FBLA Clinical Review Memorandum

Application Type	BLA Efficacy Supplement
STN	125251/454
CBER Received Date	9/2/25
PDUFA Goal Date	7/2/26
Division / Office	Division of Clinical Evaluation Hematology/Office of Clinical Evaluation
Priority Review (Yes/No)	No
Reviewer Name(s)	Christine Knoll, MD (Clinical) CBER/OTP/OCE/DCEH/BHB Xing Jing, PhD (Clinical Pharmacology)
Review Completion Date / Stamped Date	July 2, 2026
Supervisory Concurrence	Courtney Johnson, MD Acting Clinical Team Leader CBER/OTP/OCE/DCEH/BHB Xiaofei Wang, PhD Acting Clinical Pharmacology Team Leader CBER/OTP/OCE Kavita Natrajan, MD Acting Branch Chief CBER/OTP/OCE/DCEH/BHB Bindu George, MD Acting Division Director CBER/OTP/OCE/DCEH
Applicant	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Established Name	vonWillebrand Factor/Coagulation Factor VIII Complex (Human)
(Proposed) Trade Name	Wilate
Pharmacologic Class	Human Plasma Derived 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	Loading Dose and Maintenance Dose(s)

	Routine prophylaxis dosing: Age < 6 years: 30-50 IU/kg two-three times a week (dose and dosing regimen for all other indications and age groups that are already approved are not included here)
Indication(s) and Intended Population(s)	WILATE is indicated in adult and pediatric 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 This application expands the routine prophylaxis indication in VWD to include patients < 6 years of age.
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	adverse event
BE	bleeding episode
BLA	biologics license application
BW	body weight
CBER	Center for Biologics Evaluation and Research
CHR	chromogenic
CI	confidence interval
ED	exposure day
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FVIII:C	Factor VIII-coagulant
FVIII	Factor VIII
IND	investigational new drug application
iPSP	initial Pediatric Study Plan
IVR	in vivo recovery
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
OD	on-demand
OS	one-stage
PeRC	Pediatric Review Committee
PI	package insert
PK	pharmacokinetic
PP	per protocol
SABR	spontaneous annualized bleeding rate
SAE	serious adverse event
SAF	safety analysis set
TABR/od/pr	total annualized bleeding rate/for on-demand treatment/for prophylaxis
TEAE	treatment-emergent adverse event
VWD	von Willebrand disease
VWF:Ac	von Willebrand factor activity
VWF	von Willebrand factor
VWF:(b) (4)	von Willebrand factor (b) (4) assay
VWF:RCo	von Willebrand factor ristocetin cofactor assay

1. EXECUTIVE SUMMARY

Von Willebrand Factor (VWF) is a glycoprotein important in coagulation due to its role in platelet adhesion during vascular injury and it serves as a carrier protein for coagulation factor VIII (FVIII). Von Willebrand disease (VWD) is an inherited hemostatic disorder characterized by a quantitative or qualitative deficiency in VWF resulting in bleeding. VWD is classified into 3 types: Type 1 is the most common with a quantitative decrease in VWF, Type 2 has multiple subtypes (2A, 2B, 2M and 2N) and results from qualitative VWF defects, and Type 3 is a total deficiency of VWF and FVIII and a bleeding pattern similar to hemophilia A. Wilate [VWF/FVIII Complex (Human)] is a double virus inactivated human plasma derived product containing VWF and FVIII. It is currently approved for children and adults with VWD for on-demand (OD) treatment and control of bleeding episodes (BEs) and perioperative management of bleeding. It is approved in adults and children ≥ 6 years of age with VWD for routine prophylaxis (RP) to reduce the frequency of bleeding episodes. In hemophilia A, it is approved for adolescents and adults for the indications of routine prophylaxis and on-demand treatment of bleeding episodes.

The Applicant submitted this efficacy supplement on September 2, 2025, to expand the indication of routine prophylaxis to children < 6 years based on data from Study WIL-33.

Study WIL-33 was a prospective, open-label, noncontrolled, Phase 3 trial conducted in 9 centers in Europe and the US that investigated the efficacy, PK, immunogenicity, and safety of Wilate in patients < 6 years with severe VWD. Patients had to have Type 3, severe Type 2 (except 2N), or severe Type 1 VWD with severity defined as a VWF:Rco < 20%, requiring VWF replacement therapy. Patients received 30-50 IU/kg of Wilate 2–3 times per week over 12 months with the dose and frequency based on the individual patient's clinical condition with specified doses for breakthrough BEs and surgeries.

The primary endpoint was total annualized bleeding rate (TABR) calculated as the total number of BEs between the first prophylaxis dose and study completion, divided by the duration (in years) between the first prophylaxis dose and study completion. BEs during perioperative periods were excluded. There was no comparison to patients' baseline in this study. All statistical analyses were descriptive.

Secondary endpoints included pharmacokinetic (PK) profile and *in vivo* recovery (IVR) characteristics, efficacy in the prevention and treatment of spontaneous and traumatic BEs, overall efficacy in perioperative prophylaxis, consumption data, and joint health status. Secondary safety endpoints included incidence of VWF and FVIII inhibitors, thromboembolic events, and safety and tolerability assessed by monitoring AEs.

The exploratory endpoints were only in Type 3 VWD patients and included VWF multimer analysis from the PK samples taken at 15 min and 24 h following infusion.

Overall, 12 patients were enrolled; 8 with Type 3 VWD and 4 with Type 2 VWD (3 Type 2A and 1 Type 2B). All 12 patients were included in the efficacy and safety analyses.

There were 56 BEs in 10 patients during Wilate prophylaxis. The primary endpoint of TABR was a mean of 4.6 (SD 6.1) with a median of 3.0 (0-22.6). The mean and median TABR for treated bleeds was 3.7 (SD 5.1) and 2.4 (0-18.7) respectively. The mean spontaneous annualized bleeding rate (SABR) was 0.9 (SD 1.2) (0.7 [SD 1.1] for treated spontaneous BEs). Of the 45 treated BEs, all had excellent or good hemostatic efficacy consistent among all bleeding sites, type, and severity.

The estimated TABR (95% CI) using a negative binomial counting model was 4.9 (2.8–8.8) with treated estimated TABR of 4.0 (2.2–7.2).

Although, no formal hypothesis was tested, the TABR in WIL-33 is in the range for the TABR of in patients ≥ 6 years and within the range using the estimated negative binomial counting model. Therefore, Wilate is considered to have demonstrated benefit.

Ten patients (83.3%) experienced 46 adverse events (AEs) with the most reported being iron deficiency (3 [25.0%]), nasopharyngitis, cough, and pyrexia (each in 2 [16.7%]). One non-serious AE of pyrexia was assessed as not related by the investigator but possibly related by the applicant due to it starting within 24 hours after Wilate. There were no hypersensitivity reactions or thrombosis. One patient developed inhibitors to both FVIII and VWF, necessitating discontinuation of the study drug and study withdrawal. This event was not included in the Applicant's analysis of AEs but was determined to be an important AE by the clinical reviewer and is included in the label.

Four SAEs occurred in 4 patients (33.3%), all of which required hospitalization including pneumonia, soft tissue infection, iron deficiency anemia, and pyrexia (1 in each patient). The clinical reviewer determined that all SAEs were unrelated to Wilate except the soft issue infection which was considered possibly related since it occurred at the site of Wilate administration and was temporally related to product administration.

PK assessment showed that the exposure levels of both VWF:RCo and FVIII in patients < 6 years were higher than those of patients 6-16 years of age. The FVIII and VWF IVRs observed are comparable with those seen previously with Wilate.

Although this trial has limited data based on one small, single-arm trial, VWD is considered a rare disease (especially type 3 and type 2 VWD included in this study) and the TABR falls within the expected and estimated range using binomial modeling. The TABR is also in keeping with the TABR for this product in RP for patients 6 and older. The results are clinically meaningful and adequate to provide evidence of substantial efficacy. Confirmatory evidence comes from efficacy in RP (with labeled dose range of 20-40 IU/kg based on PK data) from trial WIL-31 in patients ≥ 6 years and PK studies demonstrating acceptable VWF and FVIII exposures (higher than those in older age groups) expected to decrease bleeds and consistent with known action of the product i.e., replacement of the missing coagulation protein. The safety profile is in keeping with

what is expected for the product including inhibitor development (neutralizing antibody) and has been addressed through labeling. Regulatory flexibility has been shown in accepting the results of a small, single-arm trial in a rare subset of VWD based on demonstration of efficacy and safety. The overall benefit risk assessment is favorable, and the clinical review team recommends regular approval for the use of Wilate for routine prophylaxis to reduce the frequency of BEs in children < 6 years with VWD. The Applicant has fulfilled the postmarketing requirement (PMR) #1 under STN 125251/382 by submitting final data from clinical study WIL-33 as well as the required Pediatric Assessment. Based on this final data. this approval action also extends the currently approved indication of routine prophylaxis to reduce the frequency of bleeding episodes in VWD to pediatric patients < 6 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

WIL-33 provides the basis of approval of Wilate routine prophylaxis to reduce the frequency of BEs in patients < 6 years. Twelve patients were enrolled between 1 to 5 years (median of 2 years). The population was 50% male, 83% White, 67% of patients had Type 3 VWD, and33% of patients had Type 2 VWD (3 Type 2A, 1 Type 2B).

1.2 Patient Experience Data

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☒	Observer-reported outcome	Section 6
☒	Clinician-reported outcome	Section 6
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	

☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Patient's parent(s)/legal guardian(s) rating of treatment of BEs was a secondary efficacy endpoint based on a four-point scale. See section 6.1.8 for the scale.

Minor BEs treated at home were assessed by the patient's parent(s)/legal guardian(s). Major BEs were ideally treated at the treating center and assessed by the investigator at the end of the BE. The efficacy was to be assessed for all treated BEs. All efficacy ratings assessed as either "excellent" or "good" were considered successfully treated.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

VWD is the most common inherited (predominantly autosomal dominant) bleeding disorder affecting 1% of the population with equal frequency in men and women. It is characterized by mucosal bleeding; easy bruising, epistaxis, oral bleeding,

menorrhagia, and gastrointestinal bleeding. Women are more likely to be symptomatic due to the hemostatic challenges of menstruation, pregnancy, and childbirth.

Von Willebrand factor (VWF) performs three critical functions in hemostasis. In primary hemostasis, VWF acts as a bridging molecule between platelets and vascular sub-endothelium and promotes platelet aggregation. VWF is a carrier for FVIII, increasing the FVIII half-life by fivefold, thereby maintaining normal FVIII levels in circulation.

VWD is characterized by either a quantitative or qualitative abnormality of VWF with three types of VWD:

1. Type 1–partial quantitative deficiency of VWF (~75% patients)
2. Type 2–qualitative abnormalities of VWF (~20%) with 4 subtypes:

    a. Type 2A—decreased platelet-dependent function with loss of high molecular weight multimers
    b. Type 2B—increased affinity for platelet glycoprotein 1b
    c. Type 2M—decreased platelet dependent function not associated with loss of high molecular weight multimers
    d. Type 2N—decreased affinity for FVIII

3. Type 3—total deficiency of VWF (~1% to 3%) with severe bleeding manifestations; the inheritance pattern is autosomal recessive

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

Humate-P (plasma-derived VWF/FVIII), Alphanate (plasma-derived VWF/FVIII), Vonvendi (recombinant VWF), and DDAVP (desmopressin, causes release of stored VWF) are currently licensed for treatment of bleeding in patients with VWD. Vonvendi is the only additional product approved for routine prophylaxis but only in adults with VWD.

2.3 Safety and Efficacy of Pharmacologically Related Products

Humate-P is effective in treating BEs and perioperative management in VWD. The most common AEs are allergic reactions, wound/injection-site bleeding, and epistaxis.

Alphanate is effective in VWD for perioperative management except for major surgery in severe Type 3. The most frequent AEs include respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

Vonvendi is effective in treating BEs and perioperative management in all patients with VWD and for prophylaxis in adults with VWD. The most frequent AE's include headache, vomiting, nausea, dizziness, arthralgia, joint injury, vertigo, increased alanine aminotransferase levels, and generalized pruritus.

DDAVP has been shown to be effective in mild to moderate VWD if Factor VIII levels > 5%. It is not effective in Type 3 VWD and is contraindicated in Type 2B VWD. Side effects include transient headache, nausea, mild abdominal cramps, vulval pain, local erythema, swelling or burning pain, and facial flushing.

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

Wilate has been extensively studied and used for treatment of VWD in the United States (US) and Europe for several years. EMA approval was in 2009. It is also approved in Australia, and parts of Latin America, the Middle East, and Asia. The pertinent AEs reported in the post marketing setting include inhibitors to FVIII and VWF, and hypersensitivity reactions including anaphylaxis and is in the current USPI.

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

Regulatory History

- December 4, 2009-Approved original BLA 125251/0 for OD treatment of BEs in patients (all ages) with severe VWD as well as mild or moderate VWD in whom DDAVP is known or suspected to be ineffective or contraindicated.
- August 5, 2015-Approved sBLA 125251/139 for perioperative management in patients (all ages) with VWD. This was the trigger for PeRC in 2019.
- September 25, 2019-Approved sBLA 125251/244 for RP and OD treatment of BEs in patients ≥ 12 years with hemophilia A. This was the trigger for PeRC in 2023.
- December 1, 2023-Approved sBLA 125251/382 for RP in patients ≥ 6 years.

Reviewer's Comment:

The exact indication statement from 2009 was "treatment of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease (vWD), and in mild and moderate vWD where use of DDAVP treatment is ineffective or contra-indicated." The current indication statement for OD and perioperative states "WILATE is indicated in adult and pediatric patients with von Willebrand disease for:

- *On-demand treatment and control of bleeding episodes (1)*
- *Perioperative management of bleeding (1)"*

We are unable to confirm when this indication statement changed.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Study WIL-33 was conducted under IND 11303 in the US and overseas in the Czech Republic, Germany, Moldova, North Macedonia, the Russian Federation, and Ukraine.

It was conducted according to the principles in the Declaration of Helsinki and International Conference on Harmonization Note for Guidance on Good Clinical Practice (CPMP/ICH/139/95) standards. The study aimed at fulfilling the Committee for Proprietary Medicinal Products Note for Guidance on the clinical validation of both FVIII (CPMP/BPWG/198/95 rev. 1) and VWF/FVIII products (CPMP/BPWG/220/02).

3.3 Financial Disclosures

Covered clinical study (name and/or number): WIL-33
Was a list of clinical investigators provided? **X Yes** ☐ No (Request list from applicant)
Total number of investigators identified: **13**
Number of investigators who are applicant employees (including both full-time and part-time employees): **None**
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **None**

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **Not Applicable**

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in applicant of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided?

☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3):

Not Applicable

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

There were no significant CMC issues for this supplement.

4.2 Assay Validation

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

4.3 Nonclinical Pharmacology/Toxicology (P/T)

There were no significant nonclinical P/T issues for this supplement.

4.4 Clinical Pharmacology (Based on Clinical Pharmacology Review Team)

The clinical pharmacology section of this prior approval supplement included one Phase 3, open-label, multicenter, noncontrolled Study WIL-33 to determine the efficacy, safety, and pharmacokinetics of Wilate prophylaxis in previously treated patients < 6 years of age with severe VWD (defined as VWF activity (VWF:RCo) <20%). Pharmacokinetics (PK) of VWF and FVIII were assessed after a single dose of 80 (70-85) IU/kg. The exposure levels of both VWF:RCo and FVIII in patients < 6 years were higher than those of patients 6-16 years of age. The FVIII and VWF IVRs observed in this Study WIL-33 are comparable with those seen previously with Wilate.

The proposed dosing regimen of 30 to 50 IU/kg of Wilate 2 to 3 times per week for Wilate administered by intravenous infusion has demonstrated clinical efficacy (refer to Section 6) with a tolerable safety profile (refer to Section 8); therefore, the proposed dosing regimen is acceptable for routine prophylaxis to reduce the frequency of BEs in children < 6 years of age with VWD. From a clinical pharmacology perspective, the prior approval supplement application is approvable.

4.4.1 Mechanism of Action

VWF and FVIII are normal constituents of human plasma. VWF mediates the binding between platelets and damaged subendothelium and is involved in the transport and stabilization of FVIII. Reduction in VWF concentration results in a correspondingly low FVIII and abnormal platelet function, resulting in excessive bleeding. VWF reverses these effects by promoting platelet adhesion to vascular subendothelium at the site of vascular damage and correcting the associated impairment in FVIII.

4.4.2 Human Pharmacokinetics

Pharmacokinetics (PK)
PK assessments were performed for both VWF and FVIII. VWF activity was measured by VWF ristocetin cofactor (VWF:RCo) activity assay, and FVIII activity was measured by one-stage (OS) assay.

PK analysis included 10 patients (2 patients excluded from the total 12 enrolled). For PK analysis, single dose of 80 (70-85) IU/kg BW Wilate was administered, as shown in Table 1. Among these 10 patients, 4 had VWD Type 2, 6 had VWD Type 3, as shown in Table 2.

Table 1: Study WIL-33 Nominal and Actual Doses (IU/kg) Administered for P Assessments (N = 10)

Assay	Mean (SD)	Median (range)
Nominal FVIII/VWF dose	78.5 (3.6)	79.9 (70.4-85.6)
Actual FVIII dose, OS	77.4 (9.2)	76.0 (66.7-99.7)
Actual VWF dose, VWF:RCo	79.3 (9.1)	78.1 (69.7-103.3)

OS = one stage; VWF:RCo = VWF ristocetin cofactor activity
Source: Applicant, Summary of Clinical Pharmacology

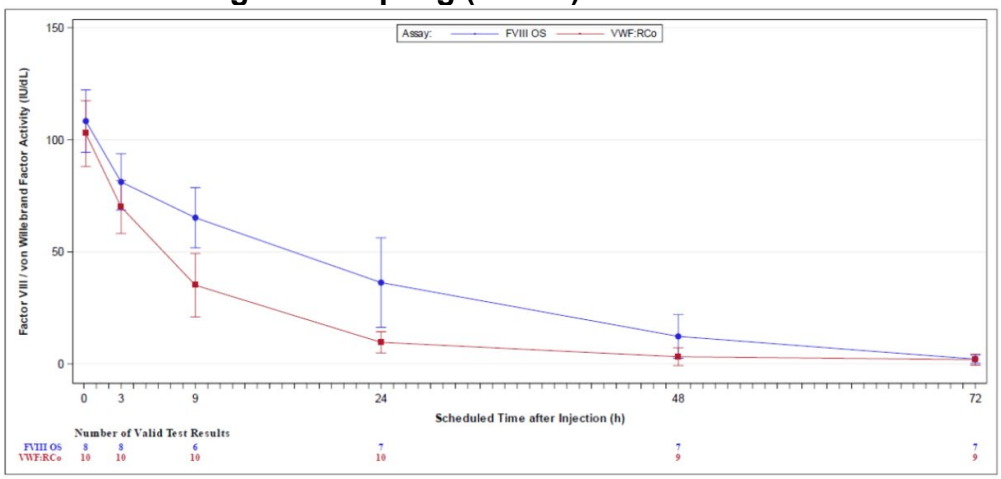
Table 2: Study WIL-33 Nominal and Actual Doses (IU/kg) Administered for PK Assessments by VWD Type (N = 10)

Assay	Type 2 (N=4)	Type 3 (N=6)
Nominal FVIII/VWF dose	80.2 (0.4)	77.4 (4.4)
Actual FVIII dose, OS	84.0 (10.9)	73.0 (4.8)
Actual VWF dose, VWF:RCo	84.3 (12.8)	76.0 (4.1)

OS = one stage; VWF:RCo = VWF ristocetin cofactor activity
Source: Applicant, Summary of Clinical Pharmacology

Mean VWF activity and FVIII activity profiles showed that administration of Wilate leads to immediate correction of both the VWF and FVIII deficiencies, as shown in Figure 1. The PK parameters of VWF and FVIII were summarized in Tables 3, 4, & 5.

Figure 1: Study WIL-33: Mean (SD) Pre-dose Adjusted VWF and FVIII Activity Obtained during PK Sampling (N = 10)



FVIII = factor VIII; OS = one stage; VWF:RCo = VWF ristocetin cofactor activity.
Sampling time points: pre-dose and 15 min, 3, 9-, 24-, 48-, and 72-hours post-dose.
Source: Applicant, Summary of Clinical Pharmacology
Wilate PK parameters, normalized to a dose of 80 IU/kg and by VWD type, are shown in Table 3, Table 4, and Table 5.

Table 3: Study WIL-33: PK Parameters Normalized to a Dose of 80 IU/kg (N = 10)

PK parameter	Mean (SD)		Geometric mean (Geo. SD)	
	VWF:RCo N = 10	FVIII OS N = 8 *	VWF:RCo N = 10	FVIII OS N = 8*
AUC, h*IU/dL	1100 (532)	2410 (1122)	1001 (1.56)	2129 (1.78)
AUCnorm, h*kg*IU/dL/IU	13.7 (6.7)	30.1 (14.2)	12.5 (1.56)	26.6 (1.78)
CL, dL/h/kg	0.09 (0.04)	0.04 (0.03)	0.08 (1.56)	0.04 (1.78)
Cmax, IU/dL	105.0 (19.7)	114.1 (27.1)	103.2 (1.2)	111.2 (1.3)
MRT, h	15.6 (9.5)	22.5 (9.4)	13.7 (1.7)	20.8 (1.6)
T1/2, h	11.7 (9.6)	15.0 (7.5)	9.6 (1.8)	13.4 (1.7)
Tmax, h	0.27 (0.04)	0.26 (0.05)	0.26 (1.19)	0.26 (1.21)
Vd, dL/kg	1.12 (0.24)	0.82 (0.28)	1.09 (1.27)	0.78 (1.42)

AUCnorm = AUC normalized for the administered dose; VWF:RCo = VWF ristocetin cofactor activity; OS = one stage.
* Data are not available for 2 patients.
Source: Applicant, Summary of Clinical Pharmacology

Table 4: Study WIL-33: PK Parameters (VWF:RCo) Normalized to a Dose of 80 IU/kg by VWD Type (N = 10)

PK parameter	Mean (SD)		Geometric mean (Geo. SD)	
	Type 2 N = 4	Type 3 N = 6	Type 2 N = 4	Type 3 N = 6
AUC, h*IU/dL	1282 (856)	978 (161)	1056 (2.1)	966 (1.2)
AUCnorm, h*kg*IU/dL/IU	16.0 (10.7)	12.2 (2.0)	13.2 (2.1)	12.1 (1.2)
CL, dL/h/kg	0.09 (0.06)	0.08 (0.02)	0.08 (2.1)	0.08 (1.2)
Cmax, IU/dL	97.8 (26.9)	109.8 (14.0)	95.0 (1.3)	109.0 (1.1)
MRT, h	19.8 (14.1)	12.8 (4.6)	16.3 (2.0)	12.2 (1.4)
T1/2, h	16.8 (14.2)	8.3 (3.0)	13.0 (2.3)	7.8 (1.5)
Tmax, h	0.28 (0.05)	0.26 (0.04)	0.27 (1.18)	0.26 (1.20)
Vd, dL/kg	1.24 (0.17)	1.03 (0.26)	1.23 (1.15)	1.01 (1.31)

AUCnorm = AUC normalized for the administered dose; VWF:RCo = VWF ristocetin cofactor activity.
Source: Applicant, Summary of Clinical Pharmacology

Table 5: Study WIL-33: PK Parameters (FVIII:C [OS]) Normalized to a Dose of 80 IU/kg by VWD Type (N = 10)

PK parameter	Mean (SD)		Geometric mean (Geo. SD)	
	Type 2 N = 4	Type 3 N = 4	Type 2 N = 4	Type 3 N = 4
AUC, h*IU/dL	1513 (645)	3306 (612)	1391 (1.7)	3258 (1.2)
AUCnorm, h*kg*IU/dL/IU	18.9 (8.1)	41.3 (7.7)	17.4 (1.7)	40.7 (1.2)
CL, dL/h/kg	0.06 (0.35)	0.02 (0.01)	0.06 (1.65)	0.03 (1.23)
Cmax, IU/dL	96.8 (20.4)	131.5 (22.2)	95.0 (1.3)	130.1 (1.2)
MRT, h	18.9 (8.9)	26.1 (9.7)	17.2 (1.7)	25.0 (1.4)
T1/2, h	13.0 (8.0)	17.0 (7.5)	11.2 (1.9)	16.0 (1.46)
Tmax, h	0.28 (0.05)	0.25 (0.05)	0.27 (1.18)	0.25 (1.25)
Vd, dL/kg	1.01 (0.24)	0.63 (0.19)	0.99 (1.26)	0.61 (1.32)

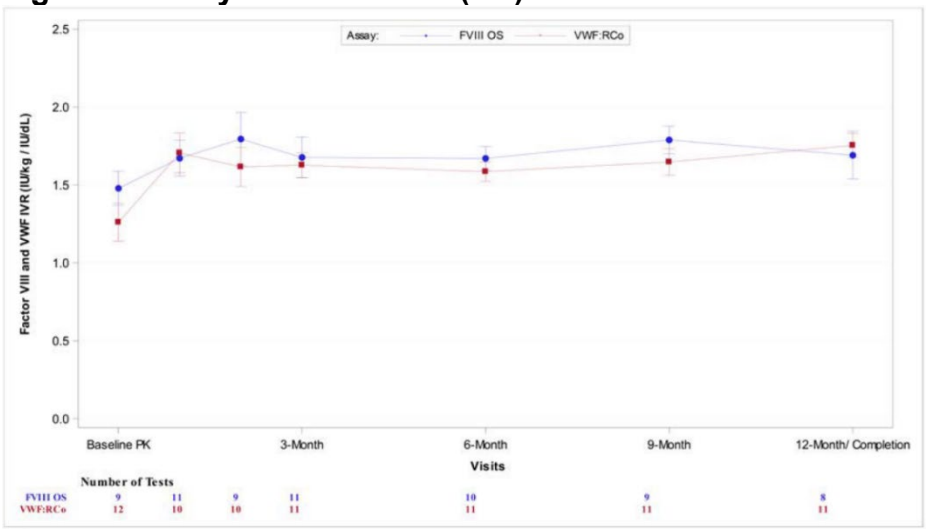
AUCnorm = AUC normalized for the administered dose; OS = one stage.
Source: Applicant, Summary of Clinical Pharmacology

Incremental in vivo recovery (IVR)

IVR assessment was performed following administration of a prophylactic dose (30-50 IU/kg). [Note: Assessment of baseline IVR was performed following administration of a single dose of 80 (70–85) IU/kg (the same dose used for the PK assessment)].

IVR of Wilate for VWF activity (VWF:RCo) and FVIII activity (OS) were measured at baseline and after 1, 2, 3, 6, 9, and 12 months of Wilate prophylaxis, as shown in Figure 2. FVIII and VWF IVRs at baseline and at the 12-month visit and by VWD type are summarized for the FVIII OS and VWF:RCo assays in Table 6 and Table 7.

Figure 2: Study WIL-33: Mean (SD) Incremental IVR for FVIII and VWF over Time



IVR = in vivo recovery; OS = one stage; VWF:RCo = VWF ristocetin cofactor activity.
Source: Applicant, Summary of Clinical Pharmacology

Table 6: Study WIL-33: Mean (95% CI) Incremental IVR at Baseline and at 12 Months

IVR, kg/dL	Baseline		12-month visit	
	N	Mean (95% CI)	N	Mean (95% CI)
VWF:RCo	12	1.26 (1.00, 1.53)	11	1.75 (1.58, 1.92)
FVIII (OS)	9	1.48 (1.23, 1.73)	8	1.69 (1.33, 2.05)

IVR = in vivo recovery; OS = one stage; VWF:RCo = VWF ristocetin cofactor activity.
Source: Applicant, Summary of Clinical Pharmacology

Table 7: Study WIL-33: Mean (95% CI) Incremental IVR at Baseline and at 12 Months by VWD Type

IVR, kg/dL	Baseline		12-month visit	
	N	Mean (95% CI)	N	Mean (95% CI)
VWF:RCo				
Type 2	4	1.22 (0.70, 1.74)	4	1.67 (1.46, 1.87)
Type 3	8	1.28 (0.88, 1.68)	7	1.80 (1.52, 2.08)
FVIII (OS)				
Type 2	4	1.23 (0.88, 1.57)	3	1.43 (0.08, 2.78)
Type 3	5	1.68 (1.36, 2.00)	5	1.85 (1.47, 2.23)

IVR = in vivo recovery; OS = one stage; VWF:RCo = VWF ristocetin cofactor activity.
Source: Applicant, Summary of Clinical Pharmacology

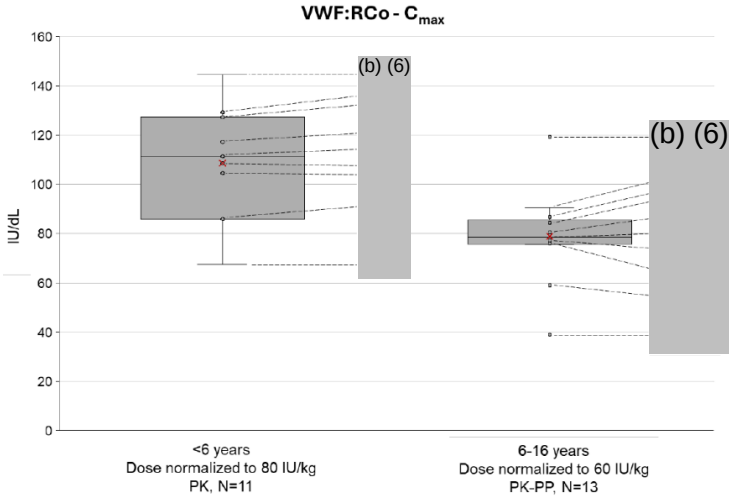
Reviewer's comments:

1. *These data showed that at 30 to 50 IU/kg dose given to pediatric patients < 6 years, IVR values for VWF:RCo and FVIII (OS) increased from baseline after Wilate prophylaxis and remained relatively constant between the 1-month and 12-month visit and were comparable with those of older populations with the*

labeled dose of 20-40 IU/kg. Thus, the proposed dose regimen of 30-50 IU/kg led to VWF:RCo and FVIII (OS) IVRs led to acceptable IVR improvement.

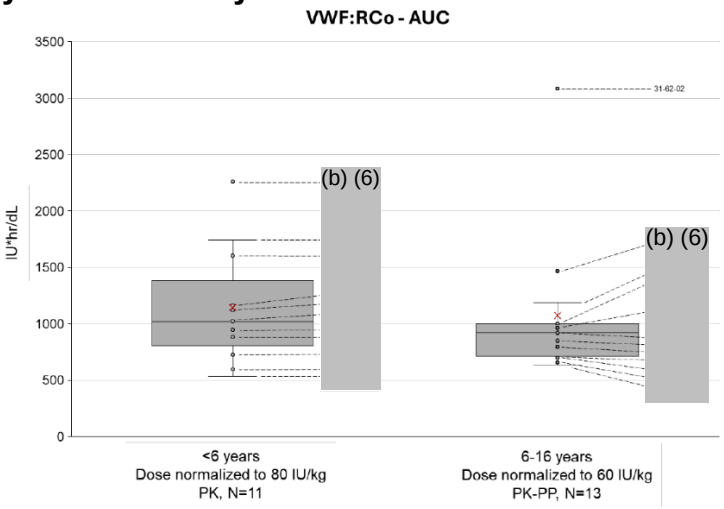
2. *The observed half-lives for VWF:RCo in WIL-33 population (< 6 years of age) was shorter than in patients ≥ 12 years of age; the FVIII half-life was also shorter than in children 6 to 16 years of age. Hence, a higher dose (30-50 IU/kg) was chosen for the patients < 6 years of age, than 20-40 IU/kg for patients 6-16 years of age. For PK assessment, 80 IU/kg was used in the younger age group (< 6 years) and 60 IU/kg in the older age group (6-16 years in Study WIL-31). According to the PK data, the VWF:RCo and FVIII (OS) exposure levels in the < 6 years at 80 IU/kg dose were higher than those in 6-16 years at 60 IU/kg dose (Figures 4-7 below). The higher dose of Wilate used in the PK study compared to the IVR study is for the purpose of overcoming endogenous baseline noise and achieving detectable plasma concentration for PK characterization. These differences in dose between the PK and IVR studies do not impact the interpretability or the conclusions from the IVR or PK assessments. These PK data indicate that a 30 to 50 IU/kg dose in < 6 years of age will have similarly higher exposures than those in 6-16 years of age given 20-40 IU/kg. Therefore, the PK data support the proposed higher prophylaxis dose of 30-50 IU/kg for < 6 years of age.*
3. *Although the different VWD types had different exposures (as shown in Tables 4 and 5), the range of exposure in patients < 6 years is above that of patients 6-16 years, as shown in Figures 4-7. Thus, given the acceptable efficacy and safety results, dose adjustment for different VWD types is not warranted.*
4. *In conclusion, based on the clinical review, the efficacy and safety outcomes, as well as the IVR results, at the proposed dose regimen in pediatric patients < 6 years of age in Study WIL-33 are acceptable (refer to Section 6 and 8 for details). Therefore, the proposed dose regimen for this age group is acceptable.*

Figure 4 Box plot comparison of VWF:RCo Cmax between pediatric patients < 6 years and 6-16 years



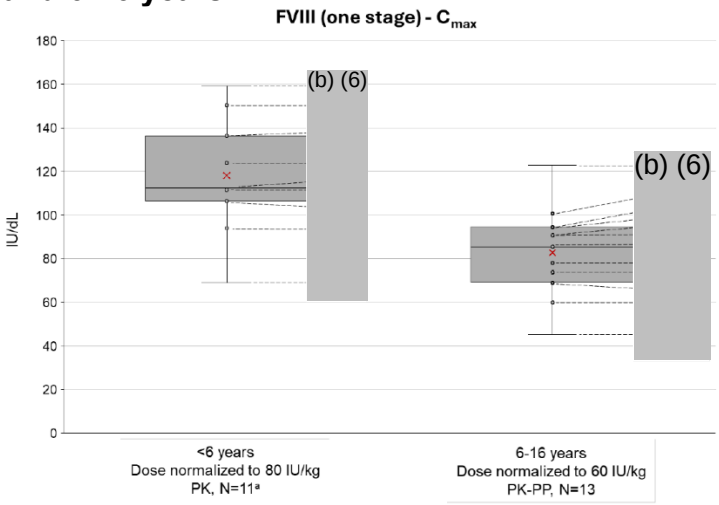
Source: Applicant's response to information request, submitted on 1/30/2026

Figure 5 Box plot comparison of VWF:RCo AUC between pediatric patients < 6 years and 6-16 years



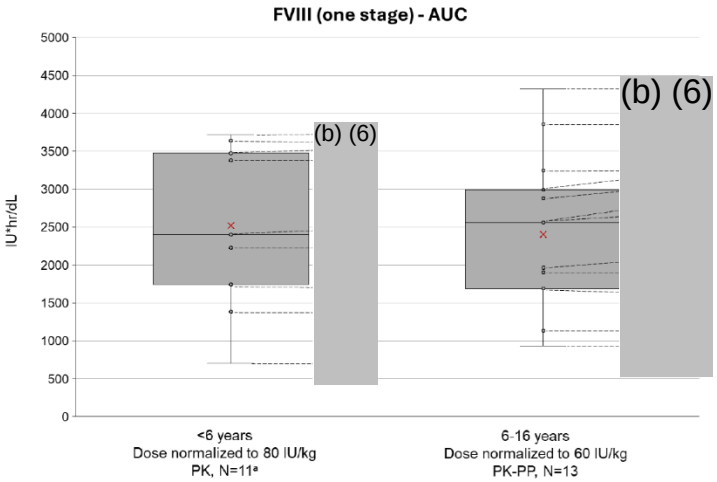
AUC refers to AUC0-inf
Source: Applicant's response to information request, submitted on 1/30/2026

Figure 6 Box plot comparison of FVIII Cmax between pediatric patients < 6 years and 6-16 years



Source: Applicant's response to information request, submitted on 1/30/2026

Figure 7 Box plot comparison of FVIII AUC between pediatric patients < 6 years and 6-16 years



AUC is AUC0-inf
Source: Applicant's response to information request, submitted on 1/30/2026

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported. Please see the Statistical Review for further details.

4.6 Pharmacovigilance

Please refer to the OBPV Review Memo for further details.

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

5.1 Review Strategy

The draft PI, and final clinical study report for study WIL-33 was reviewed. Datasets were analyzed for safety and efficacy. The final study reports for studies submitted to the original BLA and supplements and corresponding clinical review memos, responses to clinical IRs seeking clarification of information in this submission were also reviewed.

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

- Wilate draft PI
- Prior Wilate approval letters
- Final study reports for WIL-31 and WIL-33 and pooled analysis for studies TMAE-104, TMAE-105, TMAE-106, TMAE-109, WIL-12, WIL-14, WIL-21, and WIL-24
- Original BLA clinical review memos as well as summaries of clinical safety and efficacy data for the original BLA and subsequent supplements
- Information submitted by the Applicant in response to information requests

- PIs for Humate-P, Alphanate, Vonvendi, and DDAVP

5.3 Table of Studies/Clinical Trials

Data from WIL-33 is used as the basis of approval for this efficacy supplement.

Studies WIL-31, WIL-14, TMAE-104, TMAE-105, TMAE-106, and TMAE-109 support efficacy and safety. Studies WIL-12, WIL-21 and WIL-24 support safety only.

Table 8: Clinical Trials Reviewed for this sBLA

Study	Safety Population	Design	Treatment	Primary Objective
WIL-33 (pivotal study)	12 patients with inherited VWD (Type 3 or severe Type 1 or 2) requiring substitution with a VWF-containing product (age < 6 years)	Phase 3, open label, noncontrolled, multicenter trial (9 centers in US, Czech Republic, Germany, Republic of Moldova, North Macedonia, Russian Federation, Ukraine)	Wilate-Routine prophylaxis	Efficacy in the prophylaxis of previously treated patients < 6 years with VWD
WIL-31	43 patients with inherited VWD, Type 1, 2A, 2B, M, or 3 requiring substitution with a VWF-containing product (age ≥6 years)	Phase 3, open label, noncontrolled, multicenter trial (14 centers in US, Bulgaria, Belarus, Croatia, Hungary, Lebanon, Russia, Ukraine)	Wilate-Routine prophylaxis, surgical prophylaxis, and on-demand treatment	Efficacy in the prophylaxis of previously treated patients with VWD
TMAE-104	41 patients with inherited VWD, any type, not responding to DDAVP (age ≥6 and ≤85 years)	Phase 3, open label, noncontrolled, multicenter trial (15 centers in Austria, Finland, Norway, Poland, Portugal, Sweden, and the United Kingdom)	Wilate-Surgical prophylaxis and on-demand treatment	Efficacy using plasma levels of FVIII:C, VWF:Ag, VWF:CB, and VWF:RCo as a surrogate marker

Study	Safety Population	Design	Treatment	Primary Objective
TMAE-105	14 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open label, noncontrolled, multicenter trial (2 centers in Poland and Bulgaria)	Wilate-PK assessment, surgical prophylaxis, and on-demand treatment	PK for VWF:Ag, VWF:CB, VWF:RCo, and plasma level of FVIII:C as a surrogate marker for efficacy
TMAE-106	14 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open label, noncontrolled, multicenter trial (8 centers in Germany)	Wilate-PK assessment	PK of VWF:Ag, VWF:CB, VWF:RCo, and plasma level of FVIII:C
TMAE-109	16 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open label, noncontrolled, multicenter trial (2 centers in Poland and Bulgaria)	Wilate-Surgical prophylaxis treatment	Efficacy using plasma levels of FVIII:C, VWF:Ag, VWF:RCo as surrogate markers
WIL-12	22 patients with any type of inherited VWD (age ≥12 years)	Phase 2, open label, randomized, controlled, crossover, multicenter trial (6 centers in the United States)	Wilate/Humate-P-PK assessment	T1/2 of Wilate for FVIII:C, VWF:RCo, VWF:Ag, and VWF:CB
WIL-14	15 children with inherited VWD, any type, DDAVP treatment known or suspected to be inadequate	Phase 2, open label, noncontrolled, multicenter trial (7 centers in Germany, Poland, France and the Czech Republic)	Wilate-Surgical prophylaxis, on-demand treatment	Efficacy in prevention and/or treatment of BEs and during surgery
WIL-21	9 patients (age ≥12 years)	Phase 2, prospective, open label, randomized, controlled, 2-arm crossover, single-center	Wilate/Humate-P-PK assessment	T1/2 of Wilate for VWF:RCo, FVIII:C, VWF:Ag, and VWF:CB

Study	Safety Population	Design	Treatment	Primary Objective
		trial in the Slovak Republic		
WIL-24	41 patients with inherited VWD undergoing surgical procedures (age ≥6 years)	Phase 3, prospective, uncontrolled, open-label, multicenter trial (25 centers in the United States, India, Turkey, Poland, Italy, South Africa, Bulgaria, Romania, and Oman)	Wilate-Surgical prophylaxis	Overall hemostatic efficacy (success or failure) of Wilate during surgery

Source: WIL-31 Clinical Summary, Synopses of Individual Studies, 2.7.6.1 Tabular Listings of VWD Clinical Studies
Abbreviations: DDAVP = desmopressin, FVIII:C = Factor VIII-coagulant, PK = pharmacokinetic, VWD = von Willebrand disease, VWF:Ag = von Willebrand factor antigen, VWF:CB = von Willebrand factor collagen binding, VWF:RCo = von Willebrand factor ristocetin cofactor assay.

5.4 Consultations

FDA Pediatric Review Committee (PeRC) Consult Regulatory History-Prior Submission:

- May 12, 2019, PeRC reviewed the iPSP including their plan for a waiver for children with VWD from 0 to <6 years. PeRC recommended they assess children ≥ 2 years and agreed with a partial waiver in children < 2 years. Additionally, PeRC recommended increased sample size and PK studies in all pediatric age groups.
- March 25, 2021, a revised iPSP was approved by both CBER and PeRC including the plan to submit 1) assessment for patients ages 6 to 16, 2) partial waiver for patients < 2 years, and 3) deferral for patients ages 2 to <6.
- October 31, 2023, in sBLA 125251/382, a partial waiver request for children <2 years and deferral request for patients ages 2 to <6 years was agreed upon by both CBER and PeRC as well as a new Pediatric Research Equity Act (PREA) post marketing requirement timeline (stated below) due to the war in the Ukraine as there are several study sites located there.

Initial Timeline That Was Outlined in the Agreed iPSP From February 26, 2021

1. Final Protocol Submission: February 2021
2. WIL-33 pediatric trial start: Q2 2021
3. Study Completion: December 2022
4. Clinical Study Report Submission: July 2023

Updated Timeline as of October 31, 2023

1. Study Completion: May 2024
2. Clinical Study Report Submission: December 2024

Finally, there was another deferral request that was agreed upon with:

Final Updated Timeline as of July 2, 2024
1. Study Completion: December 2024
2. Clinical Study Report Submission: September 2025

FDA Pediatric Review Committee (PeRC) Consult-Current Submission:

On May 5, 2026, PeRC reviewed the iPSP, partial waiver for patients < 2 years, and deferral for patients 2 to < 6 years. WIL-33 is the current study submitted in this sBLA that satisfies fulfillment of the deferral for patients 2 to < 6 years with severe VWD, aimed to determine the efficacy, PK, immunogenicity, and safety of Wilate RP.

Although we agreed to the request for a waiver in patients <2 years of age, the Applicant was able to enroll 2 patients < 2 years in WIL-33. Therefore, the primary review team and PeRC agreed with approval for the RP indication in patients < 6 years.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1—Pivotal Study WIL-33

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective: Determine the efficacy of Wilate in prophylaxis of up to 12 patients (8 evaluable) with severe VWD (VWF:RCo <20%) < 6 years, for a period of 12 months.

Secondary Objectives:

- Determine the PK of Wilate for VWF:Ac (VWF:RCo) and FVIII:C (one-stage [OS]).
- Determine incremental in-vivo recovery (IVR) of Wilate over time.

- Evaluate traumatic and spontaneous breakthrough bleeds during prophylaxis.
- Assess the treatment response in minor and major bleeds and surgeries.
- Determine Wilate consumption data for prophylaxis, OD treatment, and surgeries.
- Investigate the immunogenic potential by screening for VWF and FVIII Inhibitors.
- Investigate the thrombogenic potential of Wilate.
- Assess the patients' joint status with the Haemophilia Joint Health Score (HJHS).
- Assess the safety and tolerability of Wilate.

Exploratory Objectives: Investigate the VWF multimer composition in the type 3 VWD.

6.1.2 Design Overview

WIL-33 was a prospective, noncontrolled, international, multicenter, Phase 3 trial. Patients received 30 to 50 IU/kg of Wilate prophylaxis 2 to 3 times per week for 12 months. This dose is higher than in the label of 20-40 IU/kg due to higher clearance and volume of distribution in patients < 6 years. The frequency was based on the clinical condition of the patient. If patients experienced ≥ 2 BEs within 30 days or 1 major BE, the dose was to be increased by 5 IU/kg and/or the treatment frequency increased.

6.1.3 Population

Inclusion Criteria:

1. Patients aged <6 years at the time of screening.

2. Type 3 (at least four patients), severe type 2 (except 2N) or severe type 1 VWD (VWF:RCo <20%) requiring substitution therapy with a VWF-containing product.

3. Minimum body weight 12.5 kg at the time of screening.

4. Voluntarily given, fully informed written and signed consent.

Reviewer's Comments:

- *Both- patients previously treated (PTP's), and previously untreated patients (PUPs) could be included in the study.*
- *Amendment 1 in Moldova and Amendment 5 in Czech Republic lowered the BW criteria from 12.5 kg to 11 kg, also decreasing blood collection volumes for laboratory tests. This was to be able to meet the established recruitment timelines due to the rare disease and challenge of identifying patients who met this requirement for the study. To achieve the lower blood collection volume*

requirement, the protocol was changed to allow for virus testing to be done later than screening but still before the first treatment with Wilate and one PK sample was omitted; neither test affected assessment of the primary endpoint.

Exclusion Criteria:

1. History, or current suspicion of VWF or FVIII inhibitors.

2. Injection of DDAVP or VWF-containing product within 72 hours prior to inclusion.

3. Medical history of a thromboembolic event.

4. Platelet count <100,000/mL at screening (except for VWD type 2B).

5. Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar.

6. Treatment with any IMP in another interventional clinical study currently or within four weeks before enrollment.

7. Other coagulation disorders or bleeding disorders.

8. Known hypersensitivity to any of the components of the study drug.

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.

PK assessment included a single dose of 80 IU/kg (70-85 IU/kg).

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.

Table 9: Wilate Dosage for the Treatment of Breakthrough 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: WIL-33 study protocol, page 4

Table 10: Definition of Minor and Major Bleeding

Bleeding severity	Description
Minor	Mild haemarthrosis (mild swelling, 'aura,' pain, warmth of the skin over the joint, change in range of motion, decrease in mobility and activity, slight difficulty in using the limb compared with baseline), superficial muscle bleed (pain and/or swelling and functional impairment compared with baseline), soft-tissue bleeding (scrapes, superficial cuts such as those cause by shaving razor, knife, or scissors, bleeding episodes that require frequent bandage changes, cutaneous bleeds with numerous bruises >1 cm), oral bleeding (superficial mouth bleeds, oozing or bleeding related to tooth eruption or extraction, spontaneous or after brushing/flossing, gum bleeding, bleeding after bites to lip or tongue), and most nose bleeds (i.e., those causing distress or interference with daily or social activities).
Major	Generally requires hospitalisation; causes incapacity, significant pain, and substantial decrease in range of motion of affected joint (in case of joint bleeds); includes symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraabdominal, intraarticular, or pericardial bleeds), intramuscular bleeds with compartment syndrome, bleeds of the pelvic muscles, periorbital bleeds, gastrointestinal bleeds, central nervous system bleeds, bleeding in the area of the neck or throat or pharynx, other major trauma, or bleeding causing a decrease in haemoglobin levels by 20 g/L (1.24 mmol/L) or more.

Source: WIL-33 study protocol, page 31

Table 11: Wilate Dosage for 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: WIL-33 study protocol, page 4

Surgeries were defined as major if any of the following criteria are met:

- General or spinal anesthesia required
- Opening into the great body cavities required
- Severe hemorrhage during surgery possible
- Hemostatic therapy for at least 6 days is required
- Orthopedic interventions involving joints
- Extraction of ≥3 teeth
- Surgeries/conditions in which the patient's life is at stake

The classification was made prospectively. All other surgeries were classified as minor.

6.1.5 Directions for Use

See above Section 6.1.4.

6.1.6 Sites and Centers

This study was conducted at 9 centers in the US, Czech Republic, Germany, Moldova, North Macedonia, Russia, and Ukraine. PI: Dr. Akshat Jain, Pediatric Hematologist-Oncologist and Medical Director of the Hemophilia Treatment Center at Loma Linda University Health at 250 E Caroline St, San Bernardino CA 92408, United States.

6.1.7 Surveillance/Monitoring

AEs were documented at each study visit by the investigator grading the severity (mild, moderate, or severe), seriousness (non-serious or serious), expectedness (expected or unexpected) and causality (probable, possible, unlikely, unrelated, or unclassified). Compliance calls were made to the parent(s)/legal guardian(s).

Table 12: Flow Chart of Assessments Performed Throughout the Study

ASSESSMENTS	Screening Visit	PK Visit (within 4 weeks after Screening)	1-Month Visit (±3 days)	2-Month Visit (±3 days)	3-Month Visit (±1 week)	Compliance Call 1 [1] (5–7 weeks after 3-Month Visit)	6-Month Visit (±2 weeks)	Compliance Call 2 [1] (5–7 weeks after 6-Month Visit)	9-Month Visit (±2 weeks)	Compliance Call 3 [1] (5–7 weeks after 9-Month Visit)	Study Completion (12-Month) Visit (+2 weeks)
Informed consent	X										
Eligibility criteria	X	X									
Demographics	X										
Body weight	X	X	X	X	X		X		X		X
Height	X										
Medical history and prior medication	X										
Family history of VWD	X										
Vital signs (blood pressure, heart rate, body temperature, respiratory rate) [2]	X	X	X	X	X		X		X		X
Physical examination	X										X
Injections at study site											
PK injection (80 IU/kg BW) [10]		X									
IVR injection			X	X	X		X		X		X
Start of prophylactic treatment phase [8]		X									
Local laboratory assessments											
Routine safety laboratory (haematology)	X										X [3]
Determination of AB0 blood group			X [4]								
Central laboratory assessments											
VWF:Ac (VWF:RCo)	X	X [6]	X [2]	X [2]	X [2]		X [2]		X [2]		X [2]
FVIII:C (OS)		X [6]	X [2]	X [2]	X [2]		X [2]		X [2]		X [2]
VWF and FVIII inhibitors [5]	X				X [3]		X [3]		X [3]		X [3]
Retention samples for virus marker testing	X										
VWF multimer analysis	X	X [7]									
Haemophilia Joint Health Score (HJHS) [9]	X										X
Assessment of compliance and adherence to treatment regimen		X	X	X	X	X	X	X	X	X	X
Bleeding Episodes monitoring	Throughout the study										
Concomitant Medication monitoring	Throughout the study										
Adverse event monitoring	Throughout the study										

Source: WIL-33 study protocol, pages 11-12

Table 13: Flow Chart of Assessments Performed Perioperatively

Assessment	For details, see Section	Within 12 hours before start	Within 3 hours before start	Surgery		POP day 1	Any POP day	End of POP period
				Intra-operatively	End [1]			
Body weight		x						
Type of surgery	7.2.2	x						
Location of surgery	7.2.2	x						
Severity of surgery	7.2.2	x						
Expected duration of surgery	7.2.2	x						
Actual duration of surgery	7.2.2				x			
Expected average/maximum blood loss during surgery	7.2.2	x						
Actual blood loss and transfusions during surgery	7.2.2				x			
Administration of *wilate*	5.4		x	(x)	(x)	(x)	(x)	(x)
FVIII:C	7.4.5		# L	(#) L	(#) L	(#) [2] L	(#) L	(#) L
VWF:Ac (VWF:RCo)	7.4.5		# L	(#) L	(#) L	(#) [2] L	(#) L	(#) L
Routine safety laboratory	7.4.5	x				(x)	(x)	(x)
Presence of wound haematomas	7.4.2					x	x	x
Vital signs	7.4.7	x		x		x		
Efficacy assessments	7.2.2				S			H
Overall efficacy assessment	7.2.2							I
Brief narrative of outcome of the intervention	7.2.2							x
Concomitant medications	7.4.2	Throughout observation period						
Adverse event monitoring	7.4.2	Throughout observation period						

Source: WIL-33 study protocol, page 52

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint— Determine TABR during Wilate prophylaxis.

TABR was calculated as the total number of BEs between the first prophylaxis dose and study completion, divided by the duration (in years) between the first prophylaxis dose of Wilate and study completion. BEs during surgery periods were excluded.

The Applicant provided separate analyses of ABRs for spontaneous, traumatic, and other BEs as well as by site, type, and severity of BE. Additionally, the Applicant provided the total number of traumatic, spontaneous, and other BEs.

Reviewer's Comment:

The applicant didn't do intrapatient comparison of the individuals' TABR on Wilate prophylaxis compared with their TABR at baseline prior to study enrollment that could have included OD treatment and or RP with Wilate or other VWF containing products.

Secondary endpoints:

PK assessments:

- PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C at baseline, 15 minutes, 3, 9, 24, 48 and 72 hours after 80 IU/kg Wilate.
- Incremental in-vivo recovery (IVR) of Wilate for VWF:Ac (VWF:RCo) and FVIII:C at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment.

Secondary Efficacy Endpoints:

- Proportion of BEs successfully treated assessed by a 4-point hemostatic efficacy scale (excellent, good, moderate, none).
- Efficacy in perioperative prophylaxis assessed at the end of the postoperative period by a 4-point hemostatic efficacy scale (excellent, good, moderate, none).
- Wilate consumption data for prophylaxis, OD treatment, and during surgery.
- Joint health status determination with the HJHS.

Table 14: Efficacy Assessment of the Treatment of Breakthrough BEs

Excellent	Bleeding was completely stopped within 3 days in case of minor bleeds, within 7 days in case of major bleeds, and within 10 days in case of gastrointestinal bleeds
Good	Bleeding was completely stopped, but time and/or dose slightly exceeded expectations
Moderate	Bleeding could be stopped only by significantly exceeding time and/or dose expectations
None	Bleeding could be stopped only by using other VWF-containing products

Source: WIL-33 protocol, page 31

Minor BEs treated at home were assessed by the patient's parent(s)/legal guardian(s). Major BEs were ideally treated at the treating center and assessed by the investigator at the end of the BE. The efficacy was to be assessed for all treated BEs. All efficacy ratings assessed as either "excellent" or "good" were considered successfully treated.

For surgery: 1) preoperative was up to 3 hours before the start of surgery, 2) end of surgery was immediately after the last surgical suture, and 3) postoperative was end of surgery to the time the patient returns to their regular VWF treatment regimen.

Table 15: Efficacy Assessment at the end of Surgery

Excellent	Intraoperative blood loss was lower than or equal to the average expected blood loss for the type of procedure performed in a patient with normal haemostasis and of the same sex, age, and stature
Good	Intraoperative blood loss was higher than the average expected blood loss but lower or equal to the maximum expected blood loss for the type of procedure in a patient with normal haemostasis
Moderate	Intraoperative blood loss was higher than the maximum expected blood loss for the type of procedure performed in a patient with normal haemostasis, but haemostasis was controlled
None	Haemostasis was uncontrolled, necessitating a change in the clotting factor replacement regimen

Source: WIL-33 protocol, page 53

Table 16: Efficacy Assessment at the end of Postoperative Period

Excellent	No postoperative bleeding or oozing that was not due to complications of surgery. All postoperative bleeding (due to complications of surgery) was controlled with *wilate* as anticipated for the type of procedure
Good	No postoperative bleeding or oozing that was not due to complications of surgery. Control of postoperative bleeding due to complications of surgery required increased dosing with *wilate* or additional injections not originally anticipated for the type of procedure
Moderate	Some postoperative bleeding and oozing that was not due to complications of surgery. Control of postoperative bleeding required increased dosing with *wilate* or additional injections not originally anticipated for the type of procedure
None	Extensive uncontrolled postoperative bleeding and oozing. Control of postoperative bleeding required use of an alternate VWF-containing product

Source: WIL-33 protocol, page 53

Table 17: Algorithm for Overall Efficacy Assessment for Surgical Prophylaxis

Algorithm for the Overall Efficacy Assessment for Surgical Prophylaxis				
Intraoperative assessment	Postoperative assessment			
	Excellent	Good	Moderate	None
Excellent	Excellent	Good	Good	Moderate
Good	Good	Good	Moderate	Moderate
Moderate	Good	Moderate	Moderate	None
None	Moderate	Moderate	None	None

Source: WIL-33 protocol, page 54

Joint health status was assessed using HJHS validated for adult patients with VWD. Target joints were defined as ≥ 3 spontaneous BEs in a single joint within 6 months.

Secondary Safety Endpoints:

- Incidence of VWF and FVIII inhibitors
- Incidence of thromboembolic events
- Safety and tolerability of Wilate assessed by monitoring adverse events (AEs)

Exploratory Endpoint:

VWF multimer analysis in hereditary type 3 VWD patients ≥14.5 kg from the PK samples at 15 minutes and 24 hours after Wilate injection.

6.1.9 Statistical Considerations & Statistical Analysis Plan

No formal sample size calculation was performed. The sample was based on communication with the FDA and EU guideline CPMP/BPWG/220/02.

Primary Endpoint Analysis: Hemostatic efficacy was assessed by TABR. The frequency and severity of BEs and the total, traumatic and spontaneous ABRs were calculated from patients' dosing and treatment frequency in different VWD types. Efficacy of prophylaxis was statistically evaluated by analyzing the primary endpoint.

Secondary Endpoint Analysis: Hemostatic efficacy in the treatment of BEs was assessed, and the frequency distribution of all successfully treated BEs and by severity, along with an exploratory 95% confidence interval (CI). Statistical analyses of other secondary endpoints were descriptive, including exploratory 95% CIs.

To assess the efficacy of Wilate in surgical prophylaxis, a frequency distribution of the efficacy rating for all surgical procedures was presented. All other surgery data (e.g., severity, type, Wilate consumption) was presented descriptively.

The PK and recovery assessments used descriptive statistics and concentration vs. time plots. The results of IVR assessments over time were presented per time point and as differences to baseline, along with 95% CIs for the mean differences.

Safety analysis was based on the occurrence of AEs, and safety laboratory testing. Analysis of AEs focused on treatment-emergent adverse events (TEAEs).

Time profiles of VWF and FVIII inhibitors were analyzed by sampling statistics for the values, frequency tables for positive findings, and 95% Pearson-Clopper CIs.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

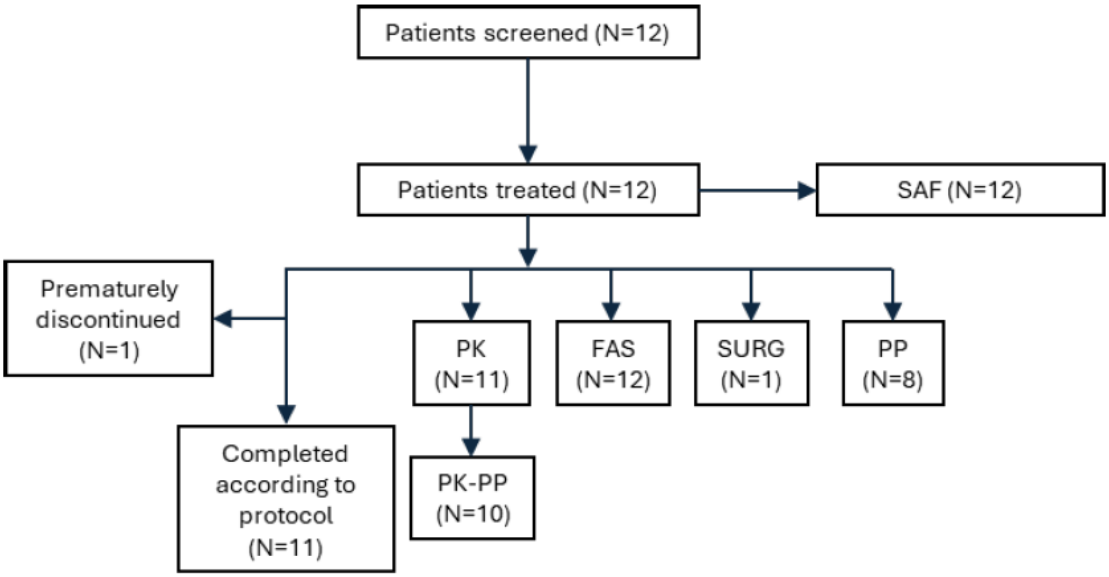
Analysis sets were the following:

The safety analysis set (SAF) included all patients who received ≥ 1 dose of Wilate.

The full analysis set (FAS), according to the intent to treat (ITT) principle, included all enrolled patients who received at least one dose of Wilate after the PK Visit.

The PP set was a subset of FAS that excluded patients with major protocol deviations which may have an impact on the evaluation of the primary study outcome.

Figure 3: WIL-33 Patient Population and Disposition



Source: WIL-33 Study report body, p. 58

Reviewer's Comment:
Patient (b) (6) *discontinued study participation after ~2 months of prophylaxis due to displacement caused by the war in Ukraine. The patient was subsequently re-enrolled after 189 days and assigned a new patient ID (ID* (b) (6) *.*

6.1.10.1.2 Demographics

The age at screening in the FAS (N=12) was a median of 2 years (range 1 to 5) with 50% being male, 83.3% White, and 66.7% with Type 3 VWD.

The PP set consisted of 8 patients excluding 4 from the FAS due to protocol deviations (see section 6.1.10.1.3). This review will focus on the FAS for efficacy analysis.

Table 18: WIL-33 Demographic Characteristics (FAS)

Parameter	Mean (SD)	Median (range)
Age (years)	2.5 (1.2)	2.0 (1.0–5.0)
Height (cm)	98.7 (10.5)	99.5 (81.0–123.0)
Weight (kg)	15.5 (3.4)	14.5 (12.0–24.3)
Body mass index (kg/m²)	15.9 (1.9)	15.8 (13.4–19.2)
	N (%)	
Sex		
Male	6 (50.0)	
Female	6 (50.0)	
Race, n (%)		
White	10 (83.3)	
Arabian	2 (16.7)	
Blood group, n (%)		
A	4 (33.3)	
B	2 (16.7)	
AB	2 (16.7)	
O	3 (25.0)	
Unknown	1 (8.3)	
VWD type		
Type 2	4 (33.3)	
Type 3	8 (66.7)	
VWF inhibitor history, n (%)[1]		
No	12 (100)	
FVIII inhibitor history, n (%)[1]		
No	12 (100)	
Family history of VWD, n (%)		
Yes	6 (50.0)	
No	6 (50.0)	

Source: WIL-33 Study report body, p. 62

6.1.10.1.3 Patient Disposition

Eleven patients completed the study with 1 discontinuing early due to AE of inhibitor development. This patient only received 3 doses of prophylaxis.

One 2-year-old patient (b) (6) had 1 major surgery of central venous port removal.

Major Protocol Deviations:

1) Patient (b) (6) (re-enrolled as (b) (6) : interruption in treatment and re-enrollment in study due to war in home country.
2) Patient (b) (6) : no increase in dose with > 2 BEs or 1 major BE within 30 days.
3) Patient (b) (6) : deviations from prophylaxis dose and withdrew from study early.
4) Patient (b) (6) deviations from prophylaxis dose.

Reviewer's Comment:

- *Patient (b) (6) experienced > 2 BEs within 30 days without an increase in the prophylaxis dose.*
- *Patient (b) (6) received higher than the recommended prophylaxis dose of 30-50 IU/kg at 133.3 IU/kg and completed only 10 days of study before discontinuing due to inhibitor development. This patient also received the highest prophylaxis dose prior to study at 137.9 IU/kg.*
- *Patient (b) (6) received higher than recommended prophylaxis dose of 30-50 IU/kg at 77.2 IU/kg.*
- *Of note, patients (b) (6) and (b) (6) who received higher than recommended doses were Type 3 VWD patients from the same center.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

There were 56 BEs in 10 patients with a mean TABR of 4.6 and median of 3.0 (range; 0-22.6). There were 45 treated BEs with a mean treated TABR of 3.7 and median of 2.4 (range; 0-18.7). The mean SABR was 0.9 (0.7 for treated BEs).

Reviewer's Comment:

47 BEs were treated with Wilate. Via IR, the applicant clarified that 2 of these BEs were prior to the start of prophylaxis. Patients (b) (6) had 1 treated BE episode each of spontaneous epistaxis prior to prophylaxis with excellent and good outcomes respectively. There were 11 minor BEs not treated with Wilate: 2 traumatic, 2 spontaneous, and 7 other (4 epistaxis secondary to pollinosis and 3 oral secondary to "eating solid food"). Five stopped spontaneously and 6 received treatment other than Wilate [epistaxis: 3 received tranexamic acid and 1 received curaspon + tranexamic acid; oral: 1 received tranexamic acid and 1 received curaspon].

Table 19: TABR during prophylaxis with Wilate vs. Estimated

Analysis Set	TABR	Treated TABR	Estimated TABR	Estimated Treated TABR
FAS (mean)	4.6	3.7		
(median)	3 (0-22.6)	2.4 (0-18.7)	4.9 (2.8-8.8)	4 (2.2-7.2)

Source: WIL-33 CSR page 63-64 and datasets ADCE, ADABR. FAS N = 12 and PP set N = 8

Estimated TABR was calculated using a negative binomial counting regression model.

Reviewer's Comment:

- *This model has been used to estimate ABR's in several studies including WIL-31 and hemophilia studies for Nuwiq, Fitusiran, Altuviiio, Eloctate, and Adynovate.*
- *Patient* (b) (6) *with Type 3 VWD had a higher TABR compared to other patients at 22.6. This patient was on Wilate prophylaxis prior to enrollment with a TABR of 14 prior to enrollment. All BEs on study were epistaxis with 1 due to a virus and 22 due to pollinosis. Per patient's past medical history, they had seasonal allergies typically in spring and summer with the majority (20; 87%) occurring between March and July with 1 in February and 2 in September. We do not know when the BEs occurred historically and whether they aligned with the epistaxis from seasonal allergies that occurred during the study. The outcome of all BEs for this patient was "excellent" with concomitant meds used in 6 of them. Excluding him, the range of the TABR of FAS ranged from 0 to 6.9 with a mean of 2.9 (SD 2.2).*

In the prior study, WIL -31, for patients 6 to 16 years, TABR was compared to the patients' TABR during a prior, non-interventional study, WIL-29, which was a 6-month prospective study where patients received OD treatment and had to have at least 6 BEs in the 6 months prior to be eligible for WIL-31. TABR decreased from 33.38 to 5.24 in all ages when switching from OD to RP. In patients 6 to < 12 years (N=9), the TABR decreased from 32.59 to 3.73 and in patients 12 to < 17 years (N=6), the TABR decreased from 28.99 to 4.28.

In WIL-33, there was no comparison of patients' TABR on-study to their historical TABR. Patients didn't require a history of BEs to be eligible. Also, the prior treatment varied with 7 patients on prior prophylaxis, 4 on prior OD, and 1 with no prior treatment.

Reviewer's Comment:

- *Per the applicant's IR response, "The prior TABR in WIL-33 was derived from a question at the screening visit regarding the number of BEs in the previous 6 months, for which the number of BEs was recorded, based on parent recall,*

without information on the type of BE or whether the BE required treatment. For patients who switched from on demand treatment to prophylaxis at any time before the screening visit, the number of BEs in the 6 months prior to switching was also documented. However, historical data were considered unreliable and inappropriate for determining conclusive prior ABRs, and descriptive statistics on prior ABRs were not performed." Also, only the number of BEs was reported without details about the type, severity, location, and if treatment received.

- *Unlike WIL-31, WIL-33 was not designed to compare the patients' TABR with their historical TABR. Via IR communication, the applicant clarified reasons for this approach stating "The sample size of WIL-33 (N=12) was considerably smaller than in WIL-31 (N=33), due to the rarity of the disease and limited availability of children in this age group who might already be receiving prophylaxis, and the convincing data from the WIL-31 study. In addition, because von Willebrand disease (VWD) has been significantly less explored in clinical research than, for example, hemophilia A, the quality of the historical bleeding data available in patient records is very poor."*
- *Patient* (b) (6) *received no prior VWF treatment or concomitant medications to treat bleeding.*
- *Patient* (b) (6) *left the Ukraine after ~2 months of prophylaxis due to war, interrupted the study and was re-enrolled* (b) (6) *) after 189 days. This patient was originally on OD prior to first enrollment then switched to prophylaxis per the study and remained on prophylaxis prior to second enrollment.*

While historical comparison was not done in WIL-33 and understanding that recall bias and inaccuracy was likely for the data reported, this review did include comparison for the patients that had historical data reported. Of the 7 people on prior prophylaxis, 5 had BEs reported for the 6 months (182.63 days) prior to enrollment with 2 patients switching to prophylaxis during this timeframe; (b) (6) started prophylaxis 168 days prior to enrollment and (b) (6) started prophylaxis 21 days prior to enrollment.

Table 20: On study TABR compared to TABR prior to enrollment (treated and untreated)

Analysis Set	TABR on study N = 12	Treated TABR on study N = 12	TABR prior to study (prophylaxis) N = 7
FAS (mean)	4.6	3.7	3.2
(median)	3 (0, 22.6)	2.4 (0, 18.7)	2 (0, 14)

*Source: Clinical reviewer analysis of Dataset ADABR; TABR on study x 12 months. TABR prior to study OD (N = 11) x 6 months; TABR prior to study prophylaxis (N=7) x 6 months with 2 patients starting prophylaxis within 6 months prior to study (1 at 168 days and 1 at 21 days prior to study). The mean TABR without these two patients is 4 with median of 2 (0-14).

Reviewer's Comments:

For the 4 patients on prior OD, the TABR the 6 months prior to study was a mean of 6.5 and median of 6 (2, 12). During WIL-33, the prior OD patients had a mean TABR of 2.65 and median of 2.33 (0, 5.94).

The mean TABR on Wilate during the study in 12 patients is higher than the mean TABR in 7 patients on RP prior to study entry. However, the sample size is small to draw any conclusions and the one patient on the study with 22 episodes of epistaxis due to seasonal allergies skewed the mean TABR to be higher on study. Additionally, as described previously, the baseline data prior to study enrollment has limitations in that they were not collected prospectively. Finally, 2 of the 7 patients on prior RP started RP within the 6 months prior to study; 1 at 168 days prior to study and 1 at 21 days prior to study. The mean TABR without these two patients is 4 with median of 2 (0-14).

Table 21: TABR in patients 6 months prior to screening and during prophylaxis

Patient#	Prior treatment (screening)	Prior 6 months		WIL-33 (prophylaxis)	
		Duration (years)	TABR[c]	Duration (years)	TABR
(b) (6)	On demand	0.5	4.00	1.0	5.94
	On demand	0.5	8.00	1.2	1.68
	On demand	0.5	12.00	1.0	2.98
	On demand	0.5	2.00	1.0	0.00
	Prophylaxis	0.5	0.00	1.0	2.89
	Prophylaxis	0.5	2.00	1.0	2.97
	Prophylaxis	0.5	14.00	1.0	22.64
	Prophylaxis	0.5	2.00	1.0	4.02
	Prophylaxis	0.5	2.00	1.0	3.93
	Prophylaxis[b]	0.46	2.17	0.025	0.00
	Prophylaxis[b]	0.06	0.00	1.0	6.89
	None	0.5	0.00	1.0	0.99

[a]Patient (b) (6) was re-enrolled as (b) (6) The prior 6 months data relate to patient (b) (6) the data for WIL-33 relate to the initial enrollment period as patient (b) (6) and the second enrollment period as patient (b) (6)
[b]These patients switched from on-demand treatment to prophylaxis during the 6 months prior to the screening visit. TABRs were 2.00 (b) (6) and 4.00 (b) (6) in the 0.5 years prior to switching.
[c]Number of bleeds in the 6 months prior to the screening visit (as documented in the screening visit question) multiplied by 2.
Source: List 14.2.3.5-1, List 16.2.6.2-4, List 16.2.6.2-5, List 16.2.4-14, List 16.2.4-15.

*Source: IR response November 20, 2025

Reviewer's Comment:

- *Comparison is difficult not only due to recall bias but also 6 of the 7 patients on prior prophylaxis were on prophylaxis with commercial Wilate prior to the study with one on Humate P prophylaxis. Prior OD patients: Two received only commercial Wilate,*

one received both Immunate and commercial Wilate, and the other received both Immunate and Octanate.

- *The average prophylaxis on study for 12 patients was 54 IU/kg {median 47.2 (32–133)} comparable to 58.2 IU/kg {median 39.7 (26.9-137.9)} for the 7 patients on prophylaxis prior to study based on their weight at screening and prophylaxis dose prior to study. Five of these 7 patients prior to study received dosing per label of 30 – 50 IU/kg (one was dosed at 27 IU/kg but within standard +/- 10% based on vial size). Two received higher doses prior to the study at 88.2 and 137.9 IU/kg.*
- *Two patients at the same center received higher RP doses on study than recommended at 133.3 IU/kg and 77.2 IU/kg; these are the 2 patients who also were on higher RP dose prior to study entry. Patient* (b) (6) *receiving 133.3 IU/kg completed only 10 days of study before discontinuing due to inhibitor development. This patient also received the highest RP dose prior to study at 137.9 IU/kg. The other 10 patients in WIL-33 received RP dosing within 30-50 IU/kg per the label.*
- *Since the majority (10 of 12) of patients received RP dose between 30-50 IU/kg on the study, this dose is reflected in the USPI with recommendation to adjust based on IVR and clinical condition.*

Table 22: TABR during prophylaxis by bleeding type and VWD type

Bleeding type	ABR: mean (SD); median (range)							
	FAS (All BEs)		FAS (Treated BEs)		PP (All BEs)		PP (Treated BEs)	
	Type 2	Type 3	Type 2	Type 3	Type 2	Type 3	Type 2	Type 3
N	4	8	4	8	3	5	3	5
Total	2.1 (1.0) 2.3 (1.0–3.0)	5.8 (7.2) 4.0 (0–22.6)	2.1 (1.0) 2.3 (1.0–3.0)	4.4 (6.2) 2.5 (0–18.7)	2.3 (1.1) 2.9 (1.0–3.0)	3.4 (2.2) 3.9 (0–5.9)	2.3 (1.1) 2.9 (1.0–3.0)	2.0 (1.6) 2.0 (0–4.0)
Spontaneous	1.0 (1.4) 0.4 (0–3.0)	0.9 (1.1) 0.5 (0–3.0)	1.0 (1.4) 0.4 (0–3.0)	0.6 (1.1) 0 (0–3.0)	1.0 (1.7) 0 (0–3.0)	1.2 (1.3) 1.0 (0–3.0)	1.0 (1.7) 0 (0–3.0)	0.8 (1.3) 0 (0–3.0)
Traumatic	1.2 (1.2) 0.9 (0–2.9)	1.5 (2.0) 1.0 (0–5.9)	1.2 (1.2) 0.9 (0–2.9)	1.2 (2.0) 0.5 (0–5.9)	1.3 (1.5) 1.0 (0–2.9)	1.2 (0.8) 1.0 (0–2.0)	1.3 (1.5) 1.0 (0–2.9)	0.8 (0.8) 1.0 (0–2.0)
Other	- -	3.5 (8.0) 0 (0–22.6)	- -	2.6 (6.6) 0 (0–18.7)	- -	1.0 (2.2) 0 (0–4.9)	- -	0.4 (0.9) 0 (0–2.0)

Source: WIL-33 CSR page 77

Reviewer's Comment:

Table 12 shows total and treated ABR by VWD Type. ABRs were higher within Type 3 but largely due to patient (b) (6) *frequent epistaxis from seasonal allergies. This patient did not have their dose increased as per protocol to increase with > 2 BEs within 30 days. The PP results in the table demonstrates the total and treated ABRs excluding the 4 patients with protocol deviations, including patient* (b) (6).

6.1.11.2 Analyses of Secondary Endpoints

PK endpoints:

1) PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C at blood samples at baseline, 15 minutes, 3, 9, 24, 48 and 72 hours after dosing 80 IU/kg BW Wilate.
2) Incremental in-vivo recovery (IVR) of Wilate for VWF:Ac (VWF:RCo) and FVIII:C at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment.

Reviewer's Comment:
We investigated PK and ABR data of all individual patients to examine whether lower exposure (Cmax or AUC) would explain higher TABR in patients that had higher than average TABR. As shown by data listed in Table 23 and 24,, those patients who experienced ABR > 5 had higher exposure than average and some patients who experienced low ABR had lower exposure. Therefore, it was not the exposure issue that caused the higher TABR.

Table 23 **VWF:RCo PK parameters and ABR results of individual patients (N=11)**

	Patient										
Parameter	(b) (6)	(b) (6) *	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)
Cmax (IU/dL)	129.2	144.64	112.25	67.46	108.59	85.99	104.65	111.49	117.29	85.87	127.41
AUC(0-inf) (IU*hr/dL)	2259.4	1603.2	944.19	531.32	1740	596.3	1021.6	1123.3	1165.6	728.52	884.97
Recovery (%IU/kg)	1.615	1.808	1.403	0.843	1.357	1.075	1.308	1.394	1.466	1.073	1.593
Age (years)	3	2	2	2	4	2	3	5	1	3	1
VWD type	2	3	3	2	2	2	3	3	3	3	3
ABR	2.89	2.97	5.94	0.96 #	2.98	0.99	0.00	22.64	4.02	3.93	6.89
sABR	0.00	0.99	0.00	0.00 #	2.98	0.00	0.00	0.00	3.02	1.96	0.98

* Patient (b) (6) in the PK set was excluded from the PK-PP set presented in the draft USPI due to a deviation from the planned dose administered for the PK.
# Patient (b) (6) FAS analysis values: ABR 1.68, sABR 0.84.
sABR= spontaneous ABR
Source: Applicant's response to information request, submitted on 1/30/2026

Table 24 **FVIII PK parameters and ABR results of individual patients (N=11)**

	Patient										
Parameter	(b) (6)	(b) (6) a}	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6)	(b) (6) b}	(b) (6)	(b) (6)	(b) (6) {b}
Cmax (IU/dL)	111.58	150.38	123.98	69.05	112.53	94.05	136.27	N/A	159.28	106.4	N/A
AUC(0-inf) (IU*hr/dL)	1381.7	3382.2	3711.2	696.63	2228.5	1744.6	2400.3	N/A	3472.4	3640.7	N/A

Recovery (%IU/kg)	1.395	1.88	1.55	0.863	1.407	1.176	1.703	N/A	1.991	1.33	N/A
Age (years)	3	2	2	2	4	2	3	5	1	3	1
VWD type	2	3	3	2	2	2	3	3	3	3	3
ABR	2.89	2.97	5.94	0.96 #	2.98	0.99	0.00	22.64	4.02	3.93	6.89
sABR	0.00	0.99	0.00	0.00 #	2.98	0.00	0.00	0.00	3.02	1.96	0.98

* Patient (b) (6) in the PK set was excluded from the PK-PP set presented in the draft USPI due to a deviation from the planned dose administered for the PK.
# Patient (b) (6) FAS analysis values: ABR 1.68, sABR 0.84.
sABR= spontaneous ABR
Source: Applicant's response to information request, submitted on 1/30/2026

Efficacy Secondary Endpoints:

Efficacy of Wilate in the treatment of spontaneous and traumatic BEs based on the proportion of spontaneous and traumatic BEs successfully treated with Wilate as assessed by a 4-point ordinal hemostatic efficacy of excellent, good, moderate, or none.

There were 56 BEs (45 treated) during prophylaxis. Of the treated BEs, all had excellent or good hemostatic efficacy consistent among all bleeding sites, type, and severity. The mean dose per BE was 58.7 IU/kg with a median of 52.9 (range 30.9 – 153.8) IU/kg.

Table 23: Efficacy Assessment of Treatment of BEs

Efficacy Rating	**FAS (N=12)** **(47 BEs)**
Excellent	46 (98%)
Good	1 (2%)

Source: WIL-33 ADCE datasets

Reviewer's Comment:

- *Two treated BEs occurred on study but before RP began; 1 excellent and 1 good efficacy rating. Both were spontaneous epistaxis.*
- *The BE with efficacy rating of good treated before RP began was a major BE of spontaneous epistaxis that required 2 Wilate infusions.*
- *For treated BEs, concomitant medication was used for 14 BEs:*
  - *tranexamic acid was used for (10 epistaxis, 1 left finger cut)*
  - *commercial Wilate for 1 epistaxis*
  - *curaspon and tranexamic acid for 1 epistaxis*
  - *aminocaproic acid for 1 small peritoneal tear*

Table 24: Distribution and Characteristics of the BEs during Prophylaxis

Parameter	FAS [56 BEs]	FAS [45 treated BEs]
BEs by site, N (%)		
Nose	35 (62.5)	29 (64.4)
Oral cavity	7 (12.5)	3 (6.7)
Other non-joint	13 (23.2)	12 (26.7)
Joint	1 (1.8)	1 (2.2)
BE type, N (%)		
Spontaneous	11 (19.6)	9 (20.0)
Traumatic	17 (30.4)	15 (33.3)
Other	28 (50.0)	21 (46.7)
BE severity, N (%)		
Minor	55 (98.2)	44 (97.8)
Major	1 (1.8)	1 (2.2)

Source: WIL-33 CSR page 66

Reviewer's comment:

There was only 1 major BE of left periorbital hematoma that required 1 dose of Wilate with excellent hemostasis with the rest being minor. There was also only 1 joint bleed that required 1 dose of Wilate with excellent hemostasis. The majority (23) of "other" BEs were epistaxis with 3 oral BEs and 2 BEs secondary to port needle insertion.

Overall efficacy of Wilate in perioperative prophylaxis assessed by a 4-point ordinal hemostatic efficacy scale of excellent, good, moderate, or none.

One 2-year-old patient had major port removal surgery in WIL-33 with excellent efficacy rated by the hematologist and surgeon at end of surgery, end of perioperative period, and overall efficacy. Blood loss was not recorded.

Reviewer's Comment:

While only 1 patient underwent surgery in this age group WIL-33, in the prior clinical trials, there were 22 (17 minor and 5 major) surgeries in 13 patients ≤ 16 years (3 patients 0 to 2 years, 4 patients 2 to 5 years, 3 patients 6 to 12 years, and 3 patients 12 to 16 years). The surgery outcomes were all rated as successful. The patient from WIL-33 was added to the label to reflect pediatric surgeries within this age group.

Wilate consumption data for prophylaxis, OD, and during surgical prophylaxis.

Prophylaxis consumption:

At study start, 9 (75.0%) patients received Wilate prophylaxis 2x per week and 3 (25%) patients 3x per week. At study end, 8 (66.7%) patients were receiving Wilate 2x per week and 4 (33.3%) patients were receiving Wilate 3x per week.

Table 25: Wilate Consumption for Prophylaxis in FAS Population (N=12); Mean (SD), Median (range)

Time on prophylaxis, months	Number of EDs	Number of Injections	Dose per injection, IU/kg	Dose per week, IU/kg
11.4 (3.5) 12.2 (0.3–14.3)	109 (36.1) 111.5 (3.0–139.0)	109 (36.1) 111.5 (3.0–139.0)	54 (27.5) 47.2 (31.5–133.3)	120.1 (65) 100.2 (63.3–311.1)

Source: WIL-33 CSR page 70

Reviewer's Comment:

- *Patient* (b) (6) *received 3 doses at 133.3 IU/kg before study discontinuation and patient* (b) (6) *received a mean dose of 77.2 IU/kg per infusion. All other patients received prophylaxis dosing within 30-50 IU/kg per the protocol and label (+/- 10% of vial size, which is acceptable in clinical practice).*
- *Since most patients received routine prophylaxis dosing of 30-50 IU/kg 2-3 times per week with adequate control of bleeding episodes, this is the dosing regimen added to the label for this age group. The statement "Adjust dosage depending on the severity of VWD, clinical condition and/or pharmacokinetic data. Additionally, for on-demand treatment, adjust dosage and duration based on location and extent of the bleeding" was added to adjust the dosing based on the patients' individual profiles.*

BE Consumption:

Table 26: Wilate Consumption for BEs, (N=12 patients; 47 BEs); Mean (SD), Median (range)

Number of EDs per BE	Number of Injections per BE	Dose per injection, IU/kg	Dose per BE, IU/kg

1 (0.2) 1 (1–2)	1.1 (0.2) 1 (1–2)	55 (22.3) 52.9 (30.9–153.8)	58.7 (27.6) 52.9 (30.9–153.8)

Source: WIL-33 CSR 71

Reviewer's Comment:

- *All but 1 were minor BEs with 1 being a major BE.*
- *Recommended dosing for minor BEs per the protocol was a loading dose of 30-50 IU/kg with maintenance dose of 30-40 IU/kg every 12 to 24 hours. Dosing within +/- 10% of recommended dosing is acceptable in clinical practice. There were 10 BEs in 4 patients who received treatment for BEs with Wilate outside of this dosing. Three patients were treated with doses of 62.11, and 62.5, and 64.52 IU/kg for 3 BEs. Patient* (b) (6)*, who received higher than protocol recommended prophylaxis doses, also received higher than protocol recommended treatment doses for BEs with a mean dose per infusion/BE of 96.6 IU/kg and median of 80.7 IU/kg (range 78.7-153.8) for 7 minor BEs, all requiring 1 infusion. The other BEs were treated with a mean infusion dose of 47.6 IU/kg and median 51.28 IU/kg (30.9-64.52).*
- *1 major BE of traumatic left periorbital hematoma was treated with 1 infusion of 51.28 IU/kg of Wilate.*
- *There were 2 minor BEs of epistaxis in 2 patients that required 2 infusions for treatment with mean infusion doses of 45.27 IU/kg in patient* (b) (6) *and 64.52 IU/kg in patient* (b) (6)*.*

Surgery Consumption:

One 2-year-old patient had major port removal surgery treated with a total dose of 186.3 IU/kg (1 preoperative dose of 62.1 IU/kg and 4 postoperative doses of 31.1 IU/kg).

Reviewer's Comment:

This patient received 62.2 IU/kg (1000 unit vial) loading dose with additional 4 postoperative doses of 31.1IU/kg (500 unit vials). The patient's weight was 16 kg at time of surgery. The 62.2 IU/kg is 34 units above the upper limit of 40-60 IU/kg that is recommended for major surgery which is most likely due to the vial size of 500 vs. 1000 units. The patient would have been underdosed at 31.1 IU/kg if a 500 unit vial was used for the preoperative dose and so received 1000 units which resulted in a higher dose than that calculated..

Joint health status determination with the HJHS, given that the patient's age and constitutional development allow this assessment:

Table 27: Hemophilia Joint Health Score

Parameter/visit	FAS	
	N	Mean (SD) [Min, Max]
Global gait score		
Baseline	11	0.36 (1.21) [0, 4]
12-months	10	0.40 (0.84) [0, 2]
Change from baseline	10	0 (0.94) [-2, 2]
Total score		
Baseline	11	1.55 (3.01) [0, 10]
12-months	10	0.80 (1.93) [0, 6]
Change from baseline	10	-0.90 (1.37) [-4, 0]

Source: WIL-33 CSR page 81

The mean change from baseline was 0 for the global gait score.

Reviewer's Comment:

The HJHS is validated for adults only. While it has been used with reportable reliability in both adults and children, it is difficult to draw any conclusions based on this scale in pediatric patients at ages that require parent reporting. Also, it is unlikely for patients with VWD at this age to have target joints. The efficacy data particularly the dose in the peri-operative period and treatment of minor bleeds using the dose of 30-50 IU/kg provides supportive data for the RP indication in this cohort, in that it demonstrates that this dose albeit with a different frequency of administration from RP suggests may Wilate be sufficient to prevent bleeding.

Exploratory Endpoint:

The exploratory endpoint was solely investigated in type 3 VWD patients with ≥14.5 kg body weight. It was VWF multimer analysis from the PK samples taken at 15 minutes, and 24 hours after Wilate injection, by using multimer analysis using low- and high-resolution electrophoresis gels.

There were 4 patients who met this criteria. Patient (b) (6) was excluded from the analysis due to the development of inhibitors. Within the 3 patients included in the analysis, the majority of multimers were small and intermediate at both timepoints with an increase in smaller multimers following the infusion.

Table 28: Percentage Multimers at 15 minutes and 24 hours following the PK Infusion in Type 3 Patients (N=3)

Multimer size	Percentage of Small, Intermediate and Large Multimers, Mean (SD)	
	15 min after PK infusion	24 h after PK infusion
Small (1–5)	39.4 (6.3)	49.2 (9.8)
Intermediate (6–10)	45.8 (2.3)	41.5 (7.3)
Large (>10)	14.8 (4.1)	9.2 (2.6)

Source: WIL-33 CSR page 73

6.1.11.3 Subpopulation Analyses

NA

6.1.11.4 Dropouts and/or Discontinuations

Please see above 6.1.10.1.3 Patient Disposition for a detailed account of any patients who dropped out of or discontinued the WIL-33 study.

6.1.12 Safety Analyses

The safety endpoints were secondary endpoints including:

- Incidence of VWF and FVIII inhibitors
- Incidence of thromboembolic events
- Safety and tolerability of Wilate by monitoring adverse events (AEs)

6.1.12.1 Methods

The clinical safety of Wilate in WIL-33 was assessed by monitoring AEs, vital signs, laboratory parameters, and immunogenicity.

AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. The analysis included only TEAEs defined as AEs that started or worsened after the first Wilate infusion. All TEAEs were summarized and tabulated according to MedDRA primary system organ class and preferred term.

Reviewer's Comment:

There were no adverse events of special interest (AESIs) reported by the Applicant in this study. However, development of inhibitor to VWF and FVIII in one patient was considered an AESI by the clinical reviewer, probably related to the product and is included in the USPI. Typical AESI's in VWF Factor studies include inhibitor development, hypersensitivity reactions, and thromboembolic events, all included within this review. Inhibitor development and thromboembolic events were included in the secondary endpoints.

6.1.12.2 Overview of Adverse Events

Eleven patients (91.7%) experienced 47 treatment emergent adverse events (TEAEs). Five serious TEAEs occurred in 5 (41.7%) patients. Three serious adverse events (SAEs) occurred in 3 patients (25%). One SAE of inhibitor development determined by the reviewer in 1 (8.3%) patient led to permanent discontinuation of study medication.

Four patients (33.3%; 4 of 12) experienced 37 mild TEAEs. Four subjects had (33.3%; 4 of 12) moderate TEAEs while 3 subjects (25%; 4 of 12) had severe TEAEs (soft tissue infection, iron deficiency anemia, and VWF and Factor VIII inhibitor development).

The most common AEs were iron deficiency anemia (3 patients), nasopharyngitis, cough, and pyrexia (each in 2 patients [16.7%]).

The Applicant assessed 1 AE of pyrexia in 1 patient as probably/possibly related. Pyrexia was assessed to be possibly related by the applicant and reviewer. Soft tissue infection was assessed as possibly related by this reviewer. VWF and Factor VIII inhibitor development was assessed as probably related by this reviewer.

Table 29: Display of TEAE's by SOC

Primary SOC	N (%) of patients	Number of TEAEs
Any TEAE	11 (91.7)	47
Infections and Infections	7 (58.3)	16
Blood and lymphatic disorders	3 (25)	4
General disorders and administration site disorders	3 (25)	7
Respiratory, thoracic, and mediastinal disorders	2 (16.7)	2
Gastrointestinal disorders	2 (16.7)	10
Injury, poisoning, and procedural complications	2 (16.7)	3
Immune System Disorders	1 (8.3)	1
Metabolism and nutrition disorders	1 (8.3)	1
Psychiatric disorders	1 (8.3)	1
Vascular disorders	1 (8.3)	1
Skin and subcutaneous disorders	1 (8.3)	1

Source: WIL-33 CSR pages 97-98, AE dataset, and reviewer interpretation of AE data

6.1.12.3 Deaths

There were no deaths in WIL-33.

6.1.12.4 Nonfatal Serious Adverse Events

Non-fatal SAEs are listed in Table 30 with causality per Applicant. Five patients experienced 5 SAEs during this study. The clinical reviewer agreed with the Applicant in the causality assessment for pyrexia, soft tissue infection and VWF and FVIII inhibitor development..

Table 30: WIL-33 Nonfatal Serious Adverse Events

SAE	Reason for Seriousness	Study Day at Onset	Outcome	Causality
Pyrexia	Required hospitalization	2	Recovered/Resolved	Possibly Related
Soft tissue infection	Required hospitalization	250	Recovered/Resolved	Possibly Related
Pneumonia	Required hospitalization	17	Recovered/Resolved	Not Related
Iron Deficiency Anemia	Required hospitalization	2	Recovered/Resolved	Not Related
VWF and Factor VIII Inhibitor Development	Medically important condition requiring study drug discontinuation	3	Not Recovered/Not Resolved	Probably Related

Source: Clinical review analysis of WIL-31 Study report body

Reviewer's Comment:

Patient (b) (6) *with Type 3 was on study for 10 days and received 1 PK and 3 prophylaxis doses. The patient discontinued the study early due to VWF and FVIII inhibitor detection . This patient had been receiving commercial Wilate prior to enrollment and had > 180 EDs prior to enrollment. At screening* (b) (6) *), VWF inhibitor was negative and FVIII inhibitor was 1.4 (negative < 0.6) per central lab. At repeat* (b) (6) *, they were both negative per central lab. Following PK dose (*(b) (6) *, both were positive with VWF inhibitor of 1.2 (any detection is considered positive) and Factor VIII inhibitor of 1.6 (negative < 0.4). At study discontinuation (*(b) (6) *), both were positive with VWF inhibitor "positive" (any detection is considered positive) and Factor VIII inhibitor of 1.8 (negative < 0.6).*

Table 31: PK study results for patient (b) (6)

Timepoint	VWF (normal 37.3-106.1) (IU/dL)	FVIII (normal 70-150) (IU/dL)
Pre-infusion	6.3	4.4
15 minutes post	27.8	missing
3 +/- 1 hour post	2.5	1.5
9 +/- 2 hours post	2.5	1.5
24 +/- 2 hours post	6.2	missing
48 +/- 2 hours post	2.5	1.5
72 +/- 2 hours post	2.5	1.5
Pre-infusion at study completion	2.5	1.5

Source: Datasets ADLBS

While the repeat inhibitors were negative both locally and centrally at screening, PK data showed limited FVIII recovery indicating presence of inhibitor prior to initial PK dose per the applicant. The patient was discontinued from study; however, this was not considered a discontinuation due to TEAE nor was the inhibitor considered an AE by the applicant. An IR was sent on December 17, 2025, for further clarification. The Applicant clarified that following study discontinuation, the patient discontinued Wilate treatment and started prophylaxis with emicizumab and Factor VIIa for breakthrough treatment. Also, per the applicant, "The Wilate product used in the study was manufactured using the same production process as the commercial Wilate that the patient was on prior to the study. However, the batch number of the commercial product used was not reported by the investigator." Based on these findings, we have concluded that the development of VWF and FVIII inhibitors is probably related to Wilate, indicating a probable causal association between Wilate and inhibitor formation. Therefore, this inhibitor development will be included in the label in sections Section 5.3 Warnings and Precautions (Neutralizing Antibodies) and 12.6 Immunogenicity.

Patient (b) (6) *developed a soft tissue infection at the site of the central venous port system. Per IR response, the infection developed on August 8, 2022, with the last prophylaxis dose prior to this occurring* (b) (6) *. The patient was originally treated conservatively with oral Cefixime* (b) (6) *, through* (b) (6) *. The infection worsened September 26, 2022, with the last prophylaxis dose prior to this occurring* (b) (6) *, and the patient received prophylaxis doses twice weekly in between the original and worsening infection. Ultimately, the central venous port system was removed on* (b) (6) *. This reviewer concludes that the soft tissue infection can't be completely ruled out by other factors and therefore, the relationship with Wilate can't be ruled out entirely and is possibly related.*

Patient (b) (6) *developed pyrexia within 24 hours following Wilate and therefore is considered possibly related by the applicant and reviewer.*

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no AESI's in this study per the applicant. Typical AESI's in VWF studies include inhibitor development, hypersensitivity reactions, and thromboembolic events. Inhibitor development and thromboembolic events were included in the secondary endpoints. This review includes evaluations of these as well as hypersensitivity.

Hypersensitivity Reactions

There were no hypersensitivity reactions in WIL-33 or AE's concerning potential hypersensitivity reactions.

Thromboembolic Events

There were no thromboembolic events in WIL-33.

Neutralizing Antibodies

Please see section 6.1.12.4 Nonfatal Serious Adverse Events.

6.1.12.6 Clinical Test Results

Besides the inhibitor development described above, no other safety concerns were raised by clinical laboratory results.

6.1.12.7 Dropouts and/or Discontinuations

One patient had an AE of inhibitor development that led to permanent discontinuation of Wilate that was considered probably related and not recovered and not resolved.

6.1.13 Study Summary and Conclusions

The primary endpoint was TABR during prophylaxis with Wilate in patients < 6 years. Overall, study WIL-33 demonstrated that Wilate prophylaxis is efficacious in children < 6 years. The mean TABR was 4.6 with an SABR of 0.9. This is lower than TABR of 5.49 for RP in children 5-17 years in study WIL-31. A higher dose of 30-50 IU/kg two-three times per week is proposed in children < 6 years of age given higher clearance. Ten of 12 subjects in WIL-33 used this dose per protocol while two subjects used higher doses. The dose of 30-50 IU/kg is included in the USPI with recommendation for individual adjustment based on IVR and clinical judgement.

The safety profile is acceptable. One patient developed an inhibitor requiring discontinuation of study drug. Therefore, we will include inhibitor development in the label in sections *Section 5.3 Warnings and Precautions (Neutralizing Antibodies) and 12.6 Immunogenicity.*

The overall benefit-risk assessment is considered favorable.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Patients with VWD underwent substantial exposure to Wilate, and the safety data collected from these studies was submitted to support the safety profile of Wilate.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data are pooled for all 10 Wilate studies in patients with VWD (WIL-33, WIL-31, WIL-14, TMAE-104, TMAE-105, TMAE-106, TMAE-109, WIL-12, WIL-21, and WIL-24).

In the pooled analysis there were a total of 225 (208 individual) patients.

Table 321: Studies Used in Integrated Safety Analysis of Wilate for VWD

Study	Safety Population	Design	Treatment
WIL-33	12 patients with severe VWD receiving prophylaxis (ages < 6 years)	Phase 3, open-label, noncontrolled, multicenter trial (9 centers US, Czech Republic, Germany, Moldova, Macedonia, Russia, and Ukraine)	Wilate-Routine prophylaxis
WIL-31 (pivotal study)	43 patients with inherited VWD, Type 1, 2A, 2B, M, or 3 requiring substitution with a VWF-containing product (age ≥6 years)	Phase 3, open-label, noncontrolled, multicenter trial (14 centers in Bulgaria, Belarus, Croatia, Hungary, Lebanon, Russia, Ukraine, and the United States	Wilate-Routine prophylaxis, surgical prophylaxis, and on-demand treatment
TMAE-104	41 patients with inherited VWD, any type, not responding to DDAVP (age ≥6 and ≤85 years)	Phase 3, open-label, noncontrolled, multicenter trial (15 centers in Austria, Finland, Norway, Poland, Portugal, Sweden, and the United Kingdom)	Wilate-Surgical prophylaxis and on-demand treatment
TMAE-105	14 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open-label, noncontrolled, multicenter trial (2 centers in Poland and Bulgaria)	Wilate-PK assessment, surgical prophylaxis, and on-demand treatment
TMAE-106	14 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open-label, noncontrolled, multicenter trial (8 centers in Germany)	Wilate-PK assessment
TMAE-109	16 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open-label, noncontrolled, multicenter trial (2 centers in Poland and Bulgaria)	Wilate-Surgical prophylaxis treatment

Study	Safety Population	Design	Treatment
WIL-12	22 patients with any type of inherited VWD (age ≥12 years)	Phase 2, open-label, randomized, controlled, crossover, multicenter trial (6 centers in the United States)	Wilate/Humate-P-PK assessment
WIL-14	15 children with inherited VWD, any type, DDAVP treatment known or suspected to be inadequate	Phase 2, open-label, non-controlled, multi-center trial (7 centers in Germany, Poland, France, and the Czech Republic)	Wilate-Surgical prophylaxis, on-demand treatment
WIL-21	9 patients (age ≥12 years)	Phase 2, prospective, open-label, randomized, controlled, 2-arm crossover, single-center trial in the Slovak Republic	Wilate/Humate-P-PK assessment
WIL-24	41 patients with inherited VWD undergoing surgical procedures (age ≥6 years)	Phase 3, prospective, uncontrolled, open-label, multicenter trial (25 centers in the United States, India, Turkey, Poland, Italy, South Africa, Bulgaria, Romania, and Oman)	Wilate-Surgical prophylaxis

Source: WIL-31 Clinical Summary, Synopses of Individual Studies, 2.7.6.1 Tabular Listings of VWD Clinical Studies
Abbreviations: DDAVP = desmopressin, PK = pharmacokinetic, VWD = von Willebrand disease.

Reviewer Comment(s): The safety data submitted is adequate to assess a thorough analysis of Wilate's safety profile.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 2: Extent of Total Exposure to Wilate (All Studies)

Population Parameter	WIL-14	TMAE-104	TMAE-105	TMAE-106	TMAE-109	WIL-12	WIL-21	WIL-24	WIL-31	All Studies
Safety†										
Patients, N	15	41	14	14	16	22	9	39	43	198
Infusions, n	419	5185	211	254	345	23	9	323	3992	10761
EDs, N	389	4908	202	201	343	23	9	262	3948	10285
Total dose, IU	223,290	8,620,000	432,500	420,900	707,000	89,100	21,800	791,760	7,742,480	19,048,830

Source: Summary of clinical safety, page 4

Reviewer Comment(s): The exposure to Wilate and safety profile from these studies should accurately predict the safety of Wilate use in patients with VWD.

8.2.3 Categorization of Adverse Events

AEs were coded according to MedDRA Version 23.1 for studies WIL-33, WIL-31, TMAE-106, and WIL-14. The analysis included only TEAEs defined as AEs that started or worsened after the first Wilate infusion. All TEAEs were summarized and tabulated according to MedDRA primary system organ class and preferred term.

For TMAE-104, TMAE-109, WIL-12, WIL-21, WIL-24, there was documentation of AEs throughout the study period.

TMAE-105—AEs were coded according to the World Health Organization Adverse Drug Reactions dictionary and grouped by body system.

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

Safety data are pooled for all 10 Wilate studies in patients with VWD (WIL-33, WIL-31, WIL-14, TMAE-104, TMAE-105, TMAE-106, TMAE-109, WIL-12, WIL-21, and WIL-24). These trials were for differing indications with different doses in VWD.

Reviewer Comment(s): Pooling of data across these ten trials is challenging as they are varied populations with different dosing schedules, doses, and for different indications (PK studies, on-demand, surgical prophylaxis, regular prophylaxis, etc). However, this pooled data does provide supportive evidence to the safety and tolerability of Wilate.

8.4 Safety Results

8.4.1 Deaths

One patient died in the TMAE-104 study. This was a 48-year-old male patient with a history of Type 3 VWD enrolled into the study on (b) (6), in (b) (6). This patient had a history of gastrointestinal hemorrhages due to intestinal angiodysplasia. On (b) (6), this patient was hospitalized for a severe gastrointestinal BE that could not be controlled with Wilate, blood transfusions, cryoprecipitate, fresh frozen

plasma, and tranexamic acid. This patient had surgery on (b) (6), to remove the intestine segment that was the cause of the uncontrollable BE confirmed by an intra-operative endoscopy. The surgeon's assessment of hemostatic efficacy of Wilate as 'very good' during surgery. However, the patient developed hypotension due to intra-abdominal bleeding and underwent surgery to stop bleeding. The next day, the patient developed renal failure, and "controlled respiration" was employed and ultimately died on (b) (6). The investigator adjudicated this death as unrelated to Wilate.

No deaths were reported in the other 9 studies.

Reviewer Comment(s): There were no deaths in WIL-33. After careful review of the patient death in the TMAE-104, this reviewer considers that is unlikely related to Wilate. The patient died from complications related due to intestinal angiodysplasia that was diagnosed prior to study enrollment. FVIII levels were reported to be normal making an inhibitor to product less likely.

8.4.2 Nonfatal Serious Adverse Events

Nonfatal Serious Adverse Events from Pooled Population

Table 3: Frequency of Serious Adverse Events (All Studies)

SAE, Preferred Term	Patients With SAE–n (%)	SAEs (N)
Any class	31 (15)	91
Gastrointestinal disorders	12 (5.8)	52
Gastrointestinal hemorrhage	5 (2.4)	33
Melena	2 (1.0)	13
Food poisoning	1 (0.5)	1
Gastritis erosive	1 (0.5)	1
Hematemesis	1 (0.5)	1
Hemorrhoidal hemorrhage	1 (0.5)	1
Mouth hemorrhage	1 (0.5)	1
Pancreatitis, acute	1 (0.5)	1
Infections and infestations	6 (2.9)	7
COVID-19 pneumonia	1 (0.5)	1
Device related infection	1 (0.5)	2
Device related sepsis	1 (0.5)	1
Parotitis	1 (0.5)	1
Pneumonia	1 (0.5)	1
General disorders and administration site conditions	4 (1.9)	4
Catheter site hemorrhage	1 (0.5)	1
Chest pain	1 (0.5)	1
Multiple organ dysfunction syndrome	1 (0.5)	1

SAE, Preferred Term	Patients With SAE–n (%)	SAEs (N)
Pyrexia	1 (0.5)	1
Injury poisoning and procedural complications	3 (1.4)	3
Accident	1 (0.5)	1
Head injury	1 (0.5)	1
Scratch	1 (0.5)	1
Investigations	3 (1.4)	3
Parvovirus B19	3 (1.4)	3
Musculoskeletal and connective tissue disorders	3 (1.4)	6
Back pain	1 (0.5)	1
Hemarthrosis	1 (0.5)	3
Synovitis	1 (0.5)	1
Torticollis	1 (0.5)	1
Reproductive system and breast disorders	2 (1.0)	3
Heavy menstrual bleeding	1 (0.5)	2
Vaginal hemorrhage	1 (0.5)	1
Respiratory, thoracic, and mediastinal disorders	2 (1.0)	6
Epistaxis	2 (1.0)	6
Blood and lymphatic system disorders	3 (1.5)	3
Blood loss anemia	1 (0.5)	1
Inhibitors	1 (0.5)	1
Iron deficiency anemia	1 (0.5)	1
Immune system disorders	1 (0.5)	1
Transplant rejection	1 (0.5)	1
Nervous system disorders	1 (0.5)	1
Syncope	1 (0.5)	1
Surgical and medical procedures	1 (0.5)	1
Tooth extraction	1 (0.5)	1
Vascular disorders	1 (0.5)	1
Hemorrhage	1 (0.5)	1

Source: Summary of Clinical Safety, Table 8, pages 10-11 as well as reviewer's adjudication

8.4.3 Study Dropouts/Discontinuations

WIL-33:

- Patient (b) (6) : withdrew due to VWF and FVIII inhibitor development

8.4.4 Common Adverse Events

Overall, the most common adverse reactions to treatment with Wilate (≥1%) in patients with VWD were hypersensitivity reactions, urticaria, chest discomfort, and dizziness.

Table 4: TEAEs Possibly or Probably Related to Treatment (All Studies)

Preferred Term	**Patients With AE–n (%)**	**AEs (N)**
Any class	23 (11)	37
Infections and Infestations	1 (0.5)	1
Soft tissue infection	1 (0.5)	1
Investigations	6 (3.0)	6
Parvovirus B19 test positive	5 (2.5)	5
Blood pressure decreased	1 (0.5)	1
Nervous system disorders	5 (2.4)	6
Dizziness	3 (1.4)	4
Dysgeusia	1 (0.5)	1
Headache	1 (0.5)	1
Immune system disorders	4 (1.9) 6	4 (1.9) 6
Hypersensitivity	4 (1.9) 6	4 (1.9) 6
Skin and subcutaneous tissue disorders	4 (1.9)	4
Urticaria	2 (1.0)	2
Pruritis	1 (0.5)	1
Rash	1 (0.5)	1
Gastrointestinal disorders	3 (1.4)	3
Abdominal discomfort	1 (0.5)	1
Nausea	1 (0.5)	1
Vomiting	1 (0.5)	1
General disorders and administration site conditions	3 (1.4)	6
Chest discomfort	2 (1.0)	4
Feeling hot	1 (0.5)	1
Pyrexia	1 (0.5)	1

Preferred Term	Patients With AE–n (%)	AEs (N)
Blood and lymphatic system disorders	2 (1)	2
Anemia	1 (0.5)	1
Inhibitor	1 (0.5)	1
Ear and labyrinth disorders	1 (0.5)	1
Vertigo	1 (0.5)	1
Respiratory, thoracic, and mediastinal disorders	1 (0.5)	1
Dyspnea	1 (0.5)	1
Vascular disorders	1 (0.5)	1
Hypertension	1 (0.5)	1

Source: Summary of Clinical Safety, Table 6, pages 8 as well as reviewer's adjudication
.

Supportive Studies

Eight non-serious AEs were considered as clinically significant:

- WIL-31:
  - Patient (b) (6) : withdrew due to hypersensitivity reaction
  - Patient (b) (6) : withdrew due to chest discomfort
- TMAE-106, Patient (b) (6) discontinued due to an allergic reaction. The investigator classified this event as nonserious and probably related to Wilate.
- WIL-12, Patient (b) (6), increased liver transaminase levels. The investigator considered these laboratory changes as unrelated to Wilate.
- WIL-24, Patient (b) (6): hypersensitivity reaction (2 AEs). The investigator classified this event as unrelated to Wilate and more likely related to anxiety and the patient was withdrawn from the study.
- WIL-24, Patient (b) (6): hypersensitivity reaction. The investigator classified this event as related to Wilate. The infusion was stopped at the time of the infusion and later restarted, and the patient received the full dose. This patient did not experience any further hypersensitivity reactions with subsequent Wilate infusion.
- WIL-24, Patient (b) (6): hypersensitivity-like reaction. The investigator assessed this event as probably related to Wilate.
- WIL-24, Patient (b) (6): 2 seizures (AEs) related to hypertension following vaginal delivery with forceps. The investigator classified this event as unrelated to Wilate.

Reviewer Comment(s): The safety data from supportive studies is acceptable. Events related to immunogenicity (clinically significant adverse events) are described below.

8.5 Additional Safety Evaluations

8.5.8 Immunogenicity (Safety)

Patients with VWD may develop inhibitors (neutralizing antibodies) to VWF and FVIII.

Study WIL-33

One patient (b) (6)) with Type 3 was only on study for 10 days receiving 1 PK dose and 3 prophylaxis doses due to VWF and FVIII inhibitor detection. This patient had been receiving commercial Wilate prior to enrollment and had > 180 EDs prior to enrollment. At screening, VWF inhibitor was negative and FVIII inhibitor was 1.4 (negative < 0.6) per central lab. At repeat, they were both negative per central lab. Following PK dose, both were positive with VWF inhibitor of 1.2 (any detection is considered positive) and Factor VIII inhibitor of 1.6 (negative < 0.4). Finally, at study discontinuation, both were positive with VWF inhibitor "positive" (any detection is considered positive) and Factor VIII inhibitor of 1.8 (negative < 0.6). This inhibitor development resulted in the patient having to change their treatment for VWD to no longer receive Wilate.

Study WIL-31

Sampling for inhibitors took place during WIL-31 at baseline in adults, at screening in pediatric patients and if inhibitor development was suspected at any time. Six patients were tested for inhibitors during WIL-31; two due to SAEs that led to discontinuation of Wilate (mild chest discomfort and moderate hypersensitivity reactions) and two due to higher-than-expected bleeding rates. These four patients had negative VWF and FVIII inhibitors.

However, two patients tested positive for inhibitors at 6 months. Due to unexpected PK results (one with no rise in VWF:RCo and the other with minimal rise in VWF:RCo), their screening retention samples were tested and found to be positive for VWF inhibitors at study entry. As both patients were benefitting from treatment with prophylactic Wilate with decreased bleeding frequency, they were kept on-study. One tested positive for VWF inhibitor at the 9-month and 12-month visits and one tested positive for VWF inhibitor at the 9-month visit but tested negative at the 12-month visit. Neither had clinical implications and no changes in therapy were needed.

Study WIL-24

There were no inhibitory anti-VWF antibodies detected during the study. However, one patient tested positive for a non-inhibitory anti-VWF antibody. VWF:RCo, VWF antigen and FVIII:C for this patient were not affected during the study and the hemostatic efficacy of Wilate was rated as successful during surgery.

Reviewer Comment(s): Patients with VWD have been reported to develop inhibitory antibodies to VWF. These antibodies may render therapy ineffective and as a result,

patients may experience uncontrolled bleeding. Surveillance is recommended and is reflected in the label changes recommended with this submission. The label was updated to reflect the patient with inhibitor development in WIL-33.

8.6 Safety Conclusions

In all studies, a total of 127 (61) patients experienced 545 TEAEs. One VWF and FVIII inhibitor was not considered a TEAE or SAE by the applicant but was included as a TEAE and SAE by this reviewer. 91 SAEs occurred in 31 patients (15%). Relatedness of TEAEs and SAEs to Wilate was only collected in WIL-31 and WIL-33.

In WIL-31, 5 SAEs occurred in 4 patients (9.3%), none of which were attributed to Wilate. The SAEs included COVID-19 pneumonia, 2 episodes of menorrhagia, food poisoning and a hemorrhoidal hemorrhage. The most common AEs were headache, respiratory tract infection, and COVID-19. Two AEs (mild chest discomfort and a moderate hypersensitivity reaction) occurred in two patients which led to the discontinuation of Wilate. The investigator assessed two patients who experienced AEs as probably/possibly related to the study treatment, and the Applicant assessed four patients who experienced AEs as probably/possibly related to the study treatment.

In WIL-33, 3 SAEs occurred in 3 patients (25%). One SAE in 1 (8.3%) patient led to permanent discontinuation of study medication. The SAEs included soft tissue infection, iron deficiency anemia, and VWF and Factor VIII inhibitor development. The investigator assessed 3 patients who experienced AEs as probably/possibly related to the study treatment and the Applicant assessed 1 patient who experienced AEs as probably/possibly related to the study treatment. The most common AEs were iron deficiency anemia (3 patients), nasopharyngitis, cough, and pyrexia (each in 2 [16.7%]). Pyrexia was assessed to be possibly related by the applicant and reviewer. Soft tissue infection was assessed as possibly related by this reviewer. VWF and Factor VIII inhibitor development was assessed as probably related by this reviewer.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Animal reproduction studies have not been conducted with Wilate. Experience with pregnant or lactating women with Wilate is limited. In Study WIL-24, Wilate was administered for surgical prophylaxis to four patients (three with VWD Type 3 and one with VWD Type 2B) during labor and delivery. Two patients underwent vaginal delivery, and two patients had a cesarean section. All procedures were successful, and no AEs related to Wilate infusions were observed.

Due to the limited clinical experience in this population, Wilate should be used during pregnancy only if clearly indicated.

9.1.2 Use During Lactation

Due to the limited clinical experience in this population, Wilate should be used during lactation only if clearly indicated.

9.1.3 Pediatric Use and PREA Considerations

The Applicant has submitted safety and efficacy data for children < 6 years. Please see above Section 6.1.11.3 for this subpopulation analysis.

Please see above Section 5.4 for further details on pediatric use and Pediatric Research Equity Act considerations. The safety profile is acceptable. One patient did develop inhibitors to VWF and FVIII that will be included in the label.

10. CONCLUSIONS

Wilate has demonstrated efficacy for treatment with routine prophylaxis to reduce the frequency of BEs in children < 6 years with VWD. The primary endpoint for this study of TABR during prophylaxis with Wilate was 4.6. The TABR was 5.24 in patients 6 and older. Thus, TABR in this study is in the range for what is expected in this patient population. One patient had 22 BEs of epistaxis due to seasonal allergies; unclear if all of these BEs were related to underlying VWD. Sensitivity analysis excluding this patient results in a lower mean TABR. Wilate demonstrated efficacy (rating of excellent or good hemostasis) in treatment of 56 BEs. It was also successfully used for major surgery in 1 subject during this study. PK data showed expected increase in VWF and FVIII following infusion.

Despite the small sample size, the Applicant has provided substantial evidence of efficacy for the RP indication in children < 6 years of age in a single-arm trial. The efficacy results are in keeping with what is expected in this patient population. Confirmatory evidence of efficacy comes from the efficacy of Wilate in RP in patients 6 years and older, and mechanistic evidence of increase in the missing/decreased clotting protein i.e., increase in VWF and FVIII in subjects without inhibitors. Bleeding control was also observed with the same dose albeit with a different dosing frequency in patients treated for minor bleeding and following the immediate post-op phase providing additional supportive efficacy data. The efficacy conclusions based on the limited sample size, the confirmatory data from the PK studies and the additional efficacy data from treatment of minor bleeds and the post-surgical management to reduce or prevent post operative bleeding are consistent with review practices for evaluation of efficacy in rare diseases. The safety profile is acceptable and the risks of therapy mainly inhibitor development have been addressed through labeling. While formal hypothesis testing through statistical methods were not performed, the PK data was based on intra patient control to ensure that an appropriate dose to permit replacement of the VWF to levels associated with treatment and prevention of bleeding was reached. Based on the data and within the context of regulatory flexibility provided to rare disease review the clinical

team concludes that the Applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled clinical investigation providing compelling evidence of clinical benefit, supported by the initial clinical investigation. The overall benefit risk assessment is favorable, and the clinical review team recommends traditional approval for the indication expansion for the use of Wilate for routine prophylaxis to reduce the frequency of BEs in children < 6 years with VWD. The FDA exercised regulatory flexibility in granting the indication of RP to children < 6 years of age based on a single-arm study with a small sample size given the rarity of this subset of patients with VWD. The Applicant has fulfilled the PMR #1 under STN 125251/382 by submitting final data from clinical study WIL-33 as well as the required Pediatric Assessment. Based on the final data provided from clinical study WIL-33, this approval action also extends the currently approved indication of routine prophylaxis to reduce the frequency of bleeding episodes in VWD to pediatric patients < 6 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 5: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	VWD arises from a congenital VWF deficiency and is classified as Type 1, Type 2, or Type 3 • Type 1: partial quantitative deficiency, 70-80% of patients • Type 2: partial qualitative deficiency, 20% • Type 3: complete deficiency	Patients with congenital VWF deficiency are at risk of frequent BEs, which puts them at risk for potential morbidity and mortality.
Unmet Medical Need	• Currently, Vonvendi is approved for the use of routine prophylaxis to reduce the frequency of BEs in patients with VWD that are 18 years and older. • Wilate is currently approved for prophylaxis to reduce the frequency of BEs in patients with VWD ≥ 6 years. • There are no currently approved therapies to reduce the frequency of BEs in patients with VWD under 6 years with routine prophylaxis.	There is an unmet medical need, as there are no currently approved therapies for prophylaxis to reduce the frequency of BEs in patients with VWD under 6 years.
Clinical Benefit	Ten trials were submitted to evaluate the safety and efficacy of Wilate • The main efficacy outcome from the WIL-33 study was TABR with the use of prophylaxis Wilate that was comparable to Wilate prophylaxis in patients ≥ 6 years.	Mean TABR of 4.6 and SABR of 0.9.indicates that treatment with prophylaxis Wilate reduces the frequency of bleeding in patients with VWD < 6 years.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most common adverse reactions to treatment with Wilate (≥1%) in patients with VWD were hypersensitivity reactions, urticaria, chest discomfort, and dizziness. The most common adverse reaction to treatment with Wilate (≥1%) in previously treated patients with hemophilia A was pyrexia (fever). • The most serious adverse reactions to treatment with Wilate in patients with VWD and hemophilia A are hypersensitivity reactions.	Evidence indicated that the risk of hypersensitivity is manageable.
Risk Management	• The most substantial risks of treatment are hypersensitivity reactions, thromboembolic events, and neutralizing antibodies. • In WIL-33, 1 patient developed an inhibitor requiring withdrawal from the study and discontinuation of study drug.	The inhibitor development was added to the label within highlights, warnings and precautions (5.3), and 12.6 immunogenicity.

Abbreviations: CI = confidence interval, TABR = total annualized bleeding rate, VWD = von Willebrand disease; VWF = von Willebrand factor.

11.2 Risk-Benefit Summary and Assessment

The overall benefit risk assessment is favorable, and the clinical review team recommends approval for the indication expansion for the use of Wilate for routine prophylaxis to reduce the frequency of BEs in children < 6 years with VWD. The FDA exercised regulatory flexibility in granting the indication of RP to children < 6 years of age based on a single-arm study with a small sample size given the rarity of this subset of patients with VWD.

11.4 Recommendations on Regulatory Actions

11.5 Labeling Review and Recommendations

The USPI has been negotiated with the Applicant and approved. Key changes include the following:

Recommended revisions to the draft labeling included:

1) Change to the indication statement to add routine prophylaxis in patients 6 years and younger.
2) Addition Dosage and Administration section of the Highlights and within dosing section 2 to include dosing 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 dosing:
    Age < 6: 30-50 IU/kg

3) Addition of the inhibitor development in highlights, warnings and precautions (5.3), and immunogenicity sections (12.6).

4) Updates to Clinical Section 14 Clinical Studies to include WIL-33 results.

11.6 Recommendations on Post marketing Actions

None.