Application Type	Efficacy Supplement BLA
STN	125251/454
CBER Received Date	September 2, 2025
PDUFA Goal Date	July 3, 2026
Division / Office	DCEH/OCE/OTP
Committee Chair	Christine Knoll, MD
Clinical Reviewer(s)	Christine Knoll, MD
Project Manager	Catherine Tran
Priority Review	Standard
Reviewer Name(s)	Hairong Shi, Ph.D. Mathematical Statistician, TEB2/DB/OBPV
Supervisory Concurrence	Lin Huo, Ph.D. Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D. Branch Chief, TEB2/DB/OBPV
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	VWF:RCo, FVIII, Total protein, Glycine, Sucrose, Sodium chloride, Sodium citrate, Calcium chloride, Water for injection, Polysorbate 80
Dosage Form(s) and Route(s) of Administration	Powder for solution, Intravenous injection
Dosing Regimen (VWD)	For patients <6 years of age On-demand treatment Loading Dose: Minor 30-50 IU/kg; Major 50-80 IU/kg Maintenance Dose: Minor 30-40 IU/kg; Major 30-50 IU/kg Perioperative management Loading Dose: Minor 30-60 IU/kg; Major 40-60 IU/kg

	Maintenance Dose: Minor 15-30 IU/kg; Major 20-40 IU/kg Routine prophylaxis 30-50 IU/kg; two or three times per week (not including Dosing Regimen for Hemophilia A or patients 6 years of age and older)
Indication(s) and Intended Population(s)	indicated in pediatric and adult patients with von Willebrand disease for: • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes indicated in adolescent and adult patients with hemophilia A for: • Routine prophylaxis to reduce the frequency of bleeding episodes • On-demand treatment and control of bleeding episodes Note: The proposed PI removes "WILATE is indicated for routine prophylaxis in children 6 years of age and older and adults with von Willebrand disease" from current PI since they are seeking to extend the indication to patients under 6 years of age with von Willebrand disease.

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GLOSSARY

ABR	Annualized Bleeding Rate
AE	Adverse Event
BE	Bleeding Episode
CI	Confidence Interval
ED	Exposure Day
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVIII	Factor VIII
HJHS	Hemophilia Joint Health Score
ICH	International Council for Harmonization
ITT	Intention To Treat
IVR	In vivo recovery
IMP	Investigational Medicinal Product
OD	On-Demand
PK	Pharmacokinetics
PP	Per-Protocol
SABR	Spontaneous Annualized Bleeding Rate
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
sBLA	supplemental Biologics License Application
SD	Standard Deviation
SOC	System Organ Class
SURG	Surgery Analysis Set
TABR	Total Annualized Bleeding Rate
TEAE	Treatment Emergent Adverse Event
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor

1. Executive Summary

WILATE was initially approved in 2009 for on-demand (OD) treatment and control of bleeding episodes (BEs) in patients with von Willebrand disease (VWD). Its indications were subsequently expanded to include perioperative management in VWD (August 2015), followed by routine prophylaxis and on-demand treatment of BEs in adolescents and adults with hemophilia A (September 2019). Most recently, in December 2023, WILATE received approval for routine prophylaxis in adults and children older than 6 years with VWD.

In this BLA efficacy supplement (sBLA), the applicant sought to extend the approved the indication of WILATE to include routine prophylaxis in children under 6 years of age with severe VWD.

To support the proposed indication extension, the applicant submitted the safety and efficacy data from pivotal Study WIL-33, an open-label, prospective, non-controlled, multicenter Phase 3 study evaluating the efficacy, pharmacokinetics, immunogenicity, and safety of WILATE in patients under 6 years of age with severe VWD (defined as VWF: RCo < 20%, regardless of prior treatment history) receiving regular prophylaxis. The primary efficacy endpoint was the total annualized bleeding rate (TABR) under prophylactic treatment with WILATE.

Study WIL-33 enrolled and treated 12 patients aged 1 to 5 years. In the full analysis set (FAS), 10 of 12 patients experienced 56 bleeding episodes (BEs) during prophylaxis, resulting in a mean TABR of 4.6 and a median TABR of 3.0. Based on a negative binomial model, the estimated mean TABR was 4.9 (95% CI: 2.8–8.8). Of the 56 BEs, 45 were treated with WILATE, yielding a mean TABR for treated BEs of 3.7 and a median of 2.4.

In total, 59 BEs were recorded, including 56 during prophylaxis and 3 prior to prophylaxis initiation (all nosebleeds). Of these, 47 were treated with WILATE, all with successful hemostatic efficacy ratings: 46 (97.9%) rated "excellent" and 1 (2.1%) rated "good." One patient underwent a major surgery (removal of central venous port system) and received perioperative and post-surgical prophylactic injections; hemostatic efficacy was rated excellent by both the hematologist and the surgeon.

No deaths were reported during the study. One patient tested positive for FVIII and VWF inhibitors during the pharmacokinetic (PK) visit. No Thromboembolic events were observed.

Conclusion
There were no statistical concerns identified in this submission. The efficacy results were confirmed through the reviewer’s independent analyses. Although no pre-specified success criteria were specified for efficacy endpoints, the findings were consistent with those observed in the previously approved age groups for the VWD indication. No safety signals of concern were identified. Based on these findings, I recommend approval of the

proposed extension of the WILATE indication to include patients under 6 years of age with severe VWD.

2. Clinical and Regulatory Background

WILATE is a plasma-derived, stable, double virus inactivated, highly purified concentrate of freeze-dried active human blood coagulation factor VIII (FVIII) and VWF.

2.1 Disease or Health-Related Condition(s) Studied

VWD is a clinically heterogeneous group of disease variants, each characterized by distinct quantitative and qualitative abnormalities in VWF caused by widely heterogeneous mutations in the various domains of the VWF gene. The symptoms of VWD are typically those of platelet dysfunction and include nosebleeds, skin bruises and hematomas, prolonged bleeding from trivial wounds, oral cavity bleeding, and excessive menstrual bleeding. There are three types of known inherited VWD. Type 1 is the most common form of VWD, accounting for 70–80% of cases, followed by Type 2, which affects approximately 20% of patients. Type 3 is the most severe form of VWD.

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

Please refer to the clinical review memo.

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

WILATE was first approved in the US in 2009 for the treatment of BEs in patients with VWD. Subsequent US approvals expanded the indication to perioperative management in VWD (2015), routine prophylaxis and OD treatment in adolescents and adults with hemophilia A (2019), and routine prophylaxis and OD treatment of BEs in patients aged 6 years and older with VWD (2023). WILATE has been extensively studied and used in the US and Europe since its EMA approval in 2009, and is additionally approved in Australia, Latin America, the Middle East, and Asia.

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

- WILATE first received FDA approval in 2009 for treatment of spontaneous and trauma-induced bleeding episodes (BEs) in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated (STN #125251/0).

- In August 2015, WILATE was approved to include an additional indication for the prevention of excessive bleeding during and after minor and major surgery in VWD patients in the US (STN #125251/139).

- In September 2019, WILATE was approved for the indications of hemophilia A in adults and adolescents for routine prophylaxis to reduce the frequency of

bleeding episodes and on-demand treatment and control of bleeding episodes in the US (STN #125251/244).

- In December 2023, WILATE was approved to expand the indication in children 6 years of age and older and adult patients with von Willebrand disease (VWD) to include routine prophylaxis to reduce the frequency of bleeding episodes in the US (STN #125251/382).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

The statistical review focuses on the pivotal Phase 3 Study WIL-33.

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

The following documents in BLA 125251/454 were reviewed and served as the basis for this statistical memo:

- Module 1.14: Labeling
- Module 2.2: Introduction
- Module 2.5: Clinical overview
- Module 2.7: Clinical summary
- Module 5.3.5.2: Clinical study reports, protocols, and SAPs for WIL-33
- Module 5.3.5.2: Datasets of WIL-33 study
- Amendment under BLA 125251/454.11, response to FDA information request, received on April 27, 2026

5.3 Table of Studies/Clinical Trials

WIL-33 was the pivotal Phase 3 study evaluating the efficacy of WILATE prophylaxis in reducing the bleeding rate in pediatric patients <6 years with severe VWD. Supportive data regarding the efficacy of WILATE in prophylaxis in patients in various age groups were provided by Studies WIL-31, TMAE-104, TMAE-105, TMAE-106, TMAE-109 and WIL-14. Table 1 provides an overview of these studies.

Table 1. Overview of Relevant Clinical Studies

Study	Total population and main inclusion criteria Patients evaluable for efficacy of prophylaxis	Objectives
WIL-33	12 patients aged <6 years with severe VWD (defined as VWF:RCo <20%) regardless of prior treatment	Primary: determine the efficacy of WILATE in the prophylactic treatment of patients <6 years old Secondary: breakthrough bleeding treatment, incremental IVR, PK, safety and tolerability, immunogenicity, thrombogenic potential, WILATE consumption
WIL-31	43 patients aged ≥6 years with inherited VWD 33* patients analyzed for efficacy of prophylaxis	Primary: determine the efficacy of WILATE in the prophylactic treatment of previously treated patients Secondary: incremental IVR, PK (patients aged 6 to <17 years), safety and tolerability, WILATE consumption
WIL-14	15 patients aged <6 years with inherited VWD, any type, DDAVP treatment known or suspected to be inadequate 10 patients analyzed for efficacy of prophylaxis	Primary: efficacy in prevention and/or treatment of BEs and during surgery Secondary: IVR prior to major surgery (optional for minor surgery), immunogenicity, safety and tolerability, PK and IVR in patients with VWD Type 3 or severe VWD (optional)
TMAE-104	41 patients aged ≥6 and ≤85 years with inherited VWD, any type, not responding to DDAVP. 27 patients analyzed for efficacy of prophylaxis	Primary: plasma levels of FVIII:C, VWF:Ag, VWF:CB and VWF:RCo as surrogate markers for efficacy Secondary: PK, bleeding time, overall efficacy (including surgeries), safety and tolerability
TMAE-105	14 patients aged ≥12 and ≤65 years with inherited VWD, any type, not responding to DDAVP 5 patients analyzed for efficacy of prophylaxis	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 surrogate markers for efficacy Secondary: IVR, bleeding time, plasma levels of VWF:Ag, VWF:CB and VWF:RCo, VWF multimers, overall efficacy, safety and tolerability
TMAE-106	14 patients aged ≥12 and ≤65 years with inherited VWD, any type, not responding to DDAVP 2 patients analyzed for efficacy of prophylaxis	Primary: PK for VWF:Ag, VWF:CB, VWF:RCo and FVIII:C, plasma level of FVIII:C as surrogate markers for efficacy Secondary: IVR of VWF:RCo, VWF:Ag and VWF:CB, bleeding time, closure time, VWF multimers, overall efficacy and tolerability
TMAE-109	16 patients aged ≥12 and ≤65 years with inherited VWD, any type, not responding to DDAVP 5 patients analyzed for efficacy of prophylaxis	Primary: plasma levels of FVIII:C, VWF:Ag, VWF:RCo as surrogate markers for efficacy Secondary: bleeding time, VWF multimers, overall efficacy, safety and tolerability

Source: Adapted from Clinical Overview Table 1, Page 6.
*Excludes 10 patients from the efficacy analyses for whom laboratory results did not confirm the patient's VWD status, i.e. severe VWD Type 1, 2A, 2B, 2M or 3.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (WIL-33)

Study WIL-33 is titled "Clinical Study to Investigate the Efficacy, Pharmacokinetics, Immunogenicity and Safety of WILATE in Severe von Willebrand Disease Patients under the Age of 6 Years."

6.1.1 Objectives

Primary Objective:
The primary objective was to determine the efficacy of WILATE in the prophylactic treatment of up to 12 pediatric patients (8 evaluable) with severe VWD (defined as screening von Willebrand factor ristocetin cofactor activity [VWF:RCo] <20%) under the age of 6 years, for a period of 12 months.

Secondary Objectives:

- Determine the pharmacokinetics (PK) of WILATE for VWF activity (VWF:Ac [VWF:RCo]) and factor VIII (FVIII) activity (FVIII:C, one-stage [OS])
- Determine the incremental in-vivo recovery (IVR) over WILATE over time
- Evaluate the rate of traumatic and spontaneous breakthrough bleeds under prophylactic treatment, including the corresponding treatment efficacy
- Assess the treatment response in minor and major bleeds and surgeries
- Determine WILATE consumption data for prophylactic treatment, on-demand treatment, and surgeries
- Investigate the immunogenic potential of WILATE by screening for VWF and FVIII inhibitors
- Investigate the thrombogenic potential of WILATE
- Assess the patients' joint status with the Hemophilia Joint Health Score (HJHS)
- Assess the safety and tolerability of WILATE

6.1.2 Design Overview

This was an open-label, prospective, non-controlled, international, multicenter Phase 3 study investigating the efficacy, PK, immunogenicity, and safety of WILATE prophylaxis in pediatric patients under the age of 6 years at screening with severe VWD. The study planned to enroll 12 patients across up to 15 sites worldwide, of whom at least 8 were required to be evaluable for the primary endpoint. All patients were to receive prophylactic treatments two or three times weekly for a duration 12 months (±2 weeks).

6.1.3 Population

Eligible patients were children under the age of 6 years with severe VWD, defined as screening VWF: RCo <20%, regardless of prior treatment. At least four patients were required to have hereditary type 3 VWD, while the remaining patients could have severe type 1 or severe type 2 VWD (excluding type 2N).

6.1.4 Study Treatments or Agents Mandated by the Protocol

WILATE is produced from human donor plasma and is presented as a powder and solvent for IV injection containing 500 IU or 1000 IU human VWF and human FVIII per vial.

- For prophylaxis: WILATE prophylaxis was administered 2–3 times per week at 30–50 IU/kg over 12 months with dose and frequency based on the individual patient's clinical condition. If the patient had > 2 BEs within a 30-day period or 1 major BE, the dose was to be increased by approximately 5 IU/kg and/or the treatment frequency could be increased.

- For the treatment of BEs:

Table 2. WILATE dosage for the treatment of BEs

Dose Type	Minor BE	Major BE
Loading dose	30–50 IU/kg	50–80 IU/kg
Maintenance dose	30–40 IU/kg every 12–24 hours	30–50 IU/kg every 12–24 hours
Therapeutic goal	Maintain VWF:Ac and FVIII:C trough levels >30%	Maintain VWF:Ac and FVIII:C trough levels >50%

Source: Original Clinical Study Report V 1.0, page 7.

- For the surgical prophylaxis

Table 3. WILATE dosage for the surgical prophylaxis

Dose Type	Minor Surgeries (Includes Tooth Extraction)	Major Surgeries
Loading Dose	40–60 IU/kg	60–80 IU/kg
Maintenance Dose	20–30 IU/kg BW, or half the loading dose, every 12–24 hours for up to 3 days	30–40 IU/kg BW, or half the loading dose, every 12–24 hours for up to 6 days or longer
Therapeutic Goal	Achieve VWF:Ac peak levels of 50% after loading dose and trough levels of >30% during maintenance doses	Achieve VWF:Ac peak level of 100% after loading dose and trough levels of >50% during maintenance doses

Source: Original Clinical Study Report V 1.0, page 7.

6.1.6 Sites and Centers

Patients were enrolled and treated at 9 centers across 7 countries: Czech Republic, Germany, Moldova, North Macedonia, Russia, Ukraine, and the United States (US).

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:
The primary endpoint was the total annualized bleeding rate (TABR) during prophylactic treatment with WILATE.

Secondary Endpoints:

- PK profile characteristics of WILATE (VWF: RCo and FVIII:C [OS]) based on blood samples taken pre-dose (baseline), 15 min, 3, 9, 24, 48 and 72 h after dosing of 80 IU/kg BW WILATE
- IVR of WILATE (VWF: RCo and FVIII:C [OS]) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- Efficacy of WILATE in the prevention and treatment of spontaneous and traumatic breakthrough BEs based on their rate and the proportion of spontaneous and traumatic BEs successfully treated with WILATE as assessed by a 4-point ordinal hemostatic efficacy scale (excellent – good – moderate – none)
- The overall efficacy of WILATE in perioperative prophylaxis against excessive bleeding as assessed at the end of the postoperative period by the responsible treating Investigator. A 4-point ordinal hemostatic efficacy scale (excellent – good – moderate – none) will be used
- WILATE consumption data for prophylactic treatment, for on-demand treatment and during surgical prophylaxis

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination

No formal sample size calculation was performed. The sample size of up to 12 patients, including at least 4 patients with type 3 VWD, was based on communication with the FDA and on EU guideline CPMP/BPWG/220/02 calling for a trial in at least 8 children under the age of 6 years with VWD, at least 3 of whom should have type 3 VWD.

Primary Efficacy Analysis

The TABR was to be calculated as the total number of spontaneous, traumatic, and other bleeds occurring in the time period between the first prophylactic dose of investigational medicinal product (IMP) and the Study Completion Visit, divided by the duration (in years) of that same interval. Bleeding episodes occurring during surgery periods were to be excluded from the calculation of TABR. Exploratory 95% CIs were to be calculated using a Poisson regression model.

Analysis Populations

- **Safety Set (SAF)**: Included all patients who received at least one dose of WILATE.
- **Full Analysis Set (FAS)**: Defined according to the intention-to-treat (ITT) principle, included all enrolled patients who received at least one dose of WILATE after the pharmacokinetic (PK) visit.
- **Per-Protocol Set (PP)**: A subset of the FAS that excluded patients with major protocol deviations that may have impacted the evaluation of the primary study outcome parameter(s).
- **Surgery Set (SURG)**: A subset of the FAS containing all patients who underwent a surgical procedure treated with WILATE during their prophylactic treatment phase.

Missing data
In general, no imputation was proposed for missing data. Calculations of the TABR were based on documented time periods only.

Subgroup analyses
The efficacy analyses were planned to be summarized in the following subgroups:

- VWD type (severe Type 1, Type 2 and Type 3)
- Sex (Female, Male)

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Of the 12 screened pediatric patients, all were enrolled and treated with WILATE. The SAF and FAS sets were identical.

Table 4. Data Sets Analyzed

Data set	Number of patients
Screened	12
Safety set (SAF)	12
Full analysis set (FAS)	12
Per-protocol (PP) set	8
Surgery set (SURG)	1

Source: Adapted from Clinical Study Report V 1.0, Table 6, p.60

6.1.10.1.1 Demographics

Demographic and baseline characteristics of the FAS/SAF population are summarized in Table 5.

Patient age at screening ranged from 1 to 5 years (median: 2 years), and the population was evenly split by sex, with six males and six females (50% each). Ten of 12 patients (83.3%) were White, and 1 (8.3%) was enrolled in the United States.

Regarding VWD classification, no patient had Type 1 VWD; 4 patients (33.3%) had Type 2 VWD, and 8 patients (66.7%) had Type 3 VWD. Six patients (50.0%) had a family history of VWD.

No patient had a known inhibitor history at enrollment.

Table 5. Demographic and Baseline Characteristics of the Study Population

Parameter	**FAS (N=12)**
Age (years)	
Mean (SD)	2.5 (1.2)
Median (min, max)	2.0 (1.0, 5.0)
Height (cm)	
Mean (SD)	98.7 (10.5)
Median (min, max)	99.5 (81.0, 123.0)
Weight (kg)	
Mean (SD)	15.3 (3.3)
Median (min, max)	14.5 (12.0, 24.3)
Body mass index (kg/m2)	
Mean (SD)	15.7 (1.9)
Median (min, max)	15.3 (13.4, 19.2)
Sex, n (%)	
Female	6 (50.0%)
Male	6 (50.0%)
Race, n (%)	
White	10 (83.3%)
Other (Arab)	2 (16.7%)
Region, n (%)	
US	1 (8.3%)
Non-US	11 (91.7%)
VWD type, n (%)	
Type 2	4 (33.3%)
Type 3	8 (66.7%)
Family history of VWD, n (%)	6 (50.0%)
VWF inhibitor history, n (%)	0 (0.0%)
FVIII inhibitor history, n (%)	0 (0.0%)

Source: Adapted from Clinical Study Report V 1.0, Table 7, p.62

Reviewer's comment: Patient (b) (6) *left Ukraine after approximately 2 months of prophylactic treatment due to the war, resulting study discontinuation. The patient was subsequently re-enrolled under a new ID* (b) (6) *) after 189 days. Per the SAP, "Assessments at initial screening/initial PK visit (initial study phase before re-enrollment) are considered as baseline" (SAP v2.0, p. 11)."*

However, the applicant applied this rule inconsistently for this patient: height measured on December 6, 2021 (initial screening visit), and weight measured on September 19, 2022 (re-screening visit), were used respectively in the baseline calculations for average height, weight, and BMI. This approach is methodologically inconsistent, as it combines measurements from two distinct time points.

To align with the SAP, both height and weight from initial screening visit (December 6, 2021) were used in the current analysis when calculating the average height, weight, and BMI. This resulted in minor discrepancies compared to the applicant's Table 7 in the CSR. where the reported values were: Mean (SD) of weight: 15.5 (3.4) kg; Mean (SD) of BMI: 15.9 (1.9) kg/m².

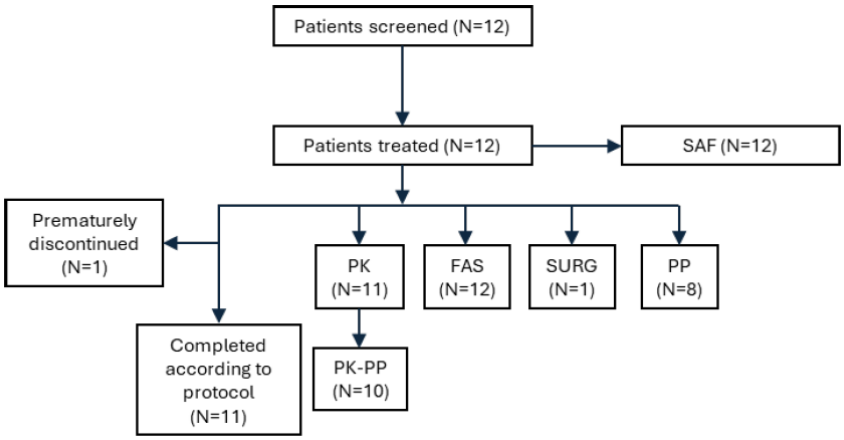
6.1.10.1.3 Subject Disposition

Subject disposition was illustrated in Figure 1. Eleven of 12 patients completed the study. One patient terminated the study early due to an adverse event (AE).
Four patients out of 12 were excluded from the PP set for the following reasons:

- One patient due to interruption of treatment and re-enrollment in the study.
- One patient because of more than two bleeding episodes (BEs) or one major BE within a 30-day period without an increase in prophylactic dose.
- One patient was found to be positive for FVIII and VWF inhibitors during the PK visit discontinued the study prematurely after receiving four treatments. This patient was excluded from both the PK analysis and the PP analysis.
- One patient due to overdose (> 20% above upper limit/> 60 IU/kg) for all prophylactic infusions.

One patient underwent a major surgery (removal of a central venous port system) while receiving WILATE treatment.

Figure 1. Disposition of Patients



Source: Original CSR Figure 1. Page 58.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

In the FAS, 10 patients experienced a total of 56 BEs during prophylaxis, and 2 patients reported no bleeding episodes. The mean and median TABR were 4.6 and 3.0, respectively. Of the 56 BEs, 45 were treated with WILATE, yielding a mean treated TABR of 3.7 and a median of 2.4; the remaining 11 BEs were minor and not treated.

In the PP set, 8 patients experienced 24 BEs, which resulted in a mean and median TABR of 3.0 for both. Of the 24 BEs, 17 were treated with WILATE, yielding a mean treated TABR of 2.1 and a median of 2.4.

TABRs details for both the FAS and PP sets, along with estimated TABRs from a negative binomial counting model are presented in Table 6.

Table 6. TABRs during Prophylaxis

	Parameter	FAS (N = 12)	PP (N = 8)
All BEs	Mean (SD)	4.6 (6.1)	3.0 (1.8)
	Median (Range)	3.0 (0–22.6)	3.0 (0–5.9)
	Estimated TABR (95% CI)	4.9 (2.8–8.8)	3.0 (2.0–4.4)
Treated BEs	Mean (SD)	3.7 (5.1)	2.1 (1.4)
	Median (Range)	2.4 (0.0-18.7)	2.4 (0.0-4.0)
	Estimated TABR (95% CI)	4.0 (2.2-7.2)	2.1 (1.3-3.4)

Source: Adapted from Clinical Study Report V 1.0, Table 8&9, p.63-64

Reviewer's comment:

- *According to the SAP, the estimates of the TABR exploratory 95% CIs should be calculated from Poisson regression models. Given the data were over-dispersed (variance > mean), the applicant estimated TABRs and 95% CIs based on negative-binomial models in the CSR. The statistical method the applicant applied in the analysis is appropriate.*

6.1.11.2 Analyses of Secondary Endpoints

Please refer to the clinical Pharmacology review memo for the analyses of PK and IVR data. Analysis results for the other secondary efficacy endpoints are presented below for the FAS.

Efficacy of WILATE in the treatment of spontaneous and traumatic breakthrough BEs

- *Annualized Bleeding Rates (ABRs) by bleeding type*

Of the 56 BEs in the FAS, 11 were spontaneous, 17 were traumatic, and 28 were other, yielding mean ABRs of 0.9, 1.4, and 2.3, respectively, and median ABRs of 0.4, 1.0, and 0, respectively. Among the 45 treated BEs, 9 were spontaneous, 15 were traumatic, and 21 were other, yielding mean ABRs of 0.7, 1.2, and 1.7, respectively, and median ABRs of 0, 0.9, and 0, respectively. One patient had a single joint BE that was treated and included in the traumatic BE category, which yielded a mean joint ABR of 0.08 and a standard deviation (SD) of 0.28.

Table 7. ABRs during Prophylaxis by Bleeding Type (FAS)

Parameter	Spontaneous	Traumatic	Joint	Other*	Total**
All BEs (n)	11	17	1	28	56
Mean (SD)	0.9 (1.2)	1.4 (1.7)	0.08 (0.28)	2.3 (6.6)	4.6 (6.1)
Median (Range)	0.4 (0.0-3.0)	1.0 (0.0-5.9)	0.0 (0.0-1.0)	0 (0.0-22.6)	3.0 (0.0-22.6)
Treated BEs (n)	9	15	1	21	45
Mean (SD)	0.7 (1.1)	1.2 (1.7)	0.08 (0.28)	1.7 (5.4)	3.7 (5.1)
Median (Range)	0 (0.0-3.0)	0.9 (0.0-5.9)	0.0 (0.0-1.0)	0 (0.0-18.7)	2.4 (0-18.7)

Source: Adapted from Clinical Study Report V 1.0, Table 12, p.68

*Other bleeds include oral bleeds when eating solid food, bleeds during needle insertion into the port system, allergy related nose bleeds, and a nose bleed related to virosis.

**Total includes spontaneous bleeds, traumatic bleeds, and other bleeds.

- *Treatment efficacy*

A total of 59 BEs were recorded in 10 of the 12 (83.3%) patients in the FAS during the study, of which 56 occurred during prophylaxis and 3 occurred prior to prophylaxis initiation. Six (50%) patients had 0 spontaneous BEs. Of these 59 BEs, 47 were treated with WILATE. Among the treated BEs, 31(66%) were nose BEs, and 45 (96%) were minor. The overall treatment success rate was 100%, with 46 (97.9%) rated as "excellent" and 1 (2.1%) rated as "good,"

Table 8. Efficacy Assessment of Treatment of BEs with WILATE (FAS)

Bleeding Event Type	N	Excellent n (%)	Good n (%)
All treated BEs	47	46 (97.9)	1 (2.1)
Spontaneous	11	10 (90.9)	1 (9.1)
Traumatic	15	15 (100.0)	0 (0.0)
Other	21	21 (100.0)	0 (0.0)

Source: Adapted from Clinical Study Report V 1.0, Table 12, p.69.

Efficacy of WILATE as surgical prophylaxis

One patient received WILATE for a major surgery (removal of central venous port system) and was rated as excellent by the hematologist and the surgeon.

WILATE consumption

- Prophylactic treatment (IVR administrations were also considered prophylactic treatments)

  At study start, 9 of 12 (75.0%) patients in the FAS received WILATE prophylaxis twice weekly and 3 (25%) patients received it three times weekly. At study end, 8 (66.7%) patients were receiving WILATE twice weekly and 4 (33.3%) three times weekly. The mean weekly prophylactic dose was 120.1 IU/kg. Details of WILATE consumption for prophylaxis are shown in Table 9.

  Patient (b) (6) received 133.3 IU/kg per injection and tested positive for FVIII and VWF inhibitors during the PK visit, leading to premature study discontinuation after four treatments (one PK and three prophylaxis). Patient (b) (6) received an overdose of 77.2 IU/kg per injection (> 20% above upper limit; > 60 IU/kg) across all prophylactic infusions.

Table 9. Consumption of WILATE for Prophylaxis (FAS)

Statistics	Time on prophylaxis (Months)	Number of Exposure days (EDs)	Number of injections	Dose per injection (IU/kg)	Dose per week (IU/kg)
Mean (SD)	11.4 (3.5)	109.0 (36.1)	109.0 (36.1)	54.0 (27.5)	120.1 (65.0)
Median (range)	12.2 (0.3–14.3)	111.5 (3.0–139.0)	111.5 (3.0–139.0)	47.2 (31.5–133.3)	100.2 (63.3–311.1)

Source: Adapted from Clinical Study Report V 1.0, Table 14, p.70.

- Treatment of BEs

Of the 47 treated BEs, 44 (93.6%) were treated with a single infusion and 3 (6.4%) required 2 infusions. The mean dose per BE was 58.7 IU/kg, with a median of 52.9 IU/kg (range: 30.9 – 153.8 IU/kg).

Table 10. Consumption of WILATE for the Treatment of BEs (FAS)

Statistics	Number of injections/BE	Number of EDs/BE	Dose per BE (IU/kg)	Dose per injection (IU/kg)
Mean (SD)	1.1 (0.2)	1.0 (0.2)	58.7 (27.6)	55.0 (22.3)
Median (range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	52.9 (30.9–153.8)	52.9 (30.9–153.8)

Source: Adapted from Clinical Study Report V 1.0, Table 15, p.71.

- Treatment of surgery
  One surgery was treated with WILATE during the study, with a total dose of 186.3 IU/kg across 5 doses: 1 preoperative dose of 62.1 IU/kg and 4 postoperative doses of 31.1 IU/kg each.

6.1.11.3 Subpopulation Analyses

Subgroup analyses are presented below. However, because of the small sample size, these analyses are descriptive only, and no meaningful statistical conclusions can be drawn.

- TABRs by VWD type for the FAS and PP population are shown in Table 11. Notably, the TABR was numerically higher in Type 3 patients compared with Type 2 patients in the FAS, mainly driven by one male patient with Type 3 VWD (Patient (b) (6)) who experienced 25 minor BEs (ABR: 22.6), which may have been due to not increasing the prophylactic dose as specified in the protocol.

Table 11. TABRs during Prophylaxis by VWD Type (FAS, PP)

	VWD Type 2 (FAS, N = 4)	VWD Type 3 (FAS, N = 8)	VWD Type 2 (PP, N = 3)	VWD Type 3 (PP, N = 5)
All BEs (n)	9	47	7	17
Mean (SD)	2.1 (1.0)	5.8 (7.2)	2.3 (1.1)	3.4 (2.2)
Median (Range)	2.3 (1.0-3.0)	4.0 (0-22.6)	2.9 (1.0-3.0)	3.9 (0.0-5.9)
Treated BEs (n)	9	36	7	10
Mean (SD)	2.1 (1.0)	4.4 (6.2)	2.3 (1.1)	2.0 (1.6)
Median (Range)	2.3 (1.0-3.0)	2.5 (0-18.7)	2.9 (1.0-3.0)	2.0 (0.0-4.0)

Source: Adapted from Clinical Study Report V 1.0, Table 18, p.75.

- TABRs by sex are shown in Table 12. The TABR appears to be numerically higher in males compared to females, largely driven by the BEs in Patient (b) (6)

Table 12. TABRs during Prophylaxis by Sex (FAS, PP)

	Male (FAS, N = 6)	Female (FAS, N = 6)	Male (PP, N = 4)	Female (PP, N = 4)
All BEs (n)	33	23	8	16
Mean (SD)	5.4 (8.6)	3.8 (2.5)	2.0 (1.8)	4.0 (1.4)
Median (Range)	2.3 (0.0-22.6)	3.5 (0–6.9)	2.0 (0.0-3.9)	3.5 (2.9-5.9)
Treated BEs (n)	26	19	5	12
Mean (SD)	4.2 (7.2)	3.1 (2.3)	1.2 (1.3)	3.0 (0.8)
Median (Range)	1.3 (0-18.7)	2.9 (0-6.9)	1.0 (0.0-3.0)	2.9 (2.0-4.0)

Source: Adapted from Clinical Study Report V 1.0, Table 19, p.76.

6.1.11.4 Dropouts and/or Discontinuations

One patient was terminated from the study due to the development of inhibitors againstFVIII and VWF inhibitors after three prophylactic IMP treatments, representing a total treatment exposure for 9 days.. This patient did not report any BE during the study. Even though this patient was included in the FAS, the patient's contribution to the TABR estimate is minimal because of the short study duration. It is unknown how the patient's bleeding profile and contribution to the ABR estimate would have evolved with longer follow-up, and therefore impacting the TABR estimate.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Four serious treatment-emergent adverse events (TEAEs) occurred in 4 (33.3%) patients, each requiring hospitalization: pyrexia, soft tissue infection, pneumonia, and iron deficiency anemia.

6.1.12.5 Adverse Events of Special Interest (AESI)

Of 12 patients in the SAF, 10 (83.3%) experienced 46 TEAEs. One patient (8.3%) experienced a TEAE assessed as possibly related to study treatment. One patient tested positive for FVIII and VWF inhibitors during the PK visit. No thromboembolic events were reported. For further details, please refer to the clinical reviewer's memo.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

WILATE was initially approved in 2009 for on-demand (OD) treatment and control of bleeding episodes (BEs) in patients with von Willebrand disease (VWD). Its indications were subsequently expanded to include perioperative management in VWD (August 2015), followed by routine prophylaxis and on-demand treatment of BEs in adolescents and adults with hemophilia A (September 2019). Most recently, in December 2023,

WILATE received approval for routine prophylaxis in adults and children older than 6 years with VWD.

In this BLA efficacy supplement (sBLA), the applicant sought to extend the approved the indication of WILATE to include routine prophylaxis in children under 6 years of age with severe VWD.

To support the proposed indication extension, the applicant submitted the safety and efficacy data from pivotal Study WIL-33, an open-label, prospective, non-controlled, multicenter Phase 3 study evaluating the efficacy, pharmacokinetics, immunogenicity, and safety of WILATE in patients under 6 years of age with severe VWD (defined as VWF: RCo < 20%, regardless of prior treatment history) receiving regular prophylaxis. The primary efficacy endpoint was the total annualized bleeding rate (TABR) under prophylactic treatment with WILATE.

Study WIL-33 enrolled and treated 12 patients aged 1 to 5 years. In the full analysis set (FAS), 10 of 12 patients experienced 56 bleeding episodes (BEs) during prophylaxis, resulting in a mean TABR of 4.6 and a median TABR of 3.0. Based on a negative binomial model, the estimated mean TABR was 4.9 (95% CI: 2.8–8.8). Of the 56 BEs, 45 were treated with WILATE, yielding a mean TABR for treated BEs of 3.7 and a median of 2.4.

In total, 59 BEs were recorded, including 56 during prophylaxis and 3 prior to prophylaxis initiation (all nosebleeds). Of these, 47 were treated with WILATE, all with successful hemostatic efficacy ratings: 46 (97.9%) rated "excellent" and 1 (2.1%) rated "good." One patient underwent a major surgery (removal of central venous port system) and received perioperative and post-surgical prophylactic injections; hemostatic efficacy was rated excellent by both the hematologist and the surgeon.

No deaths were reported during the study. One patient tested positive for FVIII and VWF inhibitors during the pharmacokinetic (PK) visit. No Thromboembolic events were observed.

10.2 Conclusions and Recommendations

There were no statistical concerns identified in this submission. The efficacy results were confirmed through the reviewer’s independent analyses. Although no pre-specified success criteria were specified for efficacy endpoints, the findings were consistent with those observed in the previously approved age groups for the VWD indication. No safety signals of concern were identified. Based on these findings, I recommend approval of the proposed extension of the WILATE indication to include patients under 6 years of age with severe VWD.