

**BLA Clinical Review Memorandum**

Application Type	BLA Efficacy Supplement
STN	125251/382
CBER Received Date	2/1/23
PDUFA Goal Date	12/1/23
Division / Office	Division of Clinical Evaluation Hematology/Office of Clinical Evaluation
Priority Review (Yes/No)	No
Reviewer Name(s)	Courtney W. Johnson
Review Completion Date / Stamped Date	1/23/24
Supervisory Concurrence	Prasad Mathew Nicole Verdun
Applicant	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Established Name	vonWillebrand Factor/Coagulation Factor VIII Complex (Human)
(Proposed) Trade Name	Wilate
Pharmacologic Class	Coagulation Factor
Formulation(s), including Adjuvants, etc.	VWF:RCo, FVIII, Total protein, Glycine, Sucrose, Sodium chloride, Sodium citrate, Calcium chloride, Water for injection, Polysorbate 80
Dosage Form(s) and Route(s) of Administration	Powder for solution, Intravenous injection
Dosing Regimen	Loading Dose and Maintenance Dose(s)
Indication(s) and Intended Population(s)	To add routine prophylaxis to reduce the frequency of bleeding episodes
Orphan Designated (Yes/No)	No

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## GLOSSARY

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

## 1. EXECUTIVE SUMMARY

Wilate [von Willebrand Factor/Coagulation Factor VIII Complex (Human)]<sup>1</sup> was approved in 2009 for prophylaxis and treatment of spontaneous and trauma-induced bleeding episodes (BEs) in patients with severe von Willebrand disease (VWD), as well as in patients with mild or moderate VWD in whom use of desmopressin (DDAVP) is known or suspected to be ineffective or contraindicated. In August 2015, Wilate was approved for the additional indication for the prevention of excessive bleeding during and after minor and major surgery in children and adults with VWD. In September 2019, Wilate was approved for routine prophylaxis to reduce the frequency of BEs and on-demand treatment and control of BEs in adolescents and adults with hemophilia A.

This efficacy supplement is for the use of Wilate for routine prophylaxis to reduce the frequency of BEs in adults and children 6 years of age and older with VWD. Evidence to support this indication is from the open-label, noncontrolled, Phase 3 pivotal Study WIL-31.

Pivotal Study WIL-31 was a prospective, open-label, noncontrolled, Phase 3 trial conducted in 14 centers in Europe and the United States. The study was started in Q2 of 2020 and ended in Q2 2022. This study investigated the efficacy and safety of Wilate in previously treated patients with Type 3, Type 2 (except 2N), or severe Type 1 VWD  $\geq 6$  years of age at the time of screening. To be included, subjects must have had Type 1 (baseline von Willebrand factor activity [VWF:Ac] [von Willebrand factor ristocetin cofactor assay (VWF:RCo)]  $< 30$  IU/dL), 2A, 2B, 2M or 3, and require substitution therapy with a VWF-containing product to control bleeding. Patients received 20 to 40 IU/kg of prophylactic Wilate 2 to 3 times per week according to investigator's discretion and based on each patient's clinical condition. There were specified doses of Wilate that were used for both breakthrough bleeding events and for surgical prophylaxis (see below). The treatment duration per patient was 12 months.

The primary endpoint is to demonstrate that prophylactic treatment with Wilate lowers the patients' total annualized bleeding rate (TABR) observed during on-demand treatment by more than 50%. The TABR under prophylactic treatment in WIL-31 was compared to the TABR for the same patients during a prior, non-interventional study (WIL-29). TABR was calculated as the total number of traumatic, spontaneous, and other bleeds, excluding menstrual bleeds during the prophylactic treatment period.

The secondary endpoints are the spontaneous annualized bleeding rate (SABR), the incremental in vivo recovery (IVR) of Wilate for VWF:Ac (VWF:RCo and von Willebrand factor (b) (4) assay [VWF:(b) (4)]) and Factor VIII-coagulant (FVIII:C) (one-stage [OS] and chromogenic [CHR]) over time; for pediatric patients-baseline pharmacokinetic (PK) profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR) over time, the safety and tolerability of Wilate by monitoring adverse events (AEs) throughout the study and Wilate consumption data (VWF/FVIII IU/kg per month per patient) for prophylaxis.

The Applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled clinical investigation providing compelling evidence of clinical benefit, supported by the initial clinical investigation and preclinical studies. The overall benefit risk assessment is favorable, and the clinical review team recommends regular approval for the use of Wilate for routine prophylaxis to reduce the frequency of BEs in adults and children 6 years of age and older with VWD.

## 1.1 Demographic Information: Subgroup Demographics and Analysis Summary

WIL-31 provides the basis of approval of Wilate routine prophylaxis to reduce the frequency of BEs. Age at screening in the full analysis set (n=43) and the safety set (n=43) ranged from 7 to 61 years of age with a median of 17 years. Ten patients were 6 to 11 years of age, 8 patients were 12 to 16 years of age and 25 were ≥17 years of age. The population was 60.5% male, 97.7% of the population was Caucasian, and 51.2% of patients had Type 3 VWD. The modified full analysis set (mFAS) consisted of 33 patients as 10 patients from the full analysis set were excluded due to unconfirmed VWD status. In the modified analysis set, 9 patients were 6 to 11 years of age, 6 patients were 12 to 16 years of age, and 18 patients were ≥17 years of age.

## 1.2 Patient Experience Data

Quality of Life data was collected during the WIL-31 study. Quality of Life was based on the scores of Patient-Reported Outcomes Measurement Information System-29 for all patients, Short Form-36 survey for patients ≥16 years of age, and Short Form-10 survey for patients 6 to 15 years of age. The Applicant provided summary tables from baseline, 6 months, and 12 months, and included any changes from baseline.

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

VWD is the most commonly inherited bleeding disorders and affects 1% of the population and has an equal frequency in men and women. However, women are more likely to be symptomatic due to bleeding events related to menstruation, pregnancy, and childbirth. VWD is characterized by either a quantitative or qualitative abnormality of VWF, an important protein in hemostasis. Heritable VWD may be caused by genetic variants in the VWF gene (located on the short arm of chromosome 12). Most cases of VWD are inherited in an autosomal dominant fashion.

VWF performs three critical functions in hemostasis, two functions in primary hemostasis, and one function in fibrin formation. In primary hemostasis, VWF acts as a bridging molecule between platelets and vascular sub-endothelium and promotes platelet aggregation. In fibrin formation, VWF acts as carrier for FVIII in circulation which increases the FVIII half-life by fivefold, thereby maintaining normal FVIII levels in circulation.

There are three types of heritable VWD:

1. Type 1—partial quantitative deficiency of VWF (~75% patients)
2. Type 2—qualitative abnormalities of VWF (~20%)

Four subtypes have been identified:

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

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

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

Humate-P, Alphanate, Vonvendi, and DDAVP are currently licensed specifically for treatment of bleeding in patients with VWD. See below Section 2.3.

## **2.3 Safety and Efficacy of Pharmacologically Related Products**

The following excerpts are from the package inserts (PIs) of products specifically approved for VWD:

### Humate-P

- Efficacy: indicated for VWD: in adults and pediatric patients in the (1) treatment of spontaneous and trauma induced BEs, and (2) prevention of excessive bleeding during and after surgery. Applies to patients with severe VWD as well as patients with mild to moderate VWD where the use of DDAVP is known or suspected to be inadequate.
- Safety: most common adverse reactions observed by >5% of subjects after receiving Humate-P are allergic-anaphylactic reactions (e.g., urticaria, chest tightness, rash, pruritus, edema) and, in patients undergoing surgery, postoperative wound and injection-site bleeding, and epistaxis.

### Alphanate

- Efficacy: indicated for surgical and/or invasive procedures in adult and pediatric patients with VWD in whom DDAVP is either ineffective or contraindicated. Not indicated for patients with severe VWD (Type 3) undergoing major surgery.
- Safety: most frequent AEs reported with Alphanate in >5% of subjects are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain, and fatigue.

### DDAVP

- Efficacy: indicated for patients with mild to moderate (but not severe) classic VWD (Type I) with FVIII levels greater than 5%. Not effective in patients with Type 3 VWD and contraindicated in patients with Type 2B VWD. Can also be contraindicated for other clinical reasons or can be associated with significant side effects.
- Safety: most frequent AEs reported with DDAVP are transient headache, nausea, mild abdominal cramps, vulval pain, local erythema, swelling or burning pain, and facial flushing.



## Vonvendi

- Efficacy: indicated for use in adults diagnosed with VWD for on-demand treatment and control of BEs, perioperative management of bleeding and routine prophylaxis to reduce the frequency of BEs in patients with severe Type 3 VWD receiving on-demand therapy.
- Safety: The most common adverse reactions observed ( $\geq 2\%$  of subjects) were headache, vomiting, nausea, dizziness, arthralgia, joint injury, vertigo, increased alanine aminotransferase levels increased, and generalized pruritus. One subject treated with Vonvendi in perioperative setting developed deep vein thrombosis after undergoing total hip replacement surgery.

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

On December 2009, Wilate was licensed in the United States for the treatment of spontaneous and trauma induced BEs in patients with severe VWD as well as patients with mild or moderate VWD in whom the use of DDAVP is known or suspected to be ineffective or contraindicated. The initial biologics license application (BLA) was approved based on studies TMAE-101, TMAE-102, TMAE-108, and TMAE-110.

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

In September 2019, the indications hemophilia A in adolescents and adults for routine prophylaxis to reduce the frequency of BEs and on-demand treatment and control of BEs were approved for Wilate in the United States.

Wilate has been extensively studied and used for treatment of VWD in the United States and Europe for several years.

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

#### Regulatory History

- On December 4, 2009, FDA approved Wilate original BLA 125251/0 for treatment of spontaneous and trauma induced BEs in patients with severe Von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of DDAVP is known or suspected to be ineffective or contraindicated.
- On August 5, 2015, FDA approved sBLA 125251/139 to include an additional indication for the prevention of excessive bleeding during and after minor and major surgery in patients with VWD. This was the trigger for a previous review for the Pediatric Advisory Committee in 2019.
- On September 25, 2019, FDA approved sBLA 125251/244 to add an indication in adults and adolescents with hemophilia A for routine prophylaxis to reduce the frequency of BEs and on demand treatment and control of BEs. This is the trigger for the current review for the Pediatric Advisory Committee.

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

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

#### 3.2 Compliance with Good Clinical Practices and Submission Integrity

Study WIL-31 was conducted under investigational new drug application (IND) 11303 in the United States and overseas in Bulgaria, Belarus, Croatia, Hungary, Lebanon, Russia, and Ukraine.

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

#### 3.3 Financial Disclosures

Covered clinical study (name and/or number): WIL-31
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> <b>Yes</b> <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <b>13</b>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <b>None</b>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <b>None</b>

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

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

Significant payments of other sorts: \_\_\_\_\_

Proprietary interest in the product tested held by investigator: \_\_\_\_\_

Significant equity interest held by investigator in sponsor of covered study: \_\_\_\_\_

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

Is a description of the steps taken to minimize potential bias provided?  
 Yes  No (Request information from applicant)

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

**Not Applicable**

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

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

##### **4.1 Chemistry, Manufacturing, and Controls**

There were no significant chemistry, manufacturing, and controls issues for this supplement.

##### **4.2 Assay Validation**

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

##### **4.3 Nonclinical Pharmacology/Toxicology**

There were no significant nonclinical pharmacology/toxicology issues for this supplement.

##### **4.4 Clinical Pharmacology**

The clinical pharmacology section of this prior approval supplement included one Phase 3, open-label, multicenter, noncontrolled study to determine the efficacy, safety, and PK of Wilate in previous treated patients ( $\geq 6$  years of age) with VWD (Study WIL-31). Pharmacokinetics of Wilate was evaluated in pediatric subjects (6 to 16 years of age). Administration of Wilate led to

immediate correction of both the FVIII and VWF deficiencies. The observed half-lives in Study WIL-31 pediatric population (6 to 16 years of age) were shorter than those observed previously with Wilate in a population including older patients (12 to 68 years of age) as reported in the labeling of Wilate: VWF:RCo assay 8.3 (1.7) hours versus 15.8 (11.0) hours, and FVIII chromogenic assay 14.8 (1.5) hours versus 19.6 (6.9) hours. The FVIII and VWF IVRs observed in this study are consistent with those seen previously with Wilate (Study WIL-12), with slightly lower IVRs in children. Assessment of prophylaxis treatment dosing and efficacy in Study WIL-31 was conducted to address the effectiveness concern in children due to above observed PK differences. The results suggested that the proposed dose of 20 to 40 IU/kg body weight (BW) 2 to 3 times per week is acceptable for prophylaxis treatment.

The proposed dosing regimen for Wilate administered by intravenous infusion has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable for routine prophylaxis to reduce the frequency of BEs in children and adults with VWD. From a clinical pharmacology standpoint, the prior approval supplement is acceptable to support approval.

#### 4.4.1 Mechanism of Action

VWF and FVIII are normal constituents of human plasma. VWF mediates the binding between platelets and damaged subendothelium; it also is involved in the transport and stabilization of FVIII. In patients with VWD, reduction in VWF concentration results in a correspondingly low FVIII activity and abnormal platelet function, thereby resulting in excessive bleeding. Plasma-derived VWF reverses these effects by promoting platelet adhesion to vascular subendothelium at the site of vascular damage and correcting the associated impairment in FVIII activity.

#### 4.4.2 Human Pharmacokinetics

Please see above [Section 4.4](#).

### 4.5 Statistical

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

### 4.6 Pharmacovigilance

Please refer to the Office of Biostatistics and Pharmacovigilance Review Memo for further details.

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

### 5.1 Review Strategy

The draft PI was reviewed first. This was followed by review of the final study report for study WIL-31, final study reports for non-IND studies submitted to the original BLA and corresponding clinical review memos; responses to clinical information requests seeking clarification of information in the submission; and financial disclosure forms.

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

- Wilate draft PI
- December 4, 2009, Wilate approval letter
- Final study reports for WIL-29 and WIL-31
- Original BLA clinical review memos as well as summaries of clinical safety and efficacy data reviewed previously by the Medical Officer for the original BLA
- Information submitted by the Applicant in response to information requests
- PIs for Humate-P, Alphanate, DDAVP

**5.3 Table of Studies/Clinical Trials**

Data from the WIL-31 study is used as the basis of approval for this efficacy supplement.

Data from studies WIL-14, TMAE-104, TMAE-105, TMAE-106 and TMAE-109 have been submitted to support efficacy and safety. Data from studies WIL-12, WIL-21 and WIL-24 have been submitted to support safety.

**Table 1: Clinical Trials Reviewed for this sBLA**

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

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

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

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

## 5.4 Consultations

### FDA Pediatric Review Committee Regulatory History

On May 12, 2019, the FDA’s Pediatric Review Committee (PeRC) reviewed the Sponsor’s initial Pediatric Study Plan (iPSP) with a plan to request a waiver for children with VWD from 0 to 5 years of age. PeRC recommended that the Sponsor conduct an assessment in children 2 years of age and older depending on the severity of the VWD. PeRC agreed with the plan to request a partial waiver in children less than 2 years of age. Additionally, PeRC recommended that the Sponsor increase the sample size and plan to conduct PK studies in all pediatric age groups. The Sponsor addressed all of the Center for Biologics Evaluation and Research (CBER) and PeRCs comments on their iPSP and submitted an agreed iPSP on February 26, 2021. On March 25, 2021, CBER completed their review of the Agreed iPSP and agreed with the Sponsor’s planned pediatric studies and the plan to submit a pediatric assessment for the pediatric population for 6 years of age to less than 17 years of age, to request a partial waiver of the pediatric assessment for the pediatric population less than 2 years of age and the plan to request a deferral of submission of the pediatric assessment for the pediatric population 2 to 5 years of age.

### Current Submission—Partial Waiver Request

In this submission, the Sponsor requested a partial waiver for children <2 years of age. This request was presented and reviewed at PeRC on October 31, 2023. Both the Division of Clinical Hematology Evaluation and PeRC agreed to the Sponsor’s request as studies are impossible or highly impracticable (because, for example, the number of the pediatric patients is so small or geographically dispersed). Additionally, many children with VWD are not typically exposed to prophylaxis in this age group.

### Current Submission—Deferral Request

In this submission, the Sponsor requested a deferral for pediatric studies in children 2 to 5 years of age as the adult study and the study of the pediatric population 6 to 17 years of age is completed (WIL-31) and ready for approval.

WIL-33 is the current study that is open for pediatric patients 2 to 5 years of age. WIL-33 aims to determine the efficacy, PK, immunogenicity, and safety of Wilate as routine prophylaxis in pediatric patients 2 to 5 years of age with severe VWD. WIL-33 is currently in the stages of recruitment.

This request was presented and reviewed at PeRC on October 31, 2023. Both the Division of Clinical Hematology Evaluation and PeRC agreed to the Sponsor's request. In addition to the above deferral request, the Sponsor also requested a new Pediatric Research Equity Act post marketing requirement timeline (stated below) due to the war in the Ukraine as there are several study sites located there. Both the Division of Clinical Hematology Evaluation and PeRC agreed to the proposed study timeline.

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

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

### Updated Timeline

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

## **6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS**

### **6.1 Trial #1—Pivotal Study WIL-31**

#### 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 with Type 3, Type 2 (except 2N), or severe Type 1 VWD.

#### Secondary Objectives

- Assess the incremental IVR of Wilate for VWF:Ac and FVIII:C over time
- Determine the PK of Wilate for VWF:Ac and FVIII:C in pediatric patients 6 to 16 years of age
- Assess the safety and tolerability of Wilate
- Determine Wilate consumption data



### Additional Objectives

- Determine the efficacy of Wilate in the treatment of breakthrough BEs
- Determine the efficacy of Wilate in surgical prophylaxis
- Assess patients' quality of life during prophylaxis with Wilate
- Assess the patients' joint status using the Hemophilia Joint Health Score
- Assess the menstrual bleeding intensity of female patients of child-bearing potential (based on Pictorial Blood Loss Assessment Chart score)

#### 6.1.2 Design Overview

WIL-31 is a prospective, noncontrolled, international, multicenter, Phase 3 trial. Patients received prophylactic treatment with Wilate, administered 2 to 3 times per week at a dose of 20 to 40 IU/kg BW for 12 months. The frequency of Wilate was determined by the principal investigator and the clinical condition of the patient. If patients experienced frequent spontaneous breakthrough bleeding events, defined as greater than two spontaneous bleeds or one major spontaneous bleed within 30 days, the dose of Wilate was increased by 5 IU/kg. If patients experience more than two spontaneous bleeds, the dosing interval of prophylactic Wilate would be shortened from 2 times to 3 times per week if that patient was not already receiving Wilate 3 times a week. Treatment was continued for 12 months.

#### 6.1.3 Population

##### *Inclusion Criteria:*

1. Patients  $\geq 6$  years of age at the time of screening
2. VWD type 1 (baseline VWF:Ac [VWF:RCo]  $< 30$  IU/dL), 2A, 2B, 2M, or 3 according to medical history, requiring substitution therapy with a VWF-containing product to control bleeding
3. Currently receiving on-demand treatment with a VWF-containing product AND having experienced at least six BEs (excluding menstrual bleeds) over a period of 6 months, with at least two of these BEs treated with a VWF-containing product
4. AND having records available to reliably evaluate the type, frequency, and treatment of BEs in this 6-month period OR
5. Having switched to prophylactic treatment with a VWF-containing product within the past 2 years AND having records available to reliably evaluate the type, frequency, and treatment of BEs over a period of 6 months of on-demand treatment
6. Female patients of child-bearing potential must have a negative urine pregnancy test at screening and agree to use adequate birth control measures; in case hormonal contraception is used, the medication class should remain unchanged for the duration of the study
7. Voluntarily given, fully informed written and signed consent obtained before any study-related procedures are conducted

*Exclusion Criteria:*

1. Having received on-demand or prophylactic treatment with a VWF-containing product, but having *no* records available to reliably evaluate the type, frequency, and treatment of BEs over a period of at least 6 months of on-demand treatment
2. History, or current suspicion, of VWF or FVIII inhibitors
3. Medical history of a thromboembolic event within 1 year before enrollment
4. Severe liver or kidney diseases (alanine aminotransferase and aspartate transaminase levels >5 times of upper limit of normal, creatinine >120 mold/L)
5. Platelet count <100,000/ $\mu$ L at screening (except for VWD type 2B)
6. Hemoglobin level <9 g/dL at screening
7. Body weight <20 kg at screening
8. Patients receiving, or scheduled to receive, immunosuppressant drugs (other than antiretroviral chemotherapy), such as prednisone (equivalent to >10 mg/day), or similar drugs
9. Pregnant or breast-feeding at the time of enrollment
10. Cervical or uterine conditions causing abnormal uterine bleeding (including infection, dysplasia)
11. Treatment with any investigational medicinal product in another interventional clinical study currently or within 4 weeks before enrollment
12. Other coagulation disorders or bleeding disorders due to anatomical reasons
13. Known hypersensitivity to any of the components of the study drug

6.1.4 Study Treatments or Agents Mandated by the Protocol

The FVIII/VWF concentrate Wilate, produced from the plasma of human donors, was presented as a powder and solvent for intravenous injection containing nominally 500 IU or 1,000 IU human VWF and human FVIII per vial.

Wilate dosage for baseline PK assessment in pediatric patients (6 to 16 years of age): Single dose of  $60 \pm 10$  IU/kg BW.

Wilate dosage for prophylactic treatment: For prophylactic treatment, Wilate was to be administered 2 to 3 times per week at a dose of 20 to 40 IU/kg BW for 12 months.

The prophylactic dose for each patient was determined by the principal investigator based on each patient's clinical condition and at the following time points:

- At the baseline IVR visit in adult patients ( $\geq 17$  years of age):  
In adult patients, the first prophylactic dose was to be administered at the time of the baseline IVR assessment.
- At the baseline PK visit in pediatric patients (6 to 16 years of age):  
In pediatric patients, the first prophylactic dose was to be administered after completion of the PK phase.

In case of unacceptably frequent spontaneous breakthrough BEs (i.e., more than two spontaneous BEs or one major 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 needed to be reconstituted). If, after a dose increase, patients still experienced more than two spontaneous BEs, the dosing interval was to be shortened from 2 times per week to 3 times per week.

**Table 2: Wilate Dosage for the Treatment of Breakthrough Bleeding Events**

Dose Type	*Minor Hemorrhage	Major Hemorrhage
Loading dose	20-40 IU/kg	40-60 IU/kg
Maintenance dose	20-30 IU/kg every 12-24 hours	20-40 IU/kg every 12-24 hours
Therapeutic goal	Maintain VWF:Ac (VWF:RCo) and FVIII:C trough levels >30%	Maintain VWF:Ac (VWF:RCo) and FVIII:C trough levels >50%

Source: WIL-31 study protocol, Version 8, March 1, 2021

\* Menstrual bleeds of regular intensity (i.e.-minor menstrual hemorrhage) will be considered normal and are not expected to require therapy unless deemed necessary by the Investigator and/or the patient.

Abbreviations: FVIII:C = Factor VIII-coagulant, VWF:Ac = von Willebrand factor activity, VWF:RCo = von Willebrand factor ristocetin cofactor assay.

**Table 3: Wilate Dosage for Surgical Prophylaxis**

Dose Type	Minor Surgeries (Includes Tooth Extraction)	Major Surgeries
Loading Dose	30-60 IU/kg	40-60 IU/kg
Maintenance Dose	15-30 IU/kg, or half the loading dose, every 12-24 hours for up to 3 days	20-40 IU/kg, or half the loading dose every 12-24 hours for up to 6 days or longer
Therapeutic Goal	Achieve VWF:Ac (VWF:RCo) peak levels of 50% after loading dose and trough levels of >30% during maintenance doses	Achieve VWF:Ac (VWF:RCo) peak level of 100% after loading dose and maintenance trough levels of >50% during maintenance doses

Source: WIL-31 study protocol, Version 8, March 1, 2021

Abbreviations: VWF:Ac = von Willebrand factor activity, VWF:RCo = von Willebrand factor ristocetin cofactor assay.

### 6.1.5 Directions for Use

See above [Section 6.1.4.](#)

### 6.1.6 Sites and Centers

This study was conducted in 14 centers in the United States, Bulgaria, Croatia, Hungary, Ukraine, Russia, and Lebanon. The coordinating investigator on this study was Dr. Robert F. Sidonio, Jr., MD, Aflac Cancer and Blood Disorders, Emory University School of Medicine, 1760 Haygood Drive, HSRB W340, Atlanta, GA, 30322.

### 6.1.7 Surveillance/Monitoring

Subjects were monitored throughout the study. At each scheduled study visit, AEs were documented by the investigator. The investigator graded the severity (mild, moderate, or severe), the seriousness (non-serious or serious), expectedness (expected or unexpected) and the causality (probable, possible, unlikely, unrelated, or unclassified) of each AE.

PK visits occurred at baseline and then at 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months (study completion) after the first prophylactic injection of Wilate. Monthly telephone contacts were performed 4, 5, 6, 7, 8, 10, and 11 months (+/- 1 week) after the first

prophylactic injection of Wilate to review the compliance of completing the patient diaries and adherence to the infusion regimen, to monitor AEs and to keep track of any concomitant medications the patients used. If an inhibitor was suspected based on an unexplained need to increase the dose, a lack of efficacy of Wilate injections, or prolonged bleeding (among other reaction, VWF and FVIII inhibitor tests were performed at a central laboratory.

The following parameters were regularly monitored by hospital staff throughout the study: vital signs, safety laboratory assessments (hematology including hemoglobin, platelet count, liver function tests, and serum creatinine).

#### 6.1.8 Endpoints and Criteria for Study Success

**Primary Endpoint**—The primary endpoint of WIL-31 was to demonstrate that TABR, during prophylactic treatment, lowers the patients' TABR during on-demand treatment by >50%.

TABR was calculated as the total number of traumatic, spontaneous, and other bleeds (excluding menstrual bleeds) during the prophylactic treatment period. Surgery periods and bleeding events were excluded from the calculation of TABR. However, the Applicant did provide separate analyses of TABRs for spontaneous bleeds, traumatic bleeds, and menstrual bleeds. Additionally, the Applicant provided TABRs for the total number of traumatic, spontaneous, other bleeds and menstrual bleeds (see below [Section 6.1.11](#)).

The individual ABRs under prophylactic treatment (WIL-31) were compared to the ABRs recorded for the same patient during a previous non-interventional study (WIL-29).

Secondary endpoints include the following:

- SABR, calculated in analogy with TABR
- Incremental IVR of Wilate for VWF:Ac (VWF:RCo and VWF:(b) (4) and FVIII:C (OS and CHR) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)
- For pediatric patients, baseline PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR) based on blood samples taken pre-dose and 1, 3, 9, 24, 48, and 72 hours after dosing
- Safety and tolerability of Wilate by monitoring AEs throughout the study
- Wilate consumption data (VWF/FVIII IU/kg per month per patient) for prophylaxis

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

**Primary Endpoint Analysis**—As the individual mean TABRs for prophylactic treatment (TABR<sub>pr</sub>) with Wilate were compared to mean TABRs for on-demand treatment (TABR<sub>od</sub>) with Wilate for the same patient, the following pair of hypotheses were tested:

(\*) H<sub>0</sub>: mean (TABR<sub>pr</sub> / TABR<sub>od</sub>) ≥ 0.5 versus H<sub>1</sub>: mean (TABR<sub>pr</sub> / TABR<sub>od</sub>) < 0.5 at a one-sided alpha level of 2.5%. A corresponding two-sided 95% confidence interval (CI) for the different TABRs and their ratio were also provided.

Secondary Endpoint Analysis—The analysis of the secondary endpoints was descriptive and included exploratory 95% CIs.

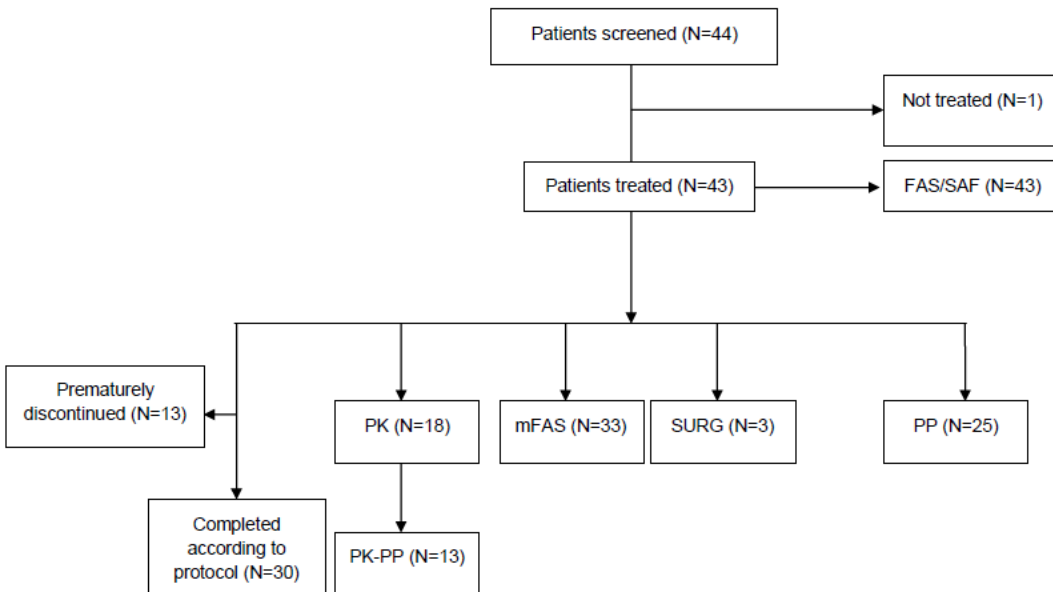
The Last Observation Carried Forward approach to calculate the dose per kg BW (IU/kg) was used in the case of missing BW documentation. No further imputations for missing data were performed.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

Forty-four patients were screened for WIL-31. Forty-three were enrolled and treated with Wilate. Patient (b) (6) was screened but subsequently lost to follow-up and was not treated with Wilate. All patients completed the non-interventional study WIL-29, in which their bleeding incidence while undergoing on-demand treatment was captured.

**Figure 1: WIL-31 Patient Population and Disposition**



Source: WIL-31 Study report body, p. 72

Abbreviations: FAS = full analysis set, mFAS = modified full analysis set, PK = study population of patients undergoing pharmacokinetic analysis, PP = per protocol, SAF = safety analysis set, SURG = surgery population.

#### 6.1.10.1.1 Demographics

For demographics, please see above Section 1.1. This is shown in the Table below.

WIL-31 Demographics

Table 4: WIL-31 Demographic Characteristics

Parameter Statistic		6-<12 yrs (N=10)	12-<17 yrs (N=8)	≥17 yrs (N=25)	Total (N=43)
Age (years)	Mean (SD)	8.9 (1.50)	14.4 (1.50)	30.4 (14.40)	22.4 (14.59)
	Median (range)	9.0 (7.0-11.0)	15.0 (12.0-16.0)	25.0 (17.0-61.0)	17.0 (7.0-61.0)
Height (cm)	Mean (SD)	133.2 (9.04)	163.6 (12.24)	171.8 (7.83)	161.3 (18.22)
	Median (range)	136.0 (118-146)	160.5 (151-182)	170.0 (155-185)	167.0 (118-185)
Weight (kg)	Mean (SD)	28.44 (6.49)	63.28 (18.74)	75.7 (17.56)	62.4 (24.96)
	Median (range)	28.3 (20.5-41.0)	64.8 (39.9-92.0)	76.0 (48.0-112.0)	62.0 (20.5-112.0)
BMI	Mean (SD)	15.9 (2.04)	23.2 (4.19)	25.6 (5.69)	22.9 (6.21)
	Median (range)	15.4 (13.3-20.3)	24.6 (16.8-27.8)	25.1 (18.8-38.8)	21.6 (13.3-38.8)
Male, n (%)		6 (60.0)	4 (50.0)	16 (64.0)	26 (60.5)
Female, n (%)		4 (40.0)	4 (50.0)	9 (36.0)	17 (39.5)
Female of childbearing potential, n (%)		NA	3 (37.5)	6 (24.0)	9 (20.9)
Race	White, n (%)	10 (100.0)	8 (100.0)	24 (96.0)	42 (97.7)
	Black or African American	0 (0)	0 (0)	1 (4.0)	1 (2.3)
Ethnicity Not Hispanic or Latino		10 (100.0)	8 (100.0)	25 (100.0)	43 (100.0)
Blood group, n (%)					
A		8 (80.0)	3 (37.5)	11 (44.0)	22 (51.2)
B		1 (10.0)	1 (12.5)	4 (16.0)	6 (14.0)
AB		1 (10.0)	0 (0)	0 (0)	1 (2.3)
O		0 (0)	4 (50.0)	10 (40.0)	14 (32.6)
VWD type, n (%)					
Severe Type 1		2 (20.0)	1 (12.5)	3 (12.0)	6 (14.0)
Type 2		2 (20.0)	1 (12.5)	2 (8.0)	5 (11.6)
Type 3		5 (50.0)	4 (50.0)	13 (52.0)	22 (51.2)
Not applicable <sup>1</sup>		1 (10.0)	2 (25.0)	7 (28.0)	10 (23.3)
Von Willebrand Factor inhibitor history, n (%) <sup>2</sup>					
No		10 (100.0)	8 (100.0)	25 (100.0)	43 (100.0)
Factor VIII inhibitor history, n (%)					
No		10 (100.0)	8 (100.0)	25 (100.0)	43 (100.0)
Family history of VWD, n (%)					
Yes		4 (40.0)	5 (62.5)	13 (52.0)	22 (51.2)
No		6 (60.0)	3 (37.5)	12 (48.0)	21 (48.8)

Source: WIL-31 Study report body, p. 76

1. Ten patients had unconfirmed von Willebrand disease status.

2. Two patients had an inhibitor detected during the study that was already present at screening.

Abbreviations: BMI = body mass index, FAS = full analysis set, SAF = safety analysis set, SD = standard deviation, VWD = von Willebrand disease, yrs = years.

#### 6.1.10.1.3 Patient Disposition

Ten patients were excluded from the mFAS due to unconfirmed VWD status. Three patients terminated the study early due to adverse reactions in two patients and “other” reasons (patient permanently left country for job opportunity abroad) in one patient.

Thirty of the 33 patients of mFAS population completed the study according to the protocol. Thirteen of the 33 patients of the mFAS population prematurely discontinued the study. Patients (b) (6) discontinued the study due to AEs. Patients (b) (6) discontinued the study due to a protocol violation as their central laboratory results did not confirm eligibility of the patient according to inclusion criteria 2. Patients (b) (6) discontinued the study due to a protocol violation as they had laboratory results that contradict results seen from patients with VWD. Patients (b) (6) withdrew consent from the study. Patient (b) (6) was lost to follow-up. Subjects (b) (6) both had laboratory results that contradict VWD and central laboratory results that didn't confirm eligibility of patient according to inclusion criterion 2. Patient (b) (6) permanently left the country for a job opportunity abroad.

The per-protocol (PP) set is a subset of the FAS which excludes patients with major protocol deviations which could have an impacted on the evaluation of the primary study outcome parameter (major protocol deviations as defined during the data review meeting). A total of 18 patients out of 43 were excluded from the Per Protocol population:

- Ten due to unconfirmed VWD status (violating inclusion criteria #2)
- Three patients discontinued the study early for other reasons (b) (6)
- Patient (b) (6) due to an underlying medical condition other than VWD (gingivitis) that significantly increases the rate of spontaneous bleeds (oral cavity bleeds)
- Patients (b) (6) as they had inhibitor to VWF already at study entry (but only detected during the 6 months study visit)
- Patient (b) (6) due to an underlying medical condition other than VWD (relapsing and remitting ulcers in small bowel) that significantly increases the rate of spontaneous bleeds (gastrointestinal bleeds due to a clip failure at a previous anastomosis site)
- Patient (b) (6) with more than two spontaneous BEs or one major spontaneous BE within 30-day period but prophylactic dose not increased without providing an explanation.

Three patients had 13 surgeries performed under Wilate treatment and were included in the surgery population.

#### Major Protocol Deviations

- Discontinuation with less than 12 months of prophylactic treatment in 13 patients.
- Inclusion criterion 2 violated (laboratory data do not support severe VWD type 1, 2A, 2B, 2M, or Type 3) in 10 patients.

- Deviations from planned dose for PK (60±10 IU/kg) - underdose (<50 IU/kg), in one patient.
- More than two spontaneous BEs or one major spontaneous BE within 30-day period but prophylactic dose not increased without explanation, in one patient.

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

The mFAS (n=33) was the primary population for efficacy analyses. The mFAS excluded 10 patients from the full analysis set (n=43) due to unconfirmed VWD status.

The TABR for treatment with prophylactic Wilate treatment was 5.49 compared to 33.38 for treatment with on-demand Wilate treatment, with a rate ratio was 0.165 (p<0.0001, 95% CI: 0.1019, 0.2656). The total bleeding rate (excluding patients with increased bleeding unrelated to VWD) was 3.96 for treatment with prophylactic Wilate compared to 33.72 for treatment with on-demand Wilate, with a rate ratio of 0.149 (p<0.001, 95% CI 0.834, 0.1649).

**Table 5: Statistics on TABR in On-Demand (WIL-29) and Prophylaxis Period (WIL-31) by Age Group (All Patients Included in the mFAS, N=33)**

Period / Age Group		Total Annualized Bleeding Rate (TABR) <sup>2</sup>								
		n <sup>1</sup>	N	Mean	Std	Min	Q1	Median	Q3	Max
On-Demand	6 - <12 Years	157	9	32.54	21.372	11.0	20.55	24.01	31.93	75.8
	12 - <17 Years	100	6	28.91	20.997	12.8	16.27	22.53	29.14	70.1
	>= 17 Years	331	18	35.29	26.338	14.8	21.84	26.57	37.51	114.5
	Total	588	33	33.38	23.614	11.0	20.55	24.46	34.02	114.5
Prophylaxis	6 - <12 Years	34	9	3.73	4.838	0.0	0.00	0.99	6.85	13.9
	12 - <17 Years	26	6	4.28	4.647	0.0	1.00	3.44	5.00	12.8
	>= 17 Years	113	18	6.31	9.634	0.0	0.00	1.46	8.39	35.8
	Total	173	33	5.24	7.745	0.0	0.00	1.92	6.85	35.8

Source: WIL-31 Summary of Clinical Efficacy, Table 1-3

1. Total number of bleeding episodes within the corresponding period.

2. The calculations of TABR is based on total number of bleeding episodes within the corresponding period relative to time in period. Abbreviations: mFAS = modified full analysis set, TABR = total annualized bleeding rate.



Additional Efficacy Data

**Table 6: Statistics on JABR in On-Demand (WIL-29) and Prophylaxis Period (WIL-31) by Age Group (All Patients Included in the mFAS, N=33)**

Period / Age Group		Joint Annualized Bleeding Rate (JABR) <sup>2</sup>								
		n <sup>1</sup>	N	Mean	Std	Min	Q1	Median	Q3	Max
On-Demand	6 - <12 Years	31	9	6.54	12.398	0.0	0.00	2.00	4.57	38.9
	12 - <17 Years	32	6	8.88	15.032	0.0	0.00	3.82	6.52	39.1
	>= 17 Years	70	18	7.63	10.466	0.0	0.00	3.26	9.93	29.6
	Total	133	33	7.56	11.513	0.0	0.00	3.43	7.97	39.1
Prophylaxis	6 - <12 Years	1	9	0.11	0.330	0.0	0.00	0.00	0.00	1.0
	12 - <17 Years	12	6	1.97	3.113	0.0	0.00	0.00	4.92	6.9
	>= 17 Years	5	18	0.27	0.556	0.0	0.00	0.00	0.00	1.9
	Total	18	33	0.53	1.477	0.0	0.00	0.00	0.00	6.9

Source: WIL-31, Summary of Clinical Efficacy, Table 1-3

1. Total number of joint bleeding episodes within the corresponding period.

2The calculations of JABR is based on total number of joint bleeding episodes within the corresponding period relative to time in period.

Abbreviations: JABR = joint annualized bleeding rates, mFAS = modified full analysis set.

Efficacy in Surgical Prophylaxis

Three patients in WIL-31 had 13 surgeries that were included in the surgery population. Ten of the surgeries were minor and three were major. The surgeries were all rated as successful. The standard dose of Wilate administered for surgery was 37.13 IU/kg per exposure day preoperatively and 20.06 IU/kg per exposure days post-operatively. There were no wound hematomas.

*Reviewer Comment(s): The product shows a significant decrease in ABR when Wilate was used in a prophylactic setting (WIL-33) versus in an on-demand setting and the primary endpoint was met for this study.*

6.1.11.2 Analyses of Secondary Endpoints

- **Secondary Endpoint #1**—SABR, calculated in analogy with TABR.

The SABR in WIL-31 (treatment with prophylactic Wilate) was 3.393 as compared with 24.417.

**Table 7: Statistics on SABR in On-Demand (WIL-29) and Prophylaxis Period (WIL-31) by Age Group (All Patients Included in mFAS, N=33)**

Period / Age Group		Spontaneous Annualized Bleeding Rate (SABR) <sup>2</sup>								
		n <sup>1</sup>	N	Mean	Std	Min	Q1	Median	Q3	Max
On-Demand	6 - <12 Years	109	9	22.84	16.090	6.8	11.01	18.86	27.94	60.2
	12 - <17 Years	74	6	21.74	15.725	4.9	12.85	18.44	25.26	50.5
	>= 17 Years	246	18	26.11	23.565	5.5	13.18	16.95	32.23	92.8
	Total	429	33	24.42	20.051	4.9	12.85	18.68	27.94	92.8
Prophylaxis	6 - <12 Years	23	9	2.53	4.145	0.0	0.00	0.98	2.96	12.9
	12 - <17 Years	9	6	1.49	1.872	0.0	0.00	0.98	1.96	5.0
	>= 17 Years	75	18	4.16	7.382	0.0	0.00	0.48	4.98	24.6
	Total	107	33	3.23	5.915	0.0	0.00	0.98	2.96	24.6

Source: WIL-31 Summary of Clinical Efficacy, Table 1-2

1. Total number of spontaneous bleeding episodes within the corresponding period

2. The calculations of SABR is based on total number of spontaneous bleeding episodes within the corresponding period relative to time in period

Abbreviations: mFAS = modified full analysis set, SABR = spontaneous annualized bleeding rate.

*Reviewer Comment(s): The product shows a significant decreased in ABR when Wilate was used in a prophylactic setting (WIL-33) versus in an on-demand setting and this secondary endpoint was met for this study.*

- **Secondary Objective #2**—Incremental IVR of Wilate for VWF:Ac (VWF:RCo and VWF:(b) (4) and FVIII:C (OS and CHR) over time (at baseline and at 1, 2, 3, 6, 9, and 12 months of treatment)

The FVIII and VWF IVRs observed in this study are consistent with those seen previously with Wilate (Study WIL-12), with slightly lower IVRs in children. Please see the clinical pharmacology review for further details.

- **Secondary Objective #3**—for pediatric patients, baseline PK profile characteristics of VWF:Ac (VWF:RCo) and FVIII:C (OS and CHR) based on blood samples taken pre-dose and 1, 3, 9, 24, 48, and 72 hours after dosing

Please see Clinical Pharmacology review memo for details regarding this secondary objective.

- **Secondary Objective #4**- Safety and tolerability of Wilate by monitoring AEs throughout the study. Please see below [Section 6.1.12](#) for safety analysis.

- **Secondary Objective #5**- Wilate consumption data (VWF/FVIII IU/kg per month per patient) for prophylaxis included:

- A total of 30 out of 33 (90.9%) of patients received Wilate 2 times per week and 3 out of 33 (9.1%) of patients received Wilate 3 times per week at the study start
- A total of 23 out of 33 (69.7%) of patients received Wilate 2 times per week and 10 out of 33 (30.3%) of patients received Wilate 3 times per week.

**Table 8: Wilate Consumption for Prophylaxis, Study WIL-31 (mFAS Population, N=33)**

Parameter	Statistic	6-<12 yrs (N=9)	12-<17 yrs (N=6)	≥17 yrs (N=18)	Total (N=33)
Number of EDs	Mean (SD)	115.89 (23.078)	103.17 (21.179)	101.17 (39.514)	105.55 (32.782)
	Median (range)	106.00 (95-159)	102.50 (78-141)	107.00 (2-145)	106.00 (2-159)
Dose per ED (IU/kg)	Mean (SD)	30.57 (7.477)	34.79 (3.999)	30.07 (6.681)	31.06 (6.589)
	Median (range)	32.95 (21.2-39.6)	35.81 (28.4-38.9)	28.84 (20.0-45.2)	32.48 (20.0-45.2)
Dose per Injection (IU/kg)	Mean (SD)	30.57 (7.477)	34.79 (3.999)	30.03 (6.619)	31.04 (6.559)
	Median (range)	32.95 (21.2-39.6)	35.81 (28.4-38.9)	28.84 (20.0-44.8)	32.48 (20.0-44.8)
Dose per Week in Study (IU/kg)	Mean (SD)	68.40 (27.461)	68.20 (17.674)	64.19 (23.919)	66.06 (23.359)
	Median (range)	66.34 (42.6-113.7)	64.44 (52.6-101.0)	53.46 (28.2-109.6)	58.28 (28.2-113.7)
Dose per Month in Study (IU/kg)	Mean (SD)	297.41 (119.407)	296.53 (76.848)	279.10 (104.005)	287.26 (101.569)
	Median (range)	288.44 (185.4-494.6)	280.20 (228.6-439.3)	232.48 (122.7-476.3)	253.42 (122.7-494.6)

Source: WIL-31 Summary of Clinical Efficacy, Table 3  
Abbreviations: ED = exposure day, mFAS = modified full analysis set, SD = standard deviation.

*Reviewer Comment(s): Secondary Objectives #2 through 5 for WIL-31 were met.*

#### 6.1.11.3 Subpopulation Analyses

The analyses of efficacy endpoints' efficacy of prophylactic treatment and efficacy in treatment in breakthrough bleeding events (BEs) were presented in age groups (6 to 11, 12 to 16, and ≥17 years of age) and VWD type (severe Type 1, Type 2, and Type 3).

The mFAS population was broken down into the following subgroup age groups (6 to 11, 12 to 16, and ≥17 years of age). There were 9 patients 6 to 11 years of age, 6 patients 12 to 16 years of age, and 18 patients ≥17 years of age.

In a subgroup analysis for pediatric patients 6 to 11 years of age, the TABR for treatment with prophylactic Wilate was 3.73 compared to 32.54 for treatment with on-demand Wilate. In pediatric patients 12 to 16 years of age the TABR for treatment with prophylactic Wilate was 4.28 compared to 28.91 for treatment with on-demand Wilate.

*Reviewer Comment(s): The primary endpoint was met in pediatric patients 6 to 16 years of age and Wilate's TABR was significantly lower for treatment under prophylactic use of Wilate, showing that the use of prophylactic Wilate in patients from 6 to 17 years of age to prevent bleeding episodes is effective.*

#### 6.1.11.4 Dropouts and/or Discontinuations

Please see above [6.1.10.1.3 Subject Disposition](#) for a detailed account of any patients who dropped out of or discontinued the WIL-31 study.

## 6.1.12 Safety Analyses

### 6.1.12.1 Methods

The clinical safety of Wilate in patients with VWD was assessed in the pivotal prophylaxis study (WIL-31) by monitoring AEs, vital signs, laboratory parameters, and immunogenicity. The total safety population of WIL-31 comprised 43 treated patients.

Additionally, safety data are pooled for all 9 Wilate studies in VWD patients (WIL-31, WIL-14, TMAE-104, TMAE-105, TMAE-106, TMAE-109, WIL-12, WIL-21, and WIL-24). In the pooled analysis there were a total of 215 (198 individual) patients.

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

This section will discuss the safety analysis of the WIL-31 trial. For the safety analysis of the pooled safety data (integrated safety analysis), please see below [Section 8](#).

### 6.1.12.2 Overview of Adverse Events

A total of 26 (60.5%) patients experienced 78 TEAEs. Five SAEs occurred in 4 (9.3%) patients. Two AEs in 2 (4.7%) patients led to permanent discontinuation of study medication (see below [Section 6.1.12.7](#)). The investigator assessed two patients who experienced AEs as probably/possibly related to the study treatment and the Applicant assessed four patients who experienced AEs as probably/possibly related to the study treatment.

Of the 43 patients in the safety analysis population, 14 (32.6%) experienced mild AEs, 8 (18.6%) experienced moderate AEs and 4 (9.3%) patients experienced severe AEs (menorrhagia, limb injury, food poisoning, and hemorrhoidal hemorrhage).

The most common AEs were headache (7 patients) and respiratory tract infection (5 patients), COVID-19 (3 patients). Hypersensitivity, allergic rhinitis, pruritis, pain in extremity pyrexia and Parvovirus B19 occurred in two patients each.

None of the headaches that occurred were thought to be related to Wilate.

### 6.1.12.3 Deaths

There were no deaths in WIL-31.

### 6.1.12.4 Nonfatal Serious Adverse Events

Four patients experienced five SAEs during this study. All SAEs were considered not related to Wilate.

**Table 9: WIL-31 Nonfatal Serious Adverse Events**

Patient	MedDRA Preferred Term	Reason for seriousness	Study day at onset	Outcome	Causality
(b) (6)	COVID-19 pneumonia	Requires or Prolongs hospitalization	146	Recovered/ Resolved	Not related
(b) (6)	Menorrhagia	Requires or Prolongs hospitalization	295	Recovered/ Resolved	Not related
	Menorrhagia	Requires or Prolongs hospitalization	344	Recovered/ Resolved	Not related
(b) (6)	Food poisoning	Requires or Prolongs hospitalization	106	Recovered/ Resolved	Not related
(b) (6)	Haemorrhoidal haemorrhage	Requires or Prolongs hospitalization	68	Recovered/ Resolved	Not related

Source: WIL-31 Study report body, Table 34

Abbreviations: COVID-19 = Coronavirus Disease 2019, MedDRA = Medical Dictionary for Regulatory Activities.

Patient (b) (6) (diagnosed with Type 3 VWD) developed COVID-19 pneumonia on Study Day 146 and required hospitalization.

Patient (b) (6) experienced two events of menorrhagia on Study Day 295 and Study Day 344.

Patient (b) (6) had food poisoning on Study Day 106.

Patient (b) (6) had a hemorrhoidal hemorrhage on Study Day 68.

*Reviewer Comment(s): The Agency agrees with the Applicant that none of the 5 SAEs that occurred to the 4 subjects are related to the study product. All SAEs recovered/resolved. Two subjects had to discontinue Wilate due to mild chest discomfort and a moderate hypersensitivity reaction.*

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

##### Hypersensitivity Reactions

Two patients had hypersensitivity reactions in WIL-31. Patient (b) (6) experienced a moderate hypersensitivity reaction that the investigator attributed to Wilate. This patient had to later discontinue treatment with Wilate. Patient WIL(b) (6) had a mild hypersensitivity reaction to dust, which the investigator considered unrelated to Wilate.

##### Thromboembolic Events

- In VWD, continued treatment using a FVIII-containing VWF product may cause an excessive rise in FVIII activity, which may increase the risk of thromboembolic events. It is recommended

to monitor plasma levels of VWF:RCo and FVIII activities in patients receiving Wilate to avoid sustained excessive VWF and FVIII activity levels.

There were no thromboembolic events in WIL-31.

### Neutralizing Antibodies

Please see below [Section 8.5.8](#).

#### 6.1.12.6 Clinical Test Results

No safety concerns were raised by clinical laboratory results.

Vital Signs—Patient (b) (6) had a potentially clinically significant tachycardia (heart rate 121 beats per minute) before the start of surgery.

#### 6.1.12.7 Dropouts and/or Discontinuations

Two patients discontinued the study, one due to a hypersensitivity reaction and the other due to mild chest discomfort after Wilate infusion.

#### 6.1.13 Study Summary and Conclusions

Overall, Wilate demonstrated efficacy with reduction in TABR with the use of prophylactic Wilate compared to on-demand Wilate. Efficacy was based on the TABR during prophylactic treatment with Wilate compared to the TABR during on-demand treatment recorded for the same patient. The primary endpoint was to demonstrate that TABR during prophylactic treatment lowers the patients' TABR during on-demand treatment by >50%. TABR was calculated as the total number of traumatic, spontaneous, and other bleeds (excluding menstrual bleeds) during the prophylactic treatment period. Surgery periods and bleeding events were excluded from the calculation of TABR.

The primary endpoint for this study was met- the TABR for treatment with prophylactic Wilate treatment was 5.49 compared to 33.38 for treatment with on-demand Wilate treatment with a rate ratio was 0.165 ( $p < 0.0001$ , 95% CI: 0.1019, 0.2656). The SABR for treatment with prophylactic Wilate treatment was 3.39 as compared with 24.42 for treatment with on-demand Wilate treatment with a rate ratio of 0.1389 ( $p < 0.0001$ , 95%CI 0.0766, 0.2519). The total bleeding rate (excluding patients with increased bleeding unrelated to VWD) was 3.96 for treatment with prophylactic Wilate compared to 33.72 for treatment with on-demand Wilate, with a rate ratio of 0.149 ( $p < 0.001$ , 95% CI 0.834, 0.1649).

The safety profile is acceptable and there were no new major safety signals were found.

## **7. INTEGRATED OVERVIEW OF EFFICACY**

Data from studies WIL-14, TMAE-104, TMAE-105, TMAE-106, and TMAE-109 was submitted to support efficacy along with the data from the pivotal study WIL-31.

**Table 10: Studies/Clinical Trials Reviewed to Support Efficacy**

<b>Study</b>	<b>Safety Population</b>	<b>Design</b>	<b>Treatment</b>	<b>Primary Objective</b>
WIL-31 (pivotal study)	43 patients with inherited VWD, Type 1, 2A, 2B, M, or 3 requiring substitution with a VWF-containing product (age ≥6 years)	Phase 3, open-label, noncontrolled, multicenter trial (14 centers in Bulgaria, Belarus, Croatia, Hungary, Lebanon, Russia, Ukraine, and the United States)	Wilate-Routine prophylaxis, surgical prophylaxis, and on-demand treatment	Efficacy in the prophylactic treatment of previously treated patients with VWD
TMAE-104	41 patients with inherited VWD, any type, not responding to DDAVP (age ≥6 and ≤85 years)	Phase 3, open-label, noncontrolled, multicenter trial (15 centers in Austria, Finland, Norway, Poland, Portugal, Sweden, and the United Kingdom)	Wilate-Surgical prophylaxis and on-demand treatment	Efficacy using plasma levels of FVIII:C, VWF:Ag, VWF:CB, and VWF:RCo as a surrogate marker
TMAE-105	14 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open-label, noncontrolled, multicenter trial (2 centers in Poland and Bulgaria)	Wilate-PK assessment, surgical prophylaxis, and on-demand treatment	PK for VWF:Ag, VWF:CB, VWF:RCo, and plasma level of FVIII:C as a surrogate marker for efficacy
TMAE-106	14 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open-label, noncontrolled, multicenter trial (8 centers in Germany)	Wilate-PK assessment	PK of VWF:Ag, VWF:CB, VWF:RCo, and plasma level of FVIII:C
TMAE-109	16 patients with inherited VWD, any type, not responding to DDAVP (age ≥12 and ≤65 years)	Phase 2, open-label, noncontrolled, multicenter trial (2 centers in Poland and Bulgaria)	Wilate-Surgical prophylaxis treatment	Efficacy using plasma levels of FVIII:C, VWF:Ag, VWF:RCo as surrogate markers

Study	Safety Population	Design	Treatment	Primary Objective
WIL-14	15 children with inherited VWD, any type, DDAVP treatment known or suspected to be inadequate	Phase 2, open-label, noncontrolled, multicenter trial (7 centers in Germany, Poland, France, and the Czech Republic)	Wilate-Surgical prophylaxis, on-demand treatment	Efficacy in prevention and/or treatment of bleeding episodes and during surgery

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

## 7.1 Indication #1—Wilate Used for Prophylaxis in Patients With VWD

### 7.1.1 Methods of Integration

Data from the WIL-31 study supports the use of Wilate for routine prophylaxis in patients with VWD 6 years of age and older. Data from TMAE-104, TMAE-105, TMAE-106, TMAE-109 and WIL-14 supports the use of Wilate for surgical prophylaxis in children and adults with VWD. In the studies TMAE-104, TMAE-105, TMAE-106, TMAE-109 and WIL-14 there were 3,352 prophylactic exposure days in 49 patients.

### 7.1.2 Demographics and Baseline Characteristics

**Table 11: Overview of Demographic Data**

	Supportive					Pivotal
	Study TMAE-104	Study TMAE-105	Study TMAE-106	Study TMAE-109	Study WIL-14	Study WIL-31
Number of patients per study	41	14	14	16	15	43 <sup>\$</sup>
Number of unique individuals	37	14	14	5	15	43
Population studied	Inherited VWD ≥6 to ≤85 years	Inherited VWD ≥12 to ≤65 years	Inherited VWD ≥12 to ≤65 years	Inherited VWD ≥12 to ≤65 years	Inherited VWD <6 years	Inherited VWD ≥6 years
VWD Type:						
3	27	9	4	8	6	22
2/2A/2B/2M/2N	1/6/3/1/0	0/1/2/0/0	0/6/0/0/2	0/2/0/0/0	0/2†/2/0/0	5
1	3	2	2	6	5	6
Mean age, years (range)	36 (5–73)	36 (13–64)	39 (16–77)	37 (14–63)	3 (1–5)	22 (7–61)
Mean height, cm (range)	161 (110–187)	171 (158–183)	167 (147–185)	171 (159–183)	99 (76–122)	161 (118–185)
Mean weight, kg (range)	64 (19–106)	74 (53–104)	72 (42–95)	72 (55–104)	16 (9–24)	62 (21–110)
Sex (male/female)	18/23	8/6	4/10	10/6	10/5	26/17

Source: Summary of Clinical Efficacy, Source 2.7.4 Appendix I

\* For all studies each individual is only listed once.

<sup>\$</sup>. 10 patients had unconfirmed VWD status.

†. Includes one patient that was classified as WWD Type 1 or 2 in the WIL-14 CSR and later reclassified as WWD Type 2A.

Abbreviations: CSR = clinical study report, VWD = von Willebrand disease.

### 7.1.3 Supportive Analysis

In total, 3352 prophylactic exposure days in 49 patients were documented in the supportive studies TMAE-104, TMAE-105, TMAE-106, TMAE-109, and WIL-14.



There were 19 patients, 12 of which had Type 3 VWD, who received prophylactic treatment for at least 10 consecutive weeks. For these patients, the mean bleeding frequency before the start of Wilate was 4.03 bleeds per month (median 3.3, range 0.8-28). This mean bleeding frequency dropped to a mean of 1.23 bleeds per months during Wilate prophylaxis (median 1.2, range 0.3 to 2.1). The median prophylactic dose was 29.9 IU/kg (range 12 to 64 IU/kg).

### Treatment of Bleeds

In total, 2,344 on-demand treatment days in 56 patients were documented for Studies TMAE-104, TMAE-105, TMAE-106, TMAE-109 and WIL-14. In these studies, 85% of a total of 1,484 bleeds were observed in patients with Type 3 VWD. A total of 160 out of 1,484 bleeds were rated as 'severe', the remainder were rated as 'mild' or 'moderate'. A total of 1,321 out of 1,484 bleeds were treated with Wilate during 2,344 exposure days. The duration of treatment for the 1,321 bleeds was 3 days or less. A total of 90% (n=832) of the bleeds resolved within 1 day, 19% (n=248) of the bleeds resolved in 2 days, and 8% (n=110) of the bleeds resolved in 3 days. Please see [Table 12](#).

**Table 12: Pooled Analysis in Supportive Studies: Efficacy Assessment and Administered Doses in Treated and Rated Bleeds**

Predominant Site of Bleeds*	No. of Bleeds† [n]	Excellent/Good Efficacy [%]‡	Mean Dose/Infusion [IU/kg]
Joints	635	93%	27.0
Epistaxis	180	68%	24.0
Gastrointestinal	140	81%	44.3
Oral	69	70%	25.7
Gynaecologic	67	91%	34.6
Other	222	97%	24.8
<b>Total</b>	<b>1313</b>	<b>88%</b>	<b>28.4</b>

Source: Module 5, Section 5.3.5.3: Pooled Analysis in VWD, August 3, 2010, Table 2.1/12

\* Pooled analysis of Studies TMAE-104, TMAE-105, TMAE-106, TMAE-109 and WIL-14.

† Only based on rated and treated bleeds.

‡ Last efficacy rating by investigator or patient per treatment episode.

Abbreviations: IU = international units, VWD = von Willebrand disease.

### Efficacy in Surgical Prophylaxis

Efficacy data was assessed in a pooled analysis of 42 patients that had 69 surgeries from Studies TMAE-104, TMAE-105, TMAE-106, TMAE-109, and WIL-14. The overall efficacy was determined at the discretion of the treating physician (excellent, good, moderate or none) in Studies TMAE-104, TMAE-105, TMAE-106, and TMAE-109. In WIL-14, efficacy was assessed per infusion rather than per overall procedure. However, as all individual infusions in all patients were rated as excellent or good (i.e., successful), the Applicant stated that it can be reasonably assumed that overall efficacy per procedure was successful (excellent or good). Overall efficacy of Wilate was judged as successful in 41 of 42 minor surgeries (97.6%) and 49 of 53 major surgeries (92.5%).

#### 7.1.4 Additional Efficacy Issues/Analyses

As above.

### 7.1.5 Efficacy Conclusions

As above.

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

In the below listed trials, patients with VWD underwent substantial exposure to Wilate, and the safety data collected from these studies was submitted to support the safety profile of Wilate.

### 8.2 Safety Database

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data are pooled for all 9 Wilate studies in patients with VWD (WIL-31, WIL-14, TMAE-104, TMAE-105, TMAE-106, TMAE-109, WIL-12, WIL-21, and WIL-24).

In the pooled analysis there were a total of 215 (198 individual) patients.

**Table 13: Studies Used in Integrated Safety Analysis of Wilate for VWD**

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

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

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

*Reviewer Comment(s): The safety data submitted from the above listed nine studies is adequate to assess a thorough analysis of Wilate's safety profile.*

## 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

**Table 14: Extent of Total Exposure to Wilate (All Studies)**

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

Source: Module 2, Section 2.7.4; Appendix I, Table 2-1

†. Includes Wilate administered for any purpose.

For Study WIL-24, all Wilate infusions that were recorded as concomitant medications were excluded.

In the presentation of total over all studies, subjects participating in more than one study were only counted once. In the surgery study WIL-24, two subjects participated twice (i.e. two subjects were treated for two surgeries) but are only counted once as well. Abbreviations: ED = exposure day, IU = international unit.

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

### 8.2.3 Categorization of Adverse Events

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

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

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

TMAE-106—AEs were grouped by body system according to MedDRA system organ class.

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

Safety data are pooled for all 9 Wilate studies in patients with VWD (WIL-31, WIL-14, TMAE-104, TMAE-105, TMAE-106, TMAE-109, WIL-12, WIL-21, and WIL-24). All of these trials were for differing indications, but only in patients with VWD. Different doses were used across these trials as well.

*Reviewer Comment(s): Pooling of data across these nine trials is problematic as it was collected in different populations; Wilate was given at different times and with differing doses. However, this pooled data does provide a thorough analysis of the safety and tolerability of Wilate.*

### 8.4 Safety Results

#### 8.4.1 Deaths

No deaths occurred in the WIL-31 or WIL-24 studies.

One patient died in the TMAE-104 study. This was a 48-year-old male patient with a history of Type 3 VWD who died from complications including renal and respiratory failure after an uncontrolled gastrointestinal bleeding event. The investigator adjudicated this death as unrelated to Wilate.

*Reviewer Comment(s): There were no deaths in the pivotal trial WIL-31. After careful review of the patient death in the TMAE-104 study, this reviewer considers that is unlikely related to Wilate.*

### 8.4.2 Nonfatal Serious Adverse Events

#### Nonfatal Serious AdversEvents From Pooled Population

**Table 15: Frequency of Serious Adverse Events**

<b>SAE, Preferred Term</b>	<b>Patients With SAE–n (%)</b>	<b>SAEs (N)</b>
Any class	26 (13.1%)	87
Gastrointestinal disorders	12 (6.1%)	53
Gastrointestinal hemorrhage	5 (2.5%)	33
Melena	2 (1%)	14
Food poisoning	1 (0.5%)	1
Gastritis erosive	1 (0.5%)	1
Hematemesis	1 (0.5%)	1
Hemorrhoidal hemorrhage	1 (0.5%)	1
Mouth hemorrhage	1 (0.5%)	1
Pancreatitis, acute	1 (0.5%)	1
Infections and infestations	4 (2%)	5
COVID-19 pneumonia	1 (0.5%)	1
Device related infection	1 (0.5%)	1
Device related sepsis	1 (0.5%)	1
Parotitis	1 (0.5%)	1
General disorders and administration site conditions	3 (1.5%)	3
Catheter site hemorrhage	1 (0.5%)	1
Chest pain	1 (0.5%)	1
Multiple organ dysfunction syndrome	1 (0.5%)	1
Injury poisoning and procedural complications	3 (1.5%)	3
Accident	1 (0.5%)	1
Head injury	1 (0.5%)	1
Scratch	1 (0.5%)	1
Investigations	3 (1.5%)	3
Parvovirus B19	3 (1.5%)	3
Musculoskeletal and connective tissue disorders	3 (1.5%)	6
Back pain	1(0.5%)	1
Hemarthrosis	1(0.5%)	1
Synovitis	1(0.5%)	1
Torticollis	1(0.5%)	1
Reproductive system and breast disorders	2 (1%)	3
Heavy menstrual bleeding	1(0.5%)	1
Vaginal hemorrhage	1(0.5%)	1
Respiratory, thoracic, and mediastinal disorders	2 (1%)	6
Epistaxis	2 (1%)	6
Blood and lymphatic system disorders	1 (0.5%)	1
Blood loss anemia	1 (0.5%)	1
Immune system disorders	1 (0.5%)	1
Transplant rejection	1 (0.5%)	1
Nervous system disorders	1 (0.5%)	1
Syncope	1 (0.5%)	1

SAE, Preferred Term	Patients With SAE-n (%)	SAEs (N)
Surgical and medical procedures	1 (0.5%)	1
Tooth extraction	1 (0.5%)	1
Vascular disorders	1 (0.5%)	1
Hemorrhage	1 (0.5%)	1

Source: Appendix I, Table 1-9

Patients with more than one adverse event of the same preferred term were counted only once.

Events with the same preferred term occurring more than once within a patient were counted as a single event for the tabulation.

AEs were considered probably/possibly related if either the investigator or the sponsor assessed the AE as related. Sponsor assessment is available in Study WIL-31 only and was not collected in previous studies.

Patients participating in more than one study were counted as one patient each. In the surgery study WIL-24, two subjects participated twice (i.e., two subjects were treated for two surgeries) but are only counted once as well.

Abbreviations: AE = adverse event, COVID-19 = Coronavirus Disease 2019 SAE = serious adverse event.

### 8.4.3 Study Dropouts/Discontinuations

#### Pivotal Trial WIL-31

- Patient (b) (6) : withdrew due to hypersensitivity reaction
- Patient (b) (6) : withdrew due to chest discomfort

See above [Section 6.1.12.7](#) for further details.

### 8.4.4 Common Adverse Events

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

**Table 16: TEAEs Possibly or Probably Related to Treatment (All Studies)**

Preferred Term	Patients With AE-n (%)	AEs (N)
Any class	20 (10.1%)	34
Investigations	6 (3%)	6
Parvovirus B19 test positive	5 (2.5%)	5
Blood pressure decreased	1 (0.5%)	1
Nervous system disorders	5 (2.5%)	6
Dizziness	3 (1.5%)	4
Dysgeusia	1 (0.5%)	1
Headache	1 (0.5%)	1
Immune system disorders	4 (2%)	6
Hypersensitivity	4 (2%)	6
Skin and subcutaneous tissue disorders	4 (2%)	4
Urticaria	2 (1%)	2
Pruritis	1 (0.5%)	1
Rash	1 (0.5%)	1
Gastrointestinal disorders	3 (1.5%)	3
Abdominal discomfort	1 (0.5%)	1
Nausea	1 (0.5%)	1
Vomiting	1 (0.5%)	1

Preferred Term	Patients With AE-n (%)	AEs (N)
General disorders and administration site conditions	2 (1%)	5
Chest discomfort	2 (1%)	4
Feeling hot	1 (0.5%)	1
Blood and lymphatic system disorders	1 (0.5%)	1
Anemia	1 (0.5%)	1
Ear and labyrinth disorders	1 (0.5%)	1
Vertigo	1 (0.5%)	1
Respiratory, thoracic, and mediastinal disorders	1 (0.5%)	1
Dyspnea	1 (0.5%)	1
Vascular disorders	1 (0.5%)	1
Dyspnea	1 (0.5%)	1

Source: Appendix I, Table 1-8

Patients with more than one adverse event of the same preferred term were counted only once.

Events with the same preferred term occurring more than once within a patient were counted as a single event for the tabulation.

AEs were considered probably/possibly related if either the investigator or the sponsor assessed the AE as related. Sponsor assessment is available in Study WIL-31 only and was not collected in previous studies.

Patients participating in more than one study were counted as one patient each. In the surgery study WIL-24, two subjects participated twice (i.e. two subjects were treated for two surgeries) but are only counted once as well.

Abbreviations: AE = adverse event, N = number of patients, n = number of AEs, TEAE = treatment-emergent adverse event.

### Supportive Studies

Six non-serious AEs were considered as clinically significant:

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

*Reviewer Comment(s): The submitted safety data from the supportive studies is acceptable and the pivotal trial's (WIL-31) safety profile is similar to that of the supportive safety study data that was submitted.*

## 8.5 Additional Safety Evaluations

### 8.5.8 Immunogenicity (Safety)

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

#### Study WIL-31

Sampling for inhibitors took place during WIL-31 at baseline in adults, at screening in pediatric patients and if inhibitor development was suspected at any time. Reasons that inhibitor development may be suspected included an unexplained need to increase the dose of Wilate and/or prolonged bleeding among others. VWF and FVIII inhibitor tests were performed at a central laboratory and if results were positive, a re-test was performed for confirmation, preferably within 15 days of the first positive test.

Six patients were tested for inhibitors during WIL-31. Only two patients tested positive for inhibitors, however, both patients' screening retention samples were tested and found to be positive for VWF inhibitors at study entry. One of these patients tested positive for VWF inhibitor at the 6, 9 and 12-month visits and the other patient tested positive for VWF inhibitor at the 6 and 9-month visits but tested negative at the 12-month visit. As both patients were benefitting from treatment with prophylactic Wilate as their bleeding frequency decreased, they were kept on-study.

#### Study WIL-14

No subject developed VWF or FVIII inhibitors.

#### Study WIL-24

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

*Reviewer Comment(s): Patients with VWD have been reported to develop inhibitory antibodies to VWF. These antibodies may render therapy ineffective and as a result, patients may experience uncontrolled bleeding. Only two subjects from WIL-31 developed an inhibitor, however, it ended up that both patients had VWF inhibitors at baseline. Routine surveillance is recommended.*

## 8.6 Safety Conclusions

A total of 26 (60.5%) patients experienced 78 TEAEs. Five SAEs occurred in 4 patients (9.3%), none of which were attributed to Wilate. The SAEs included COVID-19 pneumonia, 2 episodes of menorrhagia, food poisoning and a hemorrhoidal hemorrhage. Two AEs (mild chest discomfort and a moderate hypersensitivity reaction) occurred in two patients which led to the discontinuation of Wilate. The investigator assessed two patients who experienced AEs as



probably/possibly related to the study treatment, and the Applicant assessed four patients who experienced AEs as probably/possibly related to the study treatment.

Of the 43 patients in the safety analysis population, 14 (32.6%) experienced mild AEs, 8 (18.6%) experienced moderate AEs and 4 (9.3%) patients experienced severe AEs (menorrhagia, limb injury, food poisoning and hemorrhoidal hemorrhage).

The most common AEs were headache (seven patients) and respiratory tract infection (five patients), COVID-19 (three patients). Hypersensitivity, allergic rhinitis, pruritis, pain in extremity pyrexia, and Parvovirus B19 occurred in two patients each.

## **9. ADDITIONAL CLINICAL ISSUES**

### **9.1 Special Populations**

#### **9.1.1 Human Reproduction and Pregnancy Data**

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

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

#### **9.1.2 Use During Lactation**

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

#### **9.1.3 Pediatric Use and PREA Considerations**

The Applicant has submitted safety and efficacy data for children 6 to less than 18 years of age. Please see above [Section 6.1.11.3](#) for this subpopulation analysis.

Please see above [Section 5.4](#) for further details on pediatric use and Pediatric Research Equity Act considerations. The safety profile is acceptable and there were no new major safety signals were found.

## **10. CONCLUSIONS**

Wilate has demonstrated efficacy for treatment with routine prophylaxis to reduce the frequency of BEs in adults and children 6 years of age and older with VWD. The primary endpoint for this study was met—the TABR for treatment with prophylactic Wilate treatment was 5.49 compared to 33.38 for treatment with on-demand Wilate treatment, with a rate ratio was 0.165 ( $p < 0.0001$ , 95% CI: 0.1019, 0.2656).

The Applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled clinical investigation providing compelling evidence of clinical

benefit, supported by the initial clinical investigation and preclinical studies. The overall benefit risk assessment is favorable, and the clinical review team recommends regular approval for the use of Wilate for routine prophylaxis to reduce the frequency of BEs in adults and children 6 years of age and older with VWD.

## **11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS**

### **11.1 Risk-Benefit Considerations**

**Table 17: Risk-Benefit Considerations**

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<p>VWD arises from a congenital VWF deficiency and is classified as Type 1, Type 2, or Type 3</p> <ul style="list-style-type: none"> <li>• Type 1: partial quantitative deficiency, 70-80% of patients</li> <li>• Type 2: partial qualitative deficiency, 20%</li> <li>• Type 3: complete deficiency</li> </ul>	<p>Patients with congenital VWF deficiency are at risk of frequent bleeding episodes, which puts them at risk for potential morbidity and mortality.</p>
<b>Unmet Medical Need</b>	<ul style="list-style-type: none"> <li>• Currently, Vonvendi is approved for the use routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD receiving on-demand therapy that are 18 years of age and older.</li> <li>• There are no currently approved therapies to reduce the frequency of bleeding episodes in patients with severe Type 1 and Type 2 VWD and no currently approved therapies to reduce the frequency of bleeding episodes in patients with Type 3 VWD under 18 years of age with routine prophylaxis.</li> </ul>	<p>There is an unmet medical need, as there are no currently approved therapies that prophylactically reduce the frequency of bleeding episodes in patients with severe Type 1 and Type 2 VWD and no currently approved therapies to reduce the frequency of bleeding episodes in patients with Type 3 VWD under 18 years of age.</p>
<b>Clinical Benefit</b>	<p>Nine trials were submitted to evaluate the safety and effective of Wilate</p> <ul style="list-style-type: none"> <li>• The main efficacy outcome from the pivotal WIL-31 study demonstrated the reduction in TABR with the use of prophylactic Wilate compared to the TABR during on-demand treatment recorded for the same patient.</li> <li>• The TABR for treatment with prophylactic Wilate treatment was 5.49 compared to 33.38 for treatment with on-demand Wilate treatment, with a rate ratio of 0.165 (p&lt;0.0001, 95% CI: 0.1019, 0.2656).</li> </ul>	<p>Strong evidence indicates that treatment with prophylactic Wilate reduces the frequency of bleeding in patients with VWD 6 years of age and older.</p>
<b>Risk</b>	<ul style="list-style-type: none"> <li>• The most common adverse reactions to treatment with Wilate (≥1%) in patients with VWD were hypersensitivity reactions, urticaria, chest discomfort, and dizziness. The most common adverse reaction to treatment with Wilate (≥1%) in previously treated patients with hemophilia A was pyrexia (fever).</li> <li>• The most serious adverse reactions to treatment with Wilate in patients with VWD and hemophilia A are hypersensitivity reactions.</li> </ul>	<p>Evidence indicated the risk of hypersensitivity is manageable.</p>

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<b>Decision Factor</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<b>Risk Management</b>	<ul style="list-style-type: none"><li>• The most substantial risks of treatment are hypersensitivity reactions, thromboembolic events, and neutralizing antibodies.</li><li>• In WIL-31, 2 of the 43 patients who received routine prophylactic treatment with Wilate, no patient had thromboembolic events and 2 patients developed neutralizing antibodies to VWF; however both patients were found to have these antibodies at screening.</li></ul>	If approved, routine measures such as the package insert, and the current pharmacovigilance plan would be adequate to manage the risk.

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

### **11.2 Risk-Benefit Summary and Assessment**

The clinical benefit of Wilate for routine prophylaxis in patients with VWD 6 years of age and older exceeds the risk.

### **11.4 Recommendations on Regulatory Actions**

I recommend Approval.

### **11.5 Labeling Review and Recommendations**

I recommend Approval of labeling for the PI and carton.

### **11.6 Recommendations on Post marketing Actions**

None.