Application Type	Efficacy Supplement
STN	125251/382
CBER Received Date	Feb 1, 2023
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Division / Office	DCEH/OCE/OTP
Committee Chair	Courtney Johnson, M.D.
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Priority Review	No
Reviewer Name(s)	Jiang Hu, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lin Huo, Ph.D., Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D., Branch Chief, TEB2/DB/OBPV
Applicant	Octapharma
Established Name	von Willebrand Factor / Coagulation Factor VIII Complex (Human)
(Proposed) Trade Name	WILATE
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Powder and solvent for solution for injection
Dosage Form(s) and Route(s) of Administration	Intravenous use after reconstitution
Dosing Regimen	20–40 IU/kg two or three times per week
Indication(s) and Intended Population(s)	Indicated in children and adults 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 (new indication) Indicated in adolescents and adults with hemophilia A for:

	• Routine prophylaxis to reduce the frequency of bleeding episodes • On-demand treatment and control of bleeding episodes

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GLOSSARY

AE	Adverse event
BE	Bleeding episode
CI	Confidence interval
EDR	Electronic Document Room
ED	Exposure Day
FDA	Food and Drug Administration
GEE	Generalized estimating equation
ITT	Intention-to-treat
IVR	In vivo recovery
MABR	Menstrual annualized bleeding rate
PK	Pharmacokinetics
PTP	Previously treated patient
SABR	Spontaneous annualized bleeding rate
sBLA	supplemental Biologics License Application
SD	Standard deviation
TABR	Total annualized bleeding rate
TEAE	Treatment emergent adverse event
VWD	von Willebrand disease

1. Executive Summary

WILATE was licensed in the US in 2009 for the treatment of spontaneous and trauma-induced bleeding episodes in patients with von Willebrand disease (VWD). The applicant requested adding the indication of “routine prophylaxis to reduce the frequency of bleeding episodes” for children and adults with VWD in this BLA efficacy supplement (sBLA).

The primary evidence of efficacy comes from a comparison of results of two studies in the same patients. Study 1, WIL-29, was a non-interventional, on-demand treatment study. Study 2, WIL-31, was a prospective, non-controlled, international, multi-center Phase 3 study designed to demonstrate that WILATE is efficacious in bleeding prophylaxis in the same patients with VWD in WIL-29. The primary efficacy endpoint was the total annualized bleeding rate (TABR) under prophylactic treatment with WILATE. Study success would be declared if the TABR during prophylactic treatment lowers the TABR during on-demand treatment by more than 50%. In Study WIL-31, 43 patients were enrolled and treated with WILATE, 10 patients were excluded from the primary efficacy analysis set mFAS due to unconfirmed VWD status. With 33 subjects in mFAS, the TABR with prophylactic WILATE treatment was 5.49 as compared with 33.38 when the same patients received on-demand WILATE treatment in the previous non-interventional Study WIL-29. The TABR ratio WIL-31 over WIL-29 was 0.165 with a two-sided 95% CI (0.102, 0.266). The upper bound of the 95% CI of the TABR ratio was lower than 0.5, therefore the pre-specified success criterion was met.

The safety evaluation revealed that no subject reported inhibitory effects. No death was reported during the study.

No statistical issues were identified during the review of this application. I verified the primary efficacy endpoint analyses. The efficacy results support the proposed indication for routine prophylaxis to reduce the frequency of bleeding episodes for patients with VWD.

2. Clinical and Regulatory Background

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

2.1 Disease or Health-Related Condition(s) Studied

VWD is clinically a heterogeneous group of disease variants, each characterized by distinct quantitative and qualitative abnormalities in VWF, which are caused by widely heterogeneous mutations in the various domains of the VWF gene. The symptoms of VWD are usually those of platelet dysfunction and include nose bleeding, skin bruises and hematomas, prolonged bleeds from trivial wounds, oral cavity bleeding, and excessive menstrual bleeding.

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

Please refer to the clinical review.

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

WILATE was approved for the treatment of VWD in the US in 2009.

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

WILATE first received FDA approval in 2009 for the on-demand treatment and control of bleeding episodes in children and adults with VWD (STN #125251/0).

In August 2015 an additional indication in children and adults with VWD for perioperative management of bleedings was approved for WILATE in US (STN #125251/139).

In September 2019 indications in adolescents and adults with hemophilia A for routine prophylaxis and on-demand treatment and control of bleeding episodes (BEs) were approved for WILATE in US. (STN #125251/244)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

The statistical memo focuses on the pivotal phase 3 study WIL-31.

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

The following documents in BLA 125251/382 were reviewed and served as the basis for this statistical memo:

- Module 2.2: Introduction
- Module 2.5: Clinical overview
- Module 2.7: Clinical summary
- Module 5.3.5.2: Clinical study reports, protocols, and SAPs for WIL-31
- Datasets of single studies and pooled datasets

5.3 Table of Studies/Clinical Trials

This efficacy of WILATE prophylaxis in reducing the bleeding rate in patients with VWD was specifically assessed as the primary efficacy objective in Study WIL-31. Data from 5 additional studies (TMAE-104, TMAE-105, TMAE-106, TMAE-109 and WIL-14), in which WILATE was used prophylactically in some patients, provided supportive data. A summary of these studies is provided in Table 1.

Table 1: Clinical Studies Conducted with WILATE Prophylaxis

Study	**Total population and main inclusion criteria Patients evaluable for efficacy of prophylaxis**	**Objectives**
WIL-31	43 patients aged ≥6 years with inherited VWD enrolled 33 patients analyzed for efficacy of prophylaxis	Primary: determine the efficacy of WILATE in the prophylactic treatment of previously treated patients Secondary: incremental In vivo recovery (IVR), PK (aged 6-16 years), safety and tolerability, WILATE consumption
WIL-14	15 patients aged <6 years with inherited VWD, any type, DDAVP treatment known or suspected to be inadequate enrolled 10 patients analyzed for efficacy of prophylaxis	Primary: efficacy in prevention and/or treatment of BEs and during surgery Secondary: IVR prior to major surgery (optional for minor surgery), immunogenicity, safety and tolerability, PK and IVR in patients with VWD Type 3 or severe VWD (optional)
TMAE-104	41 patients aged ≥6 and ≤85 years with inherited VWD, any type, not responding to DDAVP enrolled 27 patients analyzed for efficacy of prophylaxis	Primary: plasma levels of FVIII:C, VWF:Ag, VWF:CB and VWF:RCo as surrogate markers for efficacy Secondary: PK, bleeding time, overall efficacy (including surgeries), safety and tolerability
TMAE-105	14 patients aged ≥12 and ≤65 years with inherited VWD, any type, not responding to DDAVP enrolled 5 patients analyzed for efficacy of prophylaxis	Primary: PK (AUC, AUCnorm, T1/2, MRT, Vss and CL) for VWF:Ag, VWF:CB, VWF:RCo, plasma level of FVIII:C as surrogate markers for efficacy Secondary: IVR, bleeding time, plasma levels of VWF:Ag, VWF:CB and VWF:RCo, VWF multimers, overall efficacy, safety and tolerability
TMAE-106	14 patients aged ≥12 and ≤65 years with inherited VWD, any type, not responding to DDAVP enrolled	Primary: PK for VWF:Ag, VWF:CB, VWF:RCo and FVIII:C, plasma level of FVIII:C as surrogate markers for efficacy Secondary: IVR of VWF:RCo, VWF:Ag and VWF:CB, bleeding

	2 patients analyzed for efficacy of prophylaxis	time, closure time, VWF multimers, overall efficacy and tolerability
TMAE-109	16 patients aged ≥12 and ≤65 years with inherited VWD, any type, not responding to DDAVP enrolled 5 patients analyzed for efficacy of prophylaxis	Primary: plasma levels of FVIII:C, VWF:Ag, VWF:RCo as surrogate markers for efficacy Secondary: bleeding time, VWF multimers, overall efficacy, safety and tolerability

Source: Adapted from BLA 125251/382 Module 2.7: summary-clin-efficacy.pdf, Table 1, page 3.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1: WIL-31

6.1.1 Objectives

The primary objective of this study was to determine the efficacy of WILATE in the prophylactic treatment of previously treated patients (PTPs) with Type 3, Type 2 (except 2N), or severe Type 1 VWD.

The secondary objectives of this study were to:

- Assess the incremental IVR of WILATE for VWF: Ac and FVIII:C over time
- Determine the pharmacokinetics (PK) of WILATE for VWF: Ac and FVIII:C in pediatric patients aged 6–16 years
- Assess the safety and tolerability of WILATE
- Determine WILATE consumption data

6.1.2 Design Overview

This was a prospective, non-controlled, international, multi-center phase 3 study investigating the efficacy and safety of WILATE in previously treated patients with Type 3, Type 2 (except 2N), or severe Type 1 VWD aged ≥6 years at the time of screening.

Overall, around 40 patients were to be enrolled by approximately 14 study sites worldwide. Of the 40 patients, at least 5 patients were to have type 3 VWD, at least 6 patients were to be aged 6–11 years, and at least 6 patients were to be aged 12–16 years. Of the 40 patients, at least 25 patients were to be evaluable for the primary endpoint.

6.1.3 Population

Please refer to the clinical review.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The investigated medical product (IMP) is WILATE, von Willebrand factor/coagulation factor VIII complex (Human) lyophilized powder for solution for intravenous injection, which was approved in 2009.

6.1.6 Sites and Centers

Patients were enrolled and treated at 14 investigational centers from 8 countries (Bulgaria, Belarus, Croatia, Hungary, Lebanon, Russia, Ukraine, and US).

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint
The primary endpoint of this study was the patients' total annualized bleeding rate (TABR).

The secondary endpoints of this study were:

- Spontaneous annualized bleeding rate (SABR), calculated in analogy with TABR
- Incremental IVR of WILATE for VWF: Ac (VWF: RCo and VWF: GPIbm) and FVIII:C (OS and CHR) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- For pediatric patients, baseline PK profile characteristics of VWF:Ac (VWF: RCo) and FVIII:C (OS and CHR) based on blood samples taken pre-dose and 1, 3, 9, 24, 48, and 72 hours after dosing
- Safety and tolerability of WILATE by monitoring adverse events (AEs) throughout the study WILATE consumption data (VWF/FVIII IU/kg per month per patient) for

Success Criterion
This study was designed to demonstrate that prophylactic treatment with WILATE lowers the patients' TABR observed during on-demand treatment (in Study WIL-29) by more than 50%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination
Let $TABR_{pr}$ be the total annualized bleeding rate in the prophylactic treatment and $TABR_{od}$ be the total annualized bleeding rate in the on-demand treatment. Assuming a mean TABR ratio ($TABR_{pr}$ / $TABR_{od}$) of 0.25 with a correlation of 0.5 between the two treatment regimes, a coefficient of variation of 10 in on-demand treatment, and a coefficient of variation of 10 in prophylactic treatment, 25 patients will be needed to reject the null hypothesis

H_0: mean ($TABR_{pr}$ / $TABR_{od}$) ≥0.5

in favor of

H_1: mean ($TABR_{pr}$ / $TABR_{od}$) <0.5

with a type I error of 0.025 and a power of 80%.

Overall, 28 patients were planned to be enrolled in this study, including at least 5 patients with VWD type 3, at least 5 patients aged 6 through 11 years, and at least 5 patients aged 12 through 16 years.

Primary Efficacy Analysis

Originally a paired t-test on log-transformed data was planned by the applicant. A corresponding two-sided 95% CI for the TABR was also planned to be provided.

However, there were some patients had documented 0 (zero) BEs during the prophylactic treatment phase, which are contradict to the assumption of a log-normally distributed TABR and make the calculation of logarithms of the TABRs impossible. Therefore, a negative binomial counting regression model (GLIM) with treatment regimen as main effect and treatment period as offset parameter was implemented for the analysis of the primary efficacy parameter.

Such negative binomial counting regression models were also used for the analysis of similarly defined secondary and exploratory endpoints, e.g. SABR.

Due to the reporting of non-confirmed eligibility, the primary and secondary efficacy analyses were performed for the modified full analysis set (mFAS).

Analysis Populations

Safety Set: The safety (SAF) set was to include all subjects who received at least one dose of IMP.

Full Analysis Set: The full analysis set (FAS) defined according to the intention-to-treat (ITT) principle was to include all enrolled subjects who received at least one dose of IMP after the Baseline IVR Visit in adults or the Baseline PK Visit in children.

Modified Full Analysis Set: The modified full analysis set (mFAS) was a subset of the FAS excluding all subjects for whom laboratory results did not confirm patient's eligibility, i.e., severe VWD type 1, 2A, 2B, 2M or 3 not confirmed.

Per Protocol Set: The per-protocol (PP) set, i.e., a subset of the FAS, excluded subjects with major protocol deviations which may have an impact on the evaluation of the primary study outcome parameter (major protocol deviations as defined during DRM).

Surgery Set: The surgery (SURG) set was to be a subset of the FAS, containing all subjects who underwent a surgical procedure treated with IMP prior to start of surgery during their Prophylactic Treatment Phase.

Subgroup Analyses

The analyses of the efficacy endpoints "efficacy of prophylactic treatment" and "efficacy in treatment of breakthrough BEs" were planned to be summarized in the following subgroups:

- Age groups (6 to 11, 12 to 16, and > 16)
- VWD types (severe type 1, type 2, and type 3)
- Sex (female, male)
- Race, according to CDISC Controlled Terminology (dependent on the number of subjects per race)

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 summarizes all analysis populations.

Table 2: Analysis Populations

Population	6 - <12 Years	12 - <17 Years	≥ 17 Years	Total
Screened subjects	10	9	25	44
FAS/SAF	10	8	25	43
mFAS	9	6	18	33
PP	7	5	13	25
PK	10	8	0	18
SURG	1	0	2	3

Source: Adapted from BLA 125251/382 Module 5.3.5.2/WIL-31: report-body.pdf, Table 8, page 75.

6.1.10.1.1 Demographics

Age at screening in the FAS/SAF population ranged from 7 to 61 years, with a median of 17 years. Ten patients were aged 6-11 years, 8 were aged 12-16 years, and 25 were aged ≥17 years. The majority of patients were male (60.5%) and all but one patient (97.7%) were white. About half of the patients (51.2%) had Type 3 VWD. Overall, 22 (51.2%) patients had a family history of VWD. The demographic and baseline characteristics of the FAS/SAF population are shown in Table 3. Data were similar in the mFAS population and PP population.

Table 3: Demographic and Baseline Characteristics for FAS/SAF

Population	6 - <12 Years (N=10)	12 - <17 Years (N=8)	≥ 17 Years (N=25)	Total (N=43)
Age				
Mean (SD)	8.9 (1.50)	14.4 (1.50)	30.4 (14.40)	22.4 (14.59)
Median (range)	9.0 (7.0-11.0)	15.0 (12.0-16.0)	25.0 (17.0-61.0)	17.0 (7.0-61.0)
Sex				
Female (%)	4 (40.0)	4 (50.0)	9 (36.0)	17 (39.5)
Male (%)	6 (60.0)	4 (50.0)	16 (64.0)	26 (60.5)
Race				
Black or African American (%)	0 (0)	0 (0)	1 (4.0)	1 (2.3)
White (%)	10 (100.0)	8 (100.0)	24 (96.0)	42 (97.7)
Ethnicity				
Not Hispanic (%)	10 (100.0)	8 (100.0)	25 (100.0)	43 (100.0)
VWD type (%)				
Severe Type 1	2 (20.0)	1 (12.5)	3 (12.0)	6 (14.0)
Type 2	2 (20.0)	1 (12.5)	2 (8.0)	5 (11.6)
Type 3	5 (50.0)	4 (50.0)	13 (52.0)	22 (51.2)
Not applicable	1 (10.0)	2 (25.0)	7 (28.0)	10 (23.3)
Family history of VWD				
Yes	4 (40.0)	5 (62.5)	13 (52.0)	22 (51.2)
No	6 (60.0)	3 (37.5)	12 (48.0)	21 (48.8)
Height (cm)				
Mean (SD)	133.2 (9.04)	163.6 (12.24)	171.8 (7.83)	161.3 (18.22)
Median (range)	136.0 (118-146)	160.5 (151-182)	170.0 (155-185)	167.0 (118-185)
Weight (kg)				
Mean (SD)	28.44 (6.49)	63.28 (18.74)	75.7 (17.56)	62.4 (24.96)
Median	28.3 (20.5-41.0)	64.8 (39.9-92.0)	76.0 (48.0-112.0)	62.0 (20.5-112.0)
BMI				
Mean (SD)	15.9 (2.04)	23.2 (4.19)	25.6 (5.69)	22.9 (6.21)
Median	15.4 (13.3-20.3)	24.6 (16.8-27.8)	25.1 (18.8-38.8)	21.6 (13.3-38.8)

Source: Adapted from BLA 125251/382 Module 5.3.5.2/WIL-31: report-body.pdf, Table 9, page 76.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The total ABRs (including traumatic bleeding, spontaneous bleeding, and other bleeding) during the on-demand phase of WIL-29 by VWD type and age group are presented for the primary efficacy population mFAS in Table 4.

Table 4: Total Annualized Bleeding Rate During the On-demand Phase of WIL-29 by VWD Type and Age Group (mFAS, N=33)

Parameters	6 - <12 Years	12 - <17 Years	≥ 17 Years	Total
Severe Type 1				
# of bleedings	47	9	27	83
# of patients	2	1	2	5
Mean	39.64	16.27	26.17	29.58
SD	29.65	-	16.04	19.62
Median	39.64	16.27	26.17	18.68
Range	18.7-60.6	16.3-16.3	14.8-37.5	14.8-60.6
Type 2				
# of bleedings	26	15	24	65
# of patients	2	1	2	5
Mean	23.18	29.14	20.45	23.28
SD	1.163	-	5.673	4.582
Median	23.18	29.14	20.45	24.01
Range	22.4-24.0	29.1-29.1	16.4-24.5	16.4-29.1
Type 3				
# of bleedings	84	76	250	410
# of patients	5	4	12	21
Mean	33.44	32.01	40.01	37.06
SD	24.97	25.86	29.48	26.91
Median	27.94	22.53	29.66	28.31
Range	11.0-75.8	12.8-70.1	17.9-114.5	11.0-114.5
Total				
# of bleedings	157	100	301	558
# of patients	9	6	16	31
Mean	32.54	28.91	35.29	33.38
SD	21.37	20.99	26.34	23.61
Median	24.01	22.53	26.57	24.46
Range	11.0-75.8	12.8-70.1	14.8-114.5	11.0-114.5

Source: Adapted from BLA 125251/382 Module 5.3.5.2/WIL-31: report-body.pdf, Table 10, page 78.

6.1.10.1.3 Subject Disposition

Of the 44 screened patients, one patient was screened but was then lost to follow-up and not treated. All other were enrolled and treated with WILATE therefore included in the FAS/SAF population. These 43 patients had completed

the non-interventional study WIL-29, in which their bleeding incidence while undergoing on-demand treatment was captured.

Of the 43 patients in the FAS, 10 patients were excluded from the mFAS due to unconfirmed VWD status. These patients were terminated early with the reason of not meeting inclusion criterion #2.

Of the 33 patients in mFAS, 3 additional patients terminated the study early due to adverse reactions in 2 patients and “other” (patient permanently left country for job opportunity abroad) in 1 patient. A total of 30 patients completed the study.

Five patients were excluded from PP population because of following reasons:

- Patient (b) (6) due to an underlying medical condition other than VWD that significantly increases the rate of spontaneous bleeds (oral cavity bleeds)
- Patients (b) (6) and (b) (6) as they had inhibitor to von Willebrand Factor already at study entry
- Patient (b) (6) due to an underlying medical condition other than VWD that significantly increases the rate of spontaneous bleeds (gastrointestinal bleeds due to a clip failure at a previous anastomosis site)
- Patient (b) (6) with more than 2 spontaneous BEs or 1 major spontaneous BE within 30-day period but prophylactic dose not increased without providing an explanation

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The comparison of TABR between WIL-31 and WIL-29 was conducted through a negative binomial counting regression model. The primary efficacy endpoint TABR was 5.49 in the WIL-31 study with prophylactic WILATE treatment, compared with 33.38 in the WIL-29 study with on-demand WILATE treatment, giving a rate ratio of 0.165 ($p<0.0001$; 95% CI: 0.102, 0.266). The upper bound of the 95% CI of the rate ratio was below 0.5 therefore the success criterion was met.

The applicant also calculated TABR including heavy menstrual events. With this definition, the TABR was 5.91 in the WIL-31 study with prophylactic WILATE treatment, compared with 35.08 in the WIL-29 study with on-demand WILATE treatment, giving a rate ratio of 0.168 ($p<0.0001$; 95% CI: 0.110, 0.258). Table 5 summarized the results of comparison of the TABR.

Table 5: Comparison of TABR in Wil-31 and Wil-29 (mFAS, N=33)

TABR	Estimated rate WIL-29	Estimated rate WIL-31	Estimate rate ratio	95% CI of ratio	p-value
Total bleeding rate (spontaneous, traumatic, and other bleeds)	33.38	5.49	0.165	0.102, 0.266	<0.0001
Total bleeding rate (spontaneous, traumatic, heavy menstrual, and other bleeds)	35.08	5.91	0.168	0.110, 0.258	<0.0001

Source: Adapted from BLA 125251/382 Module 5.3.5.2/WIL-31: report-body.pdf, Table 12, page 82, and BLA 125251/382/0258 Module 1: resp-fda-info-request.pdf.

The analysis results were similar using the FAS and PP set and led to the same conclusion.

Remark: Per protocol version 5 (dated as 2/25/2020) menstrual bleeds, regular and heavy, were excluded from the calculation of TABR. Therefore in the original BLA submission, the TABR was calculated as the total number of spontaneous, traumatic and other bleeds (excluding menstrual bleeds). CBER sent request on 8/18/2023 asking the applicant to recalculate TABR with heavy menstrual bleeds included. The applicant submitted the revised TABR on 9/1/2023 in 125251/0258.

6.1.11.2 Analyses of Secondary Endpoints

Spontaneous annualized bleeding rate (SABR)

The SABR was 3.393 in WIL-31 as compared with 24.417 in WIL-29, giving a rate ratio of 0.139 (p<0.0001; 95% CI: 0.0766; 0.2519).

Traumatic annualized bleeding rate (TRABR)

The TRABR was 1.916 in WIL-31 as compared with 8.570 in WIL-29, giving a rate ratio of 0.224 (p=0.0127 95% CI: 0.1104; 0.4527).

Heavy Menstrual Annualized Bleeding Rate (HMABR)

The HMABR was 2.953 in WIL-31 as compared with 10.187 in WIL-29, giving a rate ratio of 0.290 (p=0.1626, 95% CI: 0.0978; 0.8592).

Incremental IVR of WILATE

A total of 33 patients were included in the mFAS population and were evaluable for IVR assessment; 9 patients were aged 6 - 11 years, 6 patients were aged 12 - 16 years and 18 were aged ≥17 years. The FVIII IVRs observed in this study are consistent with those seen previously with WILATE. Table 6 summarizes the means and the 95% CIs for FVIII IVRs and VWF IVRs.

Table 6: Factor VIII and von Willebrand Factor In-Vivo Recovery at Baseline and 12-Months

	Baseline (mean [CI], n)	12-month visit (mean [CI], n)
FVIII IVR, CHR assay, kg/dL	1.697 (1.49, 1.90), 33	2.140 (1.92, 2.36), 29
FVIII IVR, OS assay, kg/dL	1.571 (1.40, 1.74), 33	2.036 (1.81, 2.26), 31
VWF: RCo IVR, kg/dL, kg/dL	1.320 (1.14, 1.50), 33	1.273 (1.04, 1.50), 29

Source: Adapted from BLA 125251/382 Module 5.3.5.2/WIL-31: report-body.pdf, Table 14, page 86.

Efficacy of WILATE in surgical prophylaxis

A total of 3 patients had 13 surgeries that were included in the SURG population. Ten of these surgeries were minor and 3 were major. All surgeries were rated as having excellent efficacy of the WILATE treatment, with one surgery rating missing.

6.1.11.3 Subpopulation Analyses

The analyses of the efficacy endpoints were presented in the following subgroups: Age groups (6 to 11, 12 to 16 and ≥17 years), VWD type (severe Type 1, Type 2 and Type 3) and Sex (Female, Male). Subgroup analysis by race is not performed because all but one subject in the study were white. Table 7 summarizes the subgroup analyses.

Table 7: Subgroup Analyses of TABR

TABR	n	Estimated rate WIL-29	Estimated rate WIL-31	Estimated rate ratio	95% CI of ratio
Age group					
6 - <12 Years	9	32.59	3.73	0.114	0.065, 0.201
12 - <17 Years	6	28.99	3.72	0.148	0.093, 0.235
≥17 Years	18	35.26	6.86	0.195	0.096, 0.396
VWD type					
Severe Type 1	6	28.34	9.94	0.351	0.110, 1.113
Type 2	5	23.25	0.98	0.042	0.007, 0.264
Type 3	22	37.05	5.19	0.140	0.092, 0.212
Sex					
Female	14	32.79	4.69	0.143	0.087, 0.236
Male	19	34.51	6.04	0.178	0.091, 0.352

Source: Adapted from BLA 125251/382 Module 5.3.5.2/WIL-31: report-body.pdf, Table 12, page 82.

6.1.12 Safety Analyses

6.1.12.3 Deaths

There were no deaths in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Five SAEs occurred in 4 (9.3%) patients. There were two SAEs of menorrhagia in one patient (b) (6) , and one COVID-19 pneumonia (b) (6) one food poisoning(b) (6) and one hemorrhoidal hemorrhage (b) (6) . All five SAEs required hospitalization.

6.1.12.5 Adverse Events of Special Interest (AESI)

Seven AEs in four patients were assessed as possibly/probably related to study medication by the Sponsor: three AEs of chest discomfort in one patient, two AEs of hypersensitivity in one patient, an AE of dizziness in one patient, and an AE of pruritus in one patient.

6.1.12.7 Dropouts and/or Discontinuations

Two AEs in 2 (4.7%) patients led to permanent discontinuation of study medication. One subject discontinued due to hypersensitivity with 2 EDs, another due to chest discomfort with 6 EDs. Both events were assessed by the investigator as nonserious but possibly or probably related to IMP, respectively.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This statistical memo reviewed the pivotal Study WIL-31, a prospective, non-controlled, international, multi-center phase 3 study designed to demonstrate that WILATE is efficacious in bleeding prophylaxis in patients with VWD.

In Study WIL-31, with 33 subjects in mFAS, when the TABR is calculated as the total number of spontaneous, traumatic and other bleeds (excluding menstrual bleeds), the TABR with prophylactic WILATE treatment was 5.49 as compared with 33.38 when the same patients received on-demand WILATE treatment in the previous non-interventional Study WIL-29. The TABR ratio is 0.165 with a 95% CI (0.102, 0.266). The TABR ratio of WIL-31 over WIL-29 was lower than 0.5 therefore the success criterion is met.

The safety evaluation revealed that no subject reported inhibitory effects. No death was reported during the study.

10.2 Conclusions and Recommendations

The statistical analysis of Study WIL-31 provides adequate statistical evidence to support the efficacy of WILATE routine prophylaxis to reduce the frequency of bleeding episodes for children and adults. I defer to the clinical reviewer on the acceptance of the safety profile of WILATE.