Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Application Type	BLA Supplement
STN	125251/244
CBER Received Date	November 30, 2018
PDUFA Goal Date	September 30, 2019
Division / Office	DB/OBE
Committee Chair	Jay Lozier, M.D., Ph.D., F.A.C.P.
Clinical Reviewer(s)	Jay Lozier, M.D., Ph.D., F.A.C.P.
Project Manager	Jean Gildner, MSHS, MT (ASCP)
Priority Review	No
Reviewer Name(s)	Shuya (Joshua) Lu, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renee Rees, Ph.D. Team Leader, FDA/CBER/OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
Applicant	Octapharma
Established Name	von Willebrand Factor / Coagulation Factor VIII Complex (Human)
(Proposed) Trade Name	WILATE
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	
Dosing Regimen	20–40 IU/kg bi-weekly
Indication(s) and Intended Population(s)	For pediatric subjects and adults with hemophilia A for: [1] Routine prophylaxis to reduce the frequency of bleeding episodes. [2] On-demand treatment and control of bleeding episodes.

Table of Contents

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
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 approved for the treatment of von Willebrand disease (VWD) in the US in 2009. This supplemental Biologics License Application (sBLA) proposes to extend the indication for WILATE to pediatric and adult patients with hemophilia A for: (1) routine prophylaxis to reduce the frequency of bleeding episodes (BEs), and (2) on-demand treatment and control of BEs.

The primary evidence is based on the pivotal study WIL-27: a prospective, international, multi-center, phase 3 study in previously treated patients (PTPs) with hemophilia A. The primary efficacy endpoint is the total annualized bleeding rate (TABR) under prophylactic treatment with WILATE, with study success declared if the TABR is less than 29 BEs per subject per year. This threshold corresponds to 50% of the TABR reported in GENA-01, the applicant's study in which previously treated adolescent and adult subjects with severe hemophilia A received on-demand FVIII treatment only.

Data for 55 subjects ≥12 years of age (5 of whom were between ≥12 and ≤16 years of age) were analyzed. A total of 25 subjects (45.5%) experienced 64 BEs under WILATE prophylaxis. For these 55 subjects, the one-sample Poisson test TABR estimate was 2.29 (95% CI was [1.80, 2.93]). The mean spontaneous annualized bleeding rate (SABR) estimate was 1.58 (95% CI was [1.17, 2.12]).

Forty-eight (75%, [95% CI: 62.60%, 84.98%]) of the 64 BEs were treated successfully with efficacy assessed as either 'excellent' or 'good'.

The safety evaluation revealed that no subject reported inhibitory effects; the two-sided 95% CI is (0, 0.044). No death was reported during the study.

No statistical issues were identified during the review of this application. I verified the primary efficacy endpoint analysis and the efficacy results seem to support the proposed indication for routine prophylaxis to reduce the frequency of bleeding episodes and on-demand treatment and control of bleeding episodes for patients with hemophilia A.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males do not produce functional coagulation FVIII in sufficient quantities to achieve satisfactory hemostasis. The incidence of congenital hemophilia A is approximately 1 in 10,000 births. Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%), or severe (<1%). The deficiency in FVIII predisposes patients with hemophilia A to recurrent BEs in joints, muscles, or internal organs, either spontaneously or as a result of accidental or surgical trauma. Without adequate treatment, these repeated hemarthroses and hematomas lead to long-term sequelae with severe disability. Less frequent but more severe bleeding sites are the central nervous system, the urinary or gastrointestinal tract, the eyes and the retroperitoneum.

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

WILATE was approved for the treatment of von Willebrand disease (VWD) in the US in 2009. The development program for hemophilia A was conducted under IND 17181. A pre-sBLA meeting was not held with the applicant. FDA/CBER received the protocol for WIL-27 on October 18, 2016. The following comments were provided to the applicant and were incorporated into the revised protocol.

1. Regarding inhibitor development:
    a. Please specify in the protocol the statistical method for calculating the 95% CI for inhibitor development.
    b. You state that you plan to pool data with other previously completed clinical studies with WILATE in hemophilia A subjects to achieve the requirement of a total of at least 80 PTPs. This pooling strategy may lead to bias as the inhibitor development of subjects in completed studies is already known and thus will affect the number of inhibitors that can be developed in WIL-27 in order to meet the 6.8% upper confidence limit success criterion

recommended in the 2003 Factor VIII FDA workshop (http://www.fda.gov/ohrms/dockets/dockets/04n0033/04n-0033-tr00001-vol3.pdf). Please clarify which completed studies and subjects you plan to pool.

c. Please consider increasing the WIL-27 sample size to meet the success criterion for inhibitor development using data from just this study. Even if no subjects in the 50 evaluable subjects develop an inhibitor, you will exceed the success criteria and this may be a review issue. Please consider enrolling at least 60 subjects; with a 10% drop-out rate, 54 subjects with 0 inhibitors can meet the criterion.

2. Please provide the formula for the calculation of TABR.
3. Please provide the null and alternative hypotheses for the study objectives in a mathematical format.
4. Please include subgroup analyses by age, race, and geographical region (US vs. non US) in the protocol.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review of the primary efficacy endpoint without unreasonable difficulty.

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

All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

5.1 Review Strategy

Seven clinical studies were included in this submission. WIL-27 is considered the pivotal study, so only WIL-27 is reviewed in this memo. Please refer to Section 5.3 for the detailed information about the other supportive studies.

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

Documents and datasets for the original BLA were reviewed.

BLA	125251/244	
	Module 1.14	Label
	Module 2.7	Clinical summary
	Module 5.2	Tabular Listing of all Clinical Studies
	Module 5.3.5.2	Clinical study reports WIL-27: Study Report Body, Protocol, Statistical Analysis Plan

Module 5.3.5.2 Data files
adsl.xpt, adbe.xpt

5.3 Table of Studies/Clinical Trials

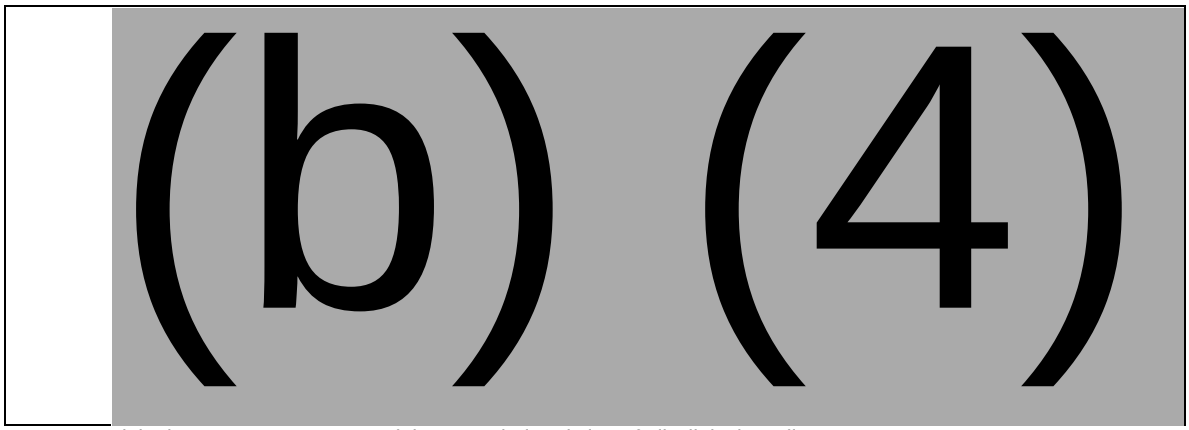
The following clinical studies, as summarized in Table 1, are included in the submission.

Table 1 Summary of clinical studies in the sBLA

Study No.	**Population No. of Patients Age**	**Design Study Sites Study Period**	**Test Product(s) Dosage Regimen Duration of Treatment**	**Study Objectives**
Pivotal Study				
WIL-27	Severe hemophilia A PTPs 55 M 12 to 64 years (<16 years n=5; ≥16years n=50)	Prospective, International Multi-center Phase 3 Bulgaria, Hungary, Poland, Russia 21-Dec-2016 to 29-Mar-2018	WILATE PK: 2 single i.v. doses for PK in 22 subjects (at baseline and 6 months) 50 ± 5 IU/kg BW Prophylaxis: 20–40 IU/kg BW every 2–3 days for 6 months. In case of unacceptably frequent spontaneous breakthrough BEs (i.e., >2 spontaneous BEs or one major or lifethreatening spontaneous BE within a 30-day period), the dose of was increased by ~5 IU/kg On-demand treatment: Early hemarthrosis, muscle bleeding or oral bleeding: Target FVIII level: 20–40%; Recommended dose: 10–20 IU/kg; Repeat every 12–24 h for ≥1 day More extensive hemarthrosis, muscle bleeding or hematoma: target FVIII level: 30–60%; Recommended dose: 15–30 IU/kg; Repeat injection every 12–24 h for 3–4 days or more until pain and disability have resolved. Life-threatening hemorrhages: Target FVIII level: 60–100%; Recommended dose: 30–50 IU/kg; Repeat injection every 8–24 h until threat has resolved. (b) (4)	<u>Primary objectives (efficacy)</u> • 50% reduction of the total annualized bleeding rate observed in the GENA-01 study, with a total of 58.1 BEs per patient per year. <u>Secondary objectives (efficacy)</u> • Spontaneous annualized bleeding rate • Bleeding episodes • WILATE consumption • Incremental IVR • PK parameters • Association between AB0 blood type and FVIII:C half-life • Association between VWF:Ag concentration and the FVIII:C half-life <u>Secondary objectives (safety)</u> • Adverse event monitoring • Safety and tolerability • Immunogenicity • Virus safety in terms of parvovirus B19 Exploratory: • (b) (4)

			(b) (4)	
Study No.	**Population No. of Patients Age**	**Design Study Sites Study Period**	**Test Product(s) Dosage Regimen Duration of Treatment**	**Study Objectives**
Supportive Studies				
TMAE-101	Severe hemophilia A PTPs N=14 M Age 18-56 (mean 33 years)	Open Non-controlled Phase II 2 centers, Israel Jul 1999 to Apr 2000	FVIII TMAE SEC (WILATE): 3 single doses of approximately 40 IU FVIII/kg BW, intravenously, for evaluation of PK and recovery.	Primary (efficacy) PK profile and IVR of FVIII levels Secondary (efficacy) • Prevention and/or treatment of bleeds • (b) (4) Secondary (safety) • Immunogenicity • Immediate tolerance (vital signs) • Virus safety • AE monitoring
TMAE-102	Severe hemophilia A PTPs N=24 M Age 11-59 (mean 24 years)	Open Non-controlled Phase II 2 centers/ Poland & Bulgaria Apr 1999 to May 2000	FVIII TMAE SEC (WILATE) single i.v. injection of 40 IU/kg BW (recovery investigation) or dose individually adapted to individual needs of the subjects.	Primary (efficacy) • IVR of FVIII levels Primary (safety) • Immunogenicity Secondary (efficacy) • Prevention and/or treatment of bleeds • (b) (4) Secondary (safety) • Virus safety • Immediate tolerance (vital signs) • AE monitoring
TMAE-108	Severe hemophilia A PTPs N=21 M Age 11-59 (mean 25 years)	Open Non-controlled Phase II 2 centers/ Poland & Bulgaria May 2000 to Mar 2001	FVIII TMAE SEC (WILATE) Single i.v. injection of 40 IU/kg BW (recovery investigation) or dose individually adapted to individual needs of the subjects.	Primary (efficacy) • IVR of FVIII levels Primary (safety) • Immunogenicity Secondary (efficacy) • Prevention and/or treatment of bleeds Secondary (safety) • Virus safety • Immediate tolerance (vital signs) • AE monitoring
TMAE-110	Severe hemophilia A PTPs N=35 M Age 12-66 (mean 31 years)	Open Non-controlled Phase III 4 centers/ Poland & Slovak Republic Feb 2002 to Jan 2003	FVIII TMAE SEC (WILATE) Single i.v. injection of 40 IU/kg BW (recovery investigation) or dose individually adapted to individual needs of the subjects.	Primary (efficacy) • IVR of FVIII levels Primary (safety) • Immunogenicity Secondary (efficacy) • Prevention and/or treatment of bleeds Secondary (safety) • Virus safety • Immediate tolerance (vital signs) • AE monitoring

(b) (4)



Source: Original sBLA 125251.244; Module 5.2, Tabular Listing of all Clinical Studies.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 WIL-27

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective of this study is:

- to determine the efficacy of WILATE in the prophylactic treatment of PTPs with severe hemophilia A.

The secondary objectives of this study are:

- Determine the efficacy of WILATE in the treatment of breakthrough BEs
- Calculate the FVIII:C pharmacokinetics (PK) for WILATE at baseline and after 6 months of prophylactic treatment
- Calculate the FVIII:C incremental in vivo recovery (IVR) of WILATE over time (at baseline, and at 3 and 6 months of treatment)
- Assess the association between ABO blood type and the FVIII:C half-life of WILATE
- Assess the association between the VWF:Ag concentration and the FVIII:C half-life of WILATE
- Assess the safety and tolerability of WILATE
- Assess the immunogenicity of WILATE

An additional objective of this study is the descriptive efficacy of WILATE in (b) (4) .

6.1.2 Design Overview

This was a prospective, international, multi-center phase 3 study that investigated the PK, efficacy, safety and immunogenicity of WILATE in PTPs with severe hemophilia A. After the screening visit, some eligible subjects participated in the PK part of the study and some subjects participated in the non-PK part. Following their initial visit (PK or non-PK), subjects had visits at Day-14, Day-30,

3-Month and 6-Month. The prophylactic treatment for each subject lasted 6 months (+ 2 weeks) and at least 50 exposure days (EDs), followed by a safety follow-up visit at 30 (±3) days after the study completion visit. Efficacy was assessed based on prophylactic treatment efficacy, successful treatment of breakthrough BEs with WILATE and successful (b) (4)
Safety and immunogenicity were monitored throughout the study.

6.1.3 Population

1. The main criteria for inclusion were diagnosis of severe hemophilia A (<1% FVIII:C) according to medical history in patients at least 12 years of age.
2. The main criteria for exclusion were diagnosis of any coagulation disorders other than hemophilia A or FVIII inhibitors.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Prophylactic Treatment:
WILATE was administered every 2 to 3 days at a dose of 20–40 IU/kg bi-weekly for 6 months.

Treatment of Breakthrough BEs:
• Early hemarthrosis, muscle bleeding or oral bleeding
  – Target FVIII level: 20–40%.
  – Recommended dose: 10–20 IU/kg.
  – Repeat every 12–24 hours. At least 1 day, until the BE as indicated by pain
    has resolved or healing has been achieved.
• More extensive hemarthrosis, muscle bleeding or hematoma
  – Target FVIII level: 30–60%.
  – Recommended dose: 15–30 IU/kg.
  – Repeat injection every 12–24 hours for 3 to 4 days or more until pain and
  – disability have resolved.
• Life-threatening hemorrhages
  – Target FVIII level: 60–100%.
  – Recommended dose: 30–50 IU/kg.
  – Repeat injection every 8–24 hours until threat has resolved.

(b) (4)

– (b) (4)

6.1.6 Sites and Centers

Participation of approximately 14 study centers from world-wide was planned. Ultimately six centers from four countries participated: Bulgaria, Hungary, Poland, and Russia.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint

- Prophylactic efficacy of WILATE was based on the TABR during WILATE treatment. TABR was calculated as the total number of BEs (treated and untreated) in the time-period between the first dose of WILATE and the study completion visit, divided by the duration (in years) between the first dose of WILATE and the study completion visit. Surgery periods and BEs occurring within these periods were excluded from the calculation of TABR.

Secondary Endpoint(s)

The following secondary efficacy endpoints were included in this study.

- SABR (calculated analogous to the TABR calculation).
- Efficacy of WILATE in the treatment of breakthrough BEs based on the proportion of BEs successfully treated with WILATE (successful includes efficacy ratings assessed as either 'excellent' or 'good'). Treatment efficacy was assessed by the subject (together with the investigator in case of on-site treatment) using the predefined criteria detailed in Table 2.

Table 2 Efficacy Assessment of the Treatment of Breakthrough BEs

Efficacy	**Criteria**
Excellent	Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 8–12 hours after an injection, requiring up to two injections for complete resolution
Moderate	Probable or slight beneficial effect within approximately 12 hours after the first injection, requiring more than two injections for complete resolution
None	No improvement within 12 hours, or worsening of symptoms, requiring more than two injections for complete resolution

- WILATE consumption data (FVIII IU/kg per week per subject) for prophylaxis
- Baseline PK parameters for FVIII:C using both the chromogenic and one stage assays and actual WILATE potencies
- Incremental IVR of WILATE over time (at baseline, and at 3 and 6 months of treatment)

- Association between ABO blood type and the FVIII:C half-life of WILATE
- Association between VWF:Ag concentration and the FVIII:C half-life of WILATE

6.1.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size:
The sample size of 55 subjects to be enrolled was based on medical and regulatory reasoning. No statistical sample size estimation was performed. The chosen sample size of 50 evaluable subjects will, however, be sufficient to reject the null hypothesis of a mean TABR >29 with a power of 90% if the mean TABR is not greater than 20 BEs per person year with a maximum standard deviation (SD) of 15.

Analysis Populations:
The safety (SAF) set: SAF includes all subjects who received at least one injection of WILATE.

The full analysis set (FAS): FAS is defined according to the intention-to-treat (ITT) principle and includes all enrolled subjects who received at least one injection of WILATE after the initial PK visit or during the initial non-PK visit.

The per-protocol (PP) set: PP is defined as a subset of the FAS, and excludes subjects with major protocol deviations which may have an impact on the evaluation of the primary study outcome parameter.

The surgery (SURG) set: SURG is defined as a subset of the FAS, containing all subjects who underwent a surgical procedure treated with WILATE during their prophylactic treatment phase.

Primary Efficacy Endpoint Analysis:
The following hypothesis was tested:

$$H_0: \mu \geq 29 \text{ vs. } H_1: \mu < 29$$

where μ denotes the mean TABR.

A one-sided, one-sample Poisson-test was used to test whether the mean TABR in subjects treated prophylactically with WILATE is below the threshold of 29 BEs per subject year. Using a generalized linear model with a Poisson error, log-link function and log (exposure time) as offset term, a corresponding two-sided 95% CI for the TABR was also provided. The null hypothesis will be rejected (at a one-sided alpha level of 2.5%) if the upper limit of the one-sided 97.5% confidence interval for μ is strictly less than 29.
.

Secondary Efficacy Endpoints Analysis:

- *SABR*:

SABR was analyzed in the same way as TABR, the only exception being that, for the comparison of mean SABRs, a predefined threshold of 19.1 per subject per year was chosen; this threshold corresponds to 50% of the SABR in GENA-01.

- *Treatment of Breakthrough Bleeds*:

The following hypothesis was tested:

$$H_0: p \leq 70\% \text{ vs. } H_1: p > 70\%$$

where p denotes the percentage of success.

The test procedure based on the GEE model took into account several BEs in one subject as correlated repeated measurements (alpha = 2.5%).

Interim Analysis:
No interim analyses were planned or carried out.

Missing Data:
There is no imputation plan for the missing data.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

There were 55 subjects in the FAS and SAF populations and 52 subjects in PP populations. One subject who underwent a surgical procedure was included in the SURG population.

6.1.10.1.1 Demographics

The subjects were male, between 12 and 64 years of age, with a median age of 35.5 years. Of the 55 subjects, 5 (9.1%) were aged between 12 and 16 years and 50 (90.9%) were older than 16 years. All subjects were White, no Hispanic or Latino. Other baseline characteristics and demographics of the safety population are shown in Table 3.

Table 3 Baseline Characteristics (SAF)

Parameter	<16 years n=5	≥16 years n=50	Total N=55
Age at screening, years			
Mean ± SD	13.6 ± 1.52	37.7 ± 10.6	35.0 ± 12.3
Median (range)	14.0 (12–15)	35.5 (21–64)	35.5 (12–64)
Weight, kg			
Mean ± SD	57.6 ± 18.9	85.9 ± 20.0	83.3 ± 21.4
Median (range)	61.0 (37–83)	84.5 (51–130)	83.0 (37–130)
BMI, kg/m^2			
Mean ± SD	21.5 ± 3.8	27.4 ± 5.7	26.8 ± 5.8
Median (range)	20.4 (17.6–27.4)	27.2 (16.5–41.8)	27.1 (16.5–41.8)
Previous ABR*			
Mean ± SD	0.40 ± 0.89	36.24 ± 39.59	32.98 ± 39.12
Median (range)	0.0 (0.0–2.0)	20.0 (0.0–120.0)	10.0 (0.0–120.0)

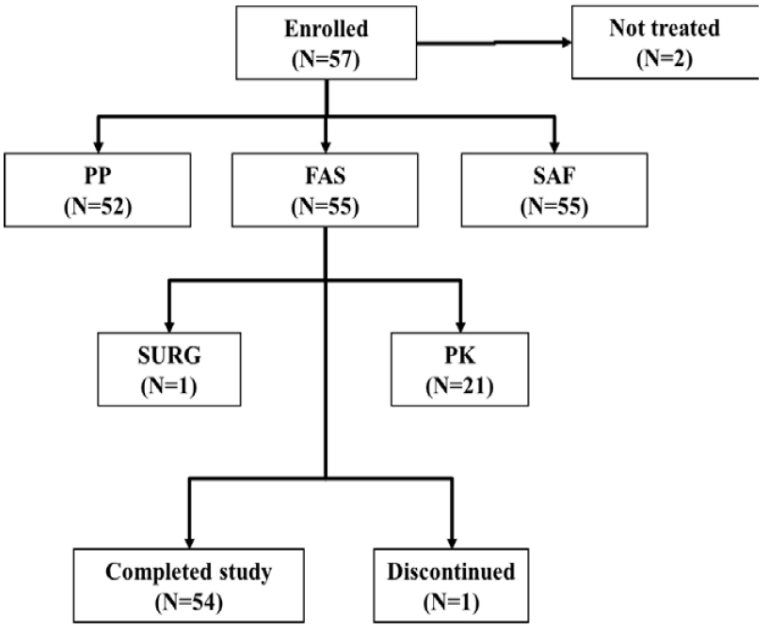
* Previous ABR based on the bleeding rate in the 6 months prior to entry into the study. ABR = annualized bleeding rate; BMI = body mass index; SD = standard deviation;
Source: Original BLA 125251.244; Module 5.3.5.1, Clinical Study Report, Table 12.

Reviewer Comment:
By happenstance, the five pediatric subjects in the study were 12, 12, 14, 15, and 15 years of age. Since none were ages 16 or 17, their breakdown into age < 16 and ≥16 is synonymous with the preferred FDA age groupings of < 18 and ≥18.

6.1.10.1.3 Subject Disposition

A total of 57 subjects were enrolled in this study. Two subjects discontinued before receiving any injections of WILATE, one due to impossibility to travel to the clinical center and one due to withdrawal of consent, leaving 55 subjects in the SAF and FAS populations. Three subjects met pre-defined criteria for exclusion from the PP population (one subject (b) (6) who also withdrew from the study, had less than 50 EDs, one (b) (6) had non-compliance in completing the patient diary and a treatment gap of >7 days and one (b) (6) had a treatment gap of >7 days). One subject did not complete the study due to an AE and the other 54 patients completed the study. A summary of subject disposition is presented in Figure 1.

Figure 1 Subject Disposition



FAS = full analysis set; PK = study population of patients who underwent pharmacokinetic analysis; PP = per-protocol; SAF = study population of patients in safety analysis; SURG = study population of surgeries treated with *Wilate*.

Source: Original BLA 125251.244; Module 5.3.5.1, Clinical Study Report, Figure 1.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

A total of 25 subjects (45.5%) experienced 64 BEs under WILATE prophylaxis and 44 of the BEs were spontaneous. The results of the TABR during prophylaxis with WILATE in the FAS population are shown in Table 4.

Table 4 TABR during WILATE Prophylaxis (FAS, N=55)

Type	Mean ± SD	Median (range)	Poisson (95% CI)
All BEs	2.21 ± 3.64	0.00 (0–15.69)	2.29 (1.80, 2.93)

Source: Original BLA 125251.244; Module 5.3.5.1, Clinical Study Report, Table 14.

Reviewer Comment:
As the upper limit of the CI for the TABR is less than 29, the prophylaxis treatment results meet the pre-specified success criterion.

6.1.11.2 Analyses of Secondary Endpoints

SABR:

The results of the SABR during prophylaxis with WILATE in the FAS population are shown in Table 5. The upper limit of the 95% CI of SABR is 2.12, which is less than the success criterion of 19.1.

Table 5 SABR during WILATE Prophylaxis (FAS)

Type	Mean ± SD	Median (range)	Poisson (95% CI)
Spontaneous BEs	1.52 ± 3.00	0.00 (0–11.76)	1.58 (1.17, 2.12)

Source: Original BLA 125251.244; Module 5.3.5.1, Clinical Study Report, Table 14.

Treatment of Breakthrough Bleeds:

The results of the treatment of breakthrough bleeds are shown in Table 6. Forty-eight (75%) of the 64 BEs were treated successfully; the 95% CI is [62.60%, 84.98%] and p-value is 0.1914 under the null hypothesis.

Table 6 Overall Assessment of Treatment Efficacy According to Severity (FAS Population, N=55; Subjects with BEs, N=25)

Severity of BE / Efficacy rating	All BEs	
	N	%
Any	64	100
Excellent	16	25
Good	32	50
Moderate	14	21.9
Unknown	2	3.1
Minor	15	100
Excellent	9	60
Good	5	33.3
Moderate	1	6.7
Moderate	34	100
Excellent	6	17.7
Good	22	64.7
Moderate	6	17.7
Major	14	100
Excellent	1	7.1
Good	5	35.7
Moderate	7	50
Unknown	1	7.1
Unknown	1	100
Unknown	1	100

Source: Original BLA 125251.244; Module 5.3.5.1, Clinical Study Report, Table 22.

6.1.11.3 Subpopulation Analyses

The primary endpoint was analyzed by age (categorized by 16 years-old) and the results are presented in Table 7. Results are similar to those for the full data set.

Table 7 Subgroup Analyses of ABRs during WILATE Prophylaxis (FAS)

Type	Mean ± SD	Median (range)	Poisson (95% CI)
<16 Years (n=5)			
All BEs	0.40 ± 0.89	0.00 (0–2)	0.40 (0.06, 2.84)
Spontaneous BEs	0	-	-
≥16 Years (n=50)			
All BEs	2.39 ± 3.77	0.00 (0–15.69)	2.48 (1.94, 3.18)
Spontaneous BEs	1.67 ± 3.11	0.00 (0–11.76)	1.73 (1.29, 2.33)

Source: Original BLA 125251.244; Module 5.3.5.1, Clinical Study Report, Table 14.

Reviewer Comment:
Because all the subjects were white male and no study center was in the US, there were no subgroup analyses for sex, race, and geographical region (US vs. non-US).

6.1.11.4 Dropouts and/or Discontinuations

Although one subject (b) (6) did not complete the study due to an AE, he had complete prophylactic data because he discontinued in the follow-up period. Therefore, there were no missing data for the primary endpoint.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during this study.

6.1.12.4 Nonfatal Serious Adverse Events

There were 17 AEs over the course of the study, 16 of which were treatment-emergent (TEAE); 11 of these (68.8%) were of mild severity and the remaining 5 (31.3%) were of moderate severity. Two of the 16 TEAEs occurred in two patients between 12 and 16 years of age. Both events were mild, non-serious thrombocytosis that were not related to treatment.

6.1.12.5 Adverse Events of Special Interest (AESI)

None of the 55 subjects in the study developed FVIII inhibitors. The two-sided 95% CI is (0, 0.044).

8. INTEGRATED OVERVIEW OF SAFETY

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Please refer to Section 5.3 for a summary of the six studies.

8.5 Additional Safety Evaluations

8.5.8 Immunogenicity (Safety)

In hemophilia A studies TMAE-101, -102, -108 and -110, and WIL-27, FVIII inhibitor development was assayed at baseline, Day 14 and Day 30 (only in study WIL-27), and 3 and 6 months after the initiation of treatment. In study ATE-111, immunogenicity was determined at baseline and at 3 months. The Bethesda method was used in studies TMAE-101 and -102 and the (b) (4) method in studies TMAE-108, -110 and -103 and ATE-111 and WIL-27.

There were 136 PTPs included in these five clinical studies and they had at least 150 EDs at the time of enrollment into the studies. Eighty-three of the 136 subjects ~~and~~ had been treated for at least 50 EDs and 6 months in the studies. None of them developed inhibitors to Factor VIII, resulting in a rate of inhibitor development of 0% (95% CI [0-4.35%]).

Results were considered negative (< 0.4 BU in studies TMAE-101, -102, -108, and -110 or < 0.6 BU in studies WIL-27 and ATE-111) for all subjects at all time-points in all studies. In study ATE-111, one subject had a temporarily detectable FVIII inhibitor level according to one laboratory after treatment with WILATE, which was undetectable on re-assay several months later. The subject was 50 years old at study entry and documented as having had more than 900 previous EDs to FVIII. It was considered unlikely that the positive inhibitor reading was a result of treatment with WILATE.

In pediatric study TMAE-103, inhibitors were observed in 8 out of 29 subjects (28%): five were low-titer inhibitors (< 5 BU) and 3 were high-titer inhibitors. Four of the inhibitors disappeared over time and one low-titer inhibitor was detected only at the subject's last inhibitor test but reappeared 3 months later. 8.6 Safety Conclusions

No previously treated subjects with hemophilia A developed clinically relevant inhibitors to FVIII in any study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

There are no statistical issues in this sBLA. This submission includes the final analysis of the pivotal study WIL-27. Data for 55 subjects ≥12 years of age (5 of whom were between ≥12 and ≤16 years of age) were analyzed. A total of 25 subjects (45.5%) experienced 64 BEs under WILATE prophylaxis. For these 55 subjects, the one-sample Poisson test TABR estimate was 2.29 (95% CI from a Poisson model was [1.80, 2.93]). The mean SABR estimate was 1.58 (95% CI

was [1.17, 2.12]). Forty-eight (75%, [95% CI: 62.60%, 84.98%]) of the 64 BEs were treated successfully with efficacy assessed as either ‘excellent’ or ‘good’; the lower limit of the 95% CI is slightly less than the success criterion of 70%. For the primary safety endpoint of inhibitor formation, no subject developed inhibitors and the two-sided 95% CI is (0, 0.044).

10.2 Conclusions and Recommendations

In this sBLA submission, the primary efficacy endpoint of the pivotal study was the mean TABR under WILATE prophylaxis. The results indicated that the lower bound of the 95% CI was less than the pre-specified criterion. No safety concerns were noted. Therefore, the statistical evidence supports the proposed indication.