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BLA Clinical Review Memorandum

Application Type	BLA Efficacy Supplement
STN	BLA 125251/244
CBER Received Date	November 30, 2018
PDUFA Goal Date	September 30, 2019
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Jay Lozier, MD, PhD, FACP
Review Completion Date / Stamped Date	September 20, 2019 Jay N. Lozier -S Digitally signed by Jay N. Lozier -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jay N. Lozier -S, 0.9.2342.19200300.100.1.1=4001014385 Date: 2019.09.20 14:30:39 -04'00'
Supervisory Concurrence	Bindu George -S Digitally signed by Bindu George -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bindu George -S, 0.9.2342.19200300.100.1.1=1300420762 Date: 2019.09.20 14:39:32 -04'00' Tejashri Purohit-Sheth, M.D. Tejashri S. Purohitsheth -S Director, DCEPT OTAT/CBER/FDA 2019.09.20 16:02:05 -04'00'
Applicant	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Established Name	von Willebrand Factor/Coagulation F VIII Complex
(Proposed) Trade Name	WILATE®
Pharmacologic Class	Coagulation Factor Concentrate
Formulation(s), including Adjuvants, etc.	
Dosage Form(s) and Route(s) of Administration	WILATE® is available as a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per single-use vial (3): • 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL • 1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL
Dosing Regimen	**Hemophilia A** • One International Unit (IU) of factor VIII (FVIII) activity per kg body weight increases the circulating FVIII level by approximately 2.0 IU/dL.

	• Use the following formula to determine required dosage (2.1): Required IU = body weight (BW) in kg x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL) • Dosing for routine prophylaxis (2.1): Subjects: Pediatric subjects and adults Dose (IU/kg): 20-40 IU/kg Frequency of infusions: Every 2 to 3 days • Individualize dosage based on the patient's weight, type and severity of hemorrhage, FVIII level, presence of inhibitors and the patient's clinical condition (2.1).
Indication(s) and Intended Population(s)	WILATE® is indicated in pediatric subjects and adults with hemophilia A for: • Routine prophylaxis to reduce the frequency of bleeding episodes • On-demand treatment and control of bleeding episodes
Orphan Designated (Yes/No)	No

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GLOSSARY

ADR	adverse drug reaction
AE	adverse event
APCC	activated prothrombin complex concentrate
ATE-111	single study of (b) (4) of WILATE® for in adults and adolescents with severe hemophilia A (b) (4)
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CR	complete response
DIC	disseminated intravascular coagulation
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full analysis set. All enrolled subjects who received at least one dose of WILATE after the baseline PK set for WIL-27 pivotal trial
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
HJHS	hemophilia joint health score
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OBE	Office of Biostatistics and Epidemiology
Octapharma	Octapharma Pharmazeutika Produktions ges.m.b.H
PCCs	prothrombin complex concentrates
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	treated per-protocol
PREA	Pediatric Research Equity Act
PTP	previously treated patient
PUP	previously untreated patient
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SABR	spontaneous annual bleeding rate
SAF	safety set, includes all subjects who received at least one dose of WILATE® in WIL-27 pivotal study
TABR	total annual bleeding rate
TEAE	treatment-emergent adverse event
TMAE-103	phase 3 study of WILATE® for prophylaxis and on-demand treatment of severe hemophilia A in previously untreated patients (PUPs)
vWD	von Willebrand disease

vWF	von Willebrand factor
WIL-27	pivotal multicenter trial of WILATE® for prophylaxis and on-demand treatment of severe hemophilia A in adults and adolescents

1. EXECUTIVE SUMMARY

WILATE® is a plasma-derived human coagulation factor concentrate produced by Octapharma Pharmazeutika (Octapharma) that contains both factor VIII and von Willebrand factor. It has been licensed since December of 2009 in the United States for treatment of von Willebrand disease. After conducting studies of WILATE® for treatment of severe hemophilia A under IND 17181 (in effect since October 2016) and conducting other studies outside the United States not under IND, Octapharma seeks approval for hemophilia A treatment indications as below:

WILATE® is indicated in pediatric subjects and adults with hemophilia A for:

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

Three phase 3 clinical trials characterize the safety, efficacy, and pharmacokinetics of factor VIII for prophylactic and on-demand treatment of severe hemophilia A in adult and adolescent previously treated patients (PTPs), previously untreated (pediatric) patients (PUPs), and for (b) (4) of bleeding in adult PTPs with severe hemophilia A (b) (4). Studies intended to support routine prophylaxis and on-demand treatment indications in the pediatric PTP population is pending completion and is in compliance with the agreed upon pediatric study plan.

The pivotal trial, WIL-27, studied prophylactic or on-demand treatment of severe hemophilia A in 55 previously treated patients (PTPs) > 12 years of age. The primary objective was to assess efficacy by comparison of the annualized bleed rate (ABR) of subjects on prophylaxis with WILATE® to the annualized bleed rate of subjects treated on-demand with the recombinant DNA factor VIII product NUWIQ (another Octapharma product). One secondary objective was to assess the safety of WILATE® by measurement of the rate of factor VIII inhibitor antibody development, which is an adverse event of special interest to the FDA. The Applicant and FDA agreed upon the study design at the time of submission of IND 17181 in October of 2016. The ABR for subjects on this study was 2.21 ± 3.64, which compared favorably to the ABR of 58.1 for the comparator on-demand treatment group in the NUWIQ licensure trial. No subjects developed inhibitors to factor VIII on this study or had seroconversion to any viral pathogens attributable to the product. Pharmacokinetic studies were performed in 21 subjects (16 adults, 5 adolescents) during this trial.

Study TMAE-103 studied prophylaxis and on-demand treatment of severe hemophilia A in 29 PUPs, 0 to 89 months of age, between July 2002 and April 2007 at study sites in Germany, Russia, and Ukraine (not under IND). The primary objective was to assess the safety of *WILATE® by measurement of the rate of factor VIII inhibitor antibody development, which is an adverse event of special interest to the FDA. One secondary objective was to assess the efficacy of WILATE® for prophylaxis and treatment of bleeding, and for* (b) (4) *. Although pharmacokinetic studies were optional in this protocol, at least one recovery*

was performed in 22 subjects with 13 subjects having a second recovery performed and several having multiple additional recoveries.

Study ATE-111 studied (b) (4) *of bleeding in 13 adult PTPs* (b) (4) *in the Slovak Republic between October 2004 and February 2007 (not under IND). The objectives were to assess safety and efficacy of WILATE® given by* (b) (4) *. The safety endpoints included measurement of factor VIII inhibitors, and seroconversion for hepatitis A virus or B19 parvovirus. The efficacy endpoints* (b) (4)

Table 1: Phase 3 Trials of WILATE®

Study	Patient Population	Phase, Study Sites	Trial Focus
WIL-27 (pivotal study)	55 PTPs with Severe Hemophilia A (ages 12-64 years)	Phase 3, multicenter, open label multicenter trial (Bulgaria, Hungary, Poland, Russia)	Prophylaxis and On-Demand Treatment, and optional PK study
TMAE-103 (PUP study)	29 PUPs with Severe Hemophilia A (ages 0-89 months)	Phase 3, non-controlled, open label, multicenter trial (Russia, Belarus, Ukraine, Germany)	Prophylaxis or On-Demand Treatment, and optional PK study
ATE-111 (b) (4) study)	13 PTPs with Severe Hemophilia A (b) (4)	Phase 3, open label, uncontrolled, single center trial (Slovak Republic)	(b) (4) thereafter, based on (b) (4) study

The Applicant discussed only the pivotal WIL-27 study with FDA in advance; data from this trial serves as the basis for approval of the routine prophylaxis and on-demand indications sought in this submission.

The design of the PUP study, TMAE-103, is like other studies of previously untreated severe hemophilia A with severe hemophilia A. The endpoints for safety (inhibitor development and seroconversion for various blood borne viral pathogens) and efficacy (ABR and hemostatic assessments) are appropriate for licensure of a factor VIII concentrate derived from plasma. However, subjects in TMAE-103 (conducted between 2002 and 2007, before routine prophylaxis was demonstrated to be clearly superior to on-demand treatment) underwent routine prophylaxis or on-demand therapy at the discretion of the Investigator. Only 4 or 5 subjects, appear to have been treated in a prophylactic manner, and there were no clear rules defining the dose and schedule for routine prophylaxis in the protocol. Enrollment for this study was skewed to children < 2 years of age, and there are relatively few children between ages 2 and 12 years, as might be expected in a PUP study. Thus, TMAE-103 provides additional safety data particularly in PUPs, but is insufficient as designed to support a routine prophylaxis and on-demand indication in pediatric PTPs (2-12 years).

Pharmacokinetic studies in WIL-27 and TMAE-103 demonstrate lower in vivo recovery (IVR) and greater clearance of factor VIII in adolescents and children <12 years of age, compared to adults. *See Pharmacology reviewer's memorandum for details.*

(b) (4)

Additionally, four supportive phase 2 trials in PTPs that studied safety, efficacy, and pharmacokinetics of factor VIII were submitted with this application. These are "legacy" studies done ~2000, and are submitted in PDF digital format, without CDISC data files, and they are not reviewed in detail.

No outside consultations were required for review of this application, nor was an Advisory Committee convened to give advice on approval of this efficacy supplement.

Licensure of this product is subject to the provisions of the Pediatric Research Equity Act. In 2017 Octapharma asked to defer studies of WILATE® in children 1-12 years of age and asked for a waiver from studies of PTPs in children 0-1 year of age, to which the FDA agreed. In this submission, Octapharma presents data from study WIL-27 in which 5 adolescents were treated successfully with WILATE as routine prophylaxis, and in which all 5 adolescents underwent pharmacokinetic studies. On July 10, 2019, the Pediatric Review Committee (PeRC) reviewed CBER's assessment that the request for the waiver (PTPs <1 year of age) and the deferral for studies of children from 1 up to 12 years of age were reasonable and agreed with our plan to grant the indications of routine prophylaxis and on-demand treatment of hemophilia A in adolescents.

There are no serious safety signals from passive surveillance (FAERS) and no special risk mitigation measures appear to be necessary if this product is licensed for treatment of hemophilia A. *See the OBE reviewer's memorandum for details.*

Although the Applicant seeks an indication for pediatric subjects and adults with hemophilia A, the pivotal trial WIL-27 only studied adolescents and adults, and the indication for routine prophylaxis and on-demand treatment of hemophilia can only be granted for adolescents and adults; the data on children under 12 years of age presented by the Applicant is insufficient to support the indications sought in children < 12 years of age.

Upon review of the clinical studies provided in the BLA submission, WILATE® appears to be safe and effective in adults and adolescents with severe hemophilia A patients for routine prophylaxis and on-demand treatment of bleeding.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The three trials that provide the basis for approval of WILATE® for treatment of adults and adolescents with severe hemophilia A are WIL-27 (pivotal study of prophylaxis and on-demand treatment in PTPs), TMAE-103 (PUP study), and ATE-111 (b) (4) in adults and adolescents). These studies were done in Europe/Russia and accordingly the subjects were uniformly Caucasian, non-Hispanic males, as shown in Table 2, below.

Table 2: Demographic Attributes of Subjects in WILATE® Phase 3 Trials

Study	N	Male (%)	White (%)	Adult (%)	Adol. (%)	Child. (%)	Infant (%)
WIL-27 (FAS)*	55	55 (100%)	55 (100%)	50 (91%)	5 (9%)	-	-
TMAE-103**	28	28 (100%	28 (100%)	-	-	5 (18%)	23 (82%)
ATE-111***	10	10 (100%)	10 (100%)	9 (90%)	1 (10%)	-	-
Total	93	93 (100%)	93 (100%)	59 (63.4%)	6 (6.5%)	5 (5.4%)	23 (24.7%)

Adult: ≥ 18 years; Adolescent: 12 to 18 years; Children: 2 to 12 years; Infants: 1 month to 2 years

*WIL-27 FAS = full analysis set (at least one dose of WILATE® administered after initial PK study; 55 of 57 enrolled comprised the FAS)

**TMAE-103 = evaluable subjects (28 of 29 enrolled)

***ATE-111 = subjects who (b) (4) (10 unique subjects, of 13 enrolled)

1.2 Patient Experience Data

Patient experience data is represented by patient reports of joint bleeding in studies WIL-27 and TMA-103 etc. and is central to the estimation of the annual bleed rate (ABR), the critical endpoint for the primary objective of these studies, which is the basis for approval.

Patient Experience Data Relevant to this Application

			Section where discussed, if applicable
☒	The patient experience data that was submitted as part of the application include:		
	☒	Clinical outcome assessment (COA) data, such as	Section 6.1 Study endpoints
		☒ Patient reported outcome (PRO)	ABR
		☒ Observer reported outcome (ObsRO)	Parent report (TMAE-103)
		☒ Clinician reported outcome (ClinRO)	Global Hemostasis Rating
		☐ Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☒	Patient-focused drug development or other stakeholder meeting summary reports	Section 2.1 Analysis of Condition
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review		

		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is a bleeding disorder due to the complete absence or partial deficiency of coagulation factor VIII. The severity of hemophilia A is inversely proportional to the circulating factor VIII level; severe hemophilia A is associated with factor VIII levels less than 1% of normal and is characterized by frequent (weekly) spontaneous bleeding into joints (hemarthroses), as well as excessive bleeding after surgery or trauma. Recurrent hemarthroses lead to crippling joint damage that can result in joint fusion and may ultimately require joint replacement. The disease is inherited in a sex-linked manner, since the factor VIII gene, is found on the long arm of the X chromosome (Xq28). Any male who inherits a defective factor VIII gene will have hemophilia A; females who are carriers have half the normal level of factor VIII, but are not usually affected with hemophilia A, since 50% factor VIII levels are enough for normal hemostasis. Approximately 1 in 5,000 males born is afflicted with hemophilia A. Factor VIII is produced from endothelial cells of all organs and hepatic sinusoidal cells in the liver and stored with von Willebrand factor in Weibel-Palade bodies after synthesis. Factor VIII is normally present in the plasma at a concentration of 100-200 ng/mL; under stress factor VIII and von Willebrand factor are released from endothelial cell stores leading to transient increases in the level of both proteins in the circulation as part of the acute response to inflammation or stress.

The natural history of untreated, severe hemophilia A is progressive damage to joints from recurrent hemarthroses, which leads to limited joint mobility and eventually joint fusion.

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

The mainstay of hemophilia A treatment is replacement therapy with factor VIII concentrates, including plasma-derived, or recombinant products that are injected intravenously. Optimal treatment is always prophylaxis with plasma-derived or recombinant factor VIII concentrates or factor VIII mimetics to maintain a level that is high enough to prevent spontaneous bleeding (typically >1% of normal) and prevent joint damage in the long term.

Other non-factor VIII hemostatic products are approved that may be used to treat hemophilia A. These include DDAVP, anti-fibrinolytics (e.g aminocaproic acid or tranexamic acid), and factor VIII mimetics (such as emicizumab).

Products such as emicizumab can serve as factor VIII mimetics through a novel mechanism, binding factor IX and factor X in close proximity, thereby enhancing the catalytic activity of activated factor IX, just as factor VIII does. Emicizumab is approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors. It is a humanized monoclonal modified IgG4, bispecific antibody produced in genetically engineered mammalian (Chinese hamster ovary) cells. Since it is a monoclonal antibody, it has a much longer half-life and is administered by subcutaneous injection. After administering a loading dose of 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, the patient continues with a maintenance dose of 1.5 mg/kg once every week, or 3 mg/kg once every two weeks, or 6 mg/kg once every four weeks. In 89 adults and adolescents with hemophilia A without factor VIII inhibitor studied in the HAVEN 3 emicizumab trial[1,2] the ABR for those receiving 1.5 mg/kg once weekly was 1.5 (95% CI 0.9-2.5) and 1.3 (95% CI 0.8-2.3) for those receiving 3 mg/kg once every two weeks, as compared to an ABR of 38.2 (95% CI 22.9-63.8) for a factor VIII on-demand control group. For subjects receiving 1.5 mg/kg of emicizumab weekly 55.6% had no bleeds during the 24-week observation period, and for the 3 mg/kg group, 60% had no bleeds during the observation period; no subject from the factor VIII on-demand group had no bleeds. For the 1.5 mg/kg weekly emicizumab group with and ABR of 1.5, their historic ABR on factor VIII prophylaxis was 4.8, indicating a 68% decrease in the ABR while on emicizumab.

Mean ABRs for emicizumab and several other, recently-approved factor VIII products is shown below in Table 3:

Table 3: Hemophilia A Routine Prophylaxis Approved Products' Mean ABRs

Product	Age of Subjects (yrs)	Year of Approval	Mean ABR (SD)
Factor VIII Mimetic			
Emicizumab HAVEN 3	≥ 12	2018	1.5
Factor VIII (Recombinant DNA)			
Kovaltry Literature	12-65	2016	4.9 (6.8)
Adynovate USPI	≥12	2015	4.7 (8.6)
Kogenate USPI	≥15-50	2015	2.0
Advate BLA Stat Review 2010	7-65	2015	2.86 (4.53)
Xyntha Literature	≥12	2008	3.9
Afstyla BLA Stat Review 2016	≥12-65	2016	3.11 (5.05)
Factor VIII-Fc Fusion Protein (Recombinant)			
Eloctate BLA Stat Review 2014	≥12	2014	2.9

PEGylated Factor VIII			
Jivi USPI	≥12	2018	3.3 (4.3)
Esperoct USPI	12-70	2019	3.3 (4.9)

2.3 Safety and Efficacy of Pharmacologically Related Products

Replacement of factor VIII activity (the mechanism of action for WILATE®) can be accomplished by numerous FDA approved products. Since factor VIII has a half-life of ~8 hours after intravenous injection, this typically requires injection of factor VIII 2 or 3 times weekly, at doses of 20-40 IU/kg to prevent joint bleeding.

Currently approved plasma-derived factor VIII concentrates may or may not contain von Willebrand factor protein in addition to factor VIII, depending on the method of purification. All plasma derived factor VIII concentrates begin with cryoprecipitation of plasma, and undergo various purification procedures thereafter, which include column chromatography; products with monoclonal antibody purification steps typically lead to homogeneous factor VIII concentrates of high specific activity that lack von Willebrand factor. Plasma derived factor VIII concentrates that contain von Willebrand factor that are FDA approved include Alphanate (Grifols) and Humate-P® (CSL Behring). Plasma-derived factor VIII products that are purified by monoclonal antibody affinity chromatography and do not contain von Willebrand factor include Monoclate® (CSL Behring) and Hemophil M® (Baxalta).

Recombinant factor VIII products contain only the factor VIII protein and non-protein stabilizers (Kovaltry®/Kogenate®, Bayer; Recombinate®, Baxter; Helixate®, CSL Behring). Some may be engineered as fusion proteins with Ig chains (ELOCTATE® Biovertiv Therapeutics) or formulated with additives like polyethylene glycol (ADYNOVATE®, Baxalta) that lead to a longer half-life than unmodified factor VIII protein. Routine prophylaxis may be achieved by administration of 25-75 IU/kg 2 times per week.

Fresh-frozen plasma, cryoprecipitate, and low-purity factor VIII concentrates are no longer considered to be acceptable treatments of hemophilia A and are not used any longer.

(b) (4) is being studied under IND by multiple sponsors, but is not currently an approved therapy for hemophilia A.

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

WILATE® was licensed in the United States in December of 2009 for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. The initial BLA was approved based on studies TMAE-101, TMAE-102, TMAE-108 and TMAE-110, which were submitted at that time in paper format (“legacy” studies).

An additional indication for prevention of excessive bleeding during and after minor and major surgery in VWD patients was approved In August 2015 in the United States.

WILATE® has therefore been extensively studied and used for treatment of von Willebrand's disease in the United States and Europe for several years.

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

Octapharma Pharmazeutika submitted an IND 17181 in October 2016 to begin studies of the use of WILATE® for treatment of hemophilia A. The plan was to conduct a pivotal study of WILATE® in approximately 50 subjects with severe hemophilia A. The Biostatistics reviewer made the following critical observation:

"The sponsor plans to pool the inhibitor data from WIL-27 with that from other WILATE® clinical studies, but does not specify which studies. However, for the other studies, the inhibitor status of these subjects is already known since the studies are complete, thus affecting the number of inhibitors that can occur in WIL-27. For example, the three clinical studies used to assess immunogenicity for the original BLA submission of WILATE® for the von Willebrand disease indication had 15 hemophilia A subjects who received WILATE®, none of whom developed an inhibitor. If the sponsor pools the inhibitor status for these 15 subjects, along with another 15 subjects with no inhibitors from other completed studies, then WIL-27 can have 1/50 inhibitors and still meet the 1/80 criterion (no more than one inhibitor in 80 subjects) recommended in the 2003 FDA workshop on Factor VIII (http://www.fda.gov/ohrms/dockets/dockets/04n0033/04n-0033-tr00001-vol3.pdf).

Therefore, pooling these previously known results, along with the WIL-27 data, would lead to bias since the results are already known.

If the sponsor does not pool the data and just uses the data in WIL-27, then the success criteria cannot be met since the upper bound of the two-sided 95% confidence interval of 0/50 (reflecting the best case scenario of no subjects with inhibitors) is 7.1%. However, if the WIL-27 sample size is 60 subjects, with a 10% drop out rate, 54 subjects with no inhibitors can meet the criterion.

The pivotal hemophilia A study (WIL-27) commenced in December of 2016.

The Applicant and FDA agreed in August of 2017 on an initial pediatric study plan in which study of subjects < 12 years of age would be deferred, with initial study of pediatric subjects ages 12-17 years.

A study of the use of WILATE® for severe hemophilia A in previously-treated pediatric subjects 1 to < 12 years of age (WIL-30) was proposed in June 2017, and the study is ongoing at the time of this review.

A pre-submission meeting was not held for this efficacy supplement.

2.6 Other Relevant Background Information

Although hemophilia A is clearly a rare disease and factor VIII therapeutics with advantages over existing hemophilia A therapeutics might qualify for orphan drug/disease designation, the Applicant has not applied for orphan drug designation of the product, WILATE® for hemophilia A. Note, Octapharma had been granted orphan drug exclusivity for WILATE® for treatment of bleeding in von Willebrand disease in 2009, however, this was revoked in 2011 following a citizen petition submitted to FDA by CSL-Behring that convinced the FDA that the claims of superiority over other products for von Willebrand disease (e.g., Humate-P®) were overstated.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

For the most part, the submission was well organized, and a complete clinical review could be conducted without unreasonable difficulty. The dataset for the phase 3 WIL-27 study was submitted in CDISC format. The dataset for TMAE-103 (PUP study) and ATE-111 (adult (b) (4) study) were submitted in digital format, but with limited STDM/ADaM file sets, which makes review of the PUP study TMAE-103 difficult. Review of the ATE-111 (b) (4) study, which only involved 14 enrolled subjects, and 11 (b) (4) in 10 unique subjects was not hindered by the format of the submitted data sets, since the safety and efficacy evaluation is easy to perform on a small study. Legacy phase 1/2 studies previously reviewed by FDA for the von Willebrand disease indication in paper format were converted to digital format for this efficacy supplement and submitted as PDFs. A pharmacovigilance plan and pediatric study plan for hemophilia A were not submitted with the original submission but both were requested by FDA through information requests and provided by the Applicant in a timely manner. An FDA audit of SDTM format data showed that the format of data submitted in study WIL-27 was largely satisfactory, aside from some missing reference ranges for viral serology testing and ABO blood type results. Other legacy (paper) studies critical to the review, such as TMA103 (phase 3 PUP study) and ATE-111 (b) (4) study), had issues with missing data, treatment start date discrepancies, duplicate bleeding events, and reference ranges for hepatitis serology data. These issues were deemed to be minor, and unlikely to prevent evaluation of the studies that are critical to the review of this application.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Study WIL-27 was conducted under IND 17181 at overseas clinical sites in Bulgaria, Hungary, Poland, and Russia. The Applicant, through authorized US representative, declares on FDA form 3674 that “the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that the requirements of 42 U.S.C. 282(j), including any applicable provisions of 42 CFR part 11, have been met. On January 4, 2019 the Applicant submitted amendment 125251/244.1, which described the Pharmacovigilance Plan (PVP) requested by OBE reviewer (Section 1.16.1). On January 15, 2019 the Applicant submitted the Pediatric Study Plan for hemophilia A (dated August 8, 2017) in Section 1.9.6, as agreed to by FDA on September 8, 2017, after an information request by the clinical reviewer.

An inspection of sites 41 (Cracow, Poland) and 21 (Sophia, Bulgaria), which studied most subjects for Study WIL-27 was conducted in April of 2019. As of the Mid-Cycle

review timepoint Site #21 received an FDA Form 483 for repeating the parvovirus testing at the 6-month visit for subjects who had previously tested positive (when no test should have been repeated).

Reviewer Comment: *Defer to BIMO reviewer for evaluation of final Establishment Inspection Report (EIR), but the inspectional findings do not suggest any problem with conduct of the study protocols that would prevent approval of the indications sought by the Applicant in this BLS.*

3.3 Financial Disclosures

<table>
<tr><td colspan="3">Covered clinical study (name and/or number): Studies WIL-27, TMAE-103, & ATE-111</td></tr>
<tr><td>Was a list of clinical investigators provided:</td><td>Yes X</td><td>No ☐ (Request list from applicant)</td></tr>
<tr><td colspan="3">Total number of investigators identified: 13

WIL-27 Investigators:
Dr. Toshko J. Lissitchkov
Dr. Lazlo Nemes
Dr. Joanna Zdziarska,
Dr. Bartosz Korczowski,
Dr. Vladimir V. Vdovin,
Dr. Andrey N. Mamaev,

ATE-111 Investigator:
Dr Angelika Batorova

TMAE-103 Investigators:
Dr W Kreuz
Dr G Auerswald
Dr T Chernova
Dr T Andreeva
Dr V Vdovin
Dr V Gapanovich
Prof P Perechrestenko
Dr K Zakirov</td></tr>
<tr><td colspan="3">Number of investigators who are sponsor employees (including both full-time and part-time employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">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)):

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 sponsor of covered study: _____</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from applicant)</td></tr>
</table>

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

No concerns were raised regarding study integrity based on review of Financial Disclosures.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

WILATE® is a factor VIII/von Willebrand factor concentrate manufactured by Octapharma Pharmazeutika Produktions ges.m.b.H., in Vienna, Austria. The Applicant verifies that WILATE® is the same product that has been marketed in the European Union under the trade name OCTATE in an amendment to BLA 125251/244, received March 9, 2019. It is purified from pooled plasma from normal donors and licensed for use in the United States for treatment of von Willebrand disease. Cryoprecipitate is prepared at (b) (4) and subjected to aluminum hydroxide adsorption; the aluminum hydroxide (b) (4) is then subject to filtration and viral inactivation with octoxynol/tri(n-butyl) phosphate, (b) (4) , ion-exchange chromatography, (b) (4) chromatography, and ultrafiltration. After viral inactivation with heat treatment, the bulk drug substance is then used to fill vials with nominal amounts of 500 IU vWF/FVIII or 1000 IU vWF/FVIII, which are then lyophilized. The final drug product is packaged with sterile 0.1% polysorbate 80 for reconstitution by the end-user. The viral inactivation procedures give a cumulative >12 log10 reduction in HIV titer, as shown in Table 4 below, from the current approved USPI.

Table 4: Wilate® Viral Clearance of Prototypical Blood-Borne Viral Pathogens

Production Step	Virus Reduction Factor [log_{10}]						
	Enveloped Viruses				Non- Enveloped Viruses		
	HIV-1	SBV	BVDV	PRV	REO 3	HAV	PPV
S/D Treatment	> 7.52	> 8.63	> 4.18	> 8.54	na	na	na
Ion-Exchange	nd	nd	nd	nd	1.86 - 2.33	1.16 - 1.93	3.29
TDH Treatment	4.91 - > 5.79	> 5.51	nd	3.99 - 4.87	> 6.40	> 5.69	2.57 - 4.12
Global Reduction Factor	> 12.43 - > 13.31	> 14.14	> 4.18	> 12.53 - > 13.41	> 8.26 - > 8.73	> 6.85 - > 7.62	5.86 - 7.41

na: not applicable
nd: not done (S/D reagents present)
HIV-1: Human Immunodeficiency Virus - 1
SBV: Sindbis Virus
BVDV: Bovine Viral Diarrhea Virus
PRV: Pseudorabies Virus
REO 3: Reovirus Type 3

WILATE is currently under the FDA lot release program, administered by the Office of Biologics Quality and Compliance (OCBQ) and factor VIII has been routinely assayed as part of that process.

4.2 Assay Validation

Assays for factor VIII coagulation activity were done using a one-stage (b) (4) assay in which the time to form a fibrin clot was the measured endpoint, and a chromogenic assay in which the rate of color development by enzymatic conversion of a colorless substrate for factor Xa was measured. Both are valid measurements of factor VIII activity and typically have similar, though not identical values for factor VIII activity. The one-stage assay is commonly used in clinical laboratories since it is an older and less expensive assay, while the chromogenic assay is less commonly used in clinical laboratory testing due to its expense and complexity. Although the activity of certain recombinant coagulation factor VIII proteins is measured and defined by the chromogenic assay as a product specification, with recombinant protein standards, no such practice applies to plasma-derived factor VIII concentrates.

Reviewer Comment*: I regard the use of the one-stage assay for measuring factor VIII activity of WILATE® and describing its use, dosing, and measurements of activity recovered in vivo to be preferable to the chromogenic assay, since the latter is not commonly available and offers no discernable advantage to physicians or other caregivers who will prescribe this product.*

The assay employed in the evaluation for factor VIII inhibitors in the Applicant's protocols is the Bethesda Inhibitor assay, with the (b) (4) . Namely, patient samples are (b) (4)

Reviewer Comment: *The* (b) (4) *Bethesda factor VIII inhibitor assay is the preferred method of inhibitor detection in the clinical laboratory.*

4.3 Nonclinical Pharmacology/Toxicology

Defer to Pharmacology/Toxicology Reviewer.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

WILATE® contains von Willebrand factor (VWF) and coagulation factor VIII (FVIII). VWF serves as a stabilizing carrier protein for the procoagulant protein FVIII. Wilate replaces these factors which are needed for effective hemostasis in Hemophilia A.

4.4.3 Human Pharmacokinetics (PK)

Limited studies of the pharmacokinetics of factor VIII were performed as part of study WIL-12, completed in 2006, in support of the 2009 BLA approval of WILATE® for von Willebrand's disease. The study in five type 1 von Willebrand disease patients given a 50 IU/kg of WILATE® showed an average factor VIII half-life of 8.9 hours (range 4.0 to 13.7) and a recovery of 2.05 IU/kg (range 1.3 to 2.69).

In the pivotal study of WILATE in adult and adolescent PTPs with hemophilia A (WIL-27), the in vivo recovery was 2.27 IU/dL per IU/kg administered for adults and 1.66 IU/dL per IU/kg administered for adolescents. In the study of WILATE in children < 12 years of age (TMAE-103) the in vivo recovery for subjects without inhibitor antibodies was 1.36 IU/dL per IU/kg administered.

Reviewer Comment(s): *The key overall finding from factor VIII pharmacokinetic studies performed in support of this efficacy supplement was that factor VIII recovery progressively decreased as the age of the subject decreased.*
Please see Pharmacology Review for details of pharmacokinetic studies.

4.5 Statistical

The statistical reviewer has verified that the primary study endpoint analyses cited by the applicant are supported by the submitted data. The two key endpoints that were analyzed were the effect of WILATE® on the annualized bleed rates (TABR & SABR) and the rate of inhibitor antibody development in WIL-27, pooled with data from other previously-conducted studies of WILATE® in PTPs. With respect to the analysis of inhibitor rates, previous review of the IND 17181 by the statistical reviewer in October 2016 indicated that

If the sponsor does not pool the [inhibitor rate] data and just uses the data in WIL-27, then the success criteria cannot be met since the upper bound of the two-sided 95% confidence interval of 0/50 (reflecting the best case scenario of no subjects with inhibitors) is 7.1%. However, if the WIL-27 sample size is 60 subjects, with a 10% drop out rate, 54 subjects with no inhibitors can meet the criterion.

In the submission the Applicant provides a Pooled Analysis of the Immunogenicity of WILATE® in Previously Treated Patients with Severe Hemophilia A, dated 2018. In this report they cite all trials of PTPs treated with WILATE® which includes TMAE-102, TMAE-108, TMAE-110, and WIL-27 (pivotal study) as the source for inhibitor analysis data (Table 5).

Table 5: PTPs with ≥ 150 Prior EDs, Rxed with WILATE® for ≥50 EDs & ≥ 6 Mos.

Study	All PTP Subjects	Subjects Meeting All Criteria for Analysis
TMAE-102	24	7
TMAE-108	21	8
TMAE-110	35	17
WIL-27	55	49
Total	**135**	**83**

The Applicant has adjusted the tally of Subjects Meeting all Criteria for Analysis in Table 5 to exclude subjects who did not meet all criteria or participated in more than one listed study.

In all, 136 PTP subjects have been treated with WILATE® in these trials. Eighty-three subjects met the strict requirements of having 150 factor VIII exposure days prior to treatment with WILATE®, 50 exposure days with WILATE®, and six months of follow-up on WILATE treatment.

4.6 Pharmacovigilance

The safety finding of special interest for this product is development of inhibitor antibodies. On January 4, 2019 the Applicant submitted amendment 125251/244.1, which described the Pharmacovigilance Plan (PVP) (Section 1.16.1). Thus far, the OBE review of adverse events associated with use of WILATE for hemophilia A, as reported

in the FAERS database, reveals few adverse events, consisting mainly of inhibitor antibodies to factor VIII in hemophilia patients with few or no prior exposure days to factor VIII.

***Reviewer Comments**: It is expected that a plasma derived factor VIII concentrate containing von Willebrand factor should have a lower inhibitor formation rate in patients with hemophilia A than recombinant factor VIII products, based on the results of the SIPPET study (Peyvandi et al,* NEJM *2016; 374:2054-2064) in which the incidence of all inhibitors was 26.8% (95% confidence interval [CI], 18.4 to 35.2) in the group that received plasma-derived factor VIII and 44.5% (95% CI, 34.7 to 54.3) in the group that received the recombinant factor VIII. For high titer inhibitors (> 5 BIAU titer) in the plasma derived factor VIII recipients and the recombinant factor VIII recipients the incidence was 18.6% (95% CI, 11.2 to 26.0) and 28.4% (95% CI, 19.6 to 37.2), respectively.*

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

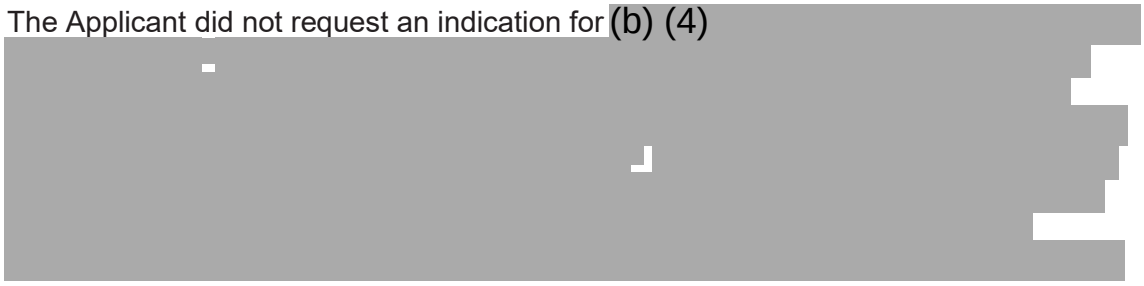
5.1 Review Strategy

The clinical review focused on the pivotal phase 3 study of WILATE® use in previously treated patients with severe hemophilia A (WIL-27). The phase 3 study of previously untreated patients with severe hemophilia A (TMA-103), and the (b) (4) study in previously treated adult and adolescents with severe hemophilia A (ATE-111), were also reviewed as supporting material for the indications sought.

For the requested indications of routine prophylaxis and on-demand treatment of bleeding, WIL-27 provides critical information (ABR data) to determine the efficacy of WILATE® adults and adolescents with severe hemophilia A and serves to establish safety in general and factor VIII inhibitor risk in particular, when combined with other studies of WILATE®. Additionally, WIL-27 provides pharmacokinetic data with which to determine the in vivo recovery of factor VIII activity and its clearance to determine dosing of the product for hemophilia A in adults and adolescents. WIL-27 does not establish efficacy, safety, or pharmacokinetics of WILATE® in children less than 12 year of age.

Study TMAE-103 provides safety data on the use of WILATE®, including factor VIII inhibitor risk, and risk of seroconversion to blood borne pathogens. Subjects were treated with WILATE® on demand or as routine prophylaxis at the discretion of the Investigators, and it appears that only four or five children were treated with WILATE® as routine prophylaxis. Further, due to the subjects having not been treated with factor VIII before, the age distribution is skewed heavily toward children less than 2 years of age (22 of 28 subjects) and only two of the six children between 2 and 12 years of age had pharmacokinetic studies. This data therefore does not allow us to extrapolate data from WIL-27 routine prophylaxis and on-demand use to children under 12 year of age.

The Applicant did not request an indication for (b) (4)



(b) (4)

Other phase 1/2 studies of safety and efficacy (TMAE-101, TMAE-102) and a phase 3 study in previously treated severe hemophilia A patients (TMAE-110) were reviewed in support of the pivotal study. Pharmacokinetic components of various studies (TMAE-101, TMAE-102,TMAE-108 & TMAE-110) were reviewed in detail by the Pharmacology reviewer. Please refer to the Clinical Pharmacology review for details.

Table 5: BLA 125251/244 Review Disciplines and Reviewers

Review Discipline	Reviewer
Regulatory Product Manager	Jean Gildner
Clinical Review; BLA Chairman	Jay Lozier
Clinical Pharmacology	Iftekhar Mahmood
Labeling Review	Alpita Popat
Statistical Review	Joshua Lu
Pharmacovigilance/Epidemiology	Firoozeh Alvandi
BIMO Review	Carla Jordan
(Chemistry, Manufacturing, Controls)	(NA)

***Reviewer Comments**: There is no review of Chemistry, Manufacturing, and Controls for this efficacy supplement since WILATE® is already licensed under BLA 125251, and there are no changes proposed for the manufacture of this product. Note, WILATE has been subject to provisions of lot release under the Office of Compliance and Biologics Quality (OCBQ) since licensure in 2009 for von Willebrand's disease, and factor VIII activity is already routinely assayed under the lot release program.*

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

BLA 125251/244 and amendments thereof served as the basis for this clinical review, with emphasis on Sections 2.5 (Clinical Overview), 2.7 (Clinical Summary), and 5.3.5 Hemophilia A, 5.3.4.2 Study Reports of Uncontrolled Clinical Studies. Reference was made to Sections 1.3 (Administrative Information) and 1.14 (Labeling) for administrative details and labeling information.

5.3 Table of Studies/Clinical Trials

Table 6: Studies in Support of Proposed Hemophilia A Indications
Primary Studies

Study	Population	Design	Treatment	eCTD
WIL-27 (pivotal study)	55 treated PTPs with Severe Hemophilia A	Phase 3, multicenter, open label multicenter trial (Bulgaria,	PK, Prophylaxis, and On-Demand Treatment	5.3.5.2

	(ages 12-64 years)	Hungary, Poland, Russia)		
TMAE-103 (PUP study)	28 evaluable PUPs with Severe Hemophilia A (ages 0-89 months)	Phase 3, non-controlled, open label, multicenter trial (Russia, Belarus, Ukraine, Germany)	Prophylaxis or On-Demand Treatment at discretion of Investigator; PK optional	5.3.5.2
(b) (4)				

Secondary Studies

Study	Population	Design	Treatment	eCTD
TMAE-101	14 PTPs with Severe Hemophilia A (age 11-59 years)	Phase 2, open label, uncontrolled, multicenter trial (Israel) Three (b) (4)	Three single bolus injections of 40 IU/kg for recovery and pharmacokinetics	5.3.5.2
TMAE-102	24 PTPs with severe hemophilia A (ages 11-59 years)	Phase 2, open label, uncontrolled, multicenter trial (Poland and Bulgaria) (1 dental, 1 arthroscopic synoviorthesis, 1 open synovectomy, 1 radiation synoviorthesis, 1 skin excision, 1 arthroscopic synovectomy; 3 (b) (4) 4 bolus (b) (4)	Single bolus injections of 40 IU/kg for recovery and pharmacokinetics	5.3.5.2

TMAE-108	21 PTPs with severe hemophilia A (ages 11-59 years)	Phase 2, open label, uncontrolled, multicenter trial (Poland and Bulgaria)	Single bolus injections of 40 IU/kg for recovery and pharmacokinetics	5.3.5.2
TMAE-110	35 PTPs with severe hemophilia A (ages 12-66 years)	Phase 3, open label, uncontrolled, multicenter trial (Poland and Slovak Republic)	Single bolus injections of 40 IU/kg for recovery and pharmacokinetics	5.3.5.2

5.4 Consultations

No consultations were required for the review of this application.

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was deemed necessary for the review of this efficacy supplement, as no novel issues were presented by its use for in patients with severe hemophilia A.

5.4.2 External Consults/Collaborations

No outside consultation was required for the review of this submission.

5.5 Literature Reviewed (if applicable)

EMICIZUMAB US Package Insert (October 16, 2018, reviewed May 28, 2019).

FDA Oncology Center of Excellence Workshop on Hemophilia Product Development, December 6, 2018, Silver Spring MD
https://www.fda.gov/media/124992/download

Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. *N Engl J Med* 2007; 357:535-544. The randomized study that demonstrated superior outcomes for routine prophylaxis in severe hemophilia A with Kogenate; included joint imaging with MRI.

NCT 02847637 (HAVEN 3 clinical trial of EMICIZUMAB)
https://clinicaltrials.gov/ct2/show/NCT02847637

Orphan Drug Exclusivity Stripped from WILATE® for vWD Treatment
http://www.fdalawblog.net/2012/08/fda-rescinds-orphan-drug-exclusivity-for-wilate-a-first-of-its-kind-decision/

Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A *N Engl J Med* 2016; 374:2054-2064. The SIPPET study which compared the rate of inhibitor antibody formation in previously

untreated patients with severe hemophilia A randomized to plasma-derived factor VIII or recombinant DNA factor VIII.

Shapiro AD, Korth-Bradley J, Poon MC. Use of pharmacokinetics in the coagulation factor treatment of patients with haemophilia. *Haemophilia* 2005;11:571-82. Study indicating that in vivo recovery of coagulation factors in hemophilia is lower in children than adults.

Verbruggen B1, Novakova I, Wessels H, et al. The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability. *Thromb Haemost.* 1995 Feb;73(2):247-51. The modified assay that is the standard method for detection of factor VIII inhibitors, particularly in clinical trials.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

WIL-27: Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of WILATE® in Previously Treated Patients with Severe Haemophilia A

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective

The primary objective of this study was to determine the efficacy of WILATE® in the prophylactic treatment of previously treated patients (PTPs) with severe hemophilia A.

Secondary

The secondary objectives of this study were to:

- Determine the efficacy of WILATE® in the treatment of breakthrough bleeding episodes (BEs)
- Calculate the factor VIII coagulant activity (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 AB0 blood type and the FVIII:C half-life of *WILATE®*
- Assess the association between the von Willebrand factor antigen (VWF:Ag) concentration and the FVIII:C half-life of WILATE®
- Assess the safety and tolerability of WILATE®
- Assess the immunogenicity of WILATE®.

Exploratory

An additional objective of this study was the descriptive efficacy of WILATE® in (b) (4)

6.1.2 Design Overview

This was a prospective, non-randomized, open-label, international, multi-center Phase 3 study that investigated the PK, efficacy, safety and immunogenicity of WILATE® in adult and adolescent PTPs with severe hemophilia A. The prophylactic treatment period for each patient lasted 6 months (+ 2 weeks) with 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 reduction of the TABR by routine WILATE prophylaxis reported by the subject and by the investigator when on-site monitoring was required (as compared to a historic control group, treated on-demand with a recombinant factor VIII product, Nuwiq)

Efficacy was assessed based on the successful treatment of breakthrough BEs with WILATE® and (b) (4) hemostatic efficacy by the (b) (4) and Investigator (b) (4). Efficacy assessments for control of bleeding were assessed by the subjects and by investigators in instances where study site monitoring was required. Hemostasis efficacy for (b) (4) and hemostasis were based on a four-point rating scale ("Excellent", "Good", "Moderate" and "None") where "Excellent" and "Good" hemostasis ratings were deemed to be successful.

The primary objective of the study was to document a 50% reduction in the total annualized bleed rate compared to a historical control of PTPs treated on-demand for Octapharma's recombinant factor VIII product Nuwiq, which was 58.1 bleeding events per year in the GENA-01 study, conducted under IND 13722.

PK assessments (which were optional) were based on a single dose of 50 (±5) international units (IU) kg body weight (BW) on Day -1 and at the 6-month visit.

Safety (adverse events) and immunogenicity (factor VIII inhibitors) were monitored throughout the study. A goal of this study was to demonstrate no inhibitors in a total of at least 80 PTPs, 50 or more of whom would be derived from this study. The remainder would be derived from other studies in which PTPs were previously studied.

Reviewer comments: *The design of the WIL-27 study is generally appropriate and typical of licensure studies of coagulation factor concentrates. The requirement for ABRs in the WILATE prophylaxis study to improve on the previously completed Nuwiq trial on-demand arm (ABR rate of 58) by 50% was a very low threshold to meet. However, this was agreed on by FDA, and the Applicant exceeded this threshold by a very wide and convincing margin. Additionally, it would have been unethical for the Applicant to encourage research subjects to switch to on-demand therapy from routine prophylaxis, so the historical control group treated on-demand was reasonable. The historic ABRs for 32 of the WIL-27 subjects who were treated on-demand prior to participation in the WIL-27 study (all adults) were compared to their ABRs while on prophylaxis, as an additional analysis. Since the selection of these 32 subjects to the WIL-27 studies was not pre-specified, the potential for selection bias exists and the use of these 32 subjects are not considered as adequately robust for inclusion in the label.*

Several changes in the planned analyses were made in the protocol. The changes were decided upon before data analysis. Key among these was that the definition of previous annual bleeding rate was modified to specify that it included the number of bleeding episodes during the prior 6 months, and the formula for calculating the annual bleeding rate was modified to: the number of bleeds under prophylaxis / days under prophylaxis / 365.25. These changes were reasonable and do not affect our ability to assess the results for granting the requested indications for hemophilia A.

6.1.3 Population

Planned enrollment was 55 patients 12 years of age or older to obtain evaluable data on 50 patients. Of these 50 patients, at least 20 patients were to undergo two 2-day PK assessments of WILATE®, one before the start and one after the end of the prophylactic

treatment phase. Of the 20 patients undergoing PK assessment, a minimum of four patients were to be between 12 and 16 years of age.

Inclusion criteria:
1. Severe hemophilia A (<1% FVIII:C) according to medical history
2. Male patients aged at least 12 years
3. Previous treatment with a coagulation factor VIII (FVIII) concentrate for at least 150 exposure days
4. Immunocompetence (CD4+ count >200/µL)
5. Good documentation of the historical bleeding rate (at least for the 6 months preceding study start)

Exclusion criteria:
1. Any coagulation disorders other than hemophilia A
2. History of FVIII inhibitor activity (≥0.6 Bethesda Units [BU]/mL) or detectable FVIII inhibitory antibodies (≥0.6 BU/mL using the (b) (4) of the Bethesda assay) at screening, as determined by the central laboratory
3. Severe liver or kidney diseases (alanine transaminase [ALT] and aspartate transaminase [AST] levels greater than five times of upper limit of normal, creatinine >120 µmol/L)
4. Patients receiving or scheduled to receive immunomodulating drugs (other than antiretroviral chemotherapy) such as alpha-interferon, prednisone (equivalent to >10 mg/day), or similar drugs

Reviewer comments: *The entry criteria for the WIL-27 study are appropriate.*

6.1.4 Study Treatments or Agents Mandated by the Protocol
The FVIII/VWF concentrate WILATE®, produced from the plasma of human donors, was provided as a powder and solvent for intravenous injection containing nominally 500 IU or 1000 IU human VWF and human FVIII per vial.
The batches of WILATE® used in the study were: A550B181I, K615B1812, K617A1816, K637B181J, K646A1813, K648B1817, K701A1812, K701B1812, K702A1811, K702C1812, K704A1811, K704B1811.

Dosing:

Pharmacokinetic Assessment: Single dose of WILATE® of 50 ± 5 IU/kg BW.

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

In case of unacceptably frequent spontaneous breakthrough BEs (i.e., more than two spontaneous BEs or one major or life-threatening spontaneous BE within a 30-day period), the dose of WILATE® was to be increased by approximately 5 IU/kg (depending on the entire content of the additional vial(s) that need(s) to be reconstituted).

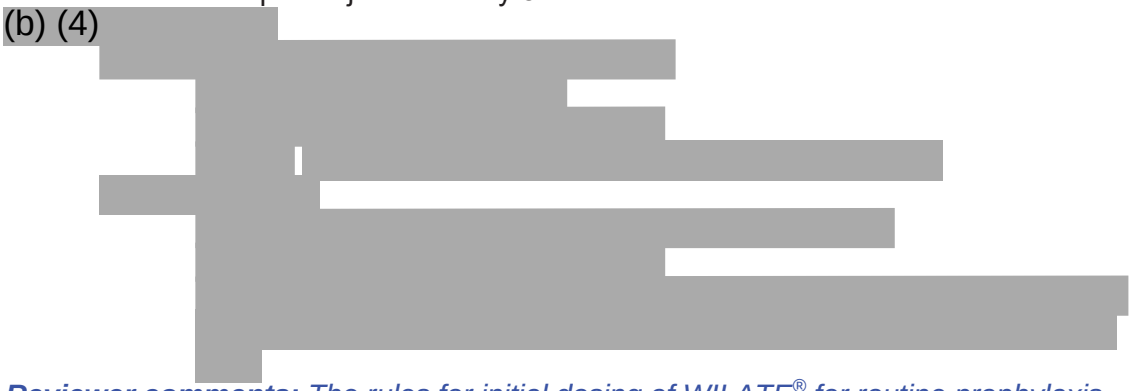
Treatment of Breakthrough BEs:

- 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)



Reviewer comments: *The rules for initial dosing of WILATE® for routine prophylaxis was typical of other approved factor VIII products and the dose increases are appropriate. The factor VIII levels were not measured after treatment, so the initial dosing was empiric. Adjustments (upward) were to be made based on bleeding frequency.*

6.1.5 Directions for Use
From the USPI (September 2016):
WILATE® is administered via intravenous infusion. WILATE® is provided with a Mix2Vial TM transfer device for reconstitution of the freeze-dried powder in diluent, a 10-mL syringe, an infusion set and two alcohol swabs
Reviewer Comment: *The Mix2Vial device is 510(k) cleared by FDA and is used to reconstitute many different coagulation factor concentrates.*

6.1.6 Sites and Centers

This study was conducted in six investigational sites in Bulgaria, Hungary, Poland and Russia. The coordinating investigator on this study was Dr Ellis Neufeld, MD, PhD, St. Jude Children's Research Hospital 262 Danny Thomas Place, MS 282, Memphis, TN 38105-3678, USA.

Table 6. WIL-27 Study Sites and Investigators

Site #	Location	Investigator
Site 21	Specialized Hospital of Active Treatment "Joan Pavel" OOD, Department Clinical Hematology-Hemorrhagic Diathesis and Anemia, Sofia, Bulgaria	Dr. Toshko J. Lissitchkov, Sofia, Bulgaria
Site 31	Medical Centre Hungarian Defense Forces, Military Hospital, Budapest, Hungary	Dr. Lazlo Nemes, Budapest, Hungary
Site 41	Cracow Medical Center, Cracow, Poland	Dr. Joanna Zdziarska, Cracow, Poland

Site 42	Korczowski Bartosz Medical Practice, Rzeszow, Poland	Dr. Bartosz Korczowski, Rzeszow, Poland
Site 61	State Budgetary Healthcare Institution of Moscow City “Morozov Pediatric City Clinical Hospital of the Moscow City Department of Healthcare”, Moscow,Russia	Dr. Vladimir V. Vdovin, Moscow, Russia
Site 62	Barnaul Branch of RAMS Hematology Center, Altai regional Hospital, Barnaul, Russia	Dr. Andrey N. Mamaev, Barnaul, Russia

6.1.7 Surveillance/Monitoring

WIL-27 subjects were screened at enrollment for eligibility and tested for factor VIII antibodies and baseline viral serology studies were drawn with routine clinical laboratory studies.

Thereafter, testing was performed at scheduled clinic visits, as listed in Table 7, taken directly from Table 3 in WIL-27 Study Report. Pharmacokinetic studies were optional in WIL-27 study.

Table 7: Schedule of Assessments for Subjects on WIL-27 Study

		PK Patients	Non-PK Patients				PK Patients	Non-PK Patients	
	Screening Visit	PK Visit	Non-PK Visit	Day-14 Visit (14-21 days)	Day-30 Visit (±3 days)	3-Month Visit (±2 weeks)	PK Study Completion Visit at 6 months (+2 weeks)	Non-PK Study Completion Visit at 6 months (+2 weeks)	Follow-up Contact 30 days (±3 days) after Study Completion Visit
Informed consent	x								
Inclusion and exclusion criteria	x								
Demographics	x								
Weight	x	x [1]	x [1]			x [1]	x [1]	x [1]	
Height	x								
Medical history (incl. FVIII treatment 6 months before screening)	x								
Vital signs	x	x [2]	x [4]			x [4]	x [2]	x [4]	
Physical examination	x						x	x	
Routine safety laboratory	x	x [3]	x [4]			x [1]	x [3]	x [4]	
Determination of CD4+ levels [8]	x								
Determination of AB0 blood group [9]	x								
HJHS, unless obtained within 3 months before screening	x								
PK injection (50 ± 5 IU/kg)		x					x		
Blood sampling for FVIII:C (OS and CHR) for PK assessment		x [5]					x [5]		
IVR injection			x [10]			x		x	
Blood sampling for FVIII:C IVR (OS and CHR)			x [6]			x [6]		x [6]	
Factor VIII inhibitor [11]	x	x [1]	x [1]	x [1]	x [1]	x [1]	x [1]	x [1]	
VWF:Ag and VWF:Ac		x [6]	x [6]	x [1]	x [1]	x [6]	x [6]	x [6]	
Parvovirus B19 antibodies		x [1]	x [1]				x [7]	x [7]	
Retention sample for possible virus marker testing		x [1]	x [1]						
Patient diary review				x	x	x	x	x	
Adverse event monitoring		x	x	»	»	»	x	x	x [12]
Concomitant medications	x	»	»	»	»	»	x	x	

PK = pharmacokinetic, IVR = in vivo recovery, HJHS = Haemophilia Joint Health Score, OS = one-stage assay, CHR = chromogenic assay, VWF:Ag = von Willebrand factor
antigen, VWF:Ac = VWF activity.
[1] Before injection.
[2] Before injection as well as 1 h (±5 min) and 48±2 h after injection.
[3] Before injection as well as 48±2 h after injection [local laboratory].
[4] Before injection as well as 15±5 min after injection.
[5] Blood sampling within 1 h before injection and 15±5 min, 1 h (±5 min), 3 h (±15 min), 6 h (±30 min), 9±1 h, 24±2 h, 30±2 h, and 48±2 h after end of injection [central laboratory].
[6] Blood sampling within 1 h before injection as well as 15±5 min after the end of injection [central laboratory].

6.1.8 Endpoints and Criteria for Study Success

Prophylactic Treatment:
Efficacy of prophylactic treatment was assessed based on the total annualized bleeding

rate (TABR), i.e., the total number of BEs per patient per year, calculated by dividing the total of all bleeds by the number of years each subject was on routine prophylaxis:

all bleeding events /(days of prophylaxis/365.25 days)

The spontaneous annualized bleeding rate (SABR), i.e., the number of spontaneous BEs per patient per year was also calculated by dividing the number of spontaneous bleeds by the number of years each subject was on routine prophylaxis:

spontaneous bleeding events /(days of prophylaxis/365.25 days)

Treatment of Breakthrough Bleeding Events:
At the end of a BE, treatment efficacy was assessed by the patient (together with the investigator in case of on-site treatment) using the predefined criteria 'excellent,' 'good,' 'moderate,' and 'none'.

The proportion of BEs successfully treated with IMP was evaluated for all BEs taken together and by BE severity. All efficacy ratings assessed as either 'excellent' or 'good' were considered 'successfully treated.'

Pharmacokinetic Analysis:
The following PK parameters for FVIII:C were determined:

- Normalized area under the curve (AUCnorm) and AUC
- In vivo half life
- Maximum plasma concentration (Cmax)
- Time to reach maximum plasma concentration (Tmax)
- Mean residence time
- Volume of distribution
- Clearance
- IVR

(b) (4)

Safety:
The following drug safety information were collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP
- Drug overdose, interaction, medication error and post study SAEs
- An adverse event of special interest, development of factor VIII inhibitors, was assessed at baseline, midway through the study, and following the six-month study period.

Reviewer comments: *The endpoints of the WIL-27 study are appropriate.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

See Biostatistics reviewer's memorandum for detailed review.

The primary approach to the statistical analysis was descriptive, presenting sampling statistics (n, mean, standard deviation [SD], quartiles and range) for continuous measurements and absolute and relative frequency counts for categorical/ordinal data. This was complemented by exploratory confidence intervals (CIs) for means or proportions.

Efficacy Analysis:
Primarily, all obtained data on treatment characteristics (IMP dosages, frequencies, total consumption) and BEs (duration, frequency, efficacy assessment) are described using the above summary statistics.

Efficacy of Routine Prophylaxis with WILATE®*:*
The efficacy of prophylactic treatment with WILATE® was statistically evaluated by comparing the primary endpoint, i.e., *total* ABR (TABR) under prophylaxis, with a predefined threshold of 29 BEs per patient per year. This threshold corresponds to 50% of the TABR reported in GENA-01, a study of Nuwiq prophylaxis (done under IND 13722) in which previously treated adolescent and adult patients with severe hemophilia A received on-demand FVIII treatment only. A confirmative one-sided, one-sample Poisson test was used to test whether the mean annualized bleeding rate (ABR) in patients treated prophylactically with WILATE® was below the threshold of 29 BEs per patient year (alpha = 2.5%). A corresponding two-sided 95% CI for the TABR was also provided.

The secondary endpoint *spontaneous* ABR (SABR) was analyzed in the manner as TABR, the only exception being that, for the comparison of mean SABRs, only spontaneous bleeds were counted and a pre-defined threshold of 19.1 per patient per year was chosen; this threshold corresponds to 50% of the SABR in GENA-01.

In addition to the comparison of ABRs to the defined thresholds, intra individual comparisons with each patient's documented pre-study ABR was performed. For this, descriptive statistics for pre-study and current ABRs and their intra-individual differences are presented, and the matched-pairs signed rank test (alpha = 5%) was used to test for a shift in ABR distributions.

Efficacy of On-Demand Treatment with WILATE® in the Treatment of Breakthrough BEs:
Confirmatory statistical testing tested the null hypotheses that the percentage of success is ≤70% (alternative hypothesis: percentage >70%); the test procedure based on the generalized estimation equation considered several BEs in one patient as correlated repeated measurements (alpha = 2.5%). The statistical analysis of other secondary endpoints are descriptive, including exploratory 95% CIs for the location parameters.

Pharmacokinetic Analysis:
The PK profiles of WILATE® and the associated PK parameters were summarized by descriptive statistics as well as the presentation of concentration vs. time plots. Similarly, the results of the IVR assessments over time were analyzed in summary tables for each time point and their differences to Baseline along with 95% CIs for the mean differences. Analysis of variance (ANOVA) was used in an exploratory sense to assess a possible association of AB0 blood type and VWF:Ag with the FVIII:C half-life of WILATE®.

Safety Analysis:
The analysis of safety was based on the occurrence of AEs, the results of safety laboratory tests, immunogenicity measurements and the occurrence of parvovirus B19 seroconversions. Analysis of AEs focused on treatment-emergent adverse events (TEAEs).

Time profiles of FVIII inhibitor testing results were analyzed by presenting sampling statistics for the values as well as frequency tables for positive findings, along with 95% Pearson-Clopper CIs. For the analysis of the FVIII inhibitor rate, to achieve a total of at least 80 PTPs, data from this study were pooled with those from previously completed clinical studies with WILATE® in hemophilia A.

Incidences of parvovirus B19 seroconversions between baseline and end of study were estimated along with 95% Pearson-Clopper CIs.

The analysis of the safety parameters recorded during surgery (laboratory values) was descriptive.
Reviewer comments: *The criterion for success in terms of efficacy of prophylaxis in the WIL-27 study (<50% of the ABR rate for the historical control group of patients treated on-demand for Nuwiq recombinant factor VIII study) was not a particularly difficult one to satisfy, but at least was surpassed by a wide margin. The critical criterion for success in terms of safety (0-1 inhibitors in the WIL-27 study, when pooled with other existing data for inhibitor formation in WILATE® recipients, is satisfactory and agreed upon in advance of the trial by FDA.*

The number of bleeding events is central to the demonstration of efficacy of routine prophylaxis, and the number of treatments required to prevent bleeding episodes or treat bleeding episodes is critical for the determination of efficacy of routine prophylaxis and on-demand treatment with WILATE. Additionally, the amount of WILATE used for routine prophylaxis and for treatment of breakthrough bleeding (on demand) is critical for creation of dosing instructions in the proposed label for prophylaxis/treatment of bleeding in patients with hemophilia A with this product.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Applicant planned to enroll at least 55 subjects 12 years of age or older to obtain data on 50 evaluable subjects. Of these 50 subjects, 20 were to undergo two 2-day PK assessments of WILATE®, one before the start and one after the end of the prophylactic treatment phase. Of the 20 subjects undergoing PK assessment, a minimum of four patients were to be between 12 and 18 years of age.

Fifty-seven subjects were enrolled, of which two were not treated with WILATE®. The full analysis set (FAS) included 55 subjects, of which 52 were treated per protocol (PP). Twenty-one underwent pharmacokinetic analysis (PK dataset), and one underwent surgery. Fifty-four subjects completed the study, and one dropped out. The safety analysis set (SAF) included the 55 subjects who were treated with at least one dose of WILATE®; this subset includes the same subjects found in the full analysis set (FAS).
Reviewer comment: *The study enrolled enough subjects to reach the desired treated number of patients. The completion rate (54/55) and limited number of dropouts (1/55)*

suggests that there was no major bias from subjects enrolled and not treated, or treated and discontinued from the study.

Patients were male, between 12 and 64 years of age, with a median age of 35.5 years. Of the 55 patients, five (9.1%) were aged between 12 and 18 years (mean 13.6 years) and 50 (90.9%) were older than 18 years of age (mean 37.7 years). All patients were White, not Hispanic or Latino. No patient had a known history of FVIII inhibitors and FVIII inhibitor levels were less than 0.6 BU/mL in all patients.

Prophylactic Treatment:
Per the Applicant: All 55 patients treated started prophylactic treatment with WILATE®. Patients received a total of 4241 injections for prophylaxis during a mean (SD) of 77.1 (12.3) EDs. The mean (SD) dose per injection was 32.0 (5.0) IU/kg and the total dose of WILATE® per patient was 203,091 (68,263) IU. The mean (SD) dose per month was 407.59 (82.74) IU/kg.
Reviewer Comments: *The Applicant's summary of the number of injections administered for prophylaxis does not reflect 30 doses administered for "Other" reasons (additional prophylactic doses given by two subjects of their own accord in anticipation of increased physical activity reasons), or for "Prevention of Recurrent Bleeding" (following treatment of bleeding episodes, after bleeding had stopped). For analyses purposes, the reviewer considered the "additional prophylaxis doses" as being counted towards the total number of doses required for prophylaxis. Additional sensitivity analyses of ABR was performed excluding these subjects and the results of sensitivity analysis was consistent with the primary efficacy analysis. The corrected sum of prophylactic doses is < 1% more than the sum stated by the Applicant. Accordingly, this has no impact on our conclusions regarding efficacy of WILATE® for routine prophylaxis or the dose required to obtain the TABR/SABR results seen in WIL-27*

On Demand Treatment:
All enrolled subjects were to be treated for bleeding (spontaneous or traumatic) with WILATE®. Of the 55 subjects in the FAS population, 30 had no bleeding events and 25 subjects experienced a total of 64 bleeding episodes during the WILATE® treatment period, 44 of which were spontaneous, and 16 were traumatic, 3 were due to other causes, and one was of unknown type.

Efficacy of on demand treatment of bleeding with WILATE® was evaluated by four-point hemostasis assessment of efficacy by the subjects and the Investigator, as well as the number of treatments and amount of WILATE® used to treat each bleeding episode.

(b) (4)

Pharmacokinetics:
Pharmacokinetic studies were optional for WIL-27. The goal was to obtain pharmacokinetic studies on at least 20 subjects, of which at least five would be pediatric subjects less than 18 years of age. The Applicant presents PK data on 21 subjects from the WIL-27 trial, of which 16 were adults and 5 were pediatric subjects <18 years of age. All pediatric subjects were enrolled at one investigational site.

6.1.10.1.1 Demographics

The patients were male, between 12 and 64 years of age, with a median age of 35.5 years. Of the 55 patients, 5 (9.1%) were aged between 12 and 18 years and 50 (90.9%) were older than 18 years. All patients were White, not Hispanic or Latino (Section 14, Table 14.1-9).

Table 8: WIL-27 Subject Demographics (Age and Race)

	Age < 18 yrs	**Age ≥ 18 yrs**	**All Age Groups**
	n (%)	n (%)	n (%)
Race			
White	5 (9.1%)	50 (90.9%)	55 (100%)
Non-White	0 (0%)	0 (0%)	0 (0%)
All Races	5 (9.1%)	50 (90.9%)	55 (100%)

Modified from Table 14.1-9 on page 140 of WIL-27 Study Report

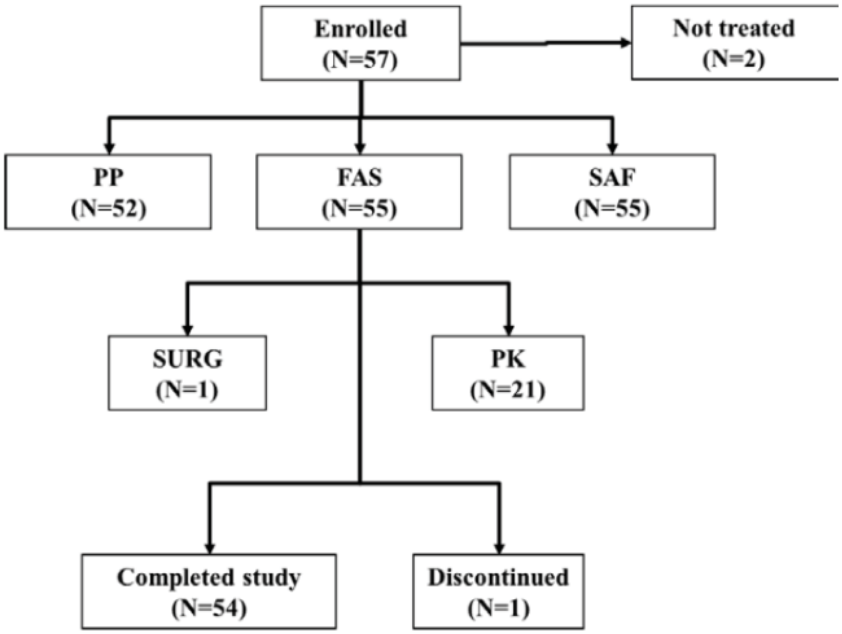
***Reviewer Comments**: Although the population was entirely White, the study conclusions are not expected to be affected by this since neither efficacy or pharmacokinetics are expected to be affected by race/ethnicity.*

6.1.10.1.3 Subject Disposition

Fifty-seven subjects enrolled in WIL-27. Two discontinued participation before receiving any WILATE® (one due to inability to travel to the study site, and one who withdrew consent before treatment). Of the fifty-five who underwent treatment with WILATE® (the Full Analysis Set (FAS), which was also the Safety population), one withdrew with less than 50 exposure days (Subject (b) (6) , one did not complete the patient diary and had a treatment gap of >7 days (Subject (b) (6) , and one had a treatment gap of >7 days (Subject (b) (6) . The FAS group minus the three subjects who were withdrawn after receiving WILATE® constitute the Per Protocol population (PP). One subject underwent a surgical procedure, and 21 underwent PK analysis and these subjects constitute the Surgical population (SURG) and Pharmacokinetics (PK) population, respectively.

Note, only 49 of the 55 FAS subjects had 150 prior factor VIII exposure days, at least 50 WILATE EDs, and at least six months of follow-up on WILATE. These are the subjects whose data is pooled for assessment of inhibitor risk in PTPs.

***Reviewer** Comments: The protocol deviations where there were gaps of >7 days in prophylaxis in 2 subjects are unlikely to cause efficacy to be over-stated; in fact, these treatment gaps would predispose subjects to have more bleeding events.*



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*.

6.1.11 Efficacy Analyses

Prophylactic Treatment

Efficacy of prophylactic treatment was assessed based on the total annualized bleeding rate (TABR), i.e., the total number of bleeding events per patient per year. No subjective rating of efficacy of prophylaxis was provided by subjects or investigators.

***Reviewer Comments:** The mean dose for all evaluable subjects may be a slight underestimate but since most subjects received the 20-30 IU/kg dose every 2-3 days, this dose is acceptable for Section 2 of the label, with further advice to adjust the dosing by 5 IU/kg for patients who experience more than 2 bleeding events per month.*

Section 14 of the label should indicate that 5 subjects did not have the protocol dose adjustments despite experiencing >2 bleeding events per month on the starting dose for prophylaxis.

As will be shown later in this review in this study there was no measurement of post-infusion levels, aside from the scheduled PK studies. These were essentially all home outpatient treatments, self-administered, on an empiric IU/kg dose. On average, the investigators treated minor bleeds with ~1 dose of ~35 IU/kg Wilate, moderate bleeds with 1-2 doses of ~35 IU/kg Wilate, and major bleeds with ~2-3 doses of ~40-45 IU/kg Wilate. So, they really did not rigorously abide by the rules for on-demand treatment of bleeding. Notwithstanding this, they met the >70% overall success rate (Good or

Excellent hemostasis rating) for treating bleeds on-demand. The label will need to reflect their empiric data.

Treatment of Breakthrough Bleeding Events

At the end of a bleeding event, treatment efficacy was assessed by the patient (together with the investigator in case of on-site treatment) using the predefined criteria 'Excellent,' 'Good,' 'Moderate,' and 'None'. The proportion of bleeding events successfully treated with IMP was evaluated for all bleeding events taken together and by bleeding event severity. All efficacy ratings assessed as either 'Excellent' or 'Good' were considered 'successfully treated.'

(b) (4)

6.1.11.1 Analyses of Primary Endpoint(s)

Efficacy results for WILATE® shown in the main report are calculated for the FAS population (n = 55) and PP population (n = 52) datasets. Efficacy during (b) (4) was analyzed for (b) (4) where (b) (4) (Section 14, Table 14.1- 5; Appendix 16.2, List 16.2.6.5-1 in WIL-27 Study Report). The SAF population included all patients who received at least one dose of WILATE® (N=55); this population was identical to the FAS population (Section 14, Table 14.1-2). PK result analysis was based on the PK population, which included all patients for whom at least one valid WILATE® PK profile has been obtained (n = 21).

Reviewer Comments: *The Applicant presents efficacy and PK data for the overall population and by two age two groups: younger than 16 years and 16 years and older. Note, there were no subjects between 16 and 18 years of age, so by happenstance the groups represented by the Applicant divided based on age 16 years corresponds exactly with the FDA preferred designation of adults being 18 and adolescents being age 12 to 18 years. In this review I refer to adults and adolescents by the FDA convention. For the WIL-27 FAS, the adults numbered 50 and the adolescents numbered 5.*

Dosing for WILATE® Prophylaxis (from the WIL-27 study report):

In the prophylactic treatment phase, the prophylactic WILATE® dosing specified in the protocol was every 2 to 3 days at a dose of 20–40 IU/kg BW. If a patient experienced more than two spontaneous BEs within a 30-day period or a major or life-threatening spontaneous BE, the prophylactic dose was to be increased by approximately 5 IU/kg. All 55 patients in the FAS population started prophylactic treatment with WILATE®.

Reviewer Comments: *The prophylactic dose that was implemented ranged from 21-41 IU/kg (mean 32 ± 5.1 IU/kg, median 31 IU/kg), based on my review of the Individual Efficacy Response Data Listing file. This reflects an average of the actual doses logged, and where there was an increase in the prophylactic dose per protocol, the higher prophylactic dose was used in the calculation. The mean (or median) was centered in the intended dose range of 20-40 IU/kg, and there were no clinically important deviations from the range specified. The target starting prophylaxis dose was administered to all trial participants. Of the 55 FAS population subjects, 49 (89%) did not meet criteria for prophylactic dose escalation. Six of the 55 FAS population subjects (11%) met criteria for dose escalation as prescribed in the protocol. Only one subject who met those*

criteria underwent the prescribed dose escalation (and thereafter had no bleeding). Five who did not undergo prescribed dose escalation represented the five highest individual TABR rates for the study population. All were adults with poor baseline joint scores, and 2 were excluded from the PP population due to noncompliance. Therefore, the prescribed starting prophylaxis regimen (20-40 IU/kg, BIW or TIW) appears to be the correct dose in the FAS subjects. In 96% (50/52) of the PP population, the starting dose and prescribed dose escalation constituted effective prophylaxis against bleeding. The superior PP population TABR results (compared to the FAS population results) reflect the fact that compliance with the recommended prophylactic regimen and dose escalation, as needed, is successful. The starting dose and dose escalation proposed in the label is justified.

The Applicant states that the total number of prophylactic injections was 4241 (Section 14, Table 14.2.1-13). Review of the Individual Efficacy Response Data Listing entries showed that Subject (b) (6) administered two other doses and Subject (b) (6) administered 21 infusions of WILATE® for "Other" reasons (not prophylaxis, treatment of bleeding, or pharmacokinetic studies). These were listed as protocol deviations and we confirmed from their reply to our May 17, 2019 information requests that these were not for undisclosed bleeding but were given by the subjects for increased physical activity (125251.244.5). Additionally, seven doses of WILATE® were given by six subjects after bleeding episodes for the stated reason "To Prevent Recurrent Bleeding". We confirmed from the Applicant's reply to our information request of May 30, 2019 that the bleeding episodes had stopped when these seven doses were administered (125251.244.8). Therefore, all these additional doses (n = 30) should be considered as part of the prophylactic treatment given to achieve the outcomes observed in WIL-27 (4271 prophylactic doses).

***Reviewer Comments**: The number of prophylactic doses stated by the Applicant to have been given as prophylaxis should be adjusted upward from 4241 to 4271. However, this does not make any practical difference in the conclusions reached for this clinical review, and this does not affect any claim made in the proposed label for the hemophilia A indications.*

The primary endpoint of this study was a 50% reduction of the historic of 58.1 observed in GENA- 01, a study of on-demand treatment with Nuwiq (Octapharma's recombinant factor VIII concentrate, licensed under BLA 125555).

From the WIL-27 Study Report*:*
"Prophylactic efficacy of WILATE® was based on the TABR during WILATE® treatment. TABR was calculated as the total number of BEs in the time between the first dose of IMP and the study completion visit, divided by the duration (in years) between the first dose of IMP and the study completion visit. (b) (4) *periods and BEs occurring within these periods were excluded from the calculation of TABR."*
***Reviewer Comment:** These assumptions are appropriate for calculation of the TABR/SABR values.*

Although the Applicant analyzed the SABR as a *secondary* endpoint; the results of this analysis is closely tied to the primary endpoint (TABR) and therefore is reviewed here; see Tables 9 and 10. The SABR for the WIL-27 study was compared to the SABR of the Nuwiq GENA-01 trial results, analogous to the primary analysis of TABR, except the threshold that was pre-specified was 50% of the 19.1 SABR rate for Nuwiq GENA-01

subjects. For the spontaneous BEs in the PP population, the one-sample Poisson test estimate was 1.51 (95% CI 1.53, 2.08, vs mean SABR >19.1: p<0.0001).
Reviewer Comments: *As expected, the spontaneous annual bleed rate (SABR) parallels the TABR and is lower because the TABR includes not only spontaneous, but also a smaller number of traumatic bleeding events. The SABR is a more valid assessment of the efficacy of routine prophylaxis than the TABR since bleeding with trauma is expected even with normal hemostasis and is not indicative of a lack of hemostatic efficacy. In any event, both TABR and SABR endpoints met pre-specified criteria for successful prophylaxis.*

A total of 25 patients (45.5%) experienced 64 BEs under WILATE® prophylaxis (Section 14, Tables 14.2.2.1-1 and 14.2.2.1-7) and 44 of the BEs were spontaneous (Section 14, Table 14.2.2.1-11). The ABRs during prophylaxis with WILATE® by age groups in the FAS population are shown in Table 9, below for the Full Analysis Set (N = 55) and subsequently in Table 10, for the Per Protocol population (N = 52).
Reviewer Comment(s): *In the Analysis Dataset file ADBE (Bleeding Events) we noted that there were 68 bleeding events listed, while only 64 were treated with WILATE®. We therefore asked the Applicant on May 16, 2019 to confirm 1) that ADBE is the analysis data set used to generate the primary efficacy analysis for ABR results to support the indication for routine prophylaxis (RP), 2) whether the 68 bleeding events constitute all treated and untreated events that occurred on the WIL-27 study, 3) whether additional WILATE® doses given for "Other reasons" represented treatment of bleeding. In response, the Applicant replied that the four bleeds occurred between screening and the start of WILATE® prophylaxis, and were actually treated with the subjects' other factor VIII product (not WILATE®) and did not count toward the ABR calculation, and that the extra doses given for "Other reasons" were additional prophylaxis doses given by the research subjects due to increased physical activity, and were not for treatment of bleeding episodes.*
Since there was some ambiguity to the response, and some bleeds may be untreated by patients on factor VIII prophylaxis, we further asked on May 23, 2019 whether 1) untreated bleeds were recorded by the subjects after investigational treatment was initiated, 2) whether these untreated bleeds were captured in the ADSL dataset, and 3) whether the efficacy analyses of ABR required inclusion of treated and untreated bleed per the protocol definition.

The response to the May 23, 2019 information request (received May 29, 2019) indicated that "All treated and untreated bleeds were to be recorded by the subject during the WIL-27 study. All bleeds that occurred after the initiation of investigational treatment were treated with Wilate; there was no untreated bleed."

We therefore evaluate the Applicant's ABR data with the assumption that there were 64 bleeds of all kinds during the 26-week routine prophylaxis period of the study, and that there are no missing or unaccounted for bleeding episodes.

The tally of bleeding episodes by the Applicant was confirmed by review of line listings for all events and comparison to the treatment log and individual case reports. All bleeding events are accounted for, and in response to our information requests the Applicant states that all bleeding events were reported by subjects and no events were censored for occurring on scheduled prophylaxis days, for instance. Review of individual patient case reports/line listings made it clear that the Applicant was (correctly) splitting

some bleeding episodes that the local Investigator treated as one event into two events due to >48 hours between treatment doses, in accordance with protocol scoring rules.
Reviewer Comment: *The review of the data submitted by the Applicant indicates that there has been no effort to minimize the number of bleeding events.*

In the WIL-27 Study Report the Sponsor has used a threshold of 16 years of age to separate the adults from the pediatric subjects for analysis. 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 (by happenstance) with our preferred age < 18 and ≥18.

Table 9: ABRs during WILATE® Prophylaxis (FAS Population, N=55)

Type	Mean ± SD	Median (range)	Poisson (95% CI)
<18 years (n = 5)			
All BEs (TABR)	0.40 ± 0.89	0.00 (0–2)	0.40 (0.06, 2.84)
Spontaneous BEs (SABR)	0	-	-
≥18 Years (n=50)			
All BEs (TABR)	2.39 ± 3.77	0.00 (0–15.69)	2.48 (1.94, 3.18)
Spontaneous BEs (SABR)	1.67 ± 3.11	0.00 (0–11.76)	1.73 (1.29, 2.33)
Total (n=55)			
All BEs (TABR)	2.21 ± 3.64	0.00 (0–15.69)	2.29 (1.80, 2.93)
Spontaneous BEs (SABR)	1.52 ± 3.00	0.00 (0–11.76)	1.58 (1.17, 2.12)

TABR = total annualized bleeding rate; SABR = spontaneous annualized bleeding rate; BE = bleeding episode; CI = confidence interval; FAS = full analysis set;
N = number of patients in full analysis set (FAS); n = number of patients in subgroup; SD = standard deviation.
Sources: Section 14, Table 14.2.3.2-1 and 14.2.3.2-5.

Reviewer Comments: *My review of the Applicant's data confirms their calculations of the total number of bleeding episodes, and mean/median TABR and SABR values, and associated standard deviations and is consistent with with the statistical reviewer's analyses, as well. The TABR rates (0.4 ± 0.89) for the five adolescents are significantly better than those (2.39 ± 3.77) for the adult subjects (n = 50). There were no spontaneous bleeding events in the adolescents, though the group was too small to draw a conclusion on its significance. This is consistent with the observation documented in Table 14.1-30 from the WIL-27 Study Report that the adolescents had better overall joint health at baseline screening (mean total joint health score: 1.2 ± 1.63) than the adults (mean total joint health score 38.6 ± 25.3). This is expected in hemophilia where joint deterioration over time is inexorable, even with optimal prophylaxis (per Marilyn Manco-Johnson, FDA Workshop on Hemophilia Product Development, December 6, 2018, Silver Spring MD). The sample size for adolescents (5) is a limitation of the efficacy data in this population, but the results in the adult population allows for extrapolation of efficacy results to the adolescent population relying on both the limited clinical data and the pharmacokinetic assessments (please refer to Table 14).*

Table 10: ABRs during WILATE® Prophylaxis (PP Population, N=52) p58 of Report

Type	Mean ± SD	Median (range)	Poisson (95% CI)
<18 years (n = 5)			
All BEs	0.40 ± 0.89	0.00 (0–2)	0.40 (0.06, 2.84)
Spontaneous BEs	0	-	-
≥18 Years (n=50)			
All BEs	2.29 ± 3.57	0.00 (0–15.69)	2.31 (1.78, 3.00)
Spontaneous BEs	1.67 ± 3.15	0.00 (0–11.76)	1.69 (1.25, 2.30)
Total (n=55)			
All BEs	2.10 ± 3.44	0.00 (0–15.69)	2.13 (1.64, 2.76)
Spontaneous BEs	1.51 ± 3.03	0.00 (0–11.76)	1.53 (1.13, 2.08)

ABR = annualized bleeding rate; BE = bleeding episode; CI = confidence interval; FAS = full analysis set; N = number of patients; n = number of patients in subgroup; SD = standard deviation.
Source: Section 14, Table 14.2.3.2-1 and 14.2.3.2-5.

Reviewer Comments: *The event rates for the FAS group was marginally worse than that of the PP group. The differences between results in the FAS and PP groups are modest, suggesting that adherence to the procedures specified by the protocol improves the outcome, but protocol deviations did not have a major impact on outcomes of the study.*

Another potential comparator to consider would be the subjects' own historical experience, which was an exploratory, post-hoc analysis. As shown in 6.1.11.5, the mean TABR of 2.39 ± 3.77 for 50 adults on the WIL-27 study was significantly better than their historical TABR of 36.24 ± 39.59 ($P < 0.0001$). The five children on WIL-27 had one bleed in the six-month study period amongst them (mean TABR = 0.4), which was exactly what was observed in the historic TABR for this group. The group was too small to draw any conclusion on this data point.

The high outliers who were not dose escalated according to the protocol also improved on their personal historic bleeding rates from prior to participation in the WIL-27 study, reflecting the value of routine prophylaxis with WILATE® to prevent bleeding. See review of the analysis of high-outliers in Section 6.1.11.2.

6.1.11.2 Analyses of Secondary Endpoints

On-Demand Treatment

Investigators' Subjective Appraisal of WILATE® Efficacy. An analysis of the efficacy of on-demand treatment was performed for the 64 bleeding events experienced on the study, using a four-point rating scale ("Excellent", "Good", "Moderate", "None") for both the FAS and PP subject groups. Per the Applicant, all treatments were rated as having some effect, which included ratings of "Excellent", "Good", or "Moderate" (there were no ratings of "None" for efficacy).

Successful treatment included hemostatic ratings of "Excellent" and "Good". For the efficacy indication for on-demand treatment, the Applicant was required to exceed a pre-specified threshold of 70% successful treatment of breakthrough bleeding episodes. Table 11 indicates the hemostasis ratings for 64 bleeding events treated with WILATE®

during the WIL-27 study, for both the 55 subject FAS (intention to treat) population and the 52-member PP (per protocol) population.

Table 11: Overall Assessment of Treatment Efficacy by Severity of Bleed

FAS Subjects (55 subjects, 26 events)			**PP Subjects (52 subjects, 25 events)**		
Severity Efficacy			**Severity** Efficacy		
	n	**%**		**n**	**%**
Any	**64**	**100**	**Any**	**57**	**100**
Excellent	16	25.0	Excellent	16	28.1
Good	32	50.0	Good	32	56.1
Moderate	14	21.9	Moderate	9	15.8
Unknown	2	3.1	Unknown	-	-
Minor	**15**	**100**	**Minor**	**15**	**100**
Excellent	9	60.0	Excellent	9	60.0
Good	5	33.3	Good	15	33.3
Moderate	1	6.7	Moderate	1	6.7
Moderate	**34**	**100**	**Moderate**	**32**	**100**
Excellent	6	17.7	Excellent	6	18.8
Good	22	64.7	Good	22	68.8
Moderate	6	17.7	Moderate	4	12.5
Major	**14**	**100**	**Major**	**10**	**100**
Excellent	1	7.1	Excellent	1	10.0
Good	5	35.7	Good	5	50.0
Moderate	7	50.0	Moderate	4	40.0
Unknown	1	7.1	Unknown	-	-
Unknown	**1**	**100**	**Unknown**	-	-
Unknown	1	100	Unknown	-	-

Reviewer Comments: *The Applicant points out that essentially all treatments for bleeding events were rated as having some efficacy, using the definition that includes "Excellent", "Good" and "Moderate" ratings as effective, as opposed to "Excellent" or "Good" for successful. Clearly, in either FAS or PP population, as the severity of the bleeding event increases the proportion with "Excellent" ratings decreases from 60% to 7-10%, while the "Moderate" hemostatic rating increases from ~7% to 40-50%. This trend is largely to be expected, since the worst efficacy was observed in adult subjects with recurrent bleeds in target joints, and with higher (worse) baseline joint scores. The analysis of hemostasis by the four-point scale is always problematic since it relies to some extent on a subjective analysis on the part of the Investigator. However, this analysis is reasonable as supporting data for the primary and secondary endpoints of this study of WILATE® efficacy.*

The use of the terms "Minor", "Moderate", and "Major" are not defined in the WIL-27 protocol. The dosing advice for the label includes the terms "Minor", "Moderate to major", and "Life-threatening" to describe categories of bleeding for which different WILATE® doses are recommended. There is not a clear correlation between the categories in the WIL-27 study and the categories in the label. The Applicant was asked to define these terms and revise Table 4 of the USPI [Dosing for Treatment of Hemorrhages] to make clear the categorization of bleeding for treatment decisions in an information request sent in July of 2019.

I performed my own analysis of the correlation between severity of bleeding, dose of administered, and the outcome of treatment to assess the proposed dosing instructions for WILATE in the USPI, since the Applicant did not perform this analysis in the materials provided. This review is summarized in Table B1, found in APPENDIX B. For this analysis I sorted the 64 bleeding events treated with WILATE® according to severity (Minor, Moderate, Major) and then sorted according to hemostatic efficacy (Excellent, Good, Moderate) on the four-point rating scale used by Investigators in WIL-27. The highest treatment dose, in IU/kg, and the number of doses required to treat each bleed is also listed.

For each severity category of bleeding I calculated the average WILATE dose (in IU/kg) and the number of doses administered that were associated with successful treatment, or for any treatment outcome.

The results of my analysis based on the findings in Table 12 are found in Table 13:

Table 13: Mean Dose (IU/kg) and Number of Doses for Various Severity Bleeding

Dose Associated with Success, Minor Bleeds				**# of Doses Associated with Success, Minor Bleeds**		
Average	**Range**	**Median**		**Average**	**Range**	**Median**
34.9	25.4-46.9	37.4		1.1	1-2	1
Dose, All Minor Bleeds				**# of Doses, All Minor Bleeds**		
Average	**Range**	**Median**		**Average**	**Range**	**Median**
35.1	25.4-46.9	37.4		1.2	1-3	1
Dose Associated with Success, Moderate Bleeds				**# of Doses Associated with Success, Moderate Bleeds**		
Average	**Range**	**Median**		**Average**	**Range**	**Median**
33.5	23-62.5	31.45		1.4	1-3	1
Dose, All Moderate Bleeds				**# of Doses, All Moderate Bleeds**		
Average	**Range**	**Median**		**Average**	**Range**	**Median**
34.1	23-62.5	33.3		2.1	1-9	1
Dose Associated with Success, Major Bleeds				**# of Doses Associated with Success, Major Bleeds**		
Average	**Range**	**Median**		**Average**	**Range**	**Median**
45.5	31.3-54.7	47.9		1	1-1	1
Average	**Range**	**Median**		**Average**	**Range**	**Median**
Dose, All Major Bleeds				**# of Doses, All Major Bleeds**		
41.6	31.3-54.7	39		2.7	1-6	2

Bleeds characterized as Minor in severity were treated with ~1 dose of ~35 IU/kg WILATE, Successful treatment was observed in 13/14 minor bleeds (93%).

Bleeds characterized as Moderate in severity were treated with ~1-2 doses of ~34 IU/kg WILATE (for 30 successful treatment or all 37 treatments). For Moderate severity bleeding episodes, the dose ranged from 23-63 IU/kg and the number of doses ranged from 1-3 for successful treatments and 1-9 for all treatments, reflecting several outliers with moderate efficacy who had 3, 5, 7, or 9 doses to treat bleeding events. These were

all adult subjects with target joints. Successful treatment was observed in 30/37 moderate bleeds (81%).

Bleeds characterized as Major in severity were treated with ~1-3 doses of ~41-45 IU/kg WILATE (for 6 successful or all 13 treatments). For Major severity bleeding episodes, the dose ranged from 31-55 IU/kg and the number of doses for all six successful treatments was 1, while the number of doses ranged from 1-6 for all 13 treatments. As for Moderate severity bleeding, the high outliers were adults with target joints. Successful treatment was observed in 6/12 minor bleeds (50%).

Analysis of the dosing of WILATE in WIL-27 indicates that Investigators largely did not abide by the protocol specified dose for different severity of bleeding. Minor and Moderate severity bleeding events were treated with the same dose and number of doses of WILATE, while Major severity bleeding episodes were treated with a higher dose of WILATE, though not many more doses than for Moderate bleeding.
Reviewer Comments: *The empiric data from the WIL-27 study shows that it was successful in >70% of all bleeding episode treatments ("Excellent" or "Good" hemostatic efficacy). The success rate fell from 93% for minor bleeds to 81% for moderate bleeds, and 50% for severe bleeds, which is not surprising, since the major bleeds treated with moderate success were all joint bleeds, in target joints, namely ankles and knees in subject* (b) (6) *. Notably, all major bleeds in soft tissues were treated successfully with WILATE®, including three soft tissue hemorrhages in that same subject. Overall, these data indicate the need to revise the proposed instructions for dosing of WILATE in Table 4 from the USPI.*

Table 4 Dosing for Treatment of Hemorrhages (from USPI)

Type of Hemorrhages	Target FVIII level (%)	Recommended dosage (IU/kg body weight)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor	20-40	20-40	Repeat every 12-24 hours	At least 1 day, until the hemorrhage has resolved
Moderate to major	30-60	15-30	Repeat every 12-24 hours	3 to 4 days or more, until the hemorrhage has resolved
Life-threatening	60-100	30-50	Repeat every 8-24 hours	Until threat has resolved

Reviewer Comments: *First, with respect to Table 4 in the proposed USPI, the types of hemorrhages do not correspond to the severity of hemorrhage as recorded in the WIL-27 study. Second, there are inconsistencies in the Target FVIII level (%) and Recommended Dosage (IU/kg body weight) column with respect to minor hemorrhage, and the recommended doses for minor hemorrhage do not reflect the empiric data from the WIL-27 study, and it makes no sense for moderate to major hemorrhage dosing to be less than that for Minor hemorrhage.*

The Applicant was asked to define the severity/type of hemorrhage, and to adjust the recommended dosage values in Table 4 of the USPI to reflect the empiric data from WIL-27 in an information request conveyed July 11, 2019. In particular, we ask that the recommended dose for a given severity of bleed not fall below the average given for that severity of bleeding in WIL-27.

In response, the Applicant provided the revised Table 4, below, which satisfies my concerns for discrepancies in dosing and severity with the WIL-27 study results:

Table 4 Dosing for Treatment of Hemorrhages (from USPI, revised)

Type of Hemorrhages	Recommended dosage (IU/kg body weight)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor	30-40	Repeat every 12-24 hours	At least 1 day, until the hemorrhage has resolved
Moderate	30-40	Repeat every 12-24 hours	3 to 4 days or more, until the hemorrhage has resolved
Major	35-50	Repeat every 12-24 hours	3 to 4 days or more, until the hemorrhage has resolved
Life-threatening	35-50	Repeat every 8-24 hours	Until threat has resolved

Pharmacokinetics

The Applicant also analyzed the area under the concentration curve (AUC) and AUC normalized to the administered dose (AUCnorm), in vivo half-life, maximum plasma concentration (Cmax), time at maximum concentration (Tmax), mean residence time, volume of distribution, clearance and IVR of WILATE® in 21 subjects in WIL-27 who underwent at least one PK study during WIL-27. The PK study data will support dosing instructions for the label and reveals critical differences between adults and adolescents.

The key pharmacokinetic parameters are listed below in Table 14, adapted from Table 29 of the WIL-27 Clinical Study Report.

Table 14: Pharmacokinetic Parameters, Adolescents and Adults, WIL-27 Study

Adolescents (≥ 12 < 18 years of age, n = 5)			
Parameter	**Baseline**	**Completion (6 months)**	**P value**
IVR (kg/dL)	1.66 ± 0.17	1.42 ± 0.36	NA
Cmax (IU/dL)	83.9 ± 9.4	72.5 ± 17.8	0.31
Half-life (h)	11.4 ± 1.93	10.5 ± 1.7	0.18
Clearance (dL/h/kg)	0.051 ± 0.008	0.05 ± 0.008	0.81
Adults (≥18 years of age, n = 16)			
Parameter	**Baseline**	**Completion (6 months)**	**P value**
IVR (kg/dL)	2.27 ± 0.41	2.17 ± 0.39	NA

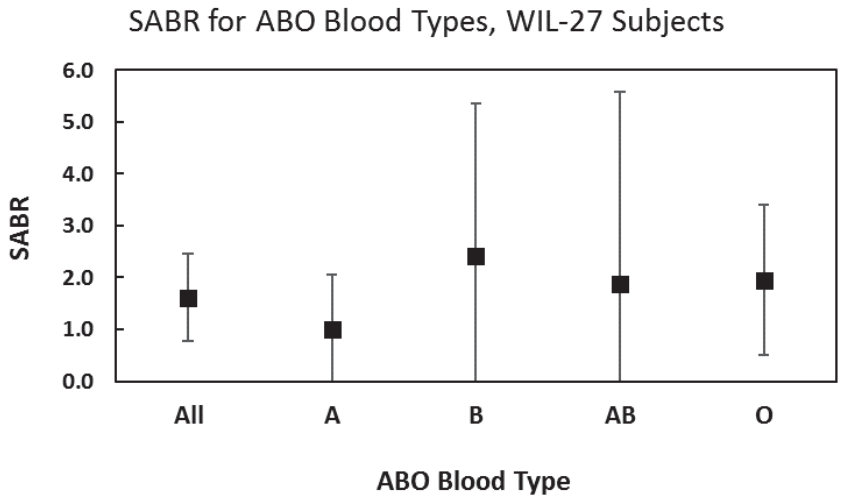
Cmax (IU/dL)	113.82 ± 20.5	113.17 ± 20.8	0.67
Half-life (h)	10.64 ± 2.69	11.81 ± 2.42	0.07
Clearance (dL/h/kg)	0.035 ± 0.013	0.032 ± 0.008	0.56

Reviewer Comments: *I defer to Pharmacology reviewer's assessment of the pharmacokinetic studies, however, there is a clear difference in IVR and clearance of WILATE between adults and adolescents. This age difference is consistent with observations of lower recovery and increased clearance in pediatric subjects found in studies of other coagulation factor products. For the label, separate description of adult and adolescent parameters should be included, rather than the aggregate data proposed by the Applicant, per the Pharmacology reviewer. This was conveyed to Octapharma in an information request on July 11, 2019.*

Effect of ABO Blood Type and vWF Antigen on WILATE Half-Life.
The Applicant assessed the relationship between ABO blood type and baseline vWF antigen levels on WILATE half-life. For adolescents, there was no significant effect of ABO blood type on WILATE half-life, and for adults there was a marginally significant effect of ABO blood on WILATE half-life (P = 0.03) for data compiled with the chromogenic assay (but not the one-stage assay, P = 0.18). No significant effect on WILATE half-life was found for baseline von Willebrand factor antigen levels.
Reviewer Comments: *There is a marginally significant difference in half-life based on ABO blood type. To assess this further, I calculated SABR values for each blood type, as shown below in Table 15. As can be seen, the SABR values are similar between all blood types, with overlapping confidence intervals. The mean SABR for each group is driven primarily by the high outlier(s) in each group. Further, since not all subjects underwent PK testing, it is worth noting that the group with the shortest mean half-life was type B, for which there was only one subject in the PK population. This might predict a higher bleeding rate in type B subjects, but although the average SABR of 2.41 is the highest of the blood groups, that value is driven by a single high outlier SABR (as for all other subsets). I do not think that this has serious clinical implications.*

Table 15: Effect of ABO Blood Type on SABR, WIL-27 Subjects

ABO Type	Average (SD)	95% CI	Median (range)
A (n = 23)	0.997 (± 2.6)	1.1	0 (0 - 11.4)
B (n = 8)	2.41 (± 4.24)	2.94	0 (0 – 11.7)
AB (n = 5)	1.83 (± 4.21)	3.69	0 (0 – 9.4)
O (n = 19)	1.95 (± 3.24)	1.46	0 (0 – 10.6)
All (n = 55)	1.61 (± 3.20)	0.85	0 (0 – 11.7)



Immunogenicity of WILATE®

The observed rate of 0 factor VIII inhibitors in a total of 83 subjects from the combined PTP pool from WIL-27, TMAE-102, TMAE-108, and TMAE-110 satisfies the FDA requirement for immunogenicity in previously treated patients with hemophilia A, which was specified in advance of the WIL-27 study.

Reviewer Comments: *Inhibitor development in hemophilia A patients is an adverse event of special interest to the FDA and the inhibitor rate in PTPs is a criterion for licensure. Our current policy is that for products to be approved, the inhibitor rate needs to be convincingly less than 5%, or, no more than one inhibitor developing in 80 research subjects with at least 150 prior exposure days to factor VIII, at least 50 exposure days to the product, and observation for at least six months while on the product. The pooled analysis of 136 PTPs finds 83 who meet these strict criteria, with no inhibitor development observed. This meets the pre-specified threshold set before the WIL-27 study was initiated. The lack of inhibitor development in any of the 136 subjects (including 53 who did not meet strict criteria) provides additional assurance of the low immunogenicity of WILATE®.*

6.1.11.3 Subpopulation Analyses

All subjects were white males (since the study was done in Europe and all subjects had severe hemophilia A, a sex-linked disease). Accordingly, there was no subpopulation analysis based on race or gender. Five subjects were adolescents between the ages of 12 and 18, so a limited analysis of adolescent pediatric subjects was possible. This is discussed in detail elsewhere, but in summary the five pediatric subjects had fewer bleeds than the adults while on prophylaxis. The ABR rates (0.4 ± 0.89) for the five children <18 years of age are significantly better than those (2.39 ± 3.77) for the larger group of adults (n = 50) who were ≥18 years of age. Further, there were no spontaneous bleeding events in the younger group, though the group was too small to draw a conclusion on its significance.

6.1.11.4 Dropouts and/or Discontinuations

Two subjects out of 57 enrolled dropped out before treatment with WILATE®. One of the 55 subjects treated on the study dropped out before completion. The dropouts and

discontinuations did not likely affect the outcome of the WIL-27 study and these were not replaced.

6.1.11.5 Exploratory and Post Hoc Analyses

The Applicant undertook numerous post-hoc analyses of bleeding events in WIL-27 study subjects. The most important of these Exploratory Analyses are reviewed, below.

Characterization of Five Highest Outliers for TABR. Per the study report, six patients experienced more than two spontaneous BEs within 30 days or a major spontaneous BE, which should have triggered an increase in their prophylactic dose. One patient (b) (6) received an increased dose according to the protocol and experienced no further BEs until the end of the study. The other five patients did not receive increased doses as outlined in the protocol and experienced further bleeding events. This post-hoc analysis of the five high outliers who did not get protocol-mandated dose adjustment is useful to review in detail. All outlier subjects were adults who had hemophilic arthropathy and/or gait disturbances at baseline. None had inhibitors to factor VIII. No doses were adjusted upward with bleeding events. Their narratives are found in the WIL-27 study report starting on page 61. The key features of these subjects are summarized in Table 16, below.

Table 16. Attributes of Five Highest TABR Outliers for WIL-27 Study

Subject	TABR	Dose	Bleeding	Compliance	Comments
(b) (6) 21 yrs	15.69	39 IU/kg (no change)	8 bleeding events (6 spontaneous, 2 traumatic)	NA	Historic TABR 120 during on-demand treatment
(b) (6) 25 yrs	12.28	35 IU/kg (no change)	7 bleeding events (3 spontaneous, 3 traumatic, 1 unknown)	Wilate interrupted during trip. Lost study diary	Historic TABR 2 while on prophylaxis & on demand treatment.
(b) (6) 35 yrs	13.21	40 IU/kg (no change)	7 bleeding events (6 spontaneous, 1 traumatic)	NA	Historic TABR 42 while on prophylaxis & on demand treatment.
(b) (6) 64 yrs	9.43	39 IU/kg (no change)	5 bleeding events (5 spontaneous)	NA	Historic TABR 14 while on prophylaxis.
(b) (6) 45 yrs	9.26	38 IU/kg (no change)	5 bleeding events (5 spontaneous)	NA	Historic TABR 86 during on demand treatment.

Reviewer Comments: *The five highest TABR outliers are seemingly explained by patient characteristics and failure to escalate the prophylaxis dose as prescribed by the protocol, rather than failure of the product. Note that four of the five high outliers had dramatically better TABRs than their historic TABR from prior to the study. It seems likely that if they had undergone dose adjustment as per the protocol, they would have had even better results.*

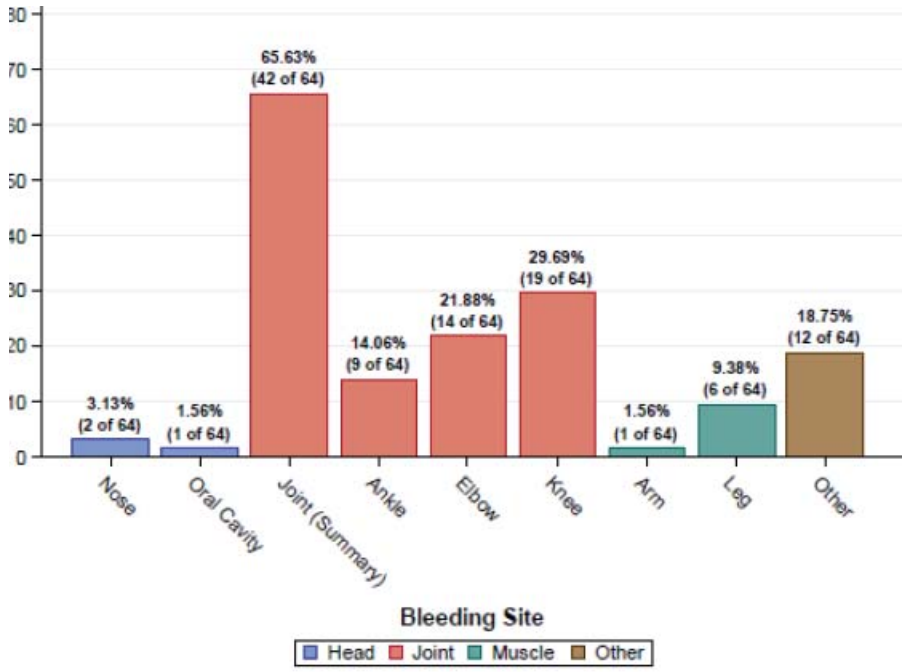
Distribution of Number of Bleeding Events. Related to the issue of high outliers is the distribution of the number of bleeding events observed for the entire FAS group of 55 subjects. As shown, below, in Table 17, modified from the WIL-27 study report (page 62), over 90% of subjects had three or fewer events during the six-month study period. Thirty, or 55% of subjects, had no bleeding during the six-month study period.

Table 17: Bleeding Episode Frequency, FAS Population (n =55)			
Frequency	**N**	**%**	**Cumulative %**
0	30	54.6	54.6
1	12	21.8	76.4
2	4	7.3	83.7
3	4	7.3	91.0
5	2	3.6	94.6
7	2	3.6	98.2
8	1	1.8	100

Modified from Table 17 in the WIL-27 Study Report; source data from Appendix 16.2

Of the 64 BEs, 15 (23.4%) were minor bleeds, 34 (53.1%) were moderate and 14 (21.9%) were major (severity of 1 BE [1.6%] was not known) (Section 14, Table 14.2.2.1-9). There were no life-threatening bleeds. Forty-four bleeds (68.8%) were spontaneous, 16 (25.0%) were traumatic bleeds, three (4.7%) were bleeds due to other causes and one (1.6%) was of unknown type (Section 14, Table 14.2.2.1-11).
Reviewer Comments: *Note that during data review by the Applicant, the subject with the 8 bleeding episodes* (b) (6) *had two events (BE007, BE008) added to his total based on the interval between dosing that the protocol specified. So, the bleeding episode numbers listed for this subject arguably was less than that listed. The difference works against the Applicant's interests in trying to minimize the number of bleeding episodes listed, indicating the Applicant is not trying to hide adverse data. The ABRs in would not change significantly by revising the bleeding episode rate up or down by the small number of cases where this occurred, in any event.*

Sites of Bleeding on WIL-27 Study. Figure 2 from WIL-27 Study Report, page 63, indicates that two thirds of bleeding occurred in joints, while the rest were soft tissue and mucosal bleeds that were scattered throughout various sites. Joint bleeds were most common in knees.



Reviewer Comments: *The distribution of sites of bleeding is typical of hemophilia bleeding, which is most common in the major weight-bearing joints, particularly the knees.*

Bleeding Rates on WIL-27 versus Historical Bleeding Rates. Another useful exploratory analysis was to compare the observed bleeding rate of each subject during the study to their individual historical bleeding rates.

This is depicted most clearly in Table 18, modified from Table 16 from page 60 of the WIL-27 Study Report:

Table 18: Historic and WIL-27 TABRs

Age, Historical Rx	Historic TABR	TABR in WIL-27	P value
<18 years (n = 5)			
Prophylaxis (n=5)			NA
Mean ± SD	0.40 ± 0.89	0.40 ± 0.89	
Median (range)	0 (0.0–2.0)	0 (0.0–2.0)	
≥18 years (n = 50)			
On-demand (n=32)			
Mean ± SD	52.19 ± 40.63	1.93 ± 3.44	
Median (range)	60.0 (0.0–120.0)	0.0 (0.0–15.7)	
Prophylaxis (n=13)			
Mean ± SD	5.23 ± 11.15	2.21 ± 2.88	
Median (range)	0.0 (0.0–40.0)	1.85 (0.0–9.4)	< 0.0001
Combination (n=5)			
Mean ± SD	14.80 ± 17.30	5.85 ± 6.35	
Median (range)	6.0 (2.0–42.0)	1.89 (0.0–13.2)	
Total TABR (n = 50)			
Mean ± SD	36.24 ± 39.59	2.39 ± 3.77	
Median (range)	20.0 (0.0–120.0)	0.0 (0.0–15.7)	

Total (n = 55)			
On-demand (n=32)			
Mean	52.19 ± 40.63	1.93 ± 3.44	
Median (range)	60.0 (0.0–120.0)	0.0 (0.0–15.7)	
Prophylaxis (n=18)			
Mean	3.89 ± 9.64	2.21 ± 2.88	
Median (range)	0.0 (0.0–40.0)	1.85 (0.0–9.4)	
Combination (n=5)			< 0.0001
Mean	14.80 ± 17.30	5.85 ± 6.35	
Median (range)	6.0 (2.0–42.0)	1.89 (0.0–13.2)	
Total TABR (n = 55)			
Mean ± SD	32.98 ± 39.12	2.21 ± 3.64	
Median (range)	10.0 (0.0–120.0)	0.0 (0.0–15.7)	

NA = not applicable; TABR = total annualized bleeding rate; SD = standard deviation; N = number of patients; n = number of patients in subgroup.
Source: Section 14, Tables 14.2.3.2-9, 14.2.3.2-3 and 14.2.3.2-11.

Reviewer Comments: *The analysis of bleeding event rates in WIL-27 trial subjects compared to their historical ABR rates indicates that the five pediatric subjects who were all previously on routine prophylaxis had low baseline bleeding event rates which remained low while on study. The adults had higher bleeding rates than the pediatric subjects both during the WIL-27 study and at baseline before the study, presumably since they had accumulated joint damage that the pediatric subjects had not yet developed. Note the higher (worse) joint scores at baseline in the adults, compared to adolescents. The greatest improvements in TABRs in adults came in those treated previously on-demand, primarily because they started with the highest historical ABR (mean 52.19/year, ± 40.63, compared to 3.89 ± 9.64 for those previously treated with routine prophylaxis). This is consistent with the observation that on-demand treatment is less efficacious than routine prophylaxis (shown in other studies for other products, e.g., Manco-Johnson, et al NEJM study of prophylaxis vs. on-demand therapy with Kogenate). For all adults, lower ABRs were seen with routine prophylaxis than on-demand or combined therapy, and for all groups the ABR during WIL-27 trial was lower than their historical baselines.*

Dosing Characteristics for Treatment of Breakthrough Bleeding. The Applicant characterized the dosing of Wilate® for treatment of breakthrough bleeding on WIL-27, as shown in Table 19, modified from Table 19 on page 64 of the Study Report, below.

Table 19: Dosing for Treatment of Breakthrough Bleeding Events
(FAS population, n = 55; Subjects with Bleeding Episodes = 25)

Parameter	Mean	SD	Median	Range
EDs per BE	1.57	1.05	1.00	1 - 5.29
Injections per BE per patient	1.60	1.08	1.00	1.00 - 5.43

Dose per BE (IU)	4645.5	3891.1	3000	1500 - 15714
Dose per BE (IU/kg)	54.5	36.8	36.4	26.7 - 182.2
Dose per Injection (IU)	2729	786	2823	1500 - 4611
Dose per Injection (IU/kg)	34.0	8.0	31.3	26.5 - 62.8

BE = bleeding episode; ED = exposure day; FAS = full analysis set
Modified from Table 19, on page 64 of the WIL-27 Study report. Source data: Section 14, Table 14.2.2.2-25 in WIL-27 Study Report

The distribution of the number of doses of WILATE® required to treat breakthrough bleeding episodes is shown in Figure can be seen, half of all bleeding events were treated with one injection of WILATE® and one exposure day of treatment.

The number of injections required to treat bleeds was also analyzed. As seen in Tables 20 (FAS subjects) and 21 (PP subjects) most bleeds were treated with one dose of WILATE®.

Table 20: Number of Injections Administered for the Treatment of Breakthrough BEs (FAS Population, N=55; Patients with BEs, N=25)

Number of injections per BE	Number of BEs	Percent of BEs
1	36	56.3
2	12	18.8
3	7	10.9
4	2	3.1
5	4	6.3
6	1	1.6
7	1	1.6
9	1	1.6

BE = bleeding episode; FAS = full analysis set.
Source: Section 14, Table 14.2.2.2-3.

Table 21: Number of Injections Administered for the Treatment of Breakthrough BEs (PP Population, N=52; Patients with BEs, N=24)

Number of injections per BE	Number of BEs	Percent of BEs
1	36	63.2
2	12	21.1
3	7	12.3
5	1	1.8
7	1	1.8

BE = bleeding episode; PP = per-protocol.
Source: Section 14, Table 14.2.2.2-4.

Reviewer Comments: *The analysis of exposure days and doses required to treat bleeding events supports the conclusion that one or two doses of WILATE is enough to*

treat bleeding events that occur while on prophylaxis. The outliers requiring more than 3 doses to control bleeding are decreased in the PP group (n = 52) as compared to the FAS group (n = 55). This is consistent with better results with better adherence to the protocol.

(b) (4)

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety analysis for WIL-27 was based on review of adverse events in the FAS population (all subjects treated at least once with WILATE) with emphasis on development of factor VIII inhibitor antibodies (an adverse event of special interest) and viral seroconversions. All information was collected by the Applicant from Investigator observations, laboratory studies, and patient diaries, entered into case report forms and presented in the WIL-27 Study Report. The Office of Biostatistics and Epidemiology was asked to review its FAERS database for reports of adverse events associated with use of WILATE for hemophilia A. They note there were 6 reports in FAERS for patients treated for hemophilia A, (from a total of 57 reports, the remainder being associated with use for its licensed indication, von Willebrand's disease). Of these 6 reports one was a transient factor VIII inhibitor in a 13-month-old patient with hemophilia A after 9 exposure days with WILATE; the antibody reportedly disappeared with further WILATE treatment at a higher dose. Another report of an antibody inhibitor appears to be drug ineffectiveness due to non-compliance. The other 4 reports included 1 report of dizziness and 1 report of hypotension associated with infusion, both of which resolved, and 1 report of exacerbation of reactive airway disease in a patient with underlying complicated course and preexisting central line infection, and 1 report of device related infection. None of these reports contained any evidence of WILATE product related issues and none raised specific safety concerns regarding WILATE in this patient population (see OBE review memorandum).

6.1.12.2 Overview of Adverse Events

Table 22 is Table 34 from the WIL-27 Study Report. It lists 16 treatment-emergent adverse events that were observed in the 55 subject safety set (SAF) population in the WIL-27 study, by organ system.

Table 22 (Table 34 from the WIL-27 Study Report):

Table 34: Display of TEAEs by System Organ Class and Preferred Term (SAF Population, N=55)

Primary system organ class Preferred term	Number of patients (%)	Number of TEAEs
Any TEAE	**12 (21.8)**	**16**
Infections and infestations	***3 (5.5)***	***3***
Erysipelas	1 (1.8)	1
Nasopharyngitis	1 (1.8)	1
Viral upper respiratory tract infection	1 (1.8)	1
Blood and lymphatic system disorders	***2 (3.6)***	***2***
Thrombocytosis	2 (3.6)	2
Immune system disorders	***2 (3.6)***	***2***
Seasonal allergy	2 (3.6)	2
Nervous system disorders	***1 (1.8)***	***1***
Headache	1 (1.8)	1
Skin and subcutaneous tissue disorders	***1 (1.8)***	***1***
Eczema	1 (1.8)	1
Musculoskeletal and connective tissue disorders	***2 (3.6)***	***5***
Arthralgia	2 (3.6)	5
General disorders and administration site conditions	***1 (1.8)***	***1***
Pain	1 (1.8)	1
Injury, poisoning and procedural complications	***1 (1.8)***	***1***
Limb injury	1 (1.8)	1

SAF = safety set; TEAE = treatment-emergent adverse event.
Source: Section 14, Table 14.3.1-1.

6.1.12.3 Deaths

There were no deaths on this study.

6.1.12.4 Nonfatal Serious Adverse Events

There were no fatal or non-fatal serious adverse events on the WIL-27 study.

6.1.12.5 Adverse Events of Special Interest (AESI)

Factor VIII Inhibitors

The key adverse event of special interest for factor VIII concentrates (factor VIII inhibitors) was not observed in any of the 55 subjects in the SAF patient data set.

Blood-Borne Pathogens.

Another adverse event of special interest for a product derived from pooled human plasma is infection with blood-borne pathogens. The risk for infection with serious enveloped viruses such as HIV that are screened for in the donor pool and subjected to a 12-13 $\log_{10}$ reduction in titer by the WILATE manufacturing procedure is negligible. The greatest risk for viral infection with a plasma-derived concentrate such as WILATE is for parvovirus B19, which is encountered by nearly all the population and is only reduced by a factor of a (b) (4) reduction in titer by the WILATE manufacturing procedure. At

screening, 53 of the 55 patients tested positive for parvovirus B19 IgG antibody and two patients aged 18 years or older tested negative (Section 14, Table 14.3.4-11). The two patients with negative tests at screening also tested negative at study completion.
Reviewer Comments: *The WIL-27 study data point to a low risk for factor VIII inhibitor development in PTPs and may be combined with data from other studies of WILATE in PTPs to meet the previously agreed upon rate of inhibitor development to ensure safety. This will be the subject of the Statistics review and the Integrated Analysis of Safety in this review. The absence of seroconversion in subjects without evidence of B19 parvovirus infection is reassuring.*

6.1.12.6 Clinical Test Results

Abnormal listings were recorded for 47 of the 55 SAF subjects during the study. All abnormal listings were classified as not clinically significant except two high measurements of platelets (reference range 130–400 x 109/L) in two patients between 12 and 18 years of age. Patient (b) (6) had a high platelet count of 610 x 109/L before injection at 3-months. Patient (b) (6) had a high platelet count of 784 x 109/L before injection at the 3-month visit. Both cases were reported as TEAEs. Neither patient had clinically significant high platelet counts at the initial PK assessment or the PK completion 6-month visit.

One clinically significant abnormality in vital signs was recorded in a patient older than 18 years of age. Subject (b) (6) had a heart rate of 127 beats per minute before injection at the initial PK assessment compared with a value of 74 beats per minute at screening. Heart rate decreased to 91 beats per minute one hour after injection and was 92 beats per minutes after 48 hours.
Reviewer Comments: *The clinical test results profile is not concerning. It would be interesting to know if the two subjects with thrombocytosis (but no thrombosis) had iron deficiency anemia, which is a common cause for acquired thrombocytosis. In reply to our information request on this point, Octapharma stated that they did not have any additional data or explanation for the two instances of thrombocytosis. I do not find these results to be of concern for product safety but should be listed as adverse events occurring in >5% of study subjects in Section 14 of the USPI.*

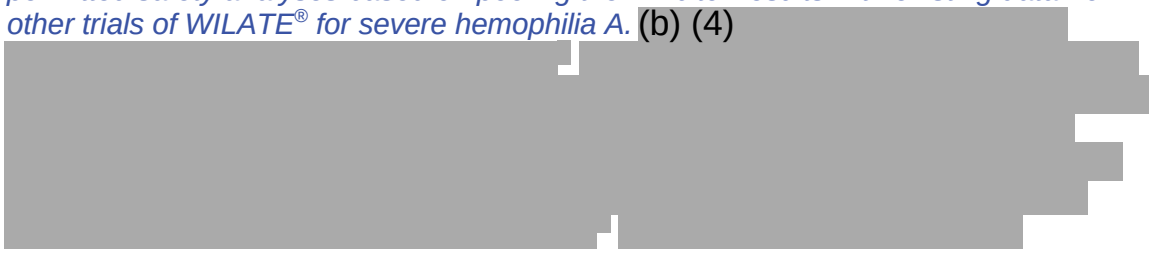
6.1.12.7 Dropouts and/or Discontinuations

Of 57 subjects enrolled, 55 underwent treatment with WILATE® , which comprise the full analysis set (FAS) and safety (SAF) dataset. Of the 55 treated subjects, one discontinued the study, and two were non-compliant with the study protocol, leaving a per-protocol (PP) set of 52 subjects. The one subject who discontinued the study (b) (6) did so due to a treatment emergent adverse event (worsening of joint pain). The Investigator characterized the worsening of the joint pain to the product, with which the Applicant did not agree. The Applicant argues that It is implausible that the injections of Wilate® were the reason for the worsening of the condition, especially in the absence of any bleeding during prophylaxis, and points to pre-existing bad joint health scores upon enrollment. The factor VIII inhibitor screen was negative (<0.6 BIAU) when tested 20 days after discontinuation of the study, hence development of an inhibitor and lack of efficacy of WILATE® was not the cause for the worsening joint pain. Two others who began treatment had deviations from the protocol, namely failure to provide diary entries for half of the study (b) (6) and one skipped prophylactic injection of WILATE® for 14 days (b) (6) . All three subjects who discontinued the study after commencing treatment were part of the FAS and SAF dataset.

Reviewer Comments: *Dropouts/discontinuations do not appear to have affected the outcome of the WILATE-27 study, and the one subject who dropped out did not do so based on a factor VIII inhibitor (and was analyzed in the FAS dataset, in any event).*

6.1.13 Study Summary and Conclusions

Pivotal trial, WIL-27, studied prophylactic and on-demand treatment of severe hemophilia A in 55 previously treated patients (PTPs) > 12 years of age (50 adults, 5 pediatric subjects 12 years of age or older). The primary objective was to assess the efficacy by comparison of ABRs of subjects on prophylaxis with WILATE® to the annualized bleed rate of subjects treated on-demand with the recombinant DNA factor VIII product NUWIQ (another Octapharma product) under IND 13722. One critical secondary objective was to assess the safety of WILATE® by measurement of the rate of factor VIII inhibitor antibody development, an adverse event of special interest for factor VIII replacement therapeutics. The ABR for subjects on this study was 2.21 ± 3.64, which compared favorably to the ABR of 58.1 for the comparator on-demand treatment group in the NUWIQ licensure trial. No subjects developed inhibitors to factor VIII on this study or had seroconversion to any viral pathogens attributable to the product. Pharmacokinetic studies done in 21 subjects demonstrated an overall in vivo recovery of 2.12 kg/dL and a half-life of 10.8 hours at baseline (one-stage factor VIII assay) that was not significantly changed after six months of treatment. The IVR in 5 subjects between 12 and 18 years of age was 1.66 kg/dL vs. 2.27 kg/dL for 16 subjects ≥ 18 years of age, as is typical for coagulation factor VIII concentrates. One subject underwent major surgery (knee arthroplasty) under WILATE® coverage on this study without bleeding.
Reviewer Comments: *WIL-27 clearly show the efficacy of WILATE® for prophylaxis of bleeding in severe hemophilia A in adults and adolescents, and appears to be safe, with no SAEs or adverse events of interest (factor VIII inhibitors). Specifically, the Applicant appears to have met the protocol specified criterion for success as per the agreements reached at the time of submission of IND 17181 in October of 2016. The protocol permitted safety analyses based on pooling the inhibitor results with existing data from other trials of WILATE® for severe hemophilia A.* (b) (4)



6.2 Trial #2

TMAE-103: International Clinical Study to Investigate the Incidence of Inhibitors in Previously Untreated Patients with Severe Haemophilia A treated with OCTATE*
**[prior product name of WILATE®]*
Reviewer Comments: *Review of TMAE-103 serves only to support safety and efficacy data in WIL-27 in adolescents and to gain insight into the inhibitor rate of WILATE® in previously untreated patients with hemophilia A. The indications for prophylaxis and on-demand treatment in children < 12 years of age will not be granted based on this review but will depend on submission of results from the ongoing WIL-30 study (a PMR under PREA).*

6.2.1 Objectives (Primary, Secondary, etc)

Primary Objective:
The primary objective of the study was to assess the immunogenicity of WILATE® in PUPs by monitoring the levels of inhibitor against FVIII (by Bethesda assay) every 3 to 4 exposure days until the 20th exposure day and thereafter every 10th exposure day or every 3 months, whichever was the soonest.

Secondary Objectives:
Secondary objectives were:

- To assess the efficacy of WILATE® for prevention and/or treatment of bleeding episodes and for use during (b) (4) .
- To assess the viral safety of WILATE® in PUPs by monitoring viral markers for HIV, HBV, HCV, HAV, Parvovirus B19 and ALAT at baseline and at 3 month intervals.
- To assess the tolerability of WILATE® by monitoring the occurrence of AEs.

6.2.2 Design Overview

Study TMAE-103 was a prospective, open-labelled, non-controlled, international multi-center study of WILATE for routine prophylaxis or on-demand treatment of bleeding in previously untreated patients (PUPs) with severe hemophilia A, at the discretion of the Investigator. Subjects' parents or guardians were required to give written informed consent and subjects had to meet the inclusion/exclusion criteria for the study.

Each subject received WILATE® exclusively as replacement therapy (except in the case of inhibitor development), either prophylactically and/or for treatment of bleeding episodes, for a minimum of 50 exposure days or for 2 years, whichever was sooner. The dosage and frequency of treatment was determined by the Investigator.

Testing for FVIII antibodies by Bethesda assay (immunogenicity testing) and virology testing was performed at study entry and at regular intervals throughout the study. Testing for FVIII recovery was optional but recommended. Patients developing an inhibitor during the study were to remain in the trial and be followed up to establish the nature of the inhibitor (e.g. transient, low responder, high responder).
Reviewer Comments: *This study was an important, phase 2 first look at the safety of WILATE in PUPs with hemophilia A. It serves primarily to ascertain the rate of inhibitor development, a critical adverse event of special interest to the FDA. Due to the non-uniform approach to treatment, lack of standardized dosing, and lack of standardized collection of data on bleeding events and efficacy, it can only suggest efficacy for routine prophylaxis or on-demand treatment of bleeding in children from 1-12 years of age. Thus, it cannot serve as the basis for approval of either indication in this age group. Several* (b) (4) *were performed on subjects under WILATE coverage on this trial. Note that the age of the children who participated in this study was skewed to ages 0-6 years; there is only one subject (age 7 years) in the age 6 to 12 years pediatric age category, which is a major gap in clinical knowledge of this product in pediatric subjects. The ongoing WIL-30 study (not available for this review) has a similar clinical trial design to WIL-27 and is meant to address efficacy and safety in children from 1-12 years of age. The recommendations for the indications for this submission will not extend to pediatric subjects and the pediatric studies are considered only as supporting evidence of safety and efficacy demonstrated in adolescents and adults*

studied in WIL-27. TMAE-103 also is the only source of information on the rate of inhibitor development in PUPs, and this will be discussed briefly in this review.

6.2.3 Population

Subjects to be included in the study were previously untreated patients (PUPs) with severe hemophilia A (FVIII:C ≤1%). Although there was no limitation of age for study admission, it was expected that most or all the subjects would be newborn or infants. The ages at time of study entry ranged from less than one month old to 7.5 years.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The dosage and frequency of treatment during the study was dependent upon the clinical situation of the patient and the decision of the investigator. Each patient received WILATE® exclusively as FVIII replacement therapy (except in the case of emergency), prophylactically and/or for treatment of bleeding episodes, for a total of 50 exposure days or for 2 years, whichever came sooner.

The dosage and duration of the replacement therapy was dependent upon the severity of the disorder of the hemostatic function, on the location and extent of the bleed and on the clinical situation of the patient.

The calculated required dosage for treatment was based on the empirical finding that 1 IU FVIII per kg body weight (bw) raises the plasma factor VIII by 1.5 to 2%. The required dosage was determined using the following formula:

Initial dose required units (IU) = Body weight (kg) x desired factor VIII rise (%) x 0.5.

For (b) (4), or after a bolus injection for treatment of major bleeding, (b) (4) was permitted. The necessary infusion rate was to be calculated from the desired FVIII level and the clearance of the patient using formulas indicated in the protocol.

6.2.5 Directions for Use

WILATE® is provided with a Mix2Vial TM transfer device for reconstitution of the freeze-dried powder in diluent, a 10-mL syringe, an infusion set and two alcohol swabs See Section 6.1.5 for previous description of WILATE® directions for use and details on Mix2Vials transfer device (from August 2010 USPI).

Thirteen batches of WILATE® were used in the study. The batch number from the carton of each vial was documented in the CRF. Table 4 provides an overview of the WILATE® batches used in the trial, showing batch numbers and expiry dates. All batches had a nominal potency of 500 IU FVIII:C. Actual potencies are shown in Section 16.2.5, List 1. Certificates of Analysis can be found in Section 16.1.6.

Table 23: WILATE® Batches Used in the Trial

Batch No.	Expiry Date	Batch No.	Expiry Date
204002180	01/2004	251012180	05/2005
217003180	04/2004	338006180	08/2005
219004180	05/2004	405001180	06/2006
224006180	06/2004	424002180	11/2006

238007180 06/2003 540012180 09/2007
248009180 10/2004 541013180 09/2007
249010180 05/2005
Source: Section 16.2.6.1, List 9

6.2.6 Sites and Centers

This study was conducted in eight investigational sites in Germany and Russia. The coordinating investigator on this study was Dr W Kreuz, University Hospital, Frankfurt Germany.

Table 24. TMAE-103 Study Sites and Investigators

Site #	**Location**	**Investigator**
Site	University Hospital Frankfurt/Main, Frankfurt, Germany	Dr W Kreuz, (Principal Investigator)
Site	Professor-Hess-Kinderklinik, Bremen, Germany	Dr G Auerswald
Site	Kirovsky Science Research Institution of Haematology and Blood Transfusion, Kirov, Russia	Dr T Chernova
Site	St.-Petersburg Haemophilia Centre, St. Petersburg, Russia	Dr T Andreeva
Site	Izmailovsky City Children's Hospital, Moscow, Russia	Dr V Vdovin
Site	Scientific Technical Centre RUP "MBI", Minsk, Russia	Dr V Gapanovich
	Science Research Institution of Haematology and Blood Transfusion, Kiev, Ukraine	Prof P Perechrestenko
	Ministry of Health of Tatarstan Children's Hospital No. 1, Kazan, Russia	Dr K Zakirov

6.2.7 Surveillance/Monitoring

After screening for eligibility and enrollment subjects in TMAE-103 underwent optional factor VIII recovery studies and factor VIII inhibitor antibody testing (after a 7-day washout period), then underwent repeat testing (and optional recovery study) every 3-4 exposure days during exposures 1-20, then every 10 exposure days for exposures 21 and upward.

Viral serologies and liver transaminases were assessed on a fixed schedule every three months after starting treatment with WILATE. See Tables 1-3 on page 15 of TMAE-103 Study Report.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoints to assess immunogenicity of WILATE® in previously untreated patients with severe hemophilia A was the Bethesda inhibitor titer assay. Although not formally stated to be the primary endpoint of the study, the results of the factor VIII

Tables 25, 26, & 27 (Tables 1, 2, & 3) from the TMAE-103 Study Report):

Table 1 Schedule for Immunogenicity Testing (Bethesda Assay) and FVIII Recovery†

Time	Frequency	Total No. of Assays
Study entry	Pre-treatment	1 assay + recovery†
Exposure Day 1 – 20	Every 3-4 exp. days	5 – 7 assays+ recovery†
Exposure Day 21 onwards	Every 10 exp. days	Depends on total number of injections, recovery†

†Optional, but recommended

Table 2 Schedule for Immunogenicity Testing (Bethesda Assay), FVIII and FVIII Recovery in rarely treated PUPs

Year	1					2			
Month after commencing treatment with WILATE	0‡	3	6	9	12	15	18	21	24
FVIII, FVIII Recovery†	+	+	+	+	+	+	+	+	+
Bethesda Assay	+	+	+	+	+	+	+	+	+

†Optional, but recommended
‡Baseline (i.e. before treatment start)

Viral safety of WILATE in PUPs was to be assessed by monitoring of viral markers for HIV, HBV, HCV, HAV and Parvovirus B19 and ALAT at baseline and at 3 month intervals.

Table 3 Virology Testing

Year	1					2			
Month after commencing treatment with WILATE	0‡	3	6	9	12	15	18	21	24
ALAT	+	+	+	+	+	+	+	+	+
Anti-HIV 1+2	+	+	+	+	+	+	+	+	+
Anti-HCV	+	+	+	+	+	+	+	+	+
Anti-HBs, anti-HBc, HBsAg	+	+	+	+	+	+	+	+	+
Anti-HAV (IgG and IgM)	+	+	+	+	+	+	+	+	+
Anti-Parvovirus B19 (IgG and IgM)	+	+	+	+	+	+	+	+	+

‡Baseline (i.e. before treatment start)

recovery studies served as a corollary to the Bethesda inhibitor assay endpoints to detect inhibitor antibodies. A rise in FVIII of less than 1% per FVIII unit/kg administered is considered indicative of inhibitor. A rise of less than 1.5% per FVIII unit/kg administered was considered suggestive.

The Bethesda inhibitor assay (b) (4) was performed every 3 to 4 exposure days until the 20th exposure day and thereafter every 10th exposure day or every 3 months, whichever was the soonest. Before inhibitor testing was performed, a wash out phase of or at least 3-4 days, but preferably 7 days was to be allowed. However, if an inhibitor was suspected, a minimum wash-out phase of 7 days was required. Patients developing an inhibitor during the study were to remain in the trial and be followed up to establish the nature of the inhibitor (e.g. transient, low responder, high responder). A cutoff point of 0.6 Bethesda inhibitor assay units (BIAU) was used for this study. Positive results for inhibitor development were to be confirmed by a second assay. If the results of the second test and the determination of recovery gave no clear results, samples were to be investigated in a second reference laboratory.

The type of mutation of the FVIII gene was determined as an unstated exploratory endpoint because previous studies have indicated that there is a relationship between inhibitor development and the FVIII mutation type [6].

6.2.9 Statistical Considerations & Statistical Analysis Plan

Since the presence of inhibitors to FVIII has a major impact on the treatment efficacy of any factor FVIII containing product, the primary efficacy endpoints were also analyzed for the following two subgroups of patients from the efficacy population:

- inhibitor patients,
- non-inhibitor patients.

The Cmax, Cmax-norm and recovery of FVIII were calculated for subjects who did not develop an inhibitor (N=20) and for subjects who developed an inhibitor (N=8) based on both the nominal and the actual potencies of the WILATE® batch infused (see Table 20 from TMAE-103 Study Report).
Efficacy assessments per treatment with WILATE® and duration of treatment of bleeding episodes were also compared for subjects with and without inhibitors.

Data management and statistical analysis were performed by (b) (4) using SAS.

This was a single-arm, open-label trial in which descriptive statistical methods (frequency distributions, descriptive statistics and figures) were to be used to analyze the data. Efficacy and safety analyses were to be based on all patients treated with WILATE® (intention-to-treat approach) with the additional possibility of performing a per-protocol analysis if there were many deviations from the protocol.

Complete individual data listings containing all reported data were to be produced. Logistic regression analyses were to be performed in addition to assess the influence of potential prognostic factors (dose, family history of inhibitors, use of other blood products) on the occurrence rate

No sample size calculation was made for this study. The planned sample size of 25 patients to be enrolled in the study complies with the recommended sample size of at

least 20 patients as given in the CPMP guidelines on clinical trials with factor VIII. The protocol recruitment of additional subjects if considered statistically necessary.

6.2.10 Study Population and Disposition

Twenty-nine subjects were enrolled in this study, one of whom did not receive WILATE® and was excluded from all further analysis. The 28 remaining subjects were all treated with WILATE® and were included in the safety analyses. Two subjects were removed from the study; one due to death (motor vehicle accident) and one due to a disqualifying transfusion before entry into the study, which was only discovered later.

6.2.10.1 Populations Enrolled/Analyzed

The Applicant planned to conduct efficacy and safety analyses on all subjects treated with WILATE ("intention to treat"), with the option to analyze results in subjects treated per protocol, in the event of numerous protocol deviations. At the end of the study, one of 29 subjects enrolled did not receive WILATE® and was not included in the analyses of efficacy and safety. Two other subjects discontinued early from the study, one for a fatal motor vehicle accident and another for a disqualifying history discovered after study entry, were included in the safety analyses.

At the end of the study, all 28 subjects treated with WILATE ("modified intention to treat") were included in all efficacy and safety analyses.

6.2.10.1.1 Demographics
All 29 subjects (100%) enrolled in TMAE-103 were Caucasian.

The age, body height, and body weight of the 28 subjects analyzed in the safety/efficacy analysis set are listed in Table 28 below, modified from Table 2 in Section 14.1 of the TMAE-Study Report (page 76):

Table 28: Statistics on age, body height and body weight

Parameter	N	Mean (±SD)	Median	Range
Age (yrs)	28	1.36 (± 1.55)	0.90	0 - 7.5
Age (mos)	28	15.93 (± 18.39)	10.5	0 - 89
Height (cm)	28	78.23 (± 17.95)	74.5	51.0 - 130.0
Weight (kg)	28	10.85 (± 5.47)	9.69	2.80 - 29.0

6.2.10.1.3 Subject Disposition
Twenty-nine subjects were enrolled in the study. Three were withdrawn: one for a fatal motor vehicle accident, another who did not commence treatment with WILATE®, and a third who had a blood transfusion at birth that was not discovered until age 4 months. See Table 10 from the TMAE-103 Study Report:

10.1 Disposition of Subjects

A total of 29 subjects from 7 centres were enrolled into the study. One subject (b) (6) did not receive treatment with WILATE during his participation in the study and has thus been excluded from both safety and efficacy analyses. (b) (4) during the study. The distribution of subjects between centres and disposition in analysis groups is shown in Table 5.

Table 5 Disposition of Subjects in Analysis Groups

Centre	No. of Subjects Enrolled	Safety Evaluable	Efficacy Evaluable	(b) (4)
B	1	1	1	(b) (4)
E	8	8	8	
F	3	3	3	
G	8	8	8	
H	6	5	5	
I	1	1	1	
L	2	2	2	
Total	**29**	**28**	**28**	

Source: Section 14.1, Table 1 and Section 16.2.3, List 1

Three subjects were withdrawn from the study prematurely.

(From Page 25 of TMAE-103 Study Report)

6.2.11 Efficacy Analyses

Hemostatic efficacy was measured as a secondary objective of this study and was assessed after each infusion of WILATE® by the physician (for hospital treatment) or the patient's parent or guardian (for home treatment) with a four-point rating scale of "none", "moderate", "good", or "excellent", as listed in Table 12 from the TMAE-103 Study Report.

Table 12 Efficacy Assessment by Reason of Administration (N=28)

Reason for treatment	Efficacy Assessment				Total No. of Injections N (%)
	Excellent N (%)	Good N (%)	Moderate N (%)	None N (%)	
Prophylaxis	635 (71.8)	250 (28.3)	0 (0.0)	0 (0.0)	885 (100.0)
Haemorrhage	264 (20.8)	995 (78.3)	10 (0.8)	2 (0.2)	1,271 (100.0)
(b) (4)	33 (55.0)	27 (45.0)	0 (0.0)	0 (0.0)	60 (100.0)
Study related (recovery)	30 (38.0)	49 (62.0)	0 (0.0)	0 (0.0)	79 (100.0)
Prophylaxis + other	3 (50.0)	3 (50.0)	0 (0.0)	0 (0.0)	6 (100.0)
Haemorrhage + other	8 (47.1)	6 (35.3)	2 (11.8)	1 (5.9)	17 (100.0)
(b) (4) study related	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Total	**973 (42.0)**	**1,331 (57.4)**	**12 (0.5)**	**3 (0.1)**	**2,319 (100.0)**

Source: Section 14.2.1, Table 19

A total of 2,319 infusions were administered, all of which were assessed. In all, 99.4% of infusions were rated as having excellent or good efficacy with only 3 infusions (0.1%) rated as having no efficacy, as they were administered to subjects with inhibitors.

Reviewer Comments: *The assessment of hemostatic efficacy is always problematic in hemophilia clinical trials, since both the quantitation of bleeding events by subjects with hemophilia and the evaluation of efficacy on the traditional 4-point efficacy scale by Investigators are subjective. In this study, there was no systematic attempt to capture the annualized bleeding rate for subjects treated with WILATE, nor any pre-specified ABR to use as a comparator to test a formal statistical hypothesis. Further, subjects were not formally assigned in any clear way to be treated with a pre-specified prophylaxis regimen. The collection of subjective efficacy assessments by the Investigators results in "Excellent" or "Good" hemostasis in virtually all (>99%) of treatments administered, which seems implausible, and there does not appear to be any formal process of auditing these assessments by study monitors as there was for the PTP study in adults and adolescents (WIL-27). The data as presented in TMAE-103 can only serve as supporting evidence of efficacy in children, and only from ages 0-6 years of age.*

6.2.11.1 Analyses of Primary Endpoint(s)

The primary objective of the study was to determine the immunogenicity of WILATE® in previously untreated patients (PUPs) with hemophilia A.

The primary endpoints therefore are the factor VIII inhibitor titers measured every 3 to 4 exposure days until the 20th exposure day and thereafter every 10th exposure day or every 3 months, (whichever was the soonest) using the Bethesda inhibitor assay, with the (b) (4)

Reviewer Comment(s): *The time points for factor VIII inhibitor antibody surveillance are appropriate, since the development of inhibitors is typically seen in the first 10 exposure days of treatment. The Bethesda inhibitor assay* (b) (4) *is the standard assay for measuring factor VIII inhibitors.*

6.2.11.2 Analyses of Secondary Endpoints

Limited pharmacokinetic evaluation in the form of a factor VIII recovery determination 15 minutes and one hour after the WILATE® dose was performed as part of this study. At least one recovery determination was performed for 22 out of 28 subjects (78.6%). Thirteen subjects had a second recovery performed, 8 subjects a third recovery and multiple subjects had further recoveries performed up to a maximum of 14 (1 subject only). Recoveries were deemed valid if at least one post-infusion measurement was available, even if a baseline measurement was not obtained. Statistics on the post infusion level of FVIII for the first 5 recovery determinations are given in Table 7 from the TMAE-103 Study Report.

Table 7 Statistics on FVIII Concentrations [%] (N = 28)

Recovery No.	Time Point	N	Mean ± SD	Mean Geom. ± SD	95% Conf limits	Median	Range
1	Pre-infusion	20	0.00 ± 0.00	-	-	0.00	0.00 – 0.00
	15 min	21	72.28 ± 62.44	52.36 ± 2.89	32.32; 84.84	57.00	0.00 – 252.00
	1 hour	22	55.77 ± 47.27	41.85 ± 2.88	26.18; 66.90	48.50	0.00 - 226.00
2	Pre-infusion	13	1.31 ± 4.71	17.00	-	0.00	0.00 – 17.00
	15 min	13	48.15 ± 31.32	45.10 ± 1.76	32.02; 63.53	38.00	0.00 – 104.00
	1 hour	13	45.08 ± 28.86	42.55 ± 1.75	30.34; 59.67	46.00	0.00 – 110.00
3	Pre-infusion	8	0.00 ± 0.00	-	-	0.00	0.00 – 0.00
	15 min	8	53.25 ± 26.95	48.17 ± 1.59	32.64; 71.09	41.00	27.00 - 99.00
	1 hour	8	39.63 ± 26.38	33.38 ± 1.84	20.00; 55.69	30.50	14.00 – 91.00
4	Pre-infusion	8	0.13 ± 0.35	1.00	-	0.00	0.00 – 1.00
	15 min	7	31.71 ± 35.77	36.57 ± 1.93	19.95; 67.03	25.00	0.00 – 105.00
	1 hour	8	37.50 ± 43.36	33.19 ± 1.93	19.15; 57.54	26.50	0.00 – 142.00
5	Pre-infusion	7	0.00 ± 0.00	-	-	0.00	0.00 -0.00
	15 min	7	44.86 ± 33.83	45.28 ± 1.82	25.98; 78.90	36.00	0.00 – 93.00
	1 hour	7	35.43 ± 27.30	36.31 ± 1.73	21.93; 60.12	28.00	0.00 – 86.00

Source: Section 14.2.1, Table 1

6.2.11.4 Dropouts and/or Discontinuations

Three subjects were withdrawn from the study for various reasons, as below.

- Subject (b) (6) suffered a fatal AE because of a head injury in a car accident.
- Subject (b) (6) was enrolled in July 2002 but was never treated with WILATE®. He did not attend for regular follow up visits after April 04 so in September 2005 he was withdrawn from the study.
- Subject (b) (6) received a blood transfusion 2 days after birth but the investigator was not aware of this when he was entered into the study. The information came to light when the subject was 4 months old, at which point he was withdrawn from the study.

6.2.11.5 Exploratory and Post Hoc Analyses

No exploratory analyses were performed for this study.

6.2.12 Safety Analyses

6.2.12.1 Methods

The primary objective of study TMAE-103 was to assess the immunogenicity of WILATE® in PUPs with severe hemophilia A. Neutralizing antibodies to factor VIII ("inhibitors") are an adverse event of special interest for factor VIII products and are reviewed before review of adverse events in general, for all 28 TMAE-103 PUP subjects who were treated with at least one dose of WILATE®.

6.2.12.2 Overview of Adverse Events

Factor VIII Inhibitors. Eight subjects (28.6%) developed FVIII inhibitors during the study (Table 28, from the TMAE-103 Study Report). One subject (b) (6) developed an inhibitor which was transitionally undetectable but reappeared 3 months later (Section 16.2.8, List 1).

Table 28 Characteristics of Subjects developing FVIII Inhibitors

Subject No.	No. of Exposure Days Prior to Inhibitor Detection	Nature of FVIII Gene Defect	Maximum Inhibitor Titre (BU)	Last Inhibitor Result (BU)
(b) (6)	3	Intron 22 inversion	33.0	24.0
	8	Intron 22 inversion	54.0	11.0
	13	Intron 22 inversion	1.6	*
	4	Small deletion (C. 6375 Delt)	1.7	<0.6
	45	Intron 22 inversion	0.6	<0.6
	7	Intron 22 inversion	2.6	<0.6
	9	Exon 24 (6682C > T R2209X)	1.6	<0.6
	25	Intron 22 inversion	33.0	10.0

*no follow up, subject died of non-related cause.

Source: Section 16.2.8, Lists 1 and 4 and 16.2.9 List 1.

Twenty-six subjects experienced at least one adverse event, each, for a total of 141 adverse events.

Adverse events by MedDRA organ system are summarized in Table 26. from the TMAE-103 Study Report.

Table 26 Adverse Events by MedDRA Coded Term Where an Event was Experienced by ≥ 10% of Subjects

MedDRA Primary SOC	Preferred Term	No. of Subjects (%)	No. of Events
Infections and Infestations	Nasopharyngitis	9 (32.1)	19
	Pharyngitis	5 (17.9)	5
	Varicella	4 (14.3)	4
	Rhinitis	3 (10.7)	3
	Tracheitis	3 (10.7)	4
Blood and Lymphatic System Disorders	Factor VIII Inhibition	8 (28.6)	9
	Iron Deficiency Anaemia	7 (25)	7
	Anaemia	5 (17.9)	5
Vascular Disorders	Haematoma	3 (10.7)	3
Respiratory, Thoracic and Mediastinal Disorders	Cough	3 (10.7)	5
Reproductive System and Breast Disorders	Phimosis	3 (10.7)	3
General Disorders and Administration Site Conditions	Pyrexia	3 (10.7)	5
Investigations	Parvovirus B19 Serology Positive	14 (50.0)	14

Source: Section 14.3.2, Table 1

6.2.12.3 Deaths

One death occurred during the study. Subject (b) (6) died on (b) (6) because of head trauma sustained in a car accident. The subject was hospitalized and treated with WILATE® but died several hours later. The autopsy described the cause of death as fracture of the occipital bone resulting in cerebral hemorrhage.

6.2.12.4 Nonfatal Serious Adverse Events

11 subjects (39.3%) experienced at least one SAE; there were a total of 16 SAEs, all categorized as *not* related to treatment with WILATE®.

Table C1, adapted from data in Tables 2 and 3 of section 14.3.2 of the TMAE-103 Study Report, is found in APPENDIX C, and lists the individual SAEs. These consist largely of bleeding events and seemingly unrelated issues like proctitis and phimosis, for instance.

Reviewer Comments: *The pattern of SAEs does not raise any special concerns about product safety. It appears that most of the hospitalizations were not due to severity of the condition, rather the need for reliable intravenous access; some of these would not have resulted in hospitalization for adults with severe hemophilia A who were practiced in self-administration of factor VIII. I agree that none were attributable to the product, and some such as paraproctitis, periostitis, or phimosis are unlikely related to hemophilia A or its treatment in any event. The fatality due to head trauma suffered in a motor vehicle accident is not attributable to safety of the product.*

6.2.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest to the FDA for plasma-derived factor VIII concentrates include inhibitor antibodies to factor VIII, and seroconversion for viral pathogens.

Inhibitors to Factor VIII. Eight subjects (28.6%) developed FVIII inhibitors during the study (Table 28). One of these subjects (b) (6) developed an inhibitor which was transitionally undetectable but reappeared 3 months later (Section 16.2.8, List 1).

The characteristics of the subjects who developed inhibitors and the titer of the inhibitor are listed in Table 28 of the TMAE-103 Study Report. Three of the eight inhibitors were high titer (> 5 BIAU), and five were low titer inhibitors (< 5 BIAU). Three were persistent, four were transient (resolved to < 0.6 BIAU), and the persistence of one low titer inhibitor remains unknown, since the subject died, and no further follow-up was possible. Five developed within 10 exposure days, and three developed between 10 and 50 exposure days; the range of exposure days for development of inhibitors was 3-34 days (median 8.5 exposure days). Six of eight subjects with inhibitors had the common intron 22 factor VIII gene inversion that is a common cause of severe hemophilia A; two had mutations that predict truncated proteins that are more likely to be associated with inhibitors.
Reviewer Comments: *Factor VIII inhibitors commonly develop in 25-30% of severe hemophilia A patients who commence factor VIII replacement therapy, most within 10 exposure days, and nearly all within 50 exposure days.*

A long-standing question is whether factor VIII inhibitors are more common in patients treated with recombinant factor VIII concentrates as compared to plasma derived concentrates. A higher rate of inhibitor development has long been noted in subjects involved in licensure trials for recombinant factor VIII products. The argument has been made that since recombinant products were licensed more recently with more rigorous surveillance for inhibitors than plasma-derived concentrates, the higher frequency of low-titer inhibitors and/or transient inhibitors is a consequence of the clinical trial design, rather than a property of the products, themselves.

A randomized trial was done to assess the inhibitor rate in previously untreated patients with severe hemophilia A (SIPPET Study) and was recently published (Peyvandi, 2016. The results indicate that inhibitors developed in 29 of 125 subjects treated with plasma-derived factor VIII (26.8%, 95% CI:18.4, 35.2%) and 47 of 126 subjects treated with recombinant factor VIII (44.5%, 95% CI:34.7%,54.3%) developed inhibitors. Of the subjects with inhibitors from plasma-derived factor VIII, 20 (16%) were high titer inhibitors, and for subjects who took recombinant products 30 (23.8%) were high titer inhibitors.

The plasma-derived products were Alphanate and Fanhdi (manufactured by Grifols), Emoclot (manufactured by Kedrion Biopharma), and Factane (manufactured by LFB), all of which contained von Willebrand factor, like WILATE®.

The observed incidence of inhibitors for WILATE® (28.6%) was comparable to that seen in the SIPPET study, and the rate of the more important high-titer inhibitors (10.7%) was less than that seen in the SIPPET study. If we were to assume that the one subject who died during the trial were to have developed a high titer inhibitor, the incidence would have been 14.7%, still within the rate observed by the SIPPET investigators for von Willebrand factor-containing factor VIII concentrates.

The observed inhibitor rate in the TMAE-103 PUP study is reassuring that the product is no more likely to induce inhibitors than similar plasma-derived products.

Seroconversion for Viral Pathogens. The 28 subjects who received WILATE that are included in the safety analysis were evaluated for HIV, hepatitis A, hepatitis B, and parvovirus antibodies. There were no positive HIV serologies in any subject at any time point. None had been vaccinated against hepatitis A and 17 had been vaccinated against hepatitis B at baseline. During the study, 18 subjects were vaccinated against hepatitis A and 11 subjects were vaccinated against hepatitis B. Immune status was monitored in this study for these viral pathogens.

Table 30, from the TMAE-103 study report lists the details of seroconversions to these three viral pathogens.

Table 30 Negative to Positive Changes in Virology Results (N=28)

Parameter	N	Comments
Anti-HAV IgG	8	All correspond to vaccination against HAV
Anti HAV IgM	1	Corresponds to vaccination against HAV
Anti-HBs	11	All correspond to vaccination against HBV
Parvovirus B19 IgG	17	Fourteen seroconversions (see Table 27); One subject had single positive result, two subjects had equivocal results followed by negative results.
Parvovirus B19 IgM	10	Eight cases were in subjects who seroconverted for B19 IgG; two cases were positive for B19 IgG at baseline.

Hepatitis A and hepatitis B seroconversions all corresponded to vaccination or re-vaccination against the specific viral pathogens.

Changes in IgG antibody to parvovirus B19 status from negative to positive occurred in 17 subjects for IgG or 10 subjects for IgM. No subject was symptomatic for parvovirus infection during the protocol. The Applicant describes 14 of these events as seroconversions and describes three others as non-seroconversions to parvovirus B19.

The non-seroconversions include:

- (b) (6) who was negative at baseline but positive at visit 2, and negative for IgG antibodies to parvovirus B19 thereafter and was always negative for IgM antibodies to parvovirus B19 at all time points.
- (b) (6) who always tested negative except at visit 19 when an equivocal positive result was obtained.
- Subject (b) (4) tested negative for IgG antibodies except at visits 9 and 10 when equivocal positive test results were obtained; 5 subsequent tests were negative for IgG antibodies and IgM antibodies were negative for all time points.

Reviewer Comments: *Parvovirus is endemic, and community acquired infection naturally occurs in children of the ages who participated in the TMAE-103 study of PUPs with severe hemophilia A. It is also the virus category least susceptible to viral inactivation measures during manufacturing; in contrast to most viruses for which viral inactivation procedures eliminate at least 10 $logs_{10}$ of viral infectivity, the inactivation of parvovirus eliminates at most ~4 $logs_{10}$. I find it much more plausible that the 14 seroconversions documented in TMAE-103 were from natural, community-acquired infection rather than infection with parvovirus B19 in WILATE®. In any event, symptomatic parvovirus infection is a mild, self-limited event in those who become infected by any means (natural or transfusion with blood products).*

6.2.12.6 Clinical Test Results

The only abnormal laboratory test results encountered during the TMAE-103 study were low factor VIII levels, long aPTT times, mild anemia (7 findings in 3 subjects undergoing (b) (4) , and variable prolongations of the prothrombin time (6 events in 1 subjects) in (b) (4) subjects. The study protocol did not require the documentation of vital signs.
Reviewer Comments: *The laboratory study abnormalities documented in study TMAE-103 are marginal and not concerning for serious safety concerns.*

6.2.12.7 Dropouts and/or Discontinuations

Three enrolled subjects were removed from study TMAE-103 prematurely. One received no treatment with WILATE®. Another was discovered after enrollment to have had a disqualifying blood transfusion shortly after birth, not disclosed at the time of enrollment. Another died of head injuries sustained in a motor vehicle accident. None of these were due to adverse events that could be attributed to use of WILATE®. All data from all treated subjects was incorporated into analyses of efficacy and safety.

6.2.13 Study Summary and Conclusions

SUMMARY OF STUDY TMAE-103*: Twenty-nine PUPs with severe hemophilia A ages <1 month to 7.5 years treated with at least 50 exposure days over at least 2 years on prophylaxis or on demand. One subject died as the result of an automobile accident due to head injuries during the study. 99.8% of 2319 infusions were evaluated as having good or excellent efficacy (non-inhibitor subjects). Eight of 28 evaluable subjects (28.6%) developed inhibitors. Of the inhibitors, 4 (14.3%) were transient low titer inhibitors that disappeared with continued use of WILATE®, 3 (10.7%) were high titer inhibitors, and 1 (3.6%) was in the last sample drawn before death from an automobile accident. There were 14 asymptomatic seroconversions for parvovirus B19 in subjects on the trial. Twenty-two subjects underwent at least one recovery study that showed an overall recovery of 1.17 IU/dl per IU/kg administered (1.36 for non-inhibitor subjects, 0.66 for inhibitor subjects).* (b) (4)

Reviewer Comments: *The preliminary findings from TMAE-103 suggests efficacy per the Investigators using the typical 4-point hemostasis evaluation scale, however the design of the study is insufficient to support an indication in the pediatric population. Definitive pediatric studies are ongoing. The safety concerns of special interest are inhibitor development and viral seroconversions. The incidence of all inhibitors in TMAE-103 (26.8%) was exactly that seen in the SIPPET study(Peyvandi et al, NEJM 2016) for two other plasma-derived factor VIII concentrates with von Willebrand factor. The rate of high titer inhibitors (10.7%) was less than that seen in the SIPPET trial 18.6% (95% CI,*

11.2 to 26.0) and 28.4% (95% CI, 19.6 to 37.2), respectively. If the inhibitor subject with one determination were to be treated as if it were a high titer inhibitor, the high titer rate would be 14.3%, still within the confidence interval for the high titer inhibitor group observed in the SIPPET study. The viral seroconversions were for parvovirus B19, not clearly due to the treatment with WILATE®, and more likely contracted from the community than the study item, given the age of the subjects in the study. Thus, in the PUP study, WILATE® appears to be safe. The interpretation of efficacy is limited by the deficiencies in the design of the study as discussed in Section 6.2.11.

6.3 Trial #3

(b) (4)

11 pages determined to be not releasable: (b)(4)

(b) (4)

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Routine prophylaxis of bleeding in hemophilia A in adults and adolescents.

Reviewer Comments: *Applicant asks for routine prophylaxis indication in adults and pediatric patients with hemophilia A, but routine prophylaxis is only systematically studied and clearly supported in adults and adolescents in the WIL-27 PTP study. The data on routine prophylaxis in children under 12 years of age in legacy study TMAE-103 is insufficient to grant a routine prophylaxis indication in children <12 years of age due to assignment to routine prophylaxis at discretion of Investigators, the small number of subjects studied on routine prophylaxis (4 or 5), the lack of children studied for routine prophylaxis between 6 and 12 years of age, and non-systematic collection of data on annual bleeding rates. Nearly all analysis of routine prophylaxis will focus on the WIL-27 pivotal study.*

7.1.1 Methods of Integration

Data from Trial 1 (WIL-27) is considered alone to determine the efficacy of routine prophylaxis in adults and adolescents with hemophilia A with WILATE®, since it is unclear which subjects in Trial 2 (TMAE-103) were on routine prophylaxis and no ABR was calculated. Trial 2 provides supporting evidence for the safety of WILATE® in adolescents with hemophilia A, treated prophylactically or on demand. Trial 2 also provides limited pharmacokinetic data in children < 12 years of age that lends support to the observation that adolescents have a lower recovery of WILATE® than adults. Trial 2 also provides insights into the effect of inhibitor antibodies on factor VIII recovery, which was not encountered in Trial 1. See discussion in Section 7.1.10 Additional Efficacy Issues/Analyses.

7.1.2 Demographics and Baseline Characteristics

All subjects (n = 55) in Trial 1 (WIL-27) were Caucasian adults (n = 50) or adolescents (n = 5) with severe hemophilia A with at least 150 exposure days to other factor VIII products, as reviewed in Section 6.1. Conversely, all subjects (n =29) in Trial 2 were Caucasian children < 12 years of age with severe hemophilia A and no prior factor VIII exposure.

7.1.3 Subject Disposition

In Trial 1 there were 57 subjects were enrolled, of which two were not treated with WILATE® (one due to inability to travel to the study site, and one due to withdrawal of consent); these two subjects were not included in any analysis. The full analysis set (FAS) included 55 subjects, of which 52 were treated per protocol (PP). The three excluded from the per-protocol (PP) population set included a patient, who also withdrew

from the study, with less than 50 exposure days, one had non-compliance in completing the patient diary and a treatment gap of >7 days, and another with a treatment gap of >7 days Twenty-one underwent pharmacokinetic analysis (PK dataset), and one underwent surgery. Fifty-four subjects completed the study, and one dropped out. The safety analysis set (SAF) included the 55 subjects who were treated with at least one dose of WILATE®; this subset includes the same subjects found in the full analysis set (FAS).

In Trial 2 only one of 29 subjects enrolled did not receive WILATE® and was not included in the analyses of efficacy and safety. Two other subjects who were discontinued (one for a fatal motor vehicle accident and another for a disqualifying history discovered after study entry), were included in the safety analyses.
Reviewer comment: *Trial 1 enrolled enough adults and adolescents to reach the desired number of subjects treated. The completion rate (54/55) and limited number of dropouts (1/55) suggests that there was no major bias from subjects enrolled and not treated, or treated and discontinued from the study. The PP population (n = 52) lost only three subjects from the FAS group (n = 55). Trial 2, though not informative with respect to the routine prophylaxis indication, likewise had only minimal attrition. Neither trial suffers from losses of recruited subjects that raise concerns about bias.*

7.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for determination of the efficacy of routine prophylaxis against bleeding with WILATE® is the bleeding rate, expressed as the number of bleeding episodes that occur during a period of routine prophylaxis. This is normalized to the number of bleeding events per year, or the ABR. This has been the standard by which all modern licensed factor VIII concentrates have been licensed for routine prophylaxis in hemophilia A. The two variants of the ABR are the spontaneous ABR (SABR), which counts only bleeding episodes that occur spontaneously, and the total ABR (TABR), which counts all bleeding episodes, traumatic or spontaneous. Though traumatic bleeding events are not the “fault” of a hemostatic product and should not be counted as a failure of the product, it is important to assess the TABR is so that Applicants cannot try to reclassify spontaneous bleeding events as traumatic, to improve the assessment of their product. The TABR is always higher than the SABR, since it includes all bleeding events, regardless of cause.

Trial 1 study results (listed in Table 9, in Section 6.1.11) indicate an overall TABR of 2.21 for all subjects (n = 55), a TABR of 2.39 for adult subjects (n = 50) and a TABR of 0.4 (n =5) for adolescents. The SABR values for all subjects, adults, and adolescents were 1.52, 1.67, and 0, respectively. These values compare favorably with annualized bleeding rates seen for other factor VIII concentrates and emicizumab, listed in Table 3 of this review in Section *2.2.*
Reviewer Comment(s): *As expected, the TABR for each group are greater than the associated SABR. Also, adults have higher ABRs than the adolescents, likely due to long-standing joint damage prior to enrollment on the study. The sample size for adolescents (5) is a limitation of the efficacy data in this population, but the results in the adult population allows for extrapolation of efficacy results to the adolescent population. Further, the pharmacokinetic studies in Trial 2 in children < 12 years of age support the dosing of Notwithstanding its limitations, the data from Trial 1 are enough to demonstrate the clinical benefit of WILATE® given as routine prophylaxis for bleeding in hemophilia A.*

7.1.5 Analysis of Secondary Endpoint(s)

The secondary endpoints that are pertinent to the routine prophylaxis indication are the immunogenicity of WILATE® during routine prophylaxis, the pharmacokinetic studies performed at baseline and after six months of routine prophylaxis, the safety and tolerability of WILATE®, and the effect of ABO blood type and half-life of factor VIII. These were all studied formally in detail in Trial 1; Trial 2 provided supporting evidence for pharmacokinetics and safety of WILATE® in children and did not formally assess the other endpoints.

No factor VIII inhibitors developed during routine prophylaxis on Trial 1, and the product was well-tolerated with few adverse events noted. Two cases of thrombocytosis in adolescent subjects were observed, which were self-limited and asymptomatic. These will be mentioned in the label as findings in Trial 1.

ABO blood group did not seem to have an important effect on the factor VIII half-life in Trial 1 and was not studied formally in Trial 2.

The pharmacokinetic findings in Trial 1 and Trial 2 are discussed in detail in Section 7.1.10 Additional Efficacy Issues/Analyses.
Reviewer Comment(s): *The secondary endpoint analyses for Trial 1 and Trial 2 (pharmacokinetics) support the safety and efficacy of WILATE® for routine prophylaxis in adults and adolescents. I do not think that WILATE® was the likely cause for transient thrombocytosis in the two adolescents in Trial 1, and this finding requires nothing more than mention in the label.*

7.1.6 Other Endpoints

An exploratory endpoint to consider in Trial 1 was the subjects' historical experience, which was an exploratory, post-hoc analysis. The mean TABR of 2.39 ± 3.77 for 50 adults in Trial 1 was significantly better than their historical TABR of 36.24 ± 39.59 ($P < 0.0001$). The five children in Trial 1 had one bleed in the six-month study period amongst them (mean TABR = 0.4), which was exactly what was observed in the historic TABR for this group. The group was too small to draw any conclusion on this data point.
Reviewer Comment(s): *This exploratory endpoint lends support to the claim of therapeutic benefit of routine prophylaxis with WILATE® and gives a context for the highest outliers in Trial 1, who were adults with pre-existing joint damage and a history of frequent bleeding events, which were reduced significantly by routine prophylaxis.*

7.1.7 Subpopulations

Subpopulation analysis in this study included adult vs. adolescent age groups and the effect of ABO blood group on pharmacokinetics.
Age Subpopulation Analysis:
Adults (n = 50) had higher recovery of factor VIII activity, TABR, SABR, and number of infusions per on-demand bleeding episode as compared to adolescents (n = 5). The higher number of bleeding events is likely due to higher rates of target joints and pre-existing joint damage, which accumulates over time in patients with hemophilia. The effect of age on in vivo factor VIII activity recovery has been explained by higher plasma volumes per kg of body weight in pediatric subjects. As noted in review of study TMAE-103 (28 pediatric subjects <12 years of age) the recovery is even less than that for adolescents, which is consistent with studies of other clotting factor concentrates.

ABO Blood Type Subpopulation Analysis:

The Applicant assessed the relationship between ABO blood type on WILATE half-life, a secondary efficacy endpoint. For adolescents, there was no significant effect of ABO blood type on WILATE half-life, and for adults there was a marginally significant effect of ABO blood on WILATE half-life (P = 0.03) for data compiled with the chromogenic assay (but not the one-stage assay, P = 0.18). As noted in Section 6.1.11.2 of this review, my analysis of SABR values for different blood groups was not significantly different, so this finding is of no apparent clinical importance.

Reviewer Comments: *Subgroup analysis does not suggest any important differences in efficacy according to subgroups that requires discussion in the label, aside from listing the clinical experience with adults and adolescents in Section 14 (CLINICAL EXPERIENCE).*

7.1.8 Persistence of Efficacy

Not applicable to these studies.

7.1.9 Product-Product Interactions

The use of additional factor VIII hemostatic agents was forbidden in Trial 1, and there was no use of anti-fibrinolytic or anti-retroviral agents in this study. The concomitant medications that were used in Trial 1 were a wide range of antibiotics, non-steroidal anti-inflammatory drugs, and allergy medications, primarily in single subjects.

Review Comment(s): *No conclusion can be reached with respect to interactions between WILATE® and other drug products.*

7.1.10 Additional Efficacy Issues/Analyses

Dosing of WILATE® is sometimes guided by factor VIII recovery as determined in pharmacokinetic studies. Pharmacokinetic studies in Trial 1 revealed a lower recovery of factor VIII in adolescents compared to adults. In general, in vivo recovery of coagulation factor activity is lower in children and adolescents than for adults due to higher plasma volumes per unit weight [Shapiro et al, *Haemophilia* 2005]. Although PK studies were optional in Trial 2, at least one recovery was performed in 22 subjects with 13 subjects having a second recovery performed and several having multiple recoveries up to a maximum of 14.

Inhibitor antibodies to FVIII were not observed in Trial 1 but are known to reduce the and efficacy of FVIII products. When pharmacokinetic data in Trial 2 were analyzed according to the presence of an inhibitor, a mean recovery of (b) (4) was found for subjects with inhibitors and (b) (4) for subjects without inhibitors.

Table 34: In Vivo Recovery for Adolescents and Adults, & Children (Trials 1 & 2)

Children < 12 years of age, with Inhibitors
(b) (4)
Children < 12 years of age, without Inhibitors
(b) (4)
Adolescents ≥ 12 < 18 years of age (n = 5)
1.66 ± 0.17 (n = 5)
Adults (≥18 years of age, n = 16)
2.27 ± 0.41 (n = 16)

Reviewer Comment(s): *The factor VIII recovery of* (b) (4) *from Trial 2 represents recovery in children less than 12 years of age. Although this recovery in children < 12 years differs from the recovery data obtained in Trial 1, in which factor VIII recovery of 1.66 ± 0.17 was observed for adolescents, and a factor VIII recovery of 2.27 ± 0.41 was observed for adults these results are consistent with the general observation that in vivo recovery of factor VIII activity decreases with decreasing age.*

7.1.11 Efficacy Conclusions

My review of the data from pivotal Trial 1 indicates that WILATE prevents bleeding in adults and adolescents with hemophilia A when administered 2-3 times weekly at a dose of 20-40 IU/kg. The evidence for this includes the overall TABR of 2.21 for all subjects (n = 55), a TABR of 2.39 for adult subjects (n = 50) and a TABR of 0.4 (n =5) for adolescents. The SABR values for all subjects, adults, and adolescents were 1.52, 1.67, and 0, respectively. These values compare favorably with annualized bleeding rates seen for other factor VIII concentrates and emicizumab, listed in Table 3 of this review in Section 2.2. These endpoints exceed all previously agreed upon target to reduce annualized bleeding rates to 50% of the observed historical bleeding rates for the Nuwiq recombinant factor VIII concentrate that was administered on-demand.

7.2 Indication #2

On-demand treatment and control of bleeding episodes in adults and adolescents with hemophilia A.

Reviewer Comments: *Applicant asks for on-demand indication in adults and pediatric patients. On demand treatment is clearly supported for adults and adolescents by results of Trial 1 (WIL-27 PTP) study, and there is some supporting data in Trial 2 (legacy PUP study TMAE-103) for safety and efficacy of on-demand treatment in children from 0-6 years of age. Only one child in the 6-12-year age group was studied in Trial 2. Integrated analysis of on-demand treatment will focus on Trial 1 and supporting data from Trial 2.*

7.2.1 Methods of Integration

Data from Trial 1 (WIL-27) is the primary basis for approval of the on-demand treatment indication, with support from Trial 2 (TMAE-103). Since Trial 2 was reported in 2008, we were provided with “legacy” data in the form of a study report and individual case report forms in PDF format (no CDISC data). The two trials studied different populations (adults and adolescents, vs. children < 12 years of age), so the data from Trial 2 could not be pooled with that from Trial 1. The data from Trial 2 should be considered complementary/supportive of the data from Trial 1, since it was collected in different patient populations, at different times, and with different methods.

Trial 2 also provides limited pharmacokinetic data in children < 12 years of age that lends support to the observation that adolescents have a lower recovery of WILATE® than adults and provides insights into the effect of inhibitor antibodies on factor VIII recovery, which was not encountered in Trial 1. See discussion in Section 7.1.10 Additional Efficacy Issues/Analyses.

7.2.2 Demographics and Baseline Characteristics

The demographic properties of Trials 1 and 2 are presented in Section 7.1.2 of this review.

7.2.3 Subject Disposition

See the description of subject dispositions for Trials 1 and 2, previously presented in Section 7.1.3 of this review.

7.2.4 Analysis of Primary Endpoint(s)

Not applicable to the on-demand treatment indication, which was a secondary endpoint of Trial 1 and Trial 2; see Analysis of Secondary Endpoints (Section 7.2.5 of this review).

7.2.5 Analysis of Secondary Endpoint(s)

The primary evidence for the efficacy of WILATE® comes from the Investigators' hemostatic efficacy rating as applied to 64 breakthrough bleeding events that occurred in Trial 1 during study of routine prophylaxis against bleeding. The overwhelming majority of bleeding events occurred in adults since routine prophylaxis was more effective in adolescents than adults; only one (traumatic) bleeding episode was documented in a single adolescent. Therefore, the data from Trial 2 where bleeding events were more commonly encountered, provides additional data that supports the extrapolation that WILATE® is effective for on-demand treatment of bleeding in adolescents.

Detailed assessments of data in Trial 1 for efficacy of on-demand treatment of bleeding in adults and adolescents with severe hemophilia A is provided in Section 6.1.11 of this review; see Tables 11 and 12 for listings of hemostatic efficacy ratings for bleeding events of different severity in the FAS (intention to treat) population and the PP (per protocol) population.

Trial 1 (WIL-27): Successful treatment included Investigator hemostatic ratings of "Excellent" and "Good" (success). For bleeds of all severity in the FAS population, 75% of episodes received a rating of "Excellent" or "Good". The success rate for this population varied according to the severity of the bleeding episode, and was 93% for Minor bleeds, 82% for Moderate bleeds, and 43% for Major bleeds. For the PP population, the successful rating was achieved in 84%, 93%, 88%, and 60% for All, Minor, Moderate, and Major bleeding events, respectively.

Reviewer Comments: *The analysis of hemostasis by the four-point scale is always problematic since it relies to some extent on a subjective analysis on the part of the Investigator. However, this analysis is reasonable as supporting data for the primary and secondary endpoints of this study of WILATE® efficacy. The observed trend for better results in Minor bleeding episodes (as opposed to Major bleeding episodes) is as expected, since the worst efficacy was observed in adult subjects with recurrent bleeds in target joints, and with higher (worse) baseline joint scores. Also, as expected, better results are seen in the PP population than the FAS population, due to better adherence to protocol-specified treatment with WILATE®. A limitation of Trial 1 with respect to on-demand treatment of bleeding is that there is only one bleeding episode treated in an adolescent subject (with "Excellent" results after one dose of WILATE®. Thus, assessment of on-demand treatment of bleeding requires support from Trial 2, in which*

there was not systematic routine prophylaxis, and in which there were more bleeding episodes were treated in children.

Trial 2 (TMAE-103): In Trial 2 there were 2319 injections of WILATE® for all purposes, including routine prophylaxis, on-demand treatment of bleeding, (b) (4) hemostasis, and various combined purposes. Of these infusions, 1271 were given for the stated purpose of treating hemorrhage Each infusion was assigned a hemostatic rating by the Investigator, parent, or guardian. These infusions were characterized by "Excellent" in 20.8% or "Good" hemostatic efficacy ratings in 78.3% of cases, for a combined success rate of 99%. It is not possible, from the legacy data presented in this study, to discern the number of *WILATE® infusions required to achieve hemostatic control in this trial*.
Reviewer Comments: *The analysis of hemostatic efficacy in children under 12 years of age in Trial 1 was limited by the non-systematic treatment, which was variably given as routine prophylaxis or on-demand at the discretion of the Investigator, as well as the lack of details on how efficacy ratings were reviewed and adjudicated, in contrast to Trial 1. One advantage of Trial 2 over Trial 1 is that subjects were followed for up to 2 years on this study. Taking all the limitations of this legacy study into account, results of Trial 2 for on-demand treatment of bleeding lends support to a labelling indication for on-demand treatment of bleeding in adolescents.*

7.2.6 Other Endpoints

See description of Other Endpoints in Section 7.1.6 of this review for a discussion of the pharmacokinetic properties of WILATE® in children < 12 years of age in Trial 2 and how this lends credence to the finding of lower in vivo recovery of factor VIII activity in adolescents compared to adults seen in Trial 1.

Additionally, Trial 2 also provides insight into immunogenicity of WILATE® in previously untreated patients (PUPs) with hemophilia A, which could not be studied in Trial 1. The overall factor VIII inhibitor rate in Trial 2 was 8/28 (29%) and the rate of high-titer inhibitors was 3/28 (10.7%). These values were consistent with those of the SIPPET study of immunogenicity of plasma-derived factor VIII vs. recombinant factor VIII inhibitors.

7.2.7 Subpopulations

Subpopulations were not analyzed in Trial 2.

7.2.8 Persistence of Efficacy

Not applicable to these studies.

7.2.9 Product-Product Interactions

See discussion of Product-Product interactions in Trials 1 & 2, in Section 7.1.9 of this review. In summary, no conclusions about product-product interactions can be made from the data in Trials 1 and 2.

7.2.10 Additional Efficacy Issues/Analyses

See Section 7.1.10 for previous discussion of pharmacokinetic data from Trials 1 and 2.

7.2.11 Efficacy Conclusions

My review of efficacy data from Trial 2 supports the conclusion that WILATE is effective for on-demand treatment of bleeding episodes in children under age 12 with severe hemophilia A. The lack of a defined routine prophylaxis regimen in the protocol and lack of systematic collection of data for annualized bleeding rates precludes any conclusion about the efficacy of WILATE for routine prophylaxis in this population. The efficacy data for on-demand treatment in children under 12 years of age may serve in this efficacy supplement to support the indication for on-demand treatment of bleeding in adolescents which was studied in Trial 1, but for which there is little data (due to the effectiveness of routine prophylaxis in the adolescent group studied).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

In both Trials 1 & 2, subjects underwent substantial exposure to WILATE® (>50 exposure days) and underwent routine physical examinations and clinical laboratory testing. Additionally, research subjects in both studies underwent specialized testing for adverse events of special interest to FDA, in particular surveillance for factor VIII inhibitors and seroconversion for blood-borne pathogens.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Table 34: Studies Used in Integrated Safety Analysis of WILATE® for Hemophilia

Study	Safety Population	Design	Treatment
Trial 1 (WIL-27, pivotal study)	55 treated PTPs with Severe Hemophilia A (ages 12-64 years)	Phase 3, multicenter, open label multicenter trial (Bulgaria, Hungary, Poland, Russia)	PK, Prophylaxis, and On-Demand Treatment
TMAE-103 (PUP study)	28 evaluable PUPs with Severe Hemophilia A (ages 0-89 months)	Phase 3, non-controlled, open label, multicenter trial (Russia, Belarus, Ukraine, Germany)	Prophylaxis or On-Demand Treatment at discretion of Investigator; PK optional

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 35: Product Exposure and Demographics of Subjects in Studies Used for Integrated Safety Analysis of WILATE for Hemophilia

Study	Number of Subjects	Exposure	Demographics
Trial 1 (WIL-27, pivotal study)	55 treated subjects	Six months of routine prophylaxis with 20-40 IU/kg WILATE® 2-3 times per week; at least 50 exposure days (median 82.3 injections,	All Caucasian PTPs 50 adults ≥18 years of age (18-64 yrs; median 35.5 yrs);

		mean total WILATE® exposure 2665.2 IU/kg) One major surgical procedure. A total of 4527 WILATE® injections, totaling 12,121,500 IU, were administered during the study period.	5 adolescents 12 to 18 years of age (median 13.6 yrs)
Trial 2 TMAE-103 (PUP study)	28 treated subjects	Up to 2 years of treatment with WILATE®, given either as prophylaxis or on-demand treatment at discretion of Investigator. Average of 70.5 exposure days per subject (range 3-246, total 1020 exposure days). (b) (4) A total of 2,319 infusions of WILATE® (1,633,600 IU, total) were administered to treat bleeding episodes, for prophylaxis (including study procedures) or for (b) (4).	All Caucasian PUPs 28 children ages 0-89 months of age

Reviewer Comment(s): *The exposure to WILATE® was substantial in both Trials 1&2 and the safety profile from these studies should reliably predict the safety of WILATE® use in hemophilia A in adults and adolescents.*

8.2.3 Categorization of Adverse Events

Trial 1 utilized MedDRA version 20.0 preferred terms for classifying adverse events. Table 34 in the WIL-27 Study Report lists all treatment emergent adverse events (TEAEs) by MedDRA terms which were observed during the study. All TEAEs were observed in one subject, except for thrombocytosis that was seen in two subjects (pre-existing, in both, though worsened and resolved during WILATE® in both cases.
Trial 2 utilized MedDRA version 9.0 preferred terms for classifying adverse events. Table 26 in the TMAE-103 Study Report lists all MedDRA adverse events which were observed in at least 10% of subjects.
Reviewer Comment(s): *Treatment emergent adverse events, in the two trials, were limited in number and quite similar in type despite being reported with different versions of MedDRA.*

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

Trial 1 was conducted in 2016-2018 in adult and adolescent previously treated patients, with systematic routine prophylaxis regimen specified in the protocol. Trial 2 was conducted from 2002-2007 in children less than 12 years of age who were previously untreated with factor VIII, and with no systematic approach to treatment. Trial 2 results were submitted in legacy PDF summary format and could not be readily combined with Trial 1 results submitted in CDISC format.

Reviewer Comment(s): *Pooling of data from Trial 1 and Trial 2 is problematic insofar as they were collected in different populations, at different times, in different ways, and submitted in different formats. However, these trials provide complementary data on different patient populations. Fortunately, both studies are relatively small (55 and 29 subjects for Trial 1 and Trial 2, respectively) and the adverse events observed are not numerous. The key adverse events of special interest to the FDA are the rate of inhibitor antibody development in PTPs (studied only in Trial 1) and transmission of blood-borne viral infections by WILATE®, which were not seen in either trial.*

8.4 Safety Results

8.4.1 Deaths

No deaths occurred in Trial 1, the pivotal (WIL-27) study of WILATE® for routine prophylaxis and on-demand treatment of hemophilia A in adult and adolescents with severe hemophilia A. There was one death of a one-year old boy in Trial 2, the study of previously untreated patients with hemophilia A due to open head trauma caused by an automobile accident. This was unrelated to use of the product. The only affect this had on the study was that this subject did not complete the required follow-up for inhibitor development. However, he had no inhibitor to factor VIII at the time of his death. This has no significant impact on evaluation of endpoints required for the indications sought.

8.4.2 Nonfatal Serious Adverse Events

There were no serious adverse events observed in Trial 1. In Trial 2, 11 subjects (39.3%) experienced a total of 16 SAEs, all categorized as unrelated to treatment with WILATE®.

See Table C1, adapted from data in Tables 2 and 3 of section 14.3.2 of the Trial 2 (TMAE-103) Study Report, which is found in APPENDIX C; this lists the individual SAEs. These consist largely of bleeding events and seemingly unrelated issues like proctitis and phimosis, for instance.

Reviewer Comments: *The SAEs in Trials 1 and 2 do not raise any product safety concerns. It appears that most of the hospitalizations in Trial 2 were not due to severity of the condition, rather the need for reliable intravenous access, which is a peculiarity of pediatric care. Some of these would not have resulted in hospitalization for adults with severe hemophilia A who were practiced in self-administration of factor VIII.*

8.4.3 Study Dropouts/Discontinuations

In Trial 1, 57 subjects were enrolled, and two dropped out for practical issues (problems traveling to the Study Site) before any WILATE® was administered. Of the 55 who were treated with at least one dose of WILATE®, two dropped before completing 50 exposure days of treatment, and between these two subjects there were not bleeding events during the time on study.

Per the Trial 1 (WIL-27) Study Report:
"One patient (b) (6) *had a TEAE (joint pain worsening) that was classified as probably related by the investigator. The TEAE led to discontinuation of study medication and discontinuation from the study upon patient's request. Following his IVR assessment at the beginning of the study on* (b) (6) *, this patient received nine prophylactic injections of 3000 IU (30.6 IU/kg) Wilate every other day until the 18-Jul-2017 (Appendix 16.2, List 16.2.6.1-2). The patient reported "worsening of joint pain", which lasted from the first day of his first Wilate exposure until 19-Jul-2017, one day after his last prophylactic injection of Wilate (Appendix 16.2, List 16.2.7-2). However, he did not report any BE during this period."*

All 55 subjects who received at least one dose of WILATE® were analyzed for adverse events (none lost to follow-up).

In Trial 2, 29 subjects were enrolled. One of the 29 subjects enrolled did not receive WILATE® and was not included in the analyses of efficacy and safety. Two other subjects discontinued early from the study, one for a fatal motor vehicle accident and another for a disqualifying history discovered after study entry, were included in the safety analyses.
***Reviewer Comment(s)**: The rate of dropouts was low, and in no case did it appear that any problem with the product was the cause for discontinuation. I agree with the Applicant that the worsening joint pain observed in subject* (b) (6) *(an adult with target joints prior to enrolling in Trial 1) is not likely to failure of the product; notably this subject reported no bleeding events during his participation in the study.*

8.4.4 Common Adverse Events

In Trial 1 there were no adverse events that occurred in more than 2 subjects. These included infections (n = 3), thrombocytosis (n = 2, both pre-existing, and resolved during treatment with WILATE®), seasonal allergy (n = 2), headache (n =1), eczema (n =1), arthralgia (n = 1), pain (n =1), and a limb injury during a surgical procedure.

In Trial 2 adverse events seen in at least 10% of subjects included a variety of infections (n =24), factor VIII inhibitors (n = 8), anemia (n =5), hematomas (n =3), cough (n = 3), fever (n = 3), phimosis (n = 3), and B19 parvovirus seroconversion (n =14, none symptomatic). See Table 26 in TMAE-103 Study Report.
***Reviewer Comment(s):** The common adverse events seen in pivotal Trial 1 were not particularly concerning. The thrombocytosis seen in two Trial 1 subjects will be mentioned in the label. In Trial 2, most common adverse events that were seen, except the factor VIII inhibitors, appear to be the typical maladies of childhood or features of hemophilia.*

8.4.5 Clinical Test Results

In Trial 1 two subjects had transient worsening of mild thrombocytosis that was pre-existing. In both subjects this resolved during continued routine prophylaxis with WILATE® with no specific treatment.

8.4.6 Systemic Adverse Events

Systemic adverse events were rare and non-serious in both Trial 1 and Trial 2.

8.4.7 Local Reactogenicity

One subject in Trial 1 had a single adverse event related to pain at the local site of administration, and no local reactions were reported in Trial 2.

8.4.8 Adverse Events of Special Interest

The key adverse events of special interest to the FDA are the rate of inhibitor antibody development in PTPs (studied only in Trial 1) and transmission of blood-borne viral infections by WILATE®.

Inhibitors:
No inhibitors were seen in the subjects in Trial 1 (adult and adolescent PTPs with 150 prior factor VIII exposure days) who completed six months of observation and experienced at least 50 WILATE® exposure days. This data, when pooled with data from other like subjects in previous clinical trials, resulted in no inhibitors in 83 pooled subjects. See Section 6.1.11.2 of this review for additional details.

Trial 2 was a study of WILATE® use in previously untreated patients (PUPs) with severe hemophilia A. WILATE® The overall factor VIII inhibitor rate in Trial 2 was 8/28 (29%) and the rate of high-titer inhibitors was 3/28 (10.7%).
Reviewer Comment(s): *The factor VIII inhibitor rate in PTPs (0/83) falls within FDA's advice on acceptable inhibitor rates in PTPs and was agreed upon in review of Trial 1 (WIL-27) statistical design prior to its initiation. Although results of PUP studies are not required for approval of a factor VIII product in adults and adolescents, it is worth noting that the data from Trial 2 was consistent with those of the SIPPET study of immunogenicity of recombinant factor VIII inhibitors.*

Transmission of Blood-Borne Pathogens:
In Trial 1 and Trial 2, no subjects seroconverted for serious blood-borne pathogens such as HIV, hepatitis, B, or hepatitis C. In Trial 1 53 of 55 subjects tested positive for B19 IgG antibodies at baseline screening and 2 of 55 subjects (both adolescents) were negative at baseline screening. The two adolescents who were negative at screening remained seronegative at the end of the study. In Trial 2, 50% of subjects seroconverted for antibodies to B19 parvovirus, though none were symptomatic for viral infection. Notably, the lots of WILATE that were used in subjects who seroconverted for B19 parvovirus were also used in subjects who remained seronegative throughout the course of the study.
Reviewer Comment(s): *No evidence of transmission of important viral diseases was seen in either Trial 1 or Trial 2. Seroconversion for B19 parvovirus that was seen in Trial 2 was unlikely to be due to contamination of the product since there were subjects who remained seronegative throughout the trial despite frequent exposure to the same lots as those who seroconverted. B19 parvovirus is an endemic, self-limited viral infection that is routinely acquired in the community in children. I think community acquired B19 parvovirus is most likely the culprit for the seroconversions seen in the children enrolled in Trial 2. I do not think this is an important safety signal.*

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not analyzed

8.5.2 Time Dependency for Adverse Events

Not analyzed

8.5.3 Product-Demographic Interactions

Not studied in these all-Caucasian study populations (Trial 1 and Trial 2)

8.5.4 Product-Disease Interactions

Not analyzed.

8.5.5 Product-Product Interactions

Since patients on other hemostatic products were excluded from Trials 1 and 2, product-product interactions were not analyzed.

8.5.6 Human Carcinogenicity
Not analyzed.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not analyzed.

8.5.8 Immunogenicity (Safety)

See Section 8.4.9 of this review for discussion of lack of factor VIII inhibitor development in Trial 1 (PTP study) and expected rate of factor VIII inhibitor development in Trial 2 (PUP study).

8.5.9 Person-to-Person Transmission, Shedding
Not analyzed.

8.6 Safety Conclusions

WILATE® does not appear to cause any serious or important adverse events, and there is no safety signal evident from review of Study 1 and Study 2 that prevents approval of WILATE® for the indications of routine prophylaxis and on-demand treatment of bleeding in adults and adolescents.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

WILATE® use during pregnancy was not studied in either Trial 1 or Trial 2, since all subjects in both studies were males with a sex-linked disease.

9.1.2 Use During Lactation

WILATE® use during lactation was not studied in either Study 1 or Study2, since all subjects in both studies were males.

9.1.3 Pediatric Use and PREA Considerations

In Trial 1 the Applicant has studied adult and adolescent (12-18 years of age) PTPs with severe hemophilia A, for the indications of 1. Routine prophylaxis to reduce the frequency of bleeding episodes, and 2. On-demand treatment and control of bleeding episodes. In this study they showed over a six-month study period of routine prophylaxis with 20-40 IU/kg WILATE® given intravenously 2-3 times per week that the annualized bleeding rate for five adolescents on the study was 0.4 per year for all bleeding events and 0 for spontaneous bleeding events (one subject had a single traumatic bleeding event). This was equal to their historic bleeding rates on other products and surpassed the pre-specified endpoint of a 50% reduction in historic bleeding rates observed for an on-demand trial (GENA-01) of a recombinant factor VIII product (Nuwiq). The single traumatic bleeding event encountered in an adolescent on this trial was successfully treated with one dose of WILATE®. Fifty other adult subjects on the same WIL-27 pivotal trial had annualized bleeding rates of 2.48 per year (total bleeding events) and 1.73 (spontaneous bleeding events), for comparison. No adolescent (or adult) developed a neutralizing antibody (inhibitor) to factor VIII during the trial and there were no serious adverse events in adolescents in this trial. Pharmacokinetics studies showed a lower in vivo recovery (2.03 vs 2.44 kg/dL), shorter half-life (10.59 vs. 11.06 hrs) and faster clearance (0.054 vs. 0.036 dL/h/kg) for adolescents compared to adults.

Trial 2 (TMAE-103) was a legacy study conducted in 2002-2004 and submitted in support of the submission by the Applicant. It studied the use of WILATE® in 29 previously untreated children with severe hemophilia A (PUPs) from ages 0-89 months. Routine prophylaxis was not studied systematically, and annualized bleeding rates were not assessed during this trial. Most children were between ages 1 and 2 years (n = 22), with one neonate (<1 month), five between ages 2 and 6 years, and one between ages 6 and 12 years. Due to the lack of systematic study of routine prophylaxis and the paucity of data for critical age groups from 2 up to 6 years and 6 up to 12 years, we cannot grant the indications of routine prophylaxis or on-demand treatment of bleeding to children less than 12 years of age.

The study of WILATE® in children less than 12 years of age will be fulfilled by WIL-30, which is a study of the use of WILATE® in 10 previously treated children with hemophilia A (PTPs) less than 12 years of age, with a study design analogous to that of Trial 1 (WIL-27). This study will likely provide data for future consideration of these indications in children less than 12 years of age.
Reviewer Comment(s): This information was presented to the Pediatric Review Committee (PeRC) on July 9, 2019, and the PeRC agreed with granting Octapharma a waiver for studies of PTPs with hemophilia under 1 year of age and deferring the study of children less than 12 years of age, to be fulfilled by WIL-30, now underway and nearing completion.

9.1.4 Immunocompromised Patients

Use of WILATE® in immunocompromised patients was not studied.

9.1.5 Geriatric Use

WILATE® was not studied in hemophilia A patients over the age of 65 years. The oldest subject in Trial 1 was 64 years of age.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not analyzed.

10. Conclusions

The safety and efficacy of routine prophylaxis and on-demand therapy with WILATE® in previously treated adult and adolescent subjects with severe hemophilia A was demonstrated in Study 1. Adolescents were shown to have decreased recovery of factor VIII compared to adults treated with WILATE® in pharmacokinetic studies; this data will appear in the US package insert to guide dosing.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

See list of elements of risk and benefit analysis for WILATE® in Table 36:

Table 36: Elements of Risk and Benefit for Use of WILATE® for Hemophilia A

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Congenital factor VIII deficiency (hemophilia A) is an X-linked bleeding condition with spontaneous hemorrhage into joints, soft tissue, and occasionally mucosal surfaces. Intracranial hemorrhage can be fatal (even with treatment after the event). • Factor VIII levels of < 1% are associated with severe disease, with frequent spontaneous bleeding. Factor VIII levels of 1-5% are associated with moderate disease, characterized by excessive bleeding with trauma and occasional spontaneous bleeding, and factor VIII activity levels of >5% are associated with mild hemophilia and rare spontaneous bleeding. • The gene for factor VIII is found on the long arm of the X chromosome, so the deficiency is inherited as a sex-linked recessive trait, meaning that a male who inherits a defective factor VIII gene will have hemophilia A. The annual incidence of hemophilia A is on the order of one case per 5000 male births per year. Females rarely have hemophilia A, due to its X-linked inheritance.	• Hemophilia A is a rare, life-threatening disease that can be ameliorated by replacement therapy with factor VIII. • Replacement of missing factor VIII to levels of > 5% should make severe hemophilia A a much less serious bleeding disorder with less frequent bleeding episodes. • Prophylaxis with factor VIII replacement to prevent major hemorrhage would be preferable to treatment after a bleeding event has occurred. • Bleeding should be treated with FVIII replacement.
Unmet Medical Need	• Factor VIII replacement therapy is the standard of care for hemophilia A. • Prophylaxis to reduce the rate of bleeding is a useful goal for patients with hemophilia. • Replacement therapy with all factor VIII products may induce of factor VIII inhibitor antibodies.	• A factor VIII concentrate with low risk of inhibitor development is desirable.
Clinical Benefit	• Clinical Trial 1 (WIL-27) demonstrated a highly significant decrease in the annualized total number of bleeding events (TABR) and in he annualized number of spontaneous bleeding events (SABR) in adults and adolescents with severe hemophilia A treated with WILATE® as routine prophylaxis, compared to historical controls from a clinical trial of he recombinant factor VIII product, NUWIQ. Subjects in Trial 1 also had improvements in heir personal historical TABR and SABR values. • Clinical Trial 1 also showed a high degree of hemostatic efficacy for treatment of breakthrough bleeding in adults and adolescents on routine prophylaxis, though the confidence in on-demand treatment of adolescents is limited by only 1 bleeding episode treated in this group. • Clinical Trial 2 (TMAE-103) showed a high degree of success for on-demand treatment of bleeding episodes in children under 12 years of age, using a four-point hemostatic efficacy rating scale (99% with Excellent or Good hemostatic efficacy ratings).	• The evidence for efficacy of WILATE® in adults and adolescents treated with routine prophylaxis is compelling. • The evidence for efficacy of WILATE® in adults with breakthrough bleeding treated on demand is good. • Although Trial 2 was done in children less than 12 years of age, the high degree of efficacy for on-demand treatment of bleeding in the 28 subjects evaluated provides support for approval of WILATE® for on-demand treatment of adolescents.
Risk	• The most important risks of routine prophylaxis and on-demand treatment of bleeding in hemophilia A are development of neutralizing antibodies to factor VIII (“inhibitors”) and transmission of blood-borne pathogens. • No factor VIII inhibitors arose in previously treated patients (PTPs) treated with WILATE routine prophylaxis in Trial 1 or in any other trial in PTPs. • No transmission of blood-borne pathogens was seen in Trial 1 or Trial 2, during which more than 12.7 million units of WILATE® were administered.	• The evidence indicates the risk of FVIII inhibitors wi h WILATE in PTPs is low/absent, and the risk of inhibitors in previously untreated patients is in line wi h other plasma-derived factor VIII concentrates. • The evidence indicates blood-borne pathogen transmission risk with WILATE® is very low or absent.
Risk Management	• Very few adverse events that are attributable to WILATE have been seen in Trial 1 or Trial 2; these are limited to factor VIII inhibitor development in PUPs and rare local infusion reactions. • Review of FAERS passive surveillance data for WILATE indicates very few adverse events have been reported since its licensure for von Willebrand disease in 2009.	• If WILATE® were approved for routine prophylaxis and on-demand treatment of bleeding in adults and adolescents with hemophilia A, the current pharmacovigilance plan would be adequate.

11.2 Risk-Benefit Summary and Assessment

Data submitted to BLA 125252.244 establish that WILATE® is effective at preventing bleeding when given as routine prophylaxis, and effective for on-demand treatment of breakthrough bleeding and traumatic bleeding in adults and adolescents with hemophilia A. The risks of treating hemophilia A with WILATE® are acceptable rates of mild/non-serious adverse events, as well as low or absent risk of factor VIII inhibitor antibody development or transmission of blood-borne viral infections.

This is typical of all similar factor VIII concentrates approved for treatment of hemophilia A and constitutes an overall favorable risk-benefit profile.

11.3 Discussion of Regulatory Options

The regulatory options available include:

1. Granting the requested indications for routine prophylaxis and on-demand treatment of bleeding in children and adults with hemophilia A, as requested
2. Granting the indications of routine prophylaxis and on-demand treatment of bleeding in adolescents and adults with hemophilia A, as supported by the data from Trial 1 and Trial 2
3. Granting the indication of routine prophylaxis OR on-demand treatment of bleeding in adolescents and adults, but not both indications
4. Granting the indications of routine prophylaxis and/or on-demand treatment of bleeding in adults, but not adolescents
5. Granting neither requested indication
6. Granting both requested indications AND the indication for management of bleeding in (b) (4) (which was not requested by the Applicant, but for which there is some support in Trial 3 (ATE-111), reviewed in Section 6.3)

11.4 Recommendations on Regulatory Actions

Reviewer Comments: *My recommendation is for granting the indications of routine prophylaxis and on-demand treatment of bleeding in adolescents and adults with hemophilia A, as supported by the data from Trial 1 and Trial 2 (option 2).*

The data provided clearly support these indications in adults and adolescents, but not children under 12 years of age. The Applicant has agreed to modifying the requested pediatric indication to adolescents in label discussions and is completing a study (WIL-30) that will address treatment of children less than 12 years of age, per the requirements of PREA.

Although the Applicant provided us with data from the (b) (4) *study, which was done by* (b) (4) *for which previous pharmacokinetic data was available, they did not ask for the* (b) (4) *indication; further, the study is limited by the need for prior pharmacokinetic studies, which may not be available for* (b) (4)

11.5 Labeling Review and Recommendations

The review team and APLB reviewed the package insert and the Applicant has modified the WILATE label accordingly.

The substantive changes are found in the following sections of the proposed label:

Section 1 (INDICATIONS AND USAGE)
WILATE® is 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

Section 2 (DOSAGE AND ADMINISTRATION)
Hemophilia A
- Calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII activity by approximately 2% of normal activity or 2 IU/dL when assessed using the one stage clotting assay. Use the following formulae to determine the required dose:

Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)

$$\text{Expected Factor VIII rise (\% of normal)} = \frac{2 \times \text{administered IU}}{\text{body weight (kg)}}$$

- Dose and duration of therapy depend on the patient's weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors. Titrate dose and frequency to the patient's clinical response, individual needs, severity of deficiency, severity of hemorrhage, desired FVIII level, and presence of inhibitor, and the patient's clinical condition. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to WILATE.

Routine Prophylaxis
A guide for dosing WILATE for routine prophylaxis to reduce the frequency of bleeding is provided in Table 3. Exact dosing should be defined by the patient's clinical status and response.

Table 3 Dosing for Routine Prophylaxis

Patients	**Recommended Dosage (IU/kg body weight)**	**Frequency of Infusions**
Adolescents and adults	20-40 IU/kg	Every 2 to 3 days

Dosing for Hemorrhages
A guide for dosing in the treatment of major and minor hemorrhages is provided in Table 4. Selected dosing regimen should maintain plasma Factor VIII activity levels at or above the plasma levels (in % of normal or in IU/dL) outlined in the table.

Table 4 Dosing for Treatment of Hemorrhages

Type of Hemorrhages	Recommended dosage (IU/kg body weight)	Frequency of Doses (hours)	Duration of Therapy (days)
Minor	30-40	Repeat every 12-24 hours	At least 1 day, until the hemorrhage has resolved
Moderate	30-40	Repeat every 12-24 hours	3 to 4 days or more, until the hemorrhage has resolved

Major	35-50	Repeat every 12-24 hours	3 to 4 days or more, until the hemorrhage has resolved
Life-threatening	35-50	Repeat every 8-24 hours	Until threat has resolved

- Monitoring parameters
  - Monitor plasma FVIII levels periodically to evaluate individual patient response to the dosage regimen.
  - If dosing studies have determined that a patient exhibits a lower/higher than expected response and shorter/longer half-life, adjust the dose and the frequency of dosing accordingly
  - Failure to achieve the expected FVIII:C level or to control bleeding after an appropriately calculated dosage may be indicative of the development of an inhibitor (an antibody to FVIII:C). Quantitate the inhibitor level by appropriate laboratory procedures and document its presence. Treatment with WILATE in such cases must be individualized.

Section 5.3 (Neutralizing Antibodies)
Hemophilia A
• Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained [see Dosage and Administration (2.1)].
• Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of Wilate. Use Bethesda Units (BU) to report inhibitor levels.

Section 6.1 (Clinical Trials Experience):

A total of 136 hemophilia A previously treated subjects (aged 11 to 66 years) received WILATE in 5 clinical studies that involved prophylactic use, treatment on demand, surgery and/or pharmacokinetics. All subjects were male. Overall, subjects received 19,317,004 IU of WILATE during 9001 exposure days. The most common adverse reaction was pyrexia (2 subjects; 1.5%). Further adverse reactions included pruritus, headache and sleeping disorder (1 subject; 0.75%). Two out of 55 subjects (3.6%) in the pivotal study of routine prophylaxis in severe hemophilia A had unexplained transient worsening of pre-existing thrombocytosis while on the study.

Section 14 (CLINICAL STUDIES)

Hemophilia A

Routine prophylaxis

The efficacy of WILATE in routine prophylaxis was evaluated in a prospective, open-label, multicenter clinical study in which adult subjects and pediatric subjects aged 12-15 years were treated during 6 months of prophylaxis with 20-40 IU/kg WILATE, mean dose 32 IU/kg. Within the group of 55 subjects, of which 50 adults and 5 pediatric subjects, there were 30 (54.6%) subjects with 0 bleeding episodes, 12 (21.8%) subjects with 1 bleeding episode, 4 (7.3%) subjects with 2 bleeding episodes, 4 (7.3%) subjects with 3 bleeding episodes, and 5 (9%) subjects with 5 or more bleeding episodes. Annualized bleeding rates for all bleeding episodes, treated and untreated, are summarized in Table 14.

Table 4 Annualized Bleeding Rate in Adult and Pediatric Subjects under Prophylaxis

	Adults (n=50)	Pediatric Subjects (n=5)

Annualized bleeding rate (per subject) - spontaneous bleeds	1.67 ± 3.11 (median 0, range 0-11.76)	0 (median 0, range 0-0)
Annualized bleeding rate (per subject) for all types of bleeds	2.39 ± 3.77 (median 0, range 0-15.69)	0.4 ± 0.89 (median 0, range 0-2)

Treatment of bleeding episodes

The study presented above also provided data on the efficacy of WILATE in the treatment of bleeding episodes. The break-through bleeds were treated with WILATE doses adjusted to the severity of the bleed. Treatment efficacy was assessed by the patient (together with the investigator in case of on-site treatment) using the predefined criteria using an ordinal scale of 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), or none (no improvement within 12 hours, or worsening of symptoms, requiring more than two injections for complete resolution).

Fifty-seven bleeding episodes were treated with WILATE, of which 15 (26.3%) bleeding episodes were minor (e.g. early onset muscle and joint bleeds with no visible symptoms, such as little or no change in the range of motion of affected joint, mild restriction of mobility and activity, scrapes, superficial cuts, bruises, superficial mouth bleeds, and most nose bleeds), 32 (56.1%) were moderate (e.g. advanced soft tissue and muscle bleeds into the limbs, bleeding into the joint space, such as the elbow, knee, ankle, wrist, shoulder, hip, foot, or finger), 10 (17.5%) were major (e.g. complicated joint bleeds, bleeds of the pelvic muscles, eyes), and 0 (0%) were life-threatening (e.g. bleedings in the abdomen, digestive system or chest, central nervous system bleeds, bleedings in the area of the neck or throat or pharynx, or other major trauma). Forty-one bleeds (71.9%) were spontaneous and 16 (28.1%) were traumatic. Thirty-six bleeding episodes (63.2%) were managed with one WILATE injection, 12 (21.1%) were managed with two injections, 7 (12.3%) were managed with 3 injections, and 2 (3.6%) required more than 3 injections. The mean dose of WILATE per injection was 34 IU/kg. Treatment efficacy was judged as excellent for 16 (28.1%) bleeding episodes, good for 32 (56.1%) bleeding episodes and moderate for 9 (15.8%) bleeding episodes. Therefore, 84.2% of all bleeding episodes were treated successfully. The one bleeding episode in one subject younger than 16 years (bleeding in finger) was treated with a single injection of 62.81 IU/kg of WILATE with excellent efficacy (successful treatment).

Further efficacy data in the treatment of bleeding episodes is available from a pooled analysis of 37 subjects with hemophilia A included in 3 additional clinical studies. These subjects had at least 150 exposure days at the time of enrollment into the study and had been treated for at least 50 exposure days and 6 months in the study. The analysis encompassed 986 bleeding episodes, of which 936 (94.9%) were treated successfully.

11.6 Recommendations on Postmarketing Actions

Thus far, the Applicant has studied routine prophylaxis and on-demand treatment of bleeding in hemophilia A in adults and adolescents. Under provision of PREA they are obligated to complete studies of WILATE® for these indications in children less than 12 years of age once these indications are granted for adults and adolescents as a PREA post-marketing requirement (PMR).

Under the agreed upon pediatric study plan Octapharma is conducting a study of routine prophylaxis and on-demand treatment of bleeding in previously treated patients with severe hemophilia A under the age of 12 years. The agreed upon study being performed under IND 17181 is WIL-30, the design of which is analogous to Trial 1 (WIL-27).

Octapharma submitted its protocol (WIL-30) on June 19, 2017, with tentative plans to complete the WIL-30 study by March 2019, and to submit the study results in September of 2019. Subsequently, Octapharma indicated in BLA amendment 125251.244.12 (July 18, 2019) that the study report will be provided in December of 2019; presumably this trial has been completed.

Octapharma previously requested deferral of pediatric studies in children under 12 years of age and waiver for pediatric studies of PTPs less than 1 year of age, based on the impossibility of finding research subjects in the latter category.

The Pediatric Review Committee reviewed these proposed plans during this review and concurred with the requested deferral and waiver requested, on July 10, 2019.

Reviewer Comment(s): *The approval letter for the routine prophylaxis and on-demand treatment of bleeding in hemophilia A should remind the Applicant (Octapharma) of their post-marketing requirement to complete the pediatric study (WIL-30) and to report the results to FDA by December of 2019.*

APPENDIX A: LIST OF AMENDMENTS TO BLA 125251.244 EFFICACY SUPPLEMENT

Amendment	Date	Topic
125251.244.1	January 4, 2019	Submission of Pharmacovigilance Plan
125251.244.2	January 15, 2019	Submission of Agreed Pediatric Study Plan
125251.244.3	March 4, 2019	Confirmed Equivalence of Trade Names WILATE and OCTATE
125251.244.4	April 15, 2019	Specified that WIL-30 is Protocol for Deferred Pediatric Studies in Hemophilia A PTPs <12 years old
125251.244.5	May 22, 2019	Clarified ADSL Dataset Used to Calculate ABRs for WIL-27 Study; Affirmed that All Bleeding Episodes Captured in Dataset
125251.244.6	May 29, 2019	Clarified Four Untreated Bleeds were Treated with Other Factor VIII Products
125251.244.7	June 4, 2019	Provided Details on Two Cases of Thrombocytosis in WIL-27
125251.244.8	June 4, 2019	Clarification that “Prevention of Recurrent Bleeding” Equals Prophylaxis in WIL-27
125251.244.9	June 7, 2019	Lists SAS Programs to Generate Tables for WIL-27
125251.244.10	June 7, 2019	Provided Draft Labeling
125251.244.11	June 19, 2019	Provided Integrated Study of Factor VIII Inhibitor Risk
125251.244.12	July 11, 2019	Clarification of AE Descriptors in Label
125251.244.13	July 18, 2019	Revision of Table 4 in Label to Conform with Results of WIL-27
125251.244.14	July 30, 2019	Revised Draft Label
125251.244.15	August 12, 2019	Revised Draft Label
125251.244.16	August 30, 2019	Revised Draft Label (final)
125251.244.17	September 4, 2019	Confirm values in Table 14

APPENDIX B: CLINICAL REVIEWER ANALYSIS OF WIL-27 BREAKTHROUGH BLEEDING BY SEVERITY, TYPE OF BLEED, DOSE, NUMBER OF DOSES, AND HEMOSTATIC EFFICACY

Table B1: WILATE® Dose, Number of Doses, and Efficacy, by Severity of Bleed

Subject	BE	Type of Bleed	Site	Severity	Dose (IU/kg)	Doses (n)	Efficacy
(b) (6)	BE001	Spont.	R. Elbow	Minor	25.4	1	Excellent
	BE001	Spont.	?	Minor	30.8	1	Excellent
	BE002	Spont.	R. Elbow	Minor	33.9	1	Excellent
	BE003	Spont.	R. Elbow	Minor	37.4	1	Excellent
	BE004	Spont.	R. Elbow	Minor	37.4	1	Excellent
	BE005	Spont.	R. Elbow	Minor	37.4	1	Excellent
	BE001	Spont.	R. Knee	Minor	38	1	Excellent
	BE001	Trauma.	R. Finger	Minor	39.8	1	Excellent
	BE001	Trauma.	R. Inguinal	Minor	27.3	1	Good
	BE002	Trauma.	L. Elbow	Minor	28.6	1	Good
	BE001	Trauma.	Oral Cavity	Minor	30.3	1	Good
	BE001	Spont.	R. Elbow	Minor	40.5	2	Good
	BE001	Spont.	L. Arm Muscle	Minor	46.9	1	Good
	BE001	Spont.	R. Knee	Minor	37.5	3	Moderate
	BE001	Spont.	R. Elbow	Moderate	26.7	1	Excellent
	BE001	Spont.	R. Hip	Moderate	29.1	1	Excellent
	BE002	Spont.	L. Knee	Moderate	29.4	1	Excellent
	BE001	Trauma.	R. Leg Muscle	Moderate	31.3	2	Excellent
	BE001	Trauma.	R. Hip	Moderate	31.6	1	Excellent
	BE001	Trauma.	R. Knee	Moderate	36.4	1	Excellent
	BE005	Spont.	L. Shoulder Blade	Moderate	37.3	1	Excellent
	BE007	Trauma.	L. Leg Muscle	Moderate	39.1	1	Excellent
	BE001	Trauma.	R. Knee	Moderate	23	1	Good
	BE001	Spont.	R. Knee	Moderate	23.8	3	Good
	BE002	Spont.	R. Hip	Moderate	23.8	2	Good
	BE002	Trauma.	L. Elbow	Moderate	27.3	1	Good
	BE001	Spont.	R. Knee	Moderate	27.8	1	Good
	BE001	Trauma.	L. Leg Muscle	Moderate	28.6	1	Good
	BE003	Spont.	R. Elbow	Moderate	28.6	1	Good
	BE001	Spont.	L. Knee	Moderate	29.4	1	Good
	BE003	Spont.	L. Knee	Moderate	29.4	2	Good
	BE001	Spont.	L. ankle	Moderate	29.7	1	Good
	BE005	Spont.	L. Hip	Moderate	31.3	1	Good
	BE001	Trauma.	L. Elbow	Moderate	33.3	1	Good
	BE002	Spont.	R. Knee	Moderate	33.3	1	Good
	BE002	Spont.	R. Knee	Moderate	37.5	2	Good
	BE001	Spont.	L. Elbow	Moderate	38	2	Good

(b) (6)

BE002	Spont.	R. Knee	Moderate	38.5	2	Good
BE004	Trauma.	R. Foot	Moderate	39	2	Good
BE007	Spont.	R. Ankle	Moderate	39	2	Good
BE002	Spont.	L. Elbow	Moderate	39.1	1	Good
BE002	Spont.	L. Ankle	Moderate	40.5	2	Good
BE003	Spont.	R. Ankle	Moderate	40.5	2	Good
BE004	Trauma.	L. Leg Muscle	Moderate	62.5	2	Good
BE002	Trauma.	L. ankle	Moderate	25	3	Moderate
BE003	Spont.	R. Knee	Moderate	31.8	7	Moderate
BE006	Spont.	L. knee	Moderate	34.5	5	Moderate
BE005	Trauma.	L. Knee	Moderate	34.5	5	Moderate
BE002	Trauma.	L. Elbow	Moderate	34.5	9	Moderate
BE003	Spont.	R. Knee	Moderate	41.7	3	Moderate
BE006	Spont.	L. Hip	Moderate	54.7	3	Moderate
BE001	Trauma.		Major	31.3	1	Excellent
BE008	Spont.	L. Leg Muscle	Major	39.1	1	Good
BE003	Spont.	L. ankle	Major	43.5	1	Good
BE001	Spont.	L. Buttock	Major	52.3	1	Good
BE002	Spont.	L. Shoulder	Major	52.3	1	Good
BE003	Spont.	L. Leg Muscle	Major	54.7	1	Good
BE004	Trauma.	L. Knee	Major	34.5	6	Moderate
BE007	Spont.	L. Knee	Major	34.5	5	Moderate
BE005	Spont.	R. Ankle	Major	39	2	Moderate
BE006	Spont.	R. Ankle	Major	39	3	Moderate
BE004	Spont.	R. Knee	Major	49.7	5	Moderate
BE009	Spont.	R. Ankle	Major	34.5	4	?
BE010	Spont.	L. Knee	?	36.4	4	?

APPENDIX C: SAEs FROM TMAE-103 STUDY OF WILATE® IN PUPS.

Table C1: Individual SAEs, TMAE-103 Study Subjects

Center/ Subject	Age (yrs)	SAE	Outcome	Related to WILATE®?	Basis for SAE
(b) (6)	1	Intramuscular Injection site hemorrhage, left arm	Resolved	No	Hospitalization
	3	Right gluteal region hematoma	Resolved	No	Hospitalization
	1	Hematoma of head	Resolved	No	Hospitalization
	1	Head injury, motor vehicle accident	Fatal	No	Fatal
	4	Retroperitoneal hematoma	Resolved	No	Hospitalization
	0.58	Neonatal encephalopathy	Resolved	No	Hospitalization
	1	Anemia	Resolved	No	Hospitalization
	1	Severe anemia	Resolved	No	Hospitalization
	4	Right knee hemarthrosis, hematoma top of right foot	Resolved	No	Hospitalization
	4	Right knee hemarthrosis, hematoma top of right foot	Resolved	No	Hospitalization
	4	Paraproctitis	Resolved	No	Hospitalization
	4	Periostitis	Resolved	No	Hospitalization
	1	Gingival bleeding	Resolved	No	Hospitalization
	1	Gingival bleeding	Resolved	No	Hospitalization
	2	Right knee hemarthrosis	Resolved	No	Hospitalization
	3	Phimosis	Resolved	No	Hospitalization