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Clinical Pharmacology BLA Review

Division of Clinical Evaluation General Medicine
Office of Clinical Evaluation
Office of Therapeutic Products

BLA	125251/382
Product	Wilate (Human coagulation F VIII and Von Willebrand Factor, von Willebrand Factor/Coagulation F VIII Complex) Powder & Solvent for solution for injection (intravenous use), 500 IU and 1000 IU
Sponsor	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Indication	Von Willebrand Disease
Date Received	01/31/2023
Reviewer	Xiaofei Wang, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation General Medicine
RPM	Catherine Tran
Through	Prasad Mathew, MD. Chief, Benign Hematology Branch Division of Clinical Evaluation Hematology

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1 EXECUTIVE SUMMARY

On January 31, 2023, OCTAPHARMA Pharmazeutika Produktionsges.m.b.H. submitted a Prior Approval Supplement (PAS) seeking an additional indication for Wilate® (Human coagulation F VIII and Von Willebrand Factor, von Willebrand Factor/Coagulation F VIII Complex) for routine prophylaxis to reduce the frequency of bleeding episodes in children and adults with von Willebrand diseases (VWD). The proposed dosing regimen for routine prophylaxis in patients age 6 and older is 20- 40 IU/kg two to three times per week.

Wilate is currently approved for 1) on-demand treatment and control of bleeding episodes and perioperative management of bleeding in children and adults with von Willebrand diseases; and 2) routine prophylaxis to reduce the frequency of bleeding episodes and on-demand treatment and control of bleeding episodes in children and adults with hemophilia A.

The clinical pharmacology section of this PAS included one Phase 3, open-label, multicenter, non-controlled study to determine the efficacy, safety, and pharmacokinetics of Wilate® in previous treated patients (≥ 6 years) with VWD (Study # Wil-31). Pharmacokinetics of Wilate® was evaluated in pediatric subjects (6 – 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 (6-16 years) were shorter than those observed previously with Wilate in a population including older patients (12 – 68 years) as reported in the labeling of Wilate: VWF:RCo assay 8.3 (1.7) hours vs. 15.8 (11.0) hours, and FVIII chromogenic assay 14.8 (1.5) hours vs. 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 – 40 IU/kg BW 2 – 3 times per week is acceptable for prophylaxis treatment.

The proposed dosing regimen for Wilate® administered by intravenous (IV) 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 bleeding episodes in children and adults with VWD. From a clinical pharmacology standpoint, the PAS is acceptable to support approval.

2 INTRODUCTION

Wilate is a plasma-derived, stable, highly purified, double virus inactivated concentrate of freeze-dried active von Willebrand factor (VWF) and factor VIII (FVIII) prepared from cryoprecipitate and intended for the treatment of patients with VWD and/or hemophilia A.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

- Administration of Wilate led to immediate correction of both the FVIII and VWF deficiencies. The observed half-lives in Study Wil-31 pediatric population (6-16 years) were shorter than those observed previously with Wilate in a population including older patients (12 – 68 years) as reported in the labeling of Wilate: VWF:RCo assay 8.3 (1.7) hours vs. 15.8 (11.0) hours, and FVIII chromogenic assay 14.8 (1.5) hours vs. 19.6 (6.9) hours. The AUC was also slightly reduced: FVIII chromogenic assay 1937 (±1.53) h*IU/dL vs 2290 (±1045) h*IU/dL, VWF:RCo assay 968 (±1.5) h*IU/dL vs 1235 (±637) h*IU/dL.

- The FVIII and VWF IVRs observed in this study are consistent with those seen previously with Wilate, 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 – 40 IU/kg BW 2 – 3 times per week is acceptable for prophylaxis treatment.

4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125251/382 and finds it acceptable pending the following revisions shown below.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

WILATE contains von Willebrand factor (VWF) and coagulation factor VIII (FVIII), constituents of normal plasma. VWF promotes platelet aggregation and platelet adhesion on damaged vascular endothelium; it also serves as a stabilizing carrier protein for the procoagulant protein FVIII, an essential cofactor in activation of factor X leading to formation of thrombin and fibrin. Patients suffering from VWD have a deficiency or abnormality of VWF. This reduction in VWF plasma concentration results in correspondingly low FVIII activity and abnormal platelet function, thereby resulting in excessive bleeding. [9] After administration, WILATE temporarily replaces missing VWF and FVIII that are needed for effective hemostasis. When infused into a patient with hemophilia A, FVIII binds to VWF in the patient´s circulation. Activated FVIII (FVIIIa) acts as a

cofactor for activated factor IX (FIXa), accelerating the conversion of factor X to activated factor X (FXa). FXa converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Hemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of FVIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of FVIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

12.2. Pharmacodynamics

There have been no specific pharmacodynamic studies on WILATE.

Reviewer's Comment:

Please include pharmacokinetic parameters results for pediatric subjects (6-16 years of age) stratified by age and VWD Type provided in current submission of Study WIL-31.

12.3. Pharmacokinetics

VWD

Pharmacokinetic (PK) profiles of WILATE were determined by FVIII activity, VWF:RCo, VWF:Ag, and VWF:CB obtained from an open label, prospective, randomized, controlled, two-arm cross-over study with WILATE and a comparator product conducted at 6 sites in the US. Twenty-two subjects (≥ 12 years of age) with inherited VWD [type 1, n=6; type 2, n=9 (6 type 2A, 1 type 2B, and 2 type 2M); and type 3, n=7] received an intravenous bolus dose of WILATE containing approximately 40 IU of VWF:RCo/kg body weight. Twenty subjects completed the study as per protocol. PK parameters for VWF:RCo and FVIII activities are summarized in Table 7 and Table 8, respectively.

The PK parameters reported in Table 7 are based on VWF:RCo values obtained using a modified Behring Coagulation System (BCS) analytical method. The modified BCS was used because of its validated lower variability compared with the standard BCS. Measured concentrations (IU VWF:RCo/mL) are higher by the modified BCS than by the standard BCS analytical method which is used in some clinical laboratories. Dose adjusted C_{max} and AUC determined by this modified BCS method are approximately 1.5 times higher than those by the standard BCS method. No difference has been found in incremental recovery.

Table 7 Pharmacokinetic Parameters of VWF:RCo:mean ± SD (range)

Parameters	VWD type I (n = 5)	VWD type II (n = 9)	VWD type III (n = 6)	Total (n = 20)
C_{max} (IU/dL)	74 ± 13 (62 - 91)	77 ± 18 (40 - 100)	79 ± 13 (65 - 102)	76 ± 15 (40 - 102)
$AUC_{(0\text{-}inf)}$ (IU*hr/dL)	1633 ± 979 (984 - 3363)	1172 ± 421 (571 - 1897)	995 ± 292 (527 - 1306)	1235 ± 637 (527 - 3363)
Half-life (hrs)	24.7 ± 17.9 (11.2 - 48.5)	15.3 ± 6.3 (6.0 - 26.4)	9.1± 2.6 (5.7 - 12.9)	15.8 ± 11.0 (5.7 - 48.5)
CL (mL/h/kg)	3.1 ± 1.1 (1.2 - 4.1)	4.1 ± 1.7 (2.0 - 7.1)	4.2 ± 1.4 (3.0 - 6.6)	3.9 ± 1.5 (1.2 - 7.1)
Vss (mL/kg)	81.7 ± 38.5 (15.3 - 74.2)	76.6 ± 35.4 (45.3 - 158.8)	49.4 ± 16.7 (29.7 - 67.1)	69.7 ± 33.2 (29.7 - 158.8)
MRT (hrs)	32.7 ± 25.8 (15.3 - 74.2)	19.7 ± 5.6 (9.9 - 27.1)	11.9 ± 2.9 (9.2 - 15.9)	20.6 ± 14.8 (9.2 - 74.2)
Recovery (%IU/kg)	1.8 ± 0.2 (1.5 - 2.0)	1.8 ± 0.5 (1.0 - 2.4)	2.1 ± 0.3 (1.8 - 2.6)	1.9 ± 0.4 (1.0 - 2.6)

C_{max} = peak concentration; AUC = area under curve; CL = clearance; Vss = volume of distribution at steady state; MRT = mean residence time

Table8 Pharmacokinetic Parameters of FVIII activity: mean ± SD (range) - chromogenic

Parameters	VWD type I (n = 5)	VWD type II (n = 8*)	VWD type III (n = 6)	Total (n = 19*)
C_{max} (IU/dL)	117.1 ± 12.1 (103 - 135)	147.2 ± 32.6 (102 - 206)	120 ± 23 (91 - 148)	112 ± 23 (59 - 148)
$AUC_{(0\text{-}inf)}$ (IU*hr/dL)	1187 ± 382 (523 - 1483)	1778 ± 1430 (544 - 4821)	2670 ± 854 (1874 - 3655)	2290 ± 1045 (464 - 4424)
Half-life (hrs)	17.5 ± 4.9 (10.9 - 23.8)	23.6 ± 8.3 (12.6 - 34.7)	16.1 ± 3.1 (11.8 - 20.1)	19.6 ± 6.9 (10.9 - 34.7)
CL (mL/h/kg)	4.4 ± 3.7 (2.5 - 11.0)	2.5 ± 0.9 (1.2 - 3.5)	2.0 ± 0.6 (1.4 - 2.8)	2.9 ± 2.1 (1.2 - 11.0)
Vss (mL/kg)	95.0 ± 53.8 (57.1 - 190.0)	79.5 ± 23.1 (52.8 - 116.2)	44.2 ± 10.4 (31.8 - 57.1)	72.4 ± 36.2 (31.8 - 190.0)
MRT (hrs)	24.1 ± 5.5 (17.2 - 31.5)	35.1 ± 14.2 (17.5 - 61.6)	23.0 ± 3.7 (18.0 - 27.7)	28.4 ± 11.1 (17.2 - 61.6)
Recovery (%IU/kg)	1.9 ± 0.5 (1.1 - 2.5)	2.2 ± 0.4 (1.6 - 2.8)	2.5 ± 0.5 (2.0 - 3.0)	2.2 ± 0.5 (1.1 - 3.0)

*One subject with implausible long half-life is not included in the summary table, except for recovery result.
C_{max} = peak concentration; AUC = area under curve; CL = clearance; Vss = volume of distribution at steady state; MRT = mean residence time

Hemophilia A

The pharmacokinetics (PK) of WILATE were evaluated in 21 (16 adults and 5 pediatric subjects aged 12-15 years) previously treated patients (PTPs) with severe Hemophilia A within a prospective, open-label, multicenter clinical study. The PK parameters (Table 9) were based on

plasma Factor VIII activity measured by the one-stage clotting assay after a single intravenous infusion of a 50 IU/kg dose.

The PK profile obtained after 6 months of repeated dosing was comparable with the PK profile obtained after the first dose.

Table 9 Pharmacokinetic Parameters of WILATE in 21 Previously Treated Patients (PTP: Mean ± SD)

PK Parameters	Adults (n=16)	Adolescents (n=5)
C_{max} (IU/dL)	113.82 ± 20.53 (77.43 - 142.00)	83.92 ± 9.40 (77.93 – 100.27)
AUC (IU*hr/dL)	1562.10 ± 451.43 (721.92 - 2271.48)	1009.74 ± 172.26 (816.23 - 1287.76)
AUC_{norm} (IU*hr/dL)	31.24 ± 9.03 (14.44 - 45.43)	20.20 ± 3.45 (16.32 - 25.76)
Half-life (hrs)	10.64 ± 2.69 (6.30 - 15.43)	11.41 ± 1.93 (9.37 – 14.57)
CL (dL/h/kg)	0.035 ± 0.013 (0.02 - 0.07)	0.051 ± 0.008 (0.04 - 0.06)
Vd (dL/kg)	0.53 ± 0.13 (0.36 - 0.82)	0.73 ± 0.13 (0.53 - 0.85)
MRT (hrs)	15.81 ± 3.63 (10.80 - 22.23)	14.39 ± 1.83 (12.85 – 17.30)
Recovery (%IU/kg)	2.27 ± 0.41 (1.54 - 2.83)	1.66 ± 0.17 (1.55 – 1.95)

C_{max} = peak concentration; AUC = area under curve; CL = clearance; Vd = volume of distribution; MRT = mean residence time

5 RECOMMENDATIONS

The clinical pharmacology information in this BLA supplement is acceptable, provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in Section 12 of the package insert. Please refer to Section 3 for detailed Labeling Recommendations.

6 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.1 Overview of Clinical Pharmacology Evaluation

The clinical pharmacology section of this PAS includes one Phase 3, open-label, multicenter, non-controlled study to determine the efficacy, safety, and pharmacokinetics of Wilate® in previous treated patients (≥ 6 years) with Type 3, Type 2 (except 2N), or severe Type 1 VWD (Study # Wil-31). Pharmacokinetics of Wilate® was evaluated in pediatric subjects (6 to 16 years of age). A total of 18 subjects were included in PK set. Five subjects were excluded from PK analysis (3 subjects were excluded due to unconfirmed VWD status and 2 subjects due to inhibitor to VWF at study entry). Thirteen subjects were included in PK analysis.

PK assessment was conducted with a single dose (60 ± 10 IU/kg body) of Wilate® prior to the prophylaxis treatment in the Study Wil-31. Blood samples were collected at pre-dose (within 60 minutes before injection), and at 60 ± 5 minutes, 3 hours (± 30 minutes), 9 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, and 72 ± 2 hours post-injection. The levels of VWF activity (VWF:Ac, measured by both VWF:RCo (ristocetin cofactor activity) and VWF:(b) (4) (assay based on the (b) (4) assays) and FVIII:C (measured by both one-stage and chromogenic assays) were measured.

Incremental in vivo recovery (IVR) of Wilate® over time were evaluated (at baseline, and at 1,2,3, 6, 9 and 12 months of treatment). For IVR assessments VWF:Ac (VWF:RCo and VWF (b) (4) and FVIII:C (measured by both one-stage and chromogenic assays) were analyzed based on actual Wilate® potency in all patients (PK was assessed only in children aged 6 to 16 years).

6.2 General Pharmacology and Pharmacokinetics

6.2.1 General Pharmacokinetic Profile

As shown in Table 1 and Figure 1, about one hour post-doing, the mean levels of VWF:RCo were 91.25 IU/dL, 63.49 IU/dL and 77.36 IU/dL for pediatric subjects with Type 1, Type 2 and Type 3 VWD, respectively. The mean values of FVIII (chromogenic assay) at one hour post administration of Wilate were 101.77 IU/dL, 71.65 IU/dL, and 94.92 IU/dL for pediatric subjects with Type 1, Type 2 and Type 3 VWD, respectively.

The observed mean (SD) half-lives were shorter than those observed previously with Wilate in a population including older patients (12 – 68 years of age), as reported in the labeling of Wilate. VWF:RCo assay 8.3 (1.7) hours vs. 15.8 (11.0) hours, and FVIII chromogenic assay 14.8 (1.5) hours vs. 19.6 (6.9) hours. The AUC was also slightly reduced: FVIII chromogenic assay 1937 (±1.53) h*IU/dL vs 2290 (±1045) h*IU/dL, VWF:RCo assay 968 (±1.5) h*IU/dL vs 1235 (±637) h*IU/dL. Subjects with VWD Type 3 are the most homogenous group due to their extremely low or unmeasurable levels of circulating VWF and FVIII.

Reviewer's Comment:

The observation of shorter half-lives of Wilate in children compared to adult subjects raised effectiveness concern of the proposed prophylaxis treatment dose (20 – 40 IU/kg BW) in pediatric subjects. To address this concern, an information request (IR) was sent to the Applicant to provide dosing and clinical efficacy information during the study for all pediatric subjects. Per the Applicant's IR response, pediatric subjects had acceptable efficacy results with recommended dosing regimen 20 – 40 IU/kg two to three time per week. Therefore, no additional dose adjustment is required for routine prophylaxis to reduce the frequency of bleeding in children.

Table 1. Study WIL-31: Mean (±SD) PK Parameters Normalized to a dose of 60 IU/kg

Parameter/assay	VWD Type 1 n=3	VWD Type 2 n=3	VWD Type 3 n=7	Total n=13
AUC (h*IU/dL)				
Chromogenic assay	1759.78 (1.791)	1376.89 (1.514)	2335.16 (1.351)	1936.52 (1 532)
One-Stage assay	1910.82 (1.861)	1302.56 (1.254)	2855.04 (1.371)	2171.3 (1.625)
VWF:RCo assay	963.462 (1.044)	1420.85 (2.206)	822.413 (1.231)	967.725 (1 526)
AUC_{norm} (h*kg*IU/dL/IU)				
Chromogenic assay	29.3292 (1.791)	22.9483 (1.514)	38.9195 (1.351)	32.2754 (1 532)
One-Stage assay	31.8472 (1.861)	21.7092 (1.254)	47.5837 (1.371)	36.1881 (1.625)
VWF:RCo assay	16.0574 (1.044)	23.6809 (2.206)	13.7068 (1.231)	16.1287 (1 526)
AUMC (h^2*IU/dL)				
Chromogenic assay	34938.6 (2.730)	49277.4 (1.457)	55475.5 (1.580)	48516.5 (1.782)
One-Stage assay	42768.1 (2.767)	37678.6 (1.610)	78784.4 (1.698)	57714.7 (1 992)
VWF:RCo assay	10423.2 (1.088)	46590.9 (2.755)	8565.44 (1.415)	13248.5 (2 382)
CL (dL/h/kg)				
Chromogenic assay	0.03407 (1.792)	0.04358 (1.514)	0.02569 (1.350)	0.03097 (1 533)
One-Stage assay	0.03136 (1.864)	0.04608 (1.254)	0.02102 (1.369)	0.02763 (1.625)
VWF:RCo assay	0.06226 (1.044)	0.04226 (2.204)	0.07296 (1.231)	0.06201 (1 525)
C_{max} (IU/dL)				
Chromogenic assay	101.772 (1.045)	71.6545 (1.437)	94.9223 (1.160)	90.3999 (1 255)
One-Stage assay	90.5768 (1.053)	59.6319 (1.314)	86.9469 (1.242)	80.4561 (1 292)
VWF:RCo assay	91.253 (1.262)	63.4862 (1.527)	77.3631 (1.147)	76.7839 (1 290)
MRT (h)				
Chromogenic assay	19.8541 (1.526)	35.7884 (1.072)	23.7566 (1.207)	25.0534 (1 361)
One-Stage assay	22.3815 (1.503)	28.9267 (1.377)	27.5951 (1.294)	26.5808 (1 345)
VWF:RCo assay	10.8185 (1.136)	32.7908 (1.381)	10.415 (1.183)	13.6903 (1.701)
$T_{1/2}$ (h)				
Chromogenic assay	14.1212 (1.375)	19.2882 (1.814)	13.4874 (1.526)	14.8043 (1 544)
One-Stage assay	15.768 (1.397)	11.3957 (2.590)	15.3198 (1.521)	14.4041 (1.690)
VWF:RCo assay	6.89733 (1.065)	17.4228 (1.957)	6.51119 (1.238)	8.28091 (1.696)
T_{max} (h)				
Chromogenic assay	0.92936 (1 122)	0.91413 (1.096)	1.13781 (1.520)	1.03241 (1 379)
One-Stage assay	0.92936 (1 122)	0.91413 (1.096)	1.55032 (2.330)	1.21954 (1 933)
VWF:RCo assay	0.92936 (1 122)	0.91413 (1.096)	0.96362 (1.041)	0.94405 (1.073)
V_d (dL/kg)				
Chromogenic assay	0.67695 (1 178)	1.55949 (1.585)	0.6104 (1.228)	0.77623 (1.600)
One-Stage assay	0.70279 (1 300)	1.33243 (1.327)	0.57993 (1.255)	0.73452 (1 514)
VWF:RCo assay	0.67372 (1 186)	1.38467 (1.932)	0.75984 (1.161)	0.84881 (1 508)

AUC=area under the curve; AUC_{norm}=AUC normalized for the administered dose; AUMC=area under the moment curve; CL=clearance; C_{max}=maximum plasma concentration; CV=coefficient of variation for geometric mean; IU=international unit; MRT=mean residence time; SD=standard deviation; $T_{1/2}$=half-life; T_{max}=time to reach maximum plasma concentration; Vd=volume of distribution at steady state.

Source: Applicant. Module 5, Study Wil-31 CSR.

Table 2 and Table 3 summarizes the PK parameters of Wilate in pediatric subjects by age group.

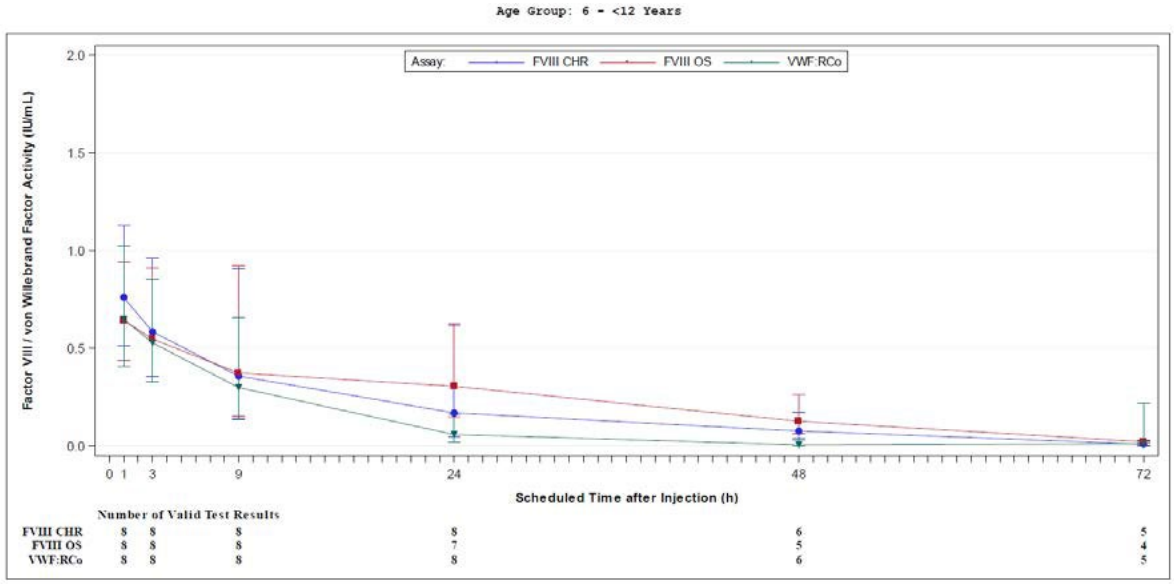
Table 2. Pharmacokinetic Parameters of VWF:RCo in children 6-16 years per age class: mean (±SD)

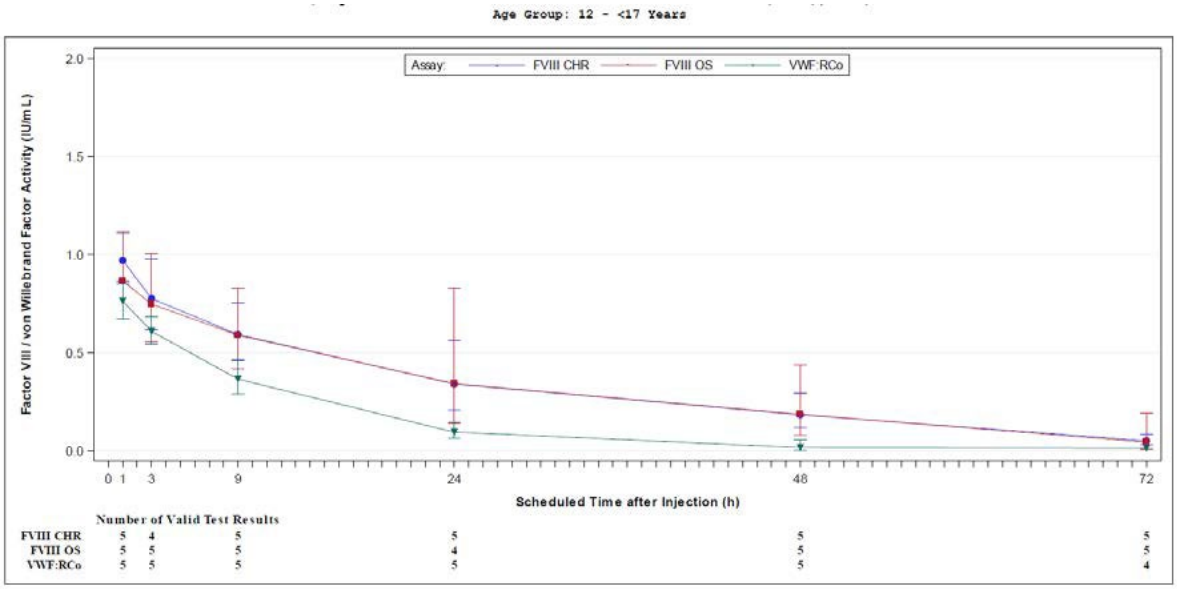
Parameters	Age 6-11 years (n = 8)	Age 12-16 years (n = 5)
C_{max} (IU/dL)	73.0 (1.4)	83.2 (1.1)
$AUC_{(0\text{-}inf)}$ (IU*hr/dL)	945 (1.7)	1005 (1.3)
Half-life (hrs)	8.4 (1.8)	8.1 (1.6)
CL (mL/h/kg)	0.1 (1.7)	0.1 (1.3)
Vss (mL/kg)	0.9 (1.7)	0.8 (1.2)
MRT (hrs)	14.2 (1.9)	13.0 (1.5)

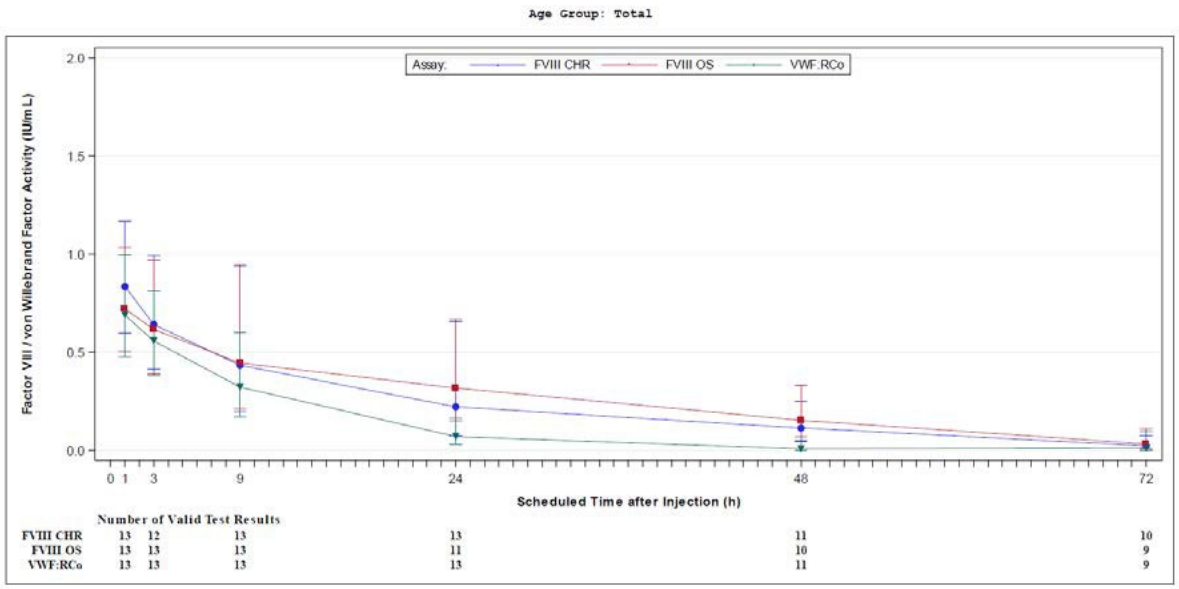
Table 3. Pharmacokinetic Parameters of FVIII (Chromogenic) in children 6-16 years per age class: mean (± SD)

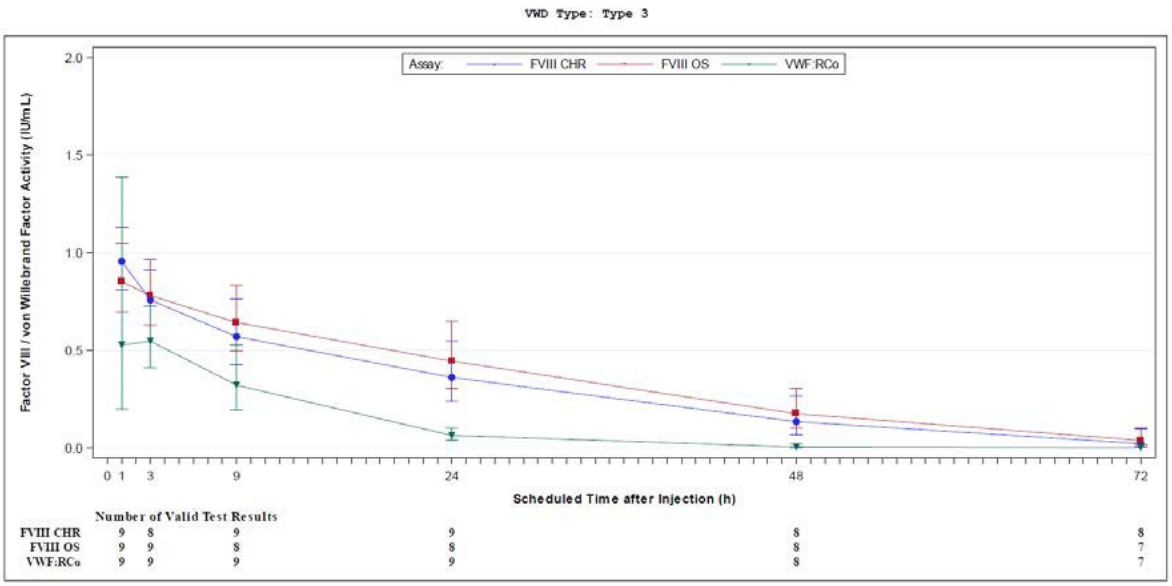
Parameters	Age 6-11 years (n = 8)	Age 12-16 years (n = 5)
C_{max} (IU/dL)	84.7 (18.1)	104.5 (7.1)
$AUC_{(0\text{-}inf)}$ (IU*hr/dL)	1734.4 (715.7)	2665.2 (623.3)
Half-life (hrs)	13.1 (5.7)	20.8 (5.6)
CL (mL/h/kg)	0.05 (0.02)	0.02 (0.01)
Vss (mL/kg)	1.0 (0.7)	0.7 (0.2)
MRT (hrs)	24.2 (8.3)	29.2 (4.7)

Figure 1. Geometric means of pre-dose adjusted Factor VIII and von Willebrand Factor activity by age group and for Type 3 VWD









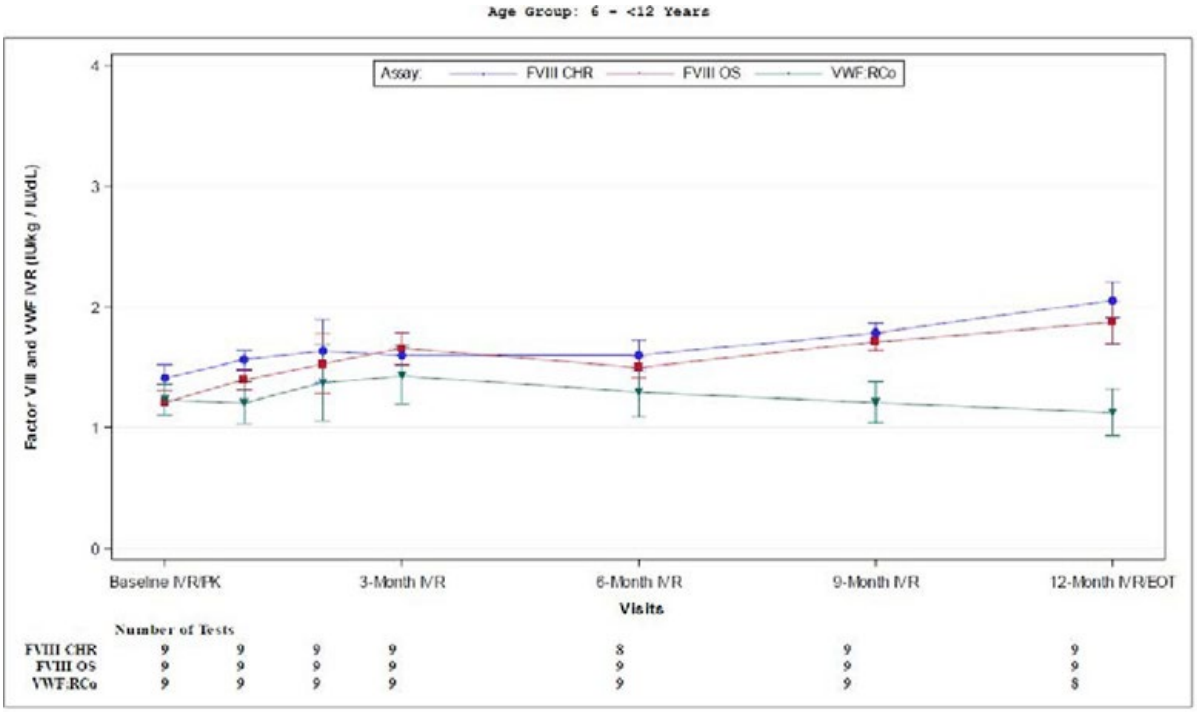
Source: Applicant. Module 5, Study Wil-31 CSR.

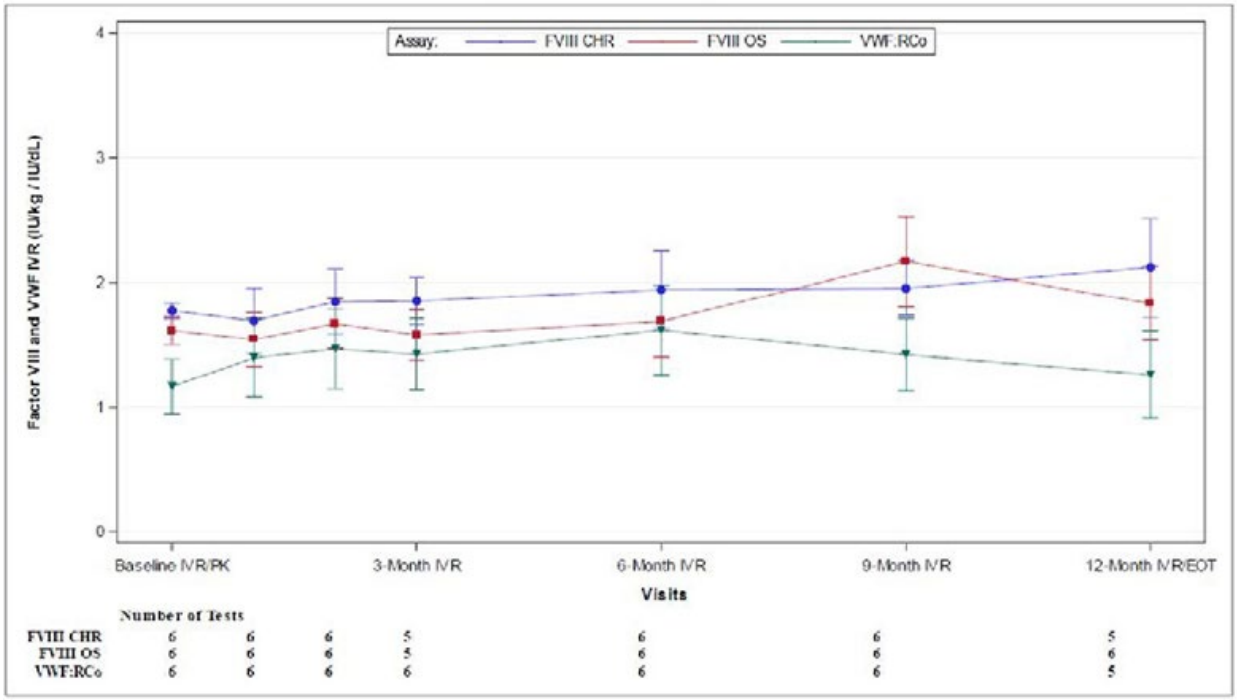
6.2.2 Incremental In Vivo Recovery (IVR) Over Time

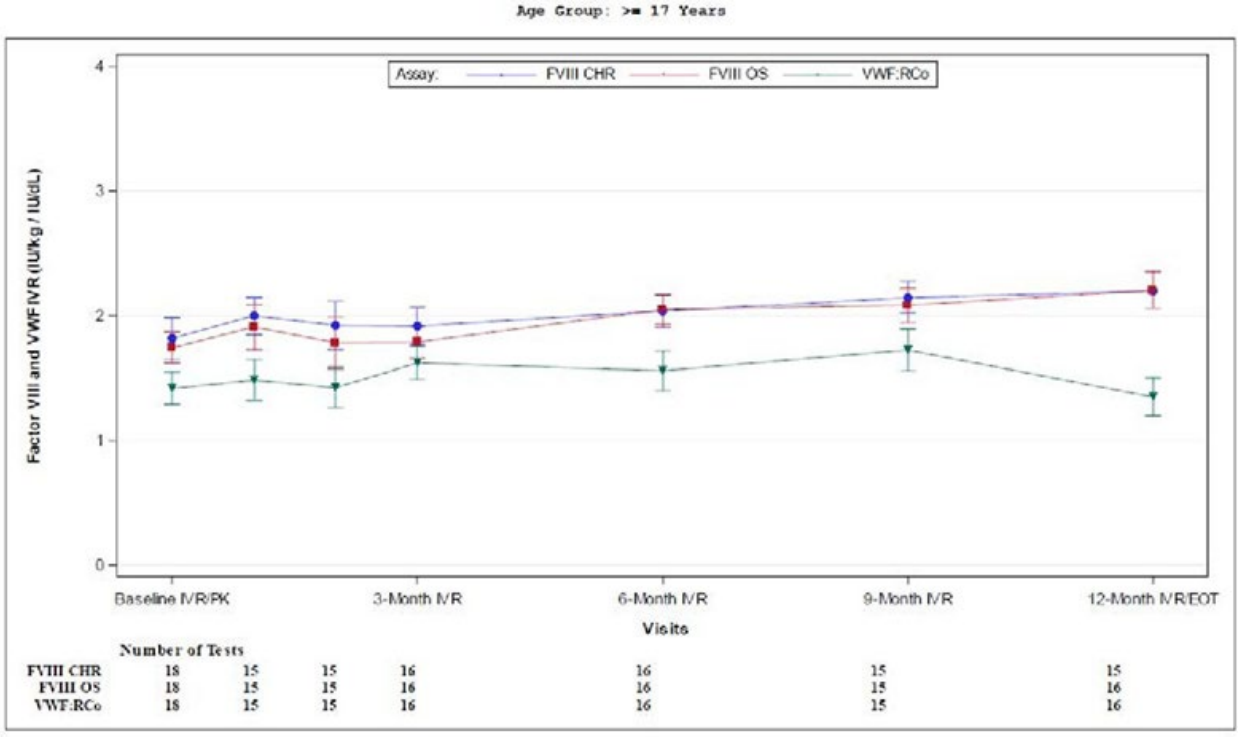
In Study Wil-31, incremental in vivo recovery (IVR) for VWF activity (VWF:Ac) and Factor VIII-coagulant (FVIII:C) over time were evaluated in modified full analysis set (mFAS) of subjects (N=33, a subset of subjects with confirmed VWD status) and per-protocol (PP) set of subjects (a subset of full analysis set, exclude subjects with major protocol deviations which have an impacted on the evaluation of the primary study outcome parameter).

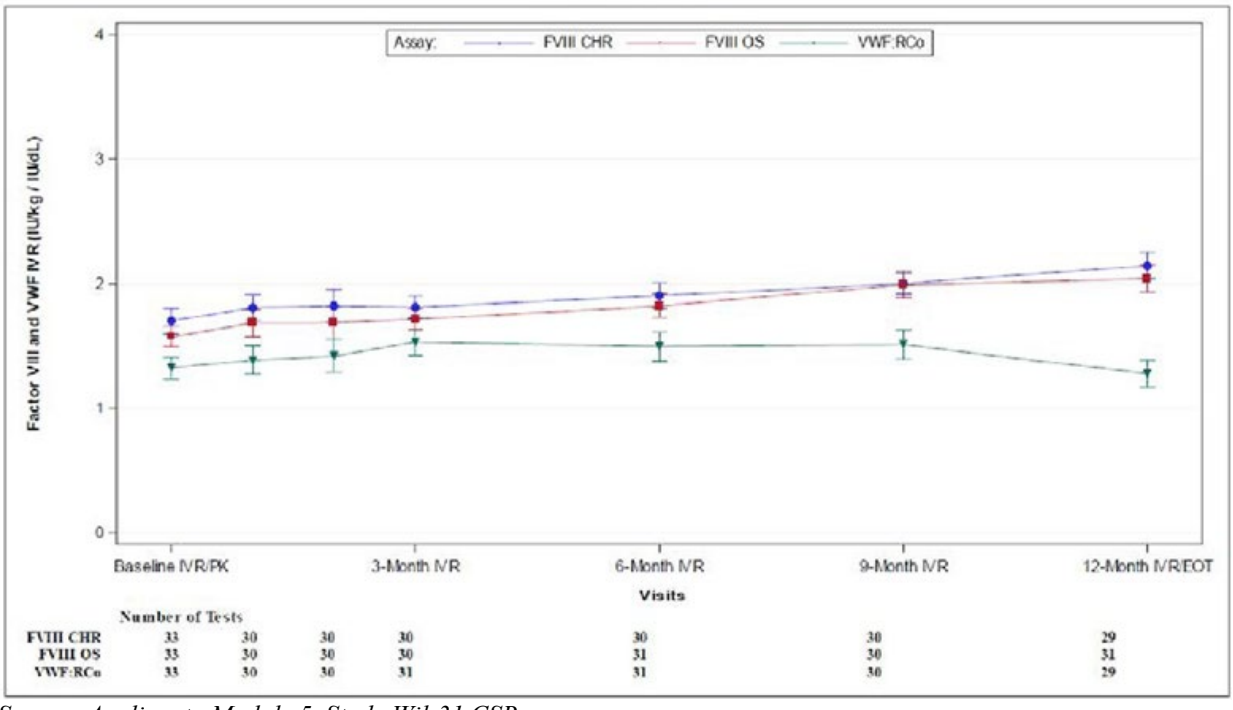
Figure 2 and Figure 3 show the incremental IVR analysis results of Wilate (FVIII:C and VWF:Ac) over time in mFAS population by age and VWD type.

Figure 2. Plot of Means of Factor VIII and von Willebrand Factor In-Vivo Recovery Over Time with Standard Deviation by Age Group (mFAS, N=33)



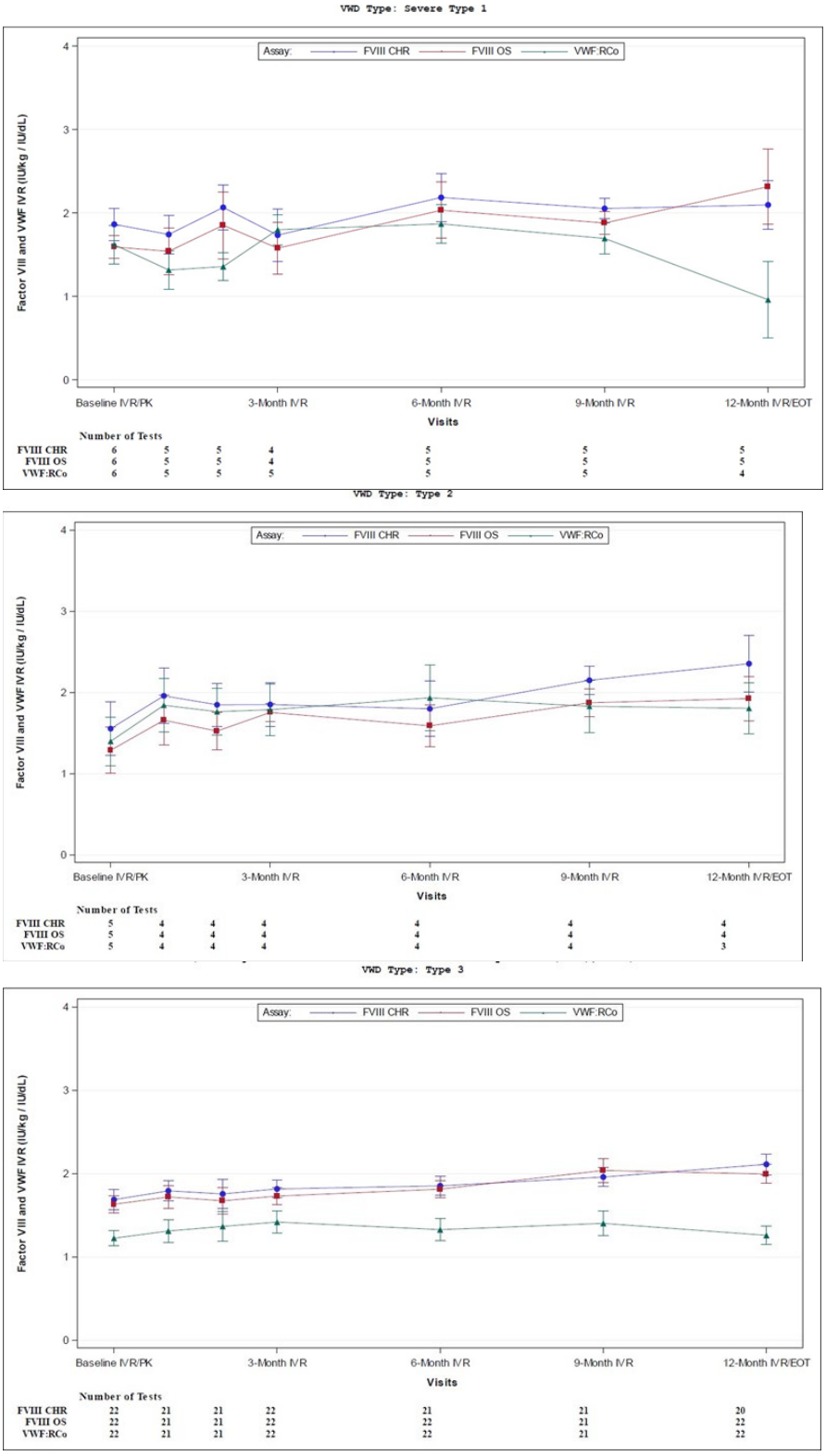






Source: Applicant. Module 5, Study Wil-31 CSR.

Figure 3. Plot of Means of Factor VIII and von Willebrand Factor In-Vivo Recovery Over Time with Standard Deviation by VWD Type (mFAS, N=33)



Source: Applicant. Module 5, Study Wil-31 CSR.

Factor VIII and VWF IVR at baseline and at the 12 months visit are summarized in Table 4. The FVIII and VWF IVRs observed in this study are consistent with those seen previously with Wilate, with slightly lower IVRs in children; this is expected, mainly due to higher volume of distribution in young children.

Table 4. Factor VIII and von Willebrand Factor In-Vivo Recovery at Baseline and 12-Months

	Mean (95% CI), n	
Parameter, Subgroup	**Baseline**	**12-Month Visit**
mFAS (N=33)		
FVIII IVR, CHR assay, kg/dL		
Total	1.697 (1.49, 1.90), 33	2.140 (1.92, 2.36), 29
6-<12 years	1.410 (1.16, 1.66), 9	2.053 (1.71, 2.40), 9
12-<17 years	1.769 (1.61, 1.93), 6	2.116 (1.01, 3.22), 5
≥17 years	1.817 (1.46, 2.17), 18	2.201 (1.89, 2.51), 15
Type 1 VWD	1.861 (1.36, 2.36), 6	2.093 (1.29, 2.90), 5
Type 2 VWD	1.553 (0.64, 2.47), 5	2.353 (1.25, 3.45), 4
Type 3 VWD	1.685 (1.43, 1.94), 22	2.110 (1.85, 2.37), 20
FVIII IVR, OS assay, kg/dL		
Total	1.571 (1.40, 1.74), 33	2.036 (1.81, 2.26), 31
6-<12 years	1.205 (0.98, 1.43), 9	1.871 (1.47, 2.28), 9
12-<17 years	1.611 (1.33, 1.90), 6	1.828 (1.07, 2.59), 6
≥17 years	1.740 (1.48, 2.00), 18	2.206 (1.88, 2.53), 16
Type 1 VWD	1.589 (1.25, 1.93), 6	2.312 (1.07, 3.56), 5
Type 2 VWD	1.287 (0.49, 2.08), 5	1.923 (1.06, 2.79), 4
Type 3 VWD	1.630 (1.42, 1.84), 22	1.993 (1.76, 2.23), 22
VWF:RCo IVR, kg/dL		
Total	1.320 (1.14, 1.50), 33	1.273 (1.04, 1.50), 29
6-<12 years	1.229 (0.94, 1.52), 9	1.124 (0.66, 1.59), 8
12-<17 years	1.162 (0.59, 1.73), 6	1.256 (0.28, 2.23), 5
≥17 years	1.419 (1.15, 1.69), 18	1.352 (1.03, 1.67), 16
Type 1 VWD	1.616 (1.02, 2.21), 6	0.956 (-0.51, 2.42), 4
Type 2 VWD	1.397 (0.56, 2.23), 5	1.804 (0.46, 3.15), 3
Type 3 VWD	1.222 (1.03, 1.41), 22	1.258 (1.02, 1.49), 22

	Mean (95% CI), n	
Parameter, Subgroup	**Baseline**	**12-Month Visit**
PP (N=25)		
FVIII IVR, CHR assay, kg/dL		
Total	1.709 (1.47, 1.95), 25	2.262 (2.04, 2.48), 24
6-<12 years	1.396 (1.06,1.74), 7	2.053 (1.58, 2.53), 7
12-<17 years	1.730 (1.57, 1.89), 5	2.423 (1.38, 3.46), 4
≥17 years	1.870 (1.43, 2.31), 13	2.325 (2.03, 2.62), 13
Type 1 VWD	1.782 (1.50, 2.06), 4	2.283 (1.39, 3.18), 4
Type 2 VWD	1.541 (0.19, 2.89), 4	2.353 (1.25, 3.45), 4
Type 3 VWD	1.731 (1.42, 2.04), 17	2.234 (1.97, 2.50), 16
FVIII IVR, OS assay, kg/dL		
Total	1.630 (1.42, 1.84), 25	2.129 (1.88, 2.38), 25
6-<12 years	1.180 (0.88, 1.48), 7	1.831 (1.31, 2.35), 7
12-<17 years	1.587 (1.22, 1.96), 5	2.054 (1.40, 2.71), 5
≥17 years	1.889 (1.58, 2.20), 13	2.319 (1.95, 2.69), 13
Type 1 VWD	1.685 (1.13, 2.24), 4	2.477 (0.77, 4.19), 4
Type 2 VWD	1.254 (0.09, 2.42), 4	1.923 (1.06, 2.79), 4
Type 3 VWD	1.706 (1.46, 1.96), 17	2.096 (1.85, 2.34), 17
VWF:RCo IVR, kg/dL		
Total	1.382 (1.21, 1.55), 25	1.440 (1.24, 1.64), 23
6-<12 years	1.253 (0.86, 1.65), 7	1.299 (0.90, 1.70), 6
12-<17 years	1.380 (1.26, 1.50), 5	1.570 (0.92, 2.22), 4
≥17 years	1.451 (1.16, 1.74), 13	1.465 (1.15, 1.78), 13
Type 1 VWD	1.538 (1.04, 2.03), 4	1.271 (-0.77, 3.32), 3
Type 2 VWD	1.419 (0.19, 2.65), 4	1.804 (0.46, 3.15), 3
Type 3 VWD	1.336 (1.16, 1.51), 17	1.405 (1.22, 1.59), 17

CI=confidence interval; mFAS=modified full analysis set; PP=per protocol set; VWD=Von Willebrand disease.

Source: Applicant. Module 5, Study Wil-31 CSR.

6.3 Clinical Pharmacology Conclusions

- Administration of Wilate led to immediate correction of both the FVIII and VWF deficiencies. Shorter half-lives and slightly lower AUC were observed in Study Wil-31 pediatric population (6-16 years) compared to that observed previously with Wilate in a population including older patients (12 – 68 years).
- The FVIII and VWF IVRs observed in this study are consistent with those seen previously with Wilate, with slightly lower IVRs in children.
- Assessment of pediatric prophylaxis treatment dosing and efficacy indicated that the dose of 20 – 40 IU/kg BW 2 – 3 times per week was sufficient for prophylaxis treatment.

7 APPENDIX - INDIVIDUAL STUDY

7.1 Study #Wil-31

Study Completion: Q2, 2022

Title: Clinical study to investigate the efficacy and safety of Wilate during prophylaxis in previous treated patients with VWD

Objectives:

Primary Objective:

To determine the efficacy of Wilate in the prophylactic treatment of previously treated patients (PTPs) with Type 3, Type 2 (except 2N), or severe Type 1 VWD.

Secondary Objectives:

- Assess the incremental IVR of *Wilate* for Von Willebrand Factor (VWF) activity (VWF:Ac) and Factor VIII-coagulant (FVIII:C) over time
- Determine the pharmacokinetics (PK) of Wilate for VWF:Ac and FVIII:C in pediatric patientsaged 6 – 16 years
- Assess the safety and tolerability of Wilate
- Determine Wilate consumption data

Additional Objectives:

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

Study Design

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

Number of Subjects:

Planned: 40; enrolled: 43 (22 patients had Type 3 VWD, 10 patients wereaged6 – 11 years, and 8 patients were aged 12- 16 years); evaluable subjects for primary endpoint: 33.

Study Treatments

Investigational medicinal product: *Wilate*

Dose for baseline PK assessment in pediatric patients (6 – 16 years): single dose of 60 ± 10 IU/kg BW
Dose for prophylaxis treatment: 20-40 IU/kg BW 2-3 times per week for 12 months
Route of Administration: intravenous injection

Pharmacokinetic Sampling Times

At pre-dose (within 60 minutes before injection), and at 60 ± 5 minutes, 3 hours (± 30 minutes), 9 ± 1 hours, 24 ± 2 hours, 48 ± 2 hours, and 72 ± 2 hours post-injection.

Pharmacokinetic Results & Conclusions:

Please refer to section 6 for details.

Source: Applicant. Module 5, Wil-31 CSR.