center, phase III clinical study that investigated efficacy and safety of Wilate in subjects who are at least 6 years of age with inherited von Willebrand disease (VWD) who underwent surgical procedures. Efficacy was assessed based on the intra- and post-surgical efficacy. In total, 28 individual subjects underwent 30 surgeries. Overall treatment of Wilate was successful in 29 of all surgeries, 9 of 9 minor surgeries and 20 of 21 major surgeries. There were no deaths in the study. Five subjects experienced a total of eight (out of 118) treatment emergent adverse events (TEAEs) that were considered probably related to treatment. No inhibitory anti-VWF antibodies occurred.

The supporting prospective, open-label, non-controlled, multicenter phase II study investigated the efficacy, safety and immunogenicity of Wilate in children <6 years of age with VWD. Seventeen subjects were enrolled; seven subjects underwent a total of nine surgical procedures, six of which were categorized as minor and three as major. Recovery assessments were performed in nine surgeries. Data for overall efficacy per surgery were not available. However, the efficacy per infusion was rated. A combined total of 45 infusions of Wilate were administered for surgical coverage. The 32 (71.1 %) were rated as excellent and 13 (28.9 %) as good, and 45 (100%) were the total of excellent or good infusions.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

The symptoms of VWD are usually those of platelet dysfunction and include nose bleeding, skin bruises and hematomas, prolonged bleeds from trivial wounds, oral cavity bleeding, and excessive menstrual bleeding. Gastrointestinal (GI) bleeds appear to be relatively rare, but may be very serious when they occur. Severe deficiency of VWF, or a specific defect in the interaction of VWF with FVIII, causes a secondary moderate deficiency of FVIII. These subjects may have symptoms that are more characteristic of hemophilia, such as bleeds into joints or soft tissues including muscle and the brain. In VWD, the principle of treatment or prevention of bleeding episodes (BEs) is the transient correction of the dual plasma deficiency of VWF and FVIII. The latter deficiency is secondary to that of VWF, FVIII's physiological carrier and stabilizer in plasma.

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

Desmopressin acetate (DDAVP) is the treatment of choice for mild and moderate VWD Type 1. DDAVP causes release of VWF from the endothelial cells resulting in an increased level of VWF and FVIII in plasma. Subjects who do not respond adequately to DDAVP, subjects who experience significant side effects to DDAVP and subjects in whom DDAVP is contraindicated are potential candidates for replacement therapy with a product containing VWF to control bleeds. In addition, if repeated infusions of DDAVP are given, tachyphylaxis may develop in initially responsive subjects, requiring VWF replacement therapy when adequate hemostasis has to be maintained for longer periods of time. Furthermore, in cases of severe bleeds and major and/or repeated surgery VWF substitution, in addition to DDAVP therapy, is required. Purified, virus inactivated, plasma-derived VWF/FVIII concentrates are currently most frequently used for VWF replacement therapy. The few available products differ in terms of purification procedures and purity (specific activity), number of virus inactivation steps, virus inactivation methods, ratio of VWF:RCo to FVIII:C and the quality of the VWF (e.g., VWF triplet structure). A purified VWF product almost deplete of FVIII:C, Wilfactin®, is also available in some countries.

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

Wilate was licensed in the US in 2009 for the treatment of spontaneous and trauma-induced bleeding episodes in subjects with severe VWD as well as subjects with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. The product is available in the US**.**

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

A previous submission to the FDA in 2006 (BLA STN #125251/0) granted approval for Wilate for the treatment of bleeding episodes (BEs). That submission also included surgery data. On the request of the FDA, all efficacy data were re-analyzed using post hoc-defined objective efficacy criteria, and the results met all pre-specified endpoints (BLA STN #125251/0, Amendment #028, Enclosure 6 - Study report Summary analysis of clinical efficacy endpoints). Further correspondence with the FDA resulted in the FDA asking to remove the five surgeries treated with continuous infusion from the re-analysis, which reduced the success rate from 0.7 to 0.68 and resulted in the surgical efficacy endpoint not being met. The already established surgical data in VWD in previous studies were thus not accepted. Therefore, an additional study (Study WIL-24) was conducted under BB-IND 11303 to assess the efficacy of Wilate specifically in surgical procedures. Thus, Study WIL-24 is the pivotal study for this submission, with Wilate efficacy assessment in surgical procedures based on prospectively-defined objective criteria.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The applicant submitted surgical data from one completed surgical study (Study WIL-24, in subjects above 6 years old) that was stopped early because the pre-specified efficacy criteria for early stopping were met. The applicant also submitted results from four completed studies (TMAE-104, TMAE-105, TMAE-106 and TMAE-109) and data and a

report from a new non-IND European study in children under 6 years old, WIL-14. All studies were very small. These trials are summarized in Table 1 below. Study WIL-24 was the pivotal Phase 3 study in 41 subjects ≥6 years of age with inherited VWD who underwent surgical procedures. Study WIL-14 included a subpopulation of seven subjects <6 years of age with inherited VWD who underwent surgical procedures. Only Study WIL-24 and the surgical subpopulation of WIL-14 have primary study objectives supporting the current supplemental BLA submission and they are reviewed in this memo.

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

The following documents (module number and title) were reviewed for this memo.

1.14 Labeling
2.5 Clinical overview
2.7.3 Summary of Clinical Efficacy
2.7.4 Summary of Clinical Safety
2.7.6 Synopses of Individual Studies
5.2 Tabular Listing of Pediatric Studies
5.3.5.2 WIL-14 Clinical Study to Investigate the Efficacy, Safety and Immunogenicity of Wilate
5.3.5.2 WIL-24 Prospective, Open-Label, Multi-Center, Phase III Clinical Study to Investigate the Efficacy and Safety of Human Factor VWF/VIII Concentrate (Wilate) in Subjects with Inherited von Willebrand Disease (VWD) Who Undergo Surgical Procedures

5.3 Table of Studies/Clinical Trials

Table 1. Summary of Studies Supporting the Surgical Indication

Study No.	Population No. of patients Age	Design Study sites Study period	Test product(s) Dosage regimen Duration of treatment	Evaluation criteria	Study objectives
WIL-24	Inherited VWD undergoing surgical procedures N=41 planned procedures (SAFETY; 39 individual patients) (12 M / 29 F) N=30 procedures (ITT; 28 individual patients) (9 M / 21 F) Age: ≥6 years	Prospective, uncontrolled, multi-center, open-label, phase III 25 centers in the USA, India, Turkey, Poland, Italy, South Africa, Bulgaria, Romania and Oman Start: August 2011 End: March 2014	Wilate ***Surgical prophylaxis***: *Minor surgeries*: loading dose 30–60 IU VWF:RCo/kg within 3 h prior to surgery to target peak level of 50%, maintenance doses of 20–40 IU VWF:RCo/kg or half of the loading dose every 12−24 h; trough level >30% for ≥2 days *Major surgeries*: loading dose 40–60 IU VWF:RCo/kg within 3 h prior to surgery to target peak level of 100%, maintenance doses of 20−40 IU VWF:RCo/kg every 12−24 h or half of the loading dose for ≥6 days; trough levels >50%; ≥2 maintenance doses within 24 h after the start of the surgery *GI surgery*: increased dosing and shorter intervals were allowed as necessary. Treatment was individualized according to the severity of the bleeding and history of the patient ***Duration***: 30 days from the day of the start of each surgery or until discharge, whatever came last	Efficacy Safety	*Primary* Overall hemostatic efficacy (success or failure) of Wilate during surgery *Secondary* • Intra- and post-operative hemostatic efficacy • Actual dosage and duration of treatment during surgical procedures • Measurement of VWF:RCo and FVIII:C plasma activity during treatment • Safety (AEs, vital signs, laboratory parameters, immunogenicity, virus safety)
WIL-14	Children with inherited VWD, any type, DDAVP treatment known or suspected to be inadequate N = 15 (ITT) (10 M / 5 F) Age: <6 years	Open-label, non-controlled, phase II Multicenter: 7 centers in Germany, Poland, France and the Czech Republic Start: April 2006 End: October 2009	Wilate ***Surgical prophylaxis***: *Minor surgeries*: start ≥30 min prior to surgery, repeat every 12−24 h until healing complete; maintain VWF:RCo plasma level >30% and FVIII:C plasma level >30% *Major surgeries:* 12−24 h prior to surgery, repeat at start of operation and every 12−24 h until healing complete; maintain VWF:RCo plasma level >60% and FVIII:C plasma level >50% ***Spontaneous bleeding episodes:*** ~20−50 IU/kg, QD or every other day ***Duration:*** treatment in accordance with clinical needs of each patient over an observation period of 1 year	Efficacy Safety	*Primary* Efficacy in prevention and/or treatment of BEs and during surgery *Secondary* • IVR prior to major surgery (optional for minor surgery) • Immunogenicity • PK and IVR in patients with VWD Type 3 or severe VWD (optional) • Safety and tolerability (AEs, vital signs, laboratory parameters, viral safety)
TMAE-104	Inherited VWD, any type, not responding to DDAVP N=41 (18 M / 23 F) Age: ≥6 and ≤85 years	Open-label, non-controlled, phase III Multicenter: 15 centers in Austria, Finland, Norway, Poland, Portugal, Sweden and the United Kingdom. Start: January 2002 End: March 2007	Wilate ***Surgical prophylaxis***: *Minor surgeries*: maintain FVIII:C >30 IU/dL until healing complete; treatment normally given QD or every other day. *Major surgeries*: maintain FVIII:C >50 IU/dL until healing complete; treatment normally given QD or bid *Dental surgery*: maintain FVIII:C >30 IU/dL ≤6 h; treatment normally consists of a single dose. ***Spontaneous or post-traumatic bleeding***: ~20−50 IU FVIII:C/kg QD or every other day normally sufficient. ***Duration:*** ≥1 dose depending on the patient's clinical needs	Efficacy Safety	*Primary* Efficacy using plasma levels of FVIII:C, VWF:Ag, VWF:CB and VWF:RCo as a surrogate marker *Secondary* • PK • Bleeding time • Investigator and/or patient overall assessment of clinical efficacy • Safety and tolerability (AEs, laboratory and viral safety, investigator and/or patient overall assessment of clinical tolerability)

TMAE-105	Inherited VWD, any type, not responding to DDAVP N=14 (8 M / 6 F) Age: ≥12 and ≤65 years	Open-label, non-controlled, phase II 2 centers in Poland and Bulgaria Start: December 1999 End: July 2000	Wilate *PK assessment*: 50 IU VWF:RCo/kg *Surgical prophylaxis*: *Minor surgeries*: QD or every other day to maintain FVIII:C >30 IU/dL until healing complete *Major surgeries:* QD or every other day to maintain FVIII:C >50 IU/dL until healing complete *Dental surgery:* single dose to maintain FVIII:C >30 IU/dL for ≤6 h *Spontaneous bleeding episodes:* ~20−50 IU/kg, QD or every other day *Duration*: PK assessment: single dose, 1 treatment day. Surgery: single dose, ≥1 treatment days	PK Efficacy Safety	*Primary* • PK (AUC, AUC_{norm}, $T_{1/2}$, MRT, V_{ss} and CL) for VWF:Ag, VWF:CB, VWF:RCo • Plasma level of FVIII:C as a surrogate marker for efficacy *Secondary* • PK parameters C_{max} and t_{max} for VWF:RCo, VWF:Ag and VWF:CB • IVR of FVIII:C, VWF:Ag and VWF:RCo • Bleeding time • Plasma levels of VWF:Ag, VWF:CB, VWF:RCo • VWF multimeric pattern • Overall assessment of efficacy • Safety and tolerability (AEs, vital signs, laboratory safety, viral safety)
TMAE-106	Inherited VWD, any type, not responding to DDAVP N=14 (4 M / 10 F) Age: ≥12 and ≤65 years	Open-label, non-controlled, phase II Multicenter: 8 centers in Germany Start: March 2002 End: July 2006	Wilate *PK assessment*: 50 IU VWF:RCo/kg *Clinical efficacy phase*: administrations and actual dose depended on clinical situation of the patient; regular treatment as prescribed by physician.iv injection or continuous infusion (surgical interventions) *Duration*: PK assessment: single dose. Clinical efficacy phase: ≥1 dose depending on the patient's clinical needs.	PK Efficacy Safety	*Primary* • PK of VWF:Ag, VWF:CB, VWF:RCo • Plasma level of FVIII:C *Secondary* • Incremental IVR and plasma levels of FVIII:C, VWF:RCo, VWF:Ag • Bleeding time • Closure time • VWF multimeric pattern • Overall assessment of efficacy • Safety, tolerability and laboratory safety, including viral safety
TMAE-109	Inherited VWD, any type, not responding to DDAVP N=16 (10 M / 6 F) Age: ≥12 and ≤65 years	Open-label, non-controlled, phase II 2 centers in Poland and Bulgaria Start: August 2000 End: May 2001	Wilate *Surgical prophylaxis*: *Minor surgeries*: QD or every other day to maintain FVIII:C >30 IU/dL until healing complete *Major surgeries:* QD or every other day to maintain FVIII:C >50 IU/dL until healing complete *Dental surgery:* single dose to maintain FVIII:C >30 IU/dL for ≤6 h *Spontaneous bleeding episodes:* ~20−50 IU/kg, QD or every other day *Duration*: Single administrations or multiple doses according to the clinical status of the patients	Efficacy Safety	*Primary* Efficacy using plasma levels of FVIII:C, VWF:Ag, VWF:RCo as surrogate markers *Secondary* • Bleeding time • VWF multimeric patterns • Overall assessment of efficacy (investigator) • Safety and tolerability (AEs, vital signs, laboratory safety, viral safety)

AE = adverse event; F = female; FVIII = factor VIII; FVIII:C = factor VIII coagulant activity; IU = international unit; IVR = in vivo recovery; M = male; N = number of subjects; VWD = von Willebrand disease; VWF = von Willebrand factor; VWF:Ag = von Willebrand factor antigen; VWF:RCo = von Willebrand factor ristocetin cofactor.
Source: "BLA 1252251/139.0, Module 5.2: TABULAR LISTING OF ALL CLINICAL STUDIES, pages 2 – 7"

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 WIL-24

Study WIL-24 is entitled "Prospective, Open-Label, Multi-Center, Phase III Clinical Study to Investigate the Efficacy and Safety of Human Factor VWF/VIII Concentrate (Wilate) in Subjects with Inherited von Willebrand Disease (VWD) Who Undergo Surgical Procedures."

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of the study is to evaluate the overall hemostatic efficacy of Wilate in preventing excessive intra and post-operative bleeding in pediatric and adult subjects with VWD who require a von Willebrand factor (VWF) product and undergo a surgical procedure.

The secondary objectives of this study are:

• To evaluate the intra- and post-operative surgical hemostatic efficacy of Wilate in preventing excessive bleeding in pediatric and adult subjects with VWD who require a VWF product and undergo a surgical procedure.
• To assess the safety of Wilate used in VWD subjects who undergo surgical procedures.
• To document the 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 factor VIII coagulant activity (FVIII:C).
• To analyze the actual dosage and duration of treatment in surgical procedures.

6.1.2 Design Overview

This was a prospective, uncontrolled, multi-center, interventional, open-label, phase III study in subjects with inherited VWD who underwent surgical procedures. Each subject could have had multiple independent surgeries that were counted as separate surgical events. All subjects used Wilate for surgical prophylaxis; dosing depended on whether it was a minor or major surgery. The subject should not have taken any VWF containing product for at least 3 days prior to the screening/baseline visit. After obtaining informed consent, inclusion and exclusion criteria were checked, and data on baseline characteristics were collected. A VWF and FVIII in vivo recovery (IVR) study (screening/baseline) was performed at least 2-4 weeks prior (3 day washout of any previous VWF containing product) to the surgical procedure using a single dose of 60 IU VWF:RCo/kg. At 30 days following the first day of the surgical procedure or at discharge, whichever came last, a final physical examination was performed, vital signs were taken, and blood was drawn for safety laboratory investigations (hematology, clinical chemistry), VWF inhibitor testing, and for HCV testing.

6.1.3 Population

Subjects older than 6 years with inherited VWD undergoing surgical procedures were eligible. They were to be negative for anti-human immunodeficiency virus (HIV); if positive, viral load <200 particles/μL or <400,000 copies/mL and CD4+ count >200/μL.

6.1.4 Study Treatments or Agents Mandated by the Protocol

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

In minor surgeries the loading dose was 30–60 VWF:RCo IU/kg to achieve peak plasma VWF:RCo level of 50%. The maintenance dose was 20–40 VWF:RCo IU/kg every 12–24 hours or half of the loading dose. The objective was to maintain VWF:RCo plasma level >30% for ≥2 days.

In major surgeries the loading dose was 40–60 IU VWF:RCo/kg within 3 hours prior to surgery to target the peak level of 100%, maintenance doses of 20−40 IU VWF:RCo/kg every 12–24 hours or half of the loading dose. The objective was to maintain VWF:RCo plasma level >50% for ≥6 days. In gastrointestinal surgery increased dosing and shorter intervals were allowed as necessary. Treatment was individualized according to the severity of the bleeding and history of the subject.

6.1.6 Sites and Centers

Twenty five centers in the USA, India, Turkey, Poland, Italy, South Africa, Bulgaria, Romania and Oman participated.

6.1.7 Surveillance/Monitoring

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint (overall success or failure of hemostatic efficacy) was derived from the adjudicated intra- and post-operative assessments according to the following algorithm shown in Table 2:

Table 2. Overall Assessment (Success or Failure) Derived From Intra-operative and Post-operative Assessments

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: "BLA 1252251/139.0, 2.7.3 WIL-24 Clinical Study Protocol, page 37."

Efficacy of Wilate in surgical procedures was assessed intra-operatively by the surgeon and post-operatively by the investigator by an objective hemostatic efficacy scale.

The intra-operative efficacy of Wilate® during the surgical procedures was assessed using a 4-point ordinal efficacy scale at the end of the surgical procedure (last suture). This scale involved assessment of the efficacy of treatment as excellent, good, moderate, or none. For all ratings, unexpected blood loss due to surgical complications was not taken into consideration when assessing intra-operative efficacy. The four definitions are as follows:

• 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 ones 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 ones 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.

The investigator conducted the post-surgery efficacy assessment from the end of the procedure to 24 hours following the last infusion of study medication using the following definition:
• Excellent: No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with Wilate® as anticipated for the type of procedure.
• Good: No post-operative bleeding or oozing that was not due to complications of surgery. Control of bleeding due to complications of surgery 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 not due to complications of surgery; 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. Control of postoperative bleeding required use of an alternate VWF:RCo/FVIII concentrate.

The IDMC conducted an independent assessment of all hemostatic efficacy results. In the event that the investigators' and surgeons' assessments fell into one of the categories marked 'primary adjudication' in Table 2 the classification of success or failure from the IDMC's assessment would take priority. Therefore, the primary endpoint of overall efficacy was based on the IDMC's adjudicated assessments.
The secondary endpoints were as follows:
• Surgeon's evaluation according to 4-point ordinal efficacy scales of the intra-operative surgical hemostatic efficacy. This scale involves assessment of the efficacy of treatment as excellent, good, moderate, or none, as described above.
• Hematologist's evaluation according to 4-point ordinal efficacy scales of the post-operative surgical hemostatic efficacy. This scale involves assessment of the efficacy of treatment as excellent, good, moderate, or none, as described above.
• Clinical safety as assessed by monitoring adverse events (AEs), vital signs, laboratory parameters and immunogenicity.
• VWF:RCo and FVIII:C plasma activity during treatment.
• Assessment of the actual dosage and duration of treatment in surgical procedures.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size
The study planned to examine up to 41 surgical procedures, with an interim analysis planned after 30 procedures were performed.

Primary endpoint
The proportion of surgeries with successful treatment was calculated and the following null and alternative primary hypotheses tested:

H_0: $p_0 < 0.6$ versus H_a: $p_0 \geq 0.6$,

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

Reviewer Comment: Protocol Amendment 5 (dated December 10, 2012) amended the null and alternative hypothesis from H_0: p_0 <0.7 versus H_a: p_0 ≥0.7 to H_0: p_0 <0.6 versus H_a: p_0 ≥0.6. According to the previous clinical reviewer for this supplement, the rationale for the change was in response to poor enrollment (email received March 2, 2015 from Stephanie Omokaro, MD, clinical reviewer, DHCR, OBRR). Assuming $p_{0=}$ 0.6, the true rate of excellent or good surgeries is 0.85 (Module 5.3.5.2 Statistical Analysis Plan, page 9) and a sample size of 41 surgeries, the power is 96%. However, assuming $p_{0=}$ 0.7, the power is 73%.

A two-sided 98.75% (Clopper-Pearson) confidence interval was constructed around the estimate of p_0 for the interim analysis. If early success was not demonstrated at the interim analysis, a two-sided 96.25% confidence interval was to be used at the end of the trial. The size of these confidence intervals kept the overall Type I error to 5%. The treatment with Wilate could be claimed as effective if the lower limit of the confidence interval was ≥0.6 at either analysis.

Secondary endpoints

For intra-operative and post-operative efficacy, a contingency table presented the number and cumulative proportions of surgeries where the efficacy is rated as excellent, good, moderate, or none. The proportion of surgeries where the classification is either excellent or good was shown, together with the two-sided 95% (Clopper-Pearson) confidence intervals.

Total dose per procedure and duration of treatment from the first to last dose was presented using summary statistics.

For each analyte (VWF:RCo and FVIII:C pre- and post-infusion), trough and peak plasma concentrations were shown graphically for each subject and summarized overall.

Analysis populations

- Safety analysis population: All subjects included in the study who received at least one dose of Wilate®. The screened subjects are included in this population because they received one dose for the IVR study. The operated subjects were counted multiple times if they underwent multiple surgeries.
- Intent to Treat (ITT) analysis population: All surgeries in the safety analysis population with the underlying disease (VWD), for whom any data were collected post treatment with Wilate®.
- Per Protocol (PP) analysis population: All surgeries in the ITT analysis population who completed the trial without major protocol violations.

The ITT analysis was considered to be the most relevant for efficacy analyses.

Missing data

If the primary endpoint remained missing after IDMC adjudication, the missing endpoint was to be imputed as a failure for the primary ITT analysis.

6.1.10 Study Population and Disposition

6.1.10.1

Populations Enrolled/Analyzed

6.1.10.1.1 Demographics
The study comprised a safety population of 41 surgeries (39 individuals).

Table 3. Demographic and Baseline Clinical Characteristics of Study Population (Safety Population, 41 surgeries (39 individuals))

Parameter	Mean	SD	Median	Range
Age at screening (years)	39.7	18.1	36.0	12–83
Height (cm)	163.5	11.4	162.0	141–187
Weight (kg)	71.1	22.6	68.0	39.0–126.0

Parameter		N*	%
Sex	Male	12	29.3
	Female	29	70.7
Race	White	24	58.5
	Asian	13	36.6
	Black or African-American	2	4.9
	Omani	2	4.9

N* -Two subjects were enrolled for 2 surgeries each; therefore, there were 39 individual subjects.
Source: "BLA 1252251/139.0, WIL-24 Clinical Study Report, page 54"

The ITT population comprised 28 individual subjects who underwent 30 surgeries (30 operated subjects). The PP population was the same as the ITT population. Among the operated subjects, 70.0% were female and age ranged from 12 to 74 years. Most operated subjects were of White (60.0%) and Asian (36.7%) race. The details are given in Table 4.

Table 4. Demographic and Baseline Clinical Characteristics of Study Population (ITT Population, 30 operated subjects (28 individuals))

Parameter	Mean	SD	Median	Range
Age at screening (years)	38.3	16.8	36.0	12–74
Height (cm)	161.9	11.2	162.0	141–187
Weight (kg)	69.4	23.6	63.7	39.0–126.0

Parameter		N*	Percentage
Sex	Male	9	30.0
	Female	21	70.0
Race	White	18	60.0
	Asian	11	36.7
	Omani	1	3.3

N* -Two subjects were enrolled for 2 surgeries each; therefore, there were 28 individual subjects.
Source: " BLA 1252251/139.0, WIL-24 Clinical Study Report, page 54"

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
None of the subjects had VWF inhibitor activity at baseline. Eleven subjects (36.7%) reported having a family history of VWD (the operated subjects were counted multiple times if they underwent multiple surgeries). Most ITT subjects (21 subjects) were Type 3 (severe disease resulting from complete absence of von Willebrand factor); the remainder were Type 1 (partial quantitative VWF deficiency, 7 subjects) or Type 2 (partial qualitative VWF deficiency, 2 subjects).

Subjects underwent the surgeries presented in Table 5.

Table 5. Summary of Surgical Procedures per Body System by Type of Surgery (ITT Population, 30 surgeries)

Body system of surgery	Minor surgery N (%)	Major surgery N (%)	All surgeries N (%)
Dental	5 (55.6)	2 (9.5)	7 (23.3)
Orthopedic	2 (22.2)	8 (38.1)	10 (33.3)
Gastrointestinal	0	4 (19.0)	4 (13.3)
Ophthalmologic	1 (11.1)	0	1 (3.3)
Obstetric/gynecological	0	5 (23.8)	5 (16.7)
Ear, nose, throat	1 (11.1)	2 (9.5)	3 (10.0)

N = number of surgeries.
Source: "BLA 1252251/139.0, 2.7.3 Summary of Clinical Efficacy, page 8."

6.1.10.1.3 Subject Disposition
A total of 39 subjects were screened for 41 surgeries, and 28 subjects (30 surgeries) completed the study according to the protocol. Two subjects had two surgeries each, thus

resulting in different numbers of surgeries and individual subjects. Thus, the safety set included 41 planned surgeries, and the ITT and PP set included 30 surgeries. Of the 11 subjects who were not included in ITT population, 9 subjects had a screening failure, 1 subject withdrew consent and 1 subject was terminated early by the sponsor due to study termination. No surgeries were excluded from the efficacy analysis. The details of disposition are given in Tables 6-8.

Table 6. Study Disposition - by Severity of Surgery (All Screened Subjects)

Number of Subjects	Minor Surgery (N = 9)	Major Surgery (N = 21)	Not Collected* (N = 11)	Total (N = 41)
Screened	9 (100.0%)	21 (100.0%)	11 (100.0%)	41 (100.0%)
Completed Study	9 (100.0%)	21 (100.0%)	0 (0.0%)	30 (73.2%)
Terminating study early	0 (0.0%)	0 (0.0%)	11 (100.0%)	11 (26.8%)
... Screening Failure	0 (0.0%)	0 (0.0%)	9 (81.8%)	9 (22.0%)
... Withdrawal by subject	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (2.4%)
... Study termination by sponsor	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (2.4%)
in Safety Set	9 (100.0%)	21 (100.0%)	11 (100.0%)	41 (100.0%)
in ITT Set	9 (100.0%)	21 (100.0%)	0 (0.0%)	30 (73.2%)
in Per Protocol Set	9 (100.0%)	21 (100.0%)	0 (0.0%)	30 (73.2%)

* Subjects did not have surgery
Source: "BLA 1252251/139.0, WIL-24 Clinical Study Report, Table 14.1.1.1."

Table 7. Study Disposition - by Age Group (All Screened Subjects)

Number of Subjects	ADOLESCENTS (N = 3)	ADULTS (N = 38)
Screened	3 (100.0%)	38 (100.0%)
Completed Study	3 (100.0%)	27 (71.1%)
Terminating study early	0 (0.0%)	11 (28.9%)
... Screening Failure	0 (0.0%)	9 (23.7%)
... Withdrawal by subject	0 (0.0%)	1 (2.6%)
... Study termination by sponsor	0 (0.0%)	1 (2.6%)
in Safety Set	3 (100.0%)	38 (100.0%)
in ITT Set	3 (100.0%)	27 (71.1%)
in Per Protocol Set	3 (100.0%)	27 (71.1%)

Adolescent (12 to 15 years). Adult (16 years or greater)
Source: "BLA 1252251/139.0, WIL-24 Clinical Study Report, Table 14.1.1.4."

Table 8. Study Disposition - by Gender (All Screened Subjects)

Number of Subjects	MALE (N = 12)	FEMALE (N = 29)
Screened	12 (100.0%)	29 (100.0%)
Completed Study	9 (75.0%)	21 (72.4%)
Terminating study early	3 (25.0%)	8 (27.6%)
... Screening Failure	2 (16.7%)	7 (24.1%)
... Withdrawal by subject	0 (0.0%)	1 (3.4%)
... Study termination by sponsor	1 (8.3%)	0 (0.0%)
in Safety Set	12 (100.0%)	29 (100.0%)
in ITT Set	9 (75.0%)	21 (72.4%)
in Per Protocol Set	9 (75.0%)	21 (72.4%)

Source: "BLA 1252251/139.0, WIL-24 Clinical Study Report, Table 14.1.1.5."

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

At the time of the interim analysis, only one procedure was adjudicated: 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 Therefore, the overall efficacy success rate was 29 out of 30 surgeries (0.967; 98.75% CI: 0.784, 1.000). Since the lower limit of the two-sided 98.75% CI was greater than 0.6 upon this analysis, the study was claimed to be successful and therefore terminated.

Reviewer Comment: The lower limit of the CI was also greater than 0.7, the original pre-specified acceptance criteria.

6.1.11.2 Analyses of Secondary Endpoints

Assessment of intra- and post-operative hemostatic efficacy by the IDMC and surgeon/investigator are presented in Table 9. Intra-operative Wilate efficacy was assessed as excellent or good in 29 procedures by the surgeon (rate of success 0.967; 95% CI 0.828, 0.999). Post-operative efficacy was assessed as excellent or good in all procedures by the investigators (rate of success 1.000; 95% CI: 0.884, 1.000). In no procedures were intra- or post-operative efficacy rated as none (Table 9).

Table 9. Intra- and Post-Operative Hemostatic Efficacy Assessment by Severity of Surgery (ITT Population; 30 surgeries)

	Major surgery			Minor surgery			All surgeries		
Efficacy grade	**N (%)**	**Rate**	**95% CI**	**N (%)**	**Rate**	**95% CI**	**N (%)**	**Rate**	**95% CI**
IDMC intra-operative assessment									
Excellent	8 (38.1)	0.857	0.637, 0.970	8 (88.9)	1.000	0.664, 1.000	16 (53.3)	0.900	0.735, 0.979
Good	10 (47.6)			1 (11.1)			11 (36.7)		
Moderate	3 (14.3)			0			3 (10.0)		
None	0			0			0		
Surgeon's intra-operative assessment									
Excellent	14 (66.7)	0.952	0.762, 0.999	8 (88.9)	1.000	0.664, 1.000	22 (73.3)	0.967	0.828, 0.999
Good	6 (28.6)			1 (11.1)			7 (23.3)		
Moderate	1 (4.8)			0			1 (3.3)		
None	0			0			0		
IDMC post-operative assessment									
Excellent	15 (71.4)	0.857	0.637, 0.970	9 (100)	1.000	0.664, 1.000	24 (80.0)	0.900	0.735, 0.979
Good	3 (14.3)			0			3 (10.0)		
Moderate	3 (14.3)			0			3 (10.0)		
None	0			0			0		
Investigator's post-operative assessment									
Excellent	15 (71.4)	1.000	0.839, 1.000	9 (100)	1.000	0.664, 1.000	24 (80.0)	1.000	0.884, 1.000
Good	6 (28.6)			0			6 (20.0)		
Moderate	0			0			0		
None	0			0			0		

CI = two-sided confidence interval; IDMC = Independent Data Monitoring Committee; N = number of surgeries; rate = overall success rate.
Source: "BLA 1252251/139.0, WIL-24 Clinical Study Report, Table 18"

The number of exposure days (EDs) for surgeries and the loading / maintenance doses were higher for major surgeries compared with minor surgeries. One loading dose of Wilate per procedure was administered for the majority of procedures (26/30, 86.7%). Two loading doses were administered for three procedures (10.0%) and three loading doses were administered for one procedure (3.3%). These additional loading doses were not administered due to any insufficiency in the efficacy of the initial dose, but rather due to delays in the start of procedures.

Average VWF and FVIII:C plasma concentrations in the ITT population as measured by the central lab remained stable during maintenance dose administrations. No accumulation of FVIII:C was observed over time.

6.1.11.3 Subpopulation Analyses

Surgery severity

Treatment with Wilate was successful in all minor surgeries (rate of success 1.000; 98.75% CI: 0.569, 1.000) and in 95.2% of major surgeries (rate of success 0.952; 98.75% CI: 0.704, 1.000) (Table 10).

Table 10. Hemostatic Efficacy Assessment by Severity of Surgery (ITT Population; 30 surgeries)

	Minor (n=9)			Major (n=21)			All surgeries (n=30)		
Efficacy grade	**N (%)**	**Rate**	**98.75% CI**	**N (%)**	**Rate**	**98.75% CI**	**N (%)**	**Rate**	**98.75% CI**
Success	9 (100)	1.000	0.569, 1.000	20 (95.2)	0.952	0.704, 1.000	29 (96.7)	0.967	0.784, 1.000
Failure	0			1 (4.8)			1 (3.3)		

CI = two-sided confidence interval; N = number of surgeries; rate = overall success rate.
Source: "BLA 1252251/139.0, WIL-24 Clinical Study Report, Table 16."

Type of VWD

Wilate treatment was also successful in all surgical procedures in subjects with VWD Type 3 and two surgeries in subjects with VWD Type 2 (rate of success 1.000; 98.75% CI: 0.785, 1.000; and rate of success 1.000; 98.75% CI: 0.079, 1.000, respectively) and in 85.7% of procedures in VWD Type 1 subjects (rate of success 0.857; 98.75% CI: 0.328, 0.999). Only one procedure was judged as a failure.

Table 11. Hemostatic Efficacy Assessment by Type of VWD (ITT Population; 30 surgeries)

	VWD Type 1			VWD Type 2			VWD Type 3		
Efficacy grade	**N (%)**	**Rate**	**98.75% CI**	**N (%)**	**Rate**	**98.75% CI**	**N (%)**	**Rate**	**98.75% CI**
Success	6 (85.7)	0.857	0.328, 0.999	2 (100)	1.000	0.079, 1.000	21 (100)	1.000	0.785, 1.000
Failure	1 (14.3)			0			0		

CI = confidence interval; N = number of surgeries; rate = overall success rate.
Source: "BLA 1252251/139.0, WIL-24 Clinical Study Report, Table 17"

Demographics

Tables 12-14 below provide hemostatic efficacy by sex, race and age in the ITT population. The difference in efficacy by sex was minor, and less so by race and age.

Table 12. Hemostatic Efficacy Rate - by Sex (ITT Population, 30 surgeries)

Gender	Rate	Lower Limit*	Upper Limit
MALE	0.89	0.43	1.00
FEMALE	1.00	0.79	1.00

*Binomial 98.75% CI

Table 13. Hemostatic Efficacy Rate - by Race (ITT Population, 30 surgeries)

Race	Rate	Lower Limit*	Upper Limit
WHITE	0.944	0.663	1.000
ASIAN	1.000	0.630	1.000
OTHER	1.000	0.006	1.000

*Binomial 98.75% CI

Table 14. Hemostatic Efficacy Rate - by Age Group (ITT Population, 30 surgeries)

Age Group	Rate	Lower Limit*	Upper Limit
12 - 17 years	1.000	0.184	1.000
18 - 65 years	0.960	0.746	1.000
> 65 years	1.000	0.079	1.000
12 - 17 years	1.000	0.184	1.000
18 - 65 years	0.960	0.746	1.000
> 65 years	1.000	0.079	1.000

*Binomial 98.75% CI

6.1.11.4 Dropouts and/or Discontinuations

All subjects had a VWF and FVIII recovery study during the screening phase of the study and 11 subjects were withdrawn from the study prior to surgery (Table 16). There was no missing data from the subjects who had surgery.

Table 16. Subject Withdrawals

Study	Center	Patient No. (sex, age at entry)	Date of withdrawal	Reason(s) for withdrawal
WIL-24	3	0301 (F, 57)	18-Nov-2013	Patient withdrew consent
	9	0901* (F, 60)	22-Apr-2013	Patient did not meet inclusion criteria
	11	1103* (F, 22)	8-Mar-2012	Patient did not undergo planned surgical procedure as per sponsor decision
	11	1105* (F, 26)	12-Aug-2013	High FVIII and VWF:RCo levels
	50	5001* (F, 83)	19-Mar-2014	Protocol violation
	50	5002 (M, 76)	8-Apr-2014	Study terminated by sponsor
	60	6001* (F, 29)	6-Jun-2012	Screening failure
	60	6004* (M, 37)	26-Apr-2013	Sponsor discontinuation
	80	8002* (M, 27)	7-Apr-2014	Surgery postponed indefinitely
	80	8003* (F, 23)	4-Feb-2014	Met exclusion criteria; surgery no longer needed
	90	9002* (F, 38)	23-Apr-2013	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 an infusion of Wilate during screening.
F = female; M = male; FVIII = coagulation factor VIII; VWF:RCo = von Willebrand factor ristocetin cofactor.
Source "BLA 1252251/139.0, WIL-24 2.7.4. Summary of Clinical Safety, Appendix Table 2.7.4.3."

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Two serious treatment emergent adverse events (TEAEs) occurred post-operatively in two subjects (vaginal hemorrhage, female, 30 years old, Asian and gastritis erosive, female, 15 years old, Asian) both of which were considered unrelated to the study drug.

6.1.12.5 Adverse Events of Special Interest (AESI)

No inhibitory anti-VWF antibodies occurred.

6.2 WIL-14

6.2.1 Objectives (Primary, Secondary, etc)

The primary objective of the study was to assess the efficacy of Wilate for the prevention and/or treatment of bleeding episodes and in surgical procedures in children <6 years of age.
Secondary objectives were:
• To determine if inhibitors occur during treatment with Wilate (VWF and FVIII inhibitors).
• To assess the clinical safety and tolerability of Wilate.
• For subjects undergoing major surgery: to assess the incremental and classical recovery prior to surgery. For subjects undergoing a minor surgery, the recovery assessment was optional and no informed consent was obtained for this assessment.
• To perform an optional PK assessment in subjects with severe VWD.

6.2.2 Design Overview
This is a prospective, open-label, non-controlled, multicenter phase II study. All subjects used Wilate for treatment or prevention of spontaneous bleeding episodes or for treatment before, during and after surgical procedures. Treatment is in accordance with the clinical needs of each subject over an observation period of one year.

For spontaneous or post-traumatic bleeding, treatment was given once daily or every other day. For major surgery, treatment began12-24 hours prior to surgery, was repeated at the start of the operation and repeated every 12-24 hours until healing was complete. For minor surgery, treatment began at least 30 minutes prior to surgery and was repeated every 12-24 hours until healing was complete.

6.2.3 Population

Subjects with inherited VWD <6 years of age, DDAVP treatment known or suspected to be inadequate, insufficient or contraindicated, and HIV-1/2 negative.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Major surgery: objective is to maintain VWF:RCo plasma levels >60 IU/dL and FVIII:C plasma levels >50 IU/dL.

Minor surgery: objective is to maintain VWF:RCo plasma levels >30 IU/dL and FVIII:C plasma levels >30 IU/dL.

6.2.6 Sites and Centers

Nine centers in Germany, Poland, France, and Czech Republic participated.

6.2.8 Endpoints and Criteria for Study Success

Primary Surgery Endpoints:
There was no single primary endpoint for the surgery procedures. Efficacy of WILATE in surgical procedures was measured by:

- amount of Wilate used
- achievement of hemostasis
- loss of blood (intra- and postoperatively)
- the requirements of additional blood or plasma transfusions.

For each surgical procedure, an efficacy assessment of the clinical response was done by the investigator using a 4-point verbal rating scale (VRS):

- none: severe uncontrolled surgical bleeding; additional injections of IMP or other styptic treatment was necessary;
- moderate: moderate control of surgical bleeding; additional injections of IMP or other styptic treatment was necessary;
- good: adequate control of surgical bleeding; did not require additional injections of IMP or other styptic treatment,
- excellent: very good control of surgical bleeding.

Furthermore, at the end of the study period, an overall efficacy assessment, to include surgeries, was performed by both the investigator and the subject's parents using a 4-point scale.

Secondary Endpoints:

- Efficacy in subjects undergoing a major surgery (optional in subjects undergoing a minor surgery), measured by: recovery (incremental and absolute) of FVIII:C, VWF:RCo, VWF:CB and VWF:Ag, the multimeric pattern and the closure time (optionally the bleeding time) prior to the surgical procedure.
- Immunogenicity measured by: the development of inhibitors against VWF and FVIII determined at baseline and every 3 months until the end of the study, as well in suspicion of inhibitor development.
- Clinical safety measured by: AEs, vital signs, laboratory parameters, and viral status.

6.2.9 Statistical Considerations & Statistical Analysis Plan

It was planned to include 12 to 20 children into the study. The CPMP guideline on the investigation of human plasma derived von Willebrand factor products (CPMP/BPWG/220/02) requires treatment of eight children below 6 years of age for an

observation period of one year. Therefore, no formal sample size calculation was performed. No a priori number of surgery subjects was specified.

For the analysis of this study, three populations are considered:
ITT Population: All subjects included in the study who received at least one dose of Wilate.
Per Protocol (PP) Population: All subjects of the ITT population who completed the study without major protocol violations. Major protocol violators were defined as subjects not having defined inherited VWD of any type, not aged <6 years at study admission, any hematological disorder other than VWD, acquired VWD, any known present or past inhibitor activity against VWF or FVIII and/or a known history of intolerance towards plasma derived or blood products.
Safety Population: All subjects who received at least one dose of Wilate.
Surgery Population: All subjects who underwent one or more surgeries and completed the surgery without major protocol violations. The analysis was based on all subjects in the PP population with a surgery.
All details of the Wilate treatment in surgeries were presented descriptively in summary tables and individual subject listings. VRS was tabulated. All analyses were performed stratified by type of surgery (major/minor) and in total.

6.2.10 Study Population and Disposition

6.2.10.1

Populations Enrolled/Analyzed

6.2.10.1.1 Demographics
The surgery subjects (four male and three female) were Caucasian except for one of Maghrebi origin. Mean age was 3.3 years (range 1.8 to 5.2 years). The details are given in Table 17.

Table 17. Demographic characteristics of the surgery subjects

Gender	Age (years)	Ethnicity
M	1.8	Caucasian
F	4.8	Caucasian
M	4.4	Caucasian
F	1.8	Caucasian
M	1.8	Caucasian
M	3.3	Maghrebi
F	5.2	Caucasian

Source: "BLA 1252251/139.0, 5.3.5.2 WIL 14 Clinical Study Report, Individual Efficacy Response Data Listing16.2.4, Demographic Data, List 16.2.4/2."

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The seven subjects in the surgery/PP population underwent a total of nine surgical procedures, six of which were categorized as minor and three as major.

6.2.10.1.3 Subject Disposition

Seventeen subjects were enrolled; 15 were included in the safety population. Surgical procedures were conducted in eight subjects; however, one subject had a protocol violation and is excluded from the surgery and PP analyses.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Analysis of the overall efficacy in surgeries was not performed due to non-availability of documentation in the CRF. However, efficacy for each infusion during surgery was assessed.

Of 49 Wilate infusions by reason of surgery 32 (65.3%) were rated as excellent and 17 (34.7) as good. Between 2 and 12 infusions were administered per subject to cover the surgical procedures and total Wilate doses ranged from 29.6 to 207.7 IU/kg per ED during surgery. Blood transfusion was needed for two (22.2%) surgeries and platelets were required in one and red blood cells in two surgeries.

In addition, all of the available efficacy ratings by the investigator and subject's parents for the overall efficacy assessment at the end of the study were either excellent or good.

6.2.11.2 Analyses of Secondary Endpoints

Recovery assessments were performed in seven subjects (those with a major surgery and those with low VWF:RCo). VWF:RCo levels were available in the blood at 30 minutes post-administration of Wilate, and these remained high for up to 6 hours. The mean incremental IVR for VWF:RCo was 1.2 ± 1.4%/IU/kg and for FVIII:C it was 1.6 ± 0.8%/IU/kg.

6.2.11.3 Subpopulation Analyses

The subpopulation analysis was not implemented because of a very small sample size and mainly ethnically homogenous population of children under six years old.

6.2.11.4 Dropouts and/or Discontinuations

One subject had a protocol violation and was excluded from the surgery analysis.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No deaths occurred during the study.

6.2.12.4 Nonfatal Serious Adverse Events

Of seven subjects included in the surgery population, four subjects experienced five SAEs: catheter sepsis, head trauma, Griselle syndrome, blood vomiting, hematemesis. All of them were classified as treatment not related or unlikely treatment related.

6.2.12.5 Adverse Events of Special Interest (AESI)

No subject developed VWF or FVIII inhibitors. No clinically significant change in thrombogenicity markers (i.e. F1+2 or D-dimer) compared with baseline were noted, and no thromboembolic events occurred.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Control of bleeding episodes by Wilate in subjects with inherited VWD, who underwent surgical procedures.

7.1.1 Methods of Integration

7.1.2 Demographics and Baseline Characteristics

Study WIL-24 included 28 subjects ≥6 years of age with inherited VWD who underwent 30 surgical procedures. Study WIL-14 included a subpopulation of seven subjects <6 years of age with inherited VWD who underwent nine surgical procedures.

Overall, a total of 35 individual subjects with VWD were treated with Wilate in a surgical setting. The subject characteristics in these studies are representative of the populations to whom Wilate would be administered in the surgical setting. In total, 39 procedures were performed.

7.1.4 Analysis of Primary Endpoint(s)

All (100%) of the Wilate infusions for surgery in children <6 years of age were rated as having excellent or good hemostatic results. More than 96% of the surgeries in subjects ≥6 years of age were rated as having excellent or good hemostatic efficacy as adjudicated by the IDMC. Results of these studies support the conclusion that Wilate has an excellent efficacy profile in children less than 6 years old, adolescents and adults, undergoing surgery.

7.1.11 Efficacy Conclusions

In the pivotal Study WIL-24 the primary endpoint of the study, hemostatic efficacy of Wilate as surgical prophylaxis, was assessed in 30 procedures in 28 individual subjects. The overall efficacy of Wilate in surgical prophylaxis (success or failure) was determined

by an IDMC-adjudicated algorithm, based on prospectively designed, objective criteria of blood loss, transfusion requirements and post-operative bleeding and oozing.

Hemostatic efficacy of each procedure was not assessed for Study WIL-14; instead, for each infusion during surgical prophylaxis, an efficacy assessment of the clinical response (excellent, good, moderate or none) was made by the investigator using a VRS. All individual infusions in all surgery subjects were rated as excellent or good. Therefore, it would be reasonably assumed that overall efficacy per procedure was successful.

A summary of efficacy evaluations of Wilate in surgical procedures for studies WIL-24 and WIL-14, according to surgery type, is shown in Table 18.

Table 18. Efficacy Assessment of Wilate in Surgical Settings across Both Studies

	Minor surgery		**Major surgery**		**All surgeries**	
Study	**Success**	**Failure**	**Success**	**Failure**	**Success**	**Failure**
WIL-24, N (%)	9 (100)	0 (0)	20 (95.2)	1 (4.8)	29 (96.7)	1 (3.3)
WIL-14*, N (%)	6 (100)	0 (0)	3 (100)	0 (0)	9 (100)	0 (0)
Total, N (%)	15 (100)	0	23 (95.8)	1 (4.2)	38 (97.4)	1 (2.6)

* Efficacy of each procedure was not assessed for Study WIL-14; instead, efficacy of each infusion administered for surgical procedures was rated and all infusions during all procedures were rated as excellent or good.
N = number of procedures.
Source: "BLA 1252251/139.0, 2.7.3 Summary of Clinical Efficacy, page 24."

Treatment with Wilate was successful in 100% of minor surgeries (15/15; 98.75% CI: 0.713, 1.000) and the rate of success in major surgeries was 95.8% (23/24; 98.75% CI: 0.73.7, 1.000).

8. INTEGRATED OVERVIEW OF SAFETY

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

WIL-24 and WIL-14

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In total, the safety population of WIL-24 comprised 41 enrolled subjects (39 individual subjects, as 2 subjects enrolled twice), of which 28 subjects underwent 30 surgical procedures. The subjects were older than 6 years. Additionally, safety data are included from the supportive study of subjects under six years (Study WIL-14). Its safety population included 15 subjects, of which seven underwent surgeries. These studies cover the range from 1 to 74 years old.

8.4 Safety Results

8.4.1 Deaths

There were no deaths.

8.4.2 Nonfatal Serious Adverse Events

Seven SAEs in six subjects were observed in the surgery population. All of them were classified as treatment not related or unlikely treatment related.

8.4.3 Study Dropouts/Discontinuations

8.4.8 Adverse Events of Special Interest

VWF inhibitors were not observed in any subject. No clinically important safety concerns, e.g., accumulation of coagulation factors over time, thromboembolic events or iatrogenic viral infection, were reported.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

According to the original statistical plan, the planned enrollment was 41 major surgeries in subjects >6 years of age at approximately 20-30 centers worldwide for study WIL-24 and 12 to 20 children <6 years of age in study WIL-14. The sample size was not justified by any statistical considerations.

The studied population included 39 individuals (41 surgeries) in Study WIL-24 and 15 individuals in Study WIL-14 for a total of 54 individuals in the safety population. In these 54 subjects, 30 surgeries (28 individuals) in Study WIL-24 and 9 surgeries (7 individuals) in Study WIL-14, for a total of 39 surgeries, were assessed.

In Study WIL-24 the Wilate treatment was overall effective in 29 of 30 surgeries, 9 of 9 minor surgeries and 20 of 21 major surgeries. Therefore, it met the pre-specified acceptance criterion. In Study WIL-14 Wilate was effective in 9 of 9 surgeries, 6 of them minor and 3 major.

Seven SAEs (no deaths) in six surgery subjects were observed in the two studies. VWF inhibitors were not observed in any subject.

10.2 Conclusions and Recommendations

There were no statistical issues in this submission. The confidence intervals were calculated correctly. Results of Studies WIL-24 and WIL-14 appear to support the use of Wilate for the treatment of surgical bleeding in pediatric and adult subjects with VWD.