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CLINICAL PHARMACOLOGY SUPPLEMENTARY BLA REVIEW
Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
Office of Tissues & Advance Therapies (OTAT)

STN 125251/244
Applicant: Octapharma
Product: von Willebrand Factor/Coagulation Factor VIII Complex (Human) (Wilate)
Indication: For on-demand treatment and control of bleeding episodes in children and adults with von Willebrand disease
Reviewer: Iftekhar Mahmood, Ph.D.
RPM: Jean Gildner
Submission Date: November 30, 2018
Through: Lei Xu, M.D., Ph.D.
Through: Ilan Irony, M.D.

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INTRODUCTION

WILATE is a human plasma-derived, sterile, purified, double virus inactivated von Willebrand Factor/Coagulation Factor VIII Complex. Von Willebrand Factor/Coagulation Factor VIII complex is the active ingredient in WILATE. It is derived from large pools of human plasma collected in U.S. plasma donation centers. WILATE contains no preservative and no albumin is added as a stabilizer. The specific activity of WILATE is ≥ 60 IU VWF:RCo and ≥ 60 IU FVIII activities per mg of total protein.

The product is manufactured from cryoprecipitate, which is reconstituted in a buffer and treated with aluminum hydroxide followed by two different chromatography steps, ultra- and diafiltration, and sterile filtration. The manufacturing process includes two virus inactivation steps, namely, treatment with an organic solvent/detergent (S/D) mixture, composed of tri-n-butyl phosphate (TNBP) and Octoxynol-9, and a terminal dry heat (TDH) treatment of the lyophilized product in final container [at +100°C (212°F) for 120 minutes at a specified residual moisture level of 0.7-1.6%]. In addition, the ion-exchange chromatography step utilized during WILATE manufacturing also removes some viruses.

RECOMMENDATION

From clinical pharmacology perspective, the study design, PK analysis, and results are acceptable.

Higher clearance (body weight adjusted) by more than 45% and lower in vivo recovery (IVR) almost by 20% in adolescents than adults warrant an increase (body weight adjusted) in FVIII dose in adolescents than adults.

Study #1

Study Title: Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety and Immunogenicity of Wilate in Previously Treated Patients with Severe Hemophilia A (WIL-27).

The primary objective of this study was to determine the efficacy of Wilate in the prophylactic treatment of previously treated patients (PTPs) with severe hemophilia A. The secondary objectives of this study were to:

• Determine the efficacy of Wilate in the treatment of breakthrough bleeding episodes (BEs)

• Evaluate the pharmacokinetics (PK) for Wilate at baseline and after 6 months of prophylactic treatment

• Assess the safety, tolerability, and immunogenicity of Wilate.

This was a prospective, international, multi-center Phase 3 study that investigated the PK, efficacy, safety and immunogenicity of Wilate in previously treated patients (PTPs) with severe hemophilia A. The prophylactic treatment for each subject lasted 6 months (±2 weeks) and at least 50 exposure days (EDs), followed by a safety follow-up visit at 30 (±3) days after the study completion. PK assessments were based on a single dose of 50 (±5) international units (IU) per kg body weight (BW) dose on Day -1 and at the 6-month visit. Efficacy was assessed based on prophylactic treatment efficacy, successful treatment of breakthrough BEs with Wilate and at the (b) (4) period. Safety and immunogenicity were monitored throughout the study.

There were 21 male subjects, at least 12 years of age in the PK study, conducted at the start and at the end of prophylactic treatment. The subjects were with severe hemophilia A (<1% FVIII:C) and were previously treated with a coagulation factor VIII (FVIII) concentrate for at least 150 exposure days. Five subjects were between ≥12 and ≤16 years of age. The subjects received a single dose of Wilate of 50 ± 5 IU/kg BW. Blood samples for PK study were taken before the drug administration (time 0), at 0.25, 1, 3, 6, 9, 24, 30, and 48 hours, postdosing. FVIII plasma concentrations were determined from chromogenic and one-stage assay methods and the PK parameters were estimated by non-compartmental analysis. The PK parameters of FVIII in subjects with hemophilia A as a function of age (12 to 16 years and >16 years) are shown in Tables 1-4. The concentration-time profiles of FVIII are shown in Figures 1-2.

Based on one-stage assay, the results of the study indicated that the half-life of FVIII was comparable between adults and adolescents. However, the clearance and in-vivo recovery of FVIII were 46% higher and 27% lower in adolescents than adults. The PK parameters of FVIII were comparable between the first dose and at month 6.

Based on chromogenic assay, the half-life of FVIII was comparable between adults and adolescents. However, the clearance and in-vivo recovery of FVIII were 47% higher and 17% lower in adolescents than adults. The PK parameters of FVIII were comparable between the first

dose and at month 6. Both assay methods indicated higher clearance and lower IVR in adolescents than adults.

Table 1: Pharmacokinetic parameters for Factor VIII in subjects >16 years of age (n = 16) (One-stage assay)

PK parameters	PK (initial)	PK (at month 6)
C_{max} (IU/dL)	123 ± 22	113 ± 17
AUC (IU*hr/dL)	1683 ± 481	1701 ± 517
Clearance (mL/h/kg)	3.5 ± 1.3	3.2 ± 0.8
Half-life (hrs)	10.6 ± 2.7	11.8 ± 2.4
MRT (hrs)	15.8 ± 3.6	16.0 ± 3.9
V_d (dL/kg)	0.53 ± 0.13	0.52 ± 0.09
IVR (Kg/dL)	2.27 ± 0.41	2.17 ± 0.39

Table 2: Pharmacokinetic parameters for Factor VIII in subjects <16 years of age (n = 5) (One-stage assay)

PK parameters	PK (initial)	PK (at month 6)
C_{max} (IU/dL)	91 ± 10	80 ± 17
AUC (IU*hr/dL)	1093 ± 194	1137 ± 149
Clearance (mL/h/kg)	5.1 ± 0.8	5.0 ± 0.8
Half-life (hrs)	11.4 ±1.9	10.5 ±1.7
MRT (hrs)	14.4 ± 1.8	15.3 ± 2.5
V_d (dL/kg)	0.73 ± 0.13	0.76 ± 0.18
IVR (Kg/dL)	1.66 ± 0.17	1.42 ± 0.36

Table 3: Pharmacokinetic parameters for Factor VIII in subjects >16 years of age (n = 16) (Chromogenic assay)

PK parameters	PK (initial)	PK (at month 6)
C_{max} (IU/dL)	131 ± 26	107 ± 16
AUC (IU*hr/dL)	1616 ± 430	1341 ± 333
Clearance (mL/h/kg)	3.6 ± 1.3	4.1 ± 0.9
Half-life (hrs)	11.1 ± 2.6	11.4 ± 2.9
MRT (hrs)	15.4 ± 3.6	15.8 ± 3.3
V_d (dL/kg)	0.53 ± 0.13	0.63 ± 0.09
IVR (Kg/dL)	2.44 ±0.51	1.96 ± 0.29

Table 4: Pharmacokinetic parameters for Factor VIII in subjects <16 years of age (n = 5) (Chromogenic assay)

PK parameters	PK (initial)	PK (at month 6)
C_{max} (IU/dL)	112 ± 38	86 ± 18
AUC (IU*hr/dL)	1061 ± 278	1104 ± 138
Clearance (mL/h/kg)	5.3 ± 1.2	5.4 ± 0.8
Half-life (hrs)	10.6 ± 4.2	11.7 ± 2.2
MRT (hrs)	14.8 ± 3.3	16.1 ± 2.6
V_d (dL/kg)	0.77 ± 0.12	0.86 ± 0.19
IVR (Kg/dL)	2.03 ± 0.61	1.44 ± 0.37

Figure 1: Concentration-time profile of FVIII in subjects >16 years of age (One-stage and chromogenic assays)

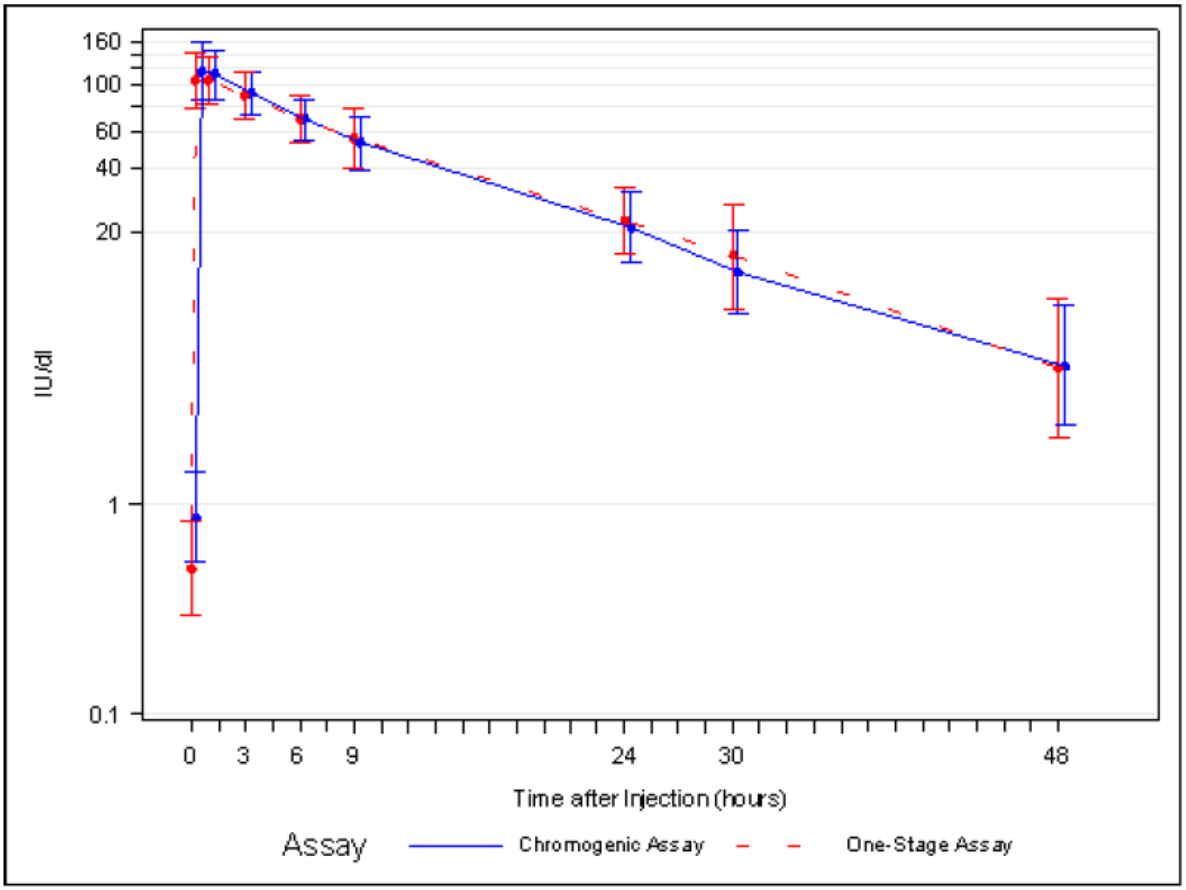
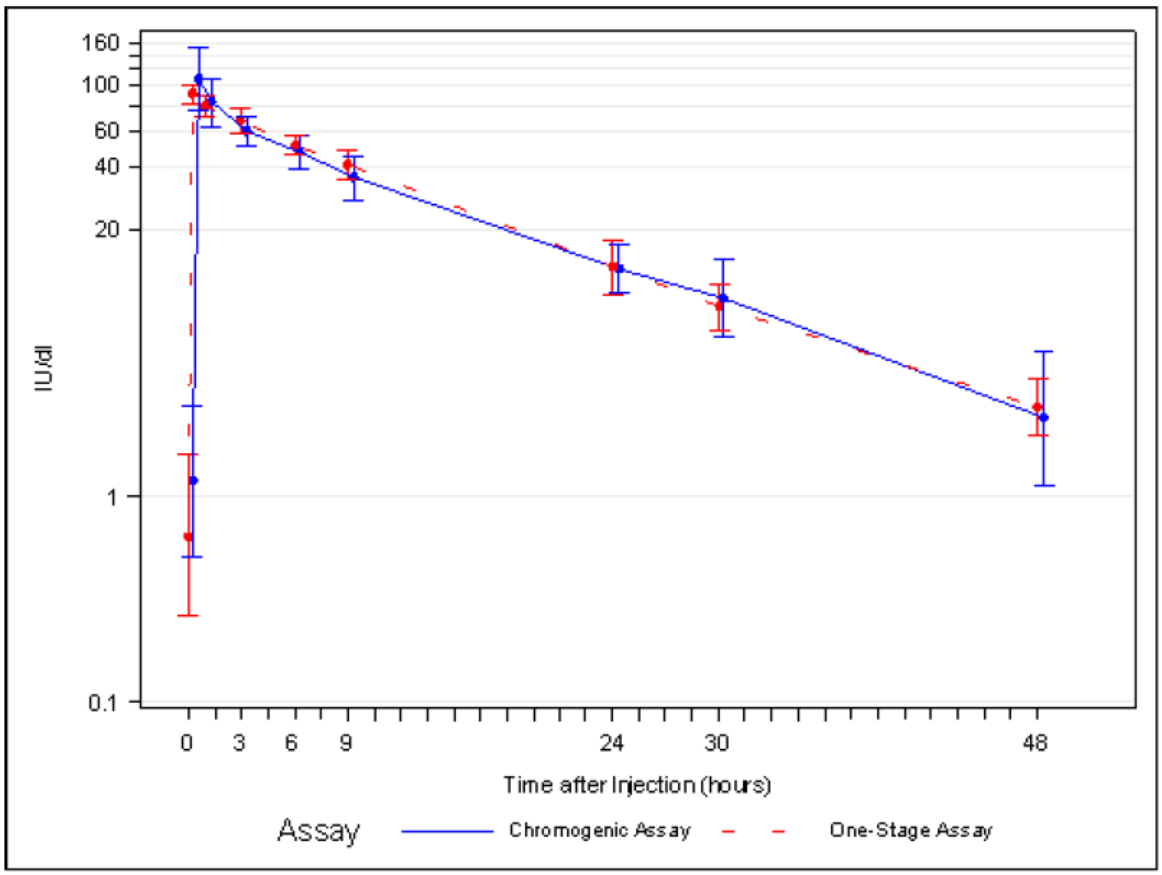


Figure 2: Concentration-time profile of FVIII in subjects <16 years of age (One-stage and chromogenic assays)



Conclusions: Higher clearance (body weight adjusted) by more than 45% and lower IVR almost by 20% in adolescents than adults warrant an increase (body weight adjusted) in FVIII dose in adolescents than adults.

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

Study #3

Study Title: International Clinical Study to Investigate the Incidence of Inhibitors in Previously Untreated Patients with Severe Hemophilia A treated with OCTATE (TAME-103).

The primary objective of the study was to assess the immunogenicity of WILATE in previously untreated patients (PUPS) with severe (FVIII:C ≤1%) hemophilia A with no inhibitor activity prior to admission. This was done by monitoring the levels of inhibitor against FVIII (by Bethesda assay) every 3 to 4 exposure days until the 20th exposure day and thereafter every 10th exposure day or every 3 months, whichever was the earlier.

This was a prospective, open-label, uncontrolled, international multi-center study. The dosage and frequency of treatment during the study was dependent upon the clinical situation of the subject and the decision of the investigator. Each subject received WILATE exclusively as replacement therapy (except in the case of inhibitor development), either prophylactically and/or for treatment of bleeding episodes, for a minimum of 50 exposure days or for 2 years, whichever was the earlier. An exposure day was defined as a day on which at least one infusion of FVIII was given. The dosage and frequency of treatment was to be determined by the clinical situation and the decision of the investigator. Testing for FVIII antibodies by Bethesda assay (immunogenicity testing) and virology testing was performed at study entry and at regular intervals throughout the study. The required dose for the treatment was determined using the following formula:

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

A total of 29 subjects from 7 centers were enrolled into the study. One subject did not receive treatment with WILATE during his participation in the study and was excluded from both safety and efficacy analyses. Subjects' age ranged from less than one month to 7.5 years (mean = 15.9 months) and with a body weight ranging from 2.8 kg to 29 kg (mean = 10.9 kg). Five subjects underwent surgery during the study. Eleven subjects (39.3%) were of blood group A, nine (32.1%) were group O, six (21.4%) were group B and 2 (7.1%) were group AB.

In order to determine the recovery, a single bolus injection of 25-30 IU per kg body weight was recommended. It was recommended that post-injection samples for FVIII measurement should be taken at 15 minutes and at 1 hour in addition to the pre-injection sample.

The C_{max}, $C_{max\text{-}normalized}$, and recovery of FVIII were calculated for subjects who did not develop an inhibitor (N=20) and for subjects who developed an inhibitor (N=8) based on both the nominal and the actual potencies of the WILATE.

The mean values for the recovery in the subjects without inhibitor was 1.36 ± 0.41%, which was approximately twice the mean recovery in subjects with inhibitor (0.66 ± 0.74%). A similar observation was noted for C_{max} and $C_{max\text{-}normalized}$ values (Table 1).

Table 1: C_{max}, $C_{max\text{-}normalized}$, and Recovery of FVIII per Recovery Analysis based on Nominal and Actual Potency (N=28)

Parameter	Potency	N	Mean ± SD	Mean Geom. ± SD	95% Conf Limits	Median	Range
Inhibitor Subjects (N = 8)							
Cmax	Nominal	21	33.42 ± 34.39	25.37 ± 3.63	14.11; 45.64	26.00	0.00 – 134.00
Cmax-norm	Nominal	21	0.67 ± 0.76	0.45 ± 4.84	0.22; 0.91	0.43	0.00 – 2.95
Recovery	Nominal	21	0.66 ± 0.74	0.44 ± 4.78	0.22; 0.90	0.43	0.00 – 2.95
Cmax	Actual	21	33.42 ± 34.39	25.37 ± 3.63	14.11; 45.64	26.00	0.00 – 134.00
Cmax-norm	Actual	21	0.67 ± 0.76	0.44 ± 4.92	0.21; 0.91	0.43	0.00 – 3.01
Recovery	Actual	21	0.66 ± 0.74	0.43 ± 4.87	0.21; 0.89	0.43	0.00 – 3.01
Non-Inhibitor Subjects (N= 20)							
Cmax	Nominal	59	60.69 ± 46.19	48.94 ± 1.91	41.36; 57.91	44.00	8.00 – 252.00
Cmax-norm	Nominal	59	1.35 ± 0.42	1.28 ± 1.42	1.17; 1.41	1.33	0.23 – 2.78
Recovery	Nominal	57	1.33 ± 0.41	1.26 ± 1.42	1.15; 1.39	1.32	0.23 – 2.78
Cmax	Actual	59	60.69 ± 46.19	48.94 ± 1.91	41.36; 57.91	44.00	8.00 – 252.00
Cmax-norm	Actual	59	1.38 ± 0.42	1.31 ± 1.42	1.19; 1.43	1.33	0.23 – 2.83
Recovery	Actual	57	1.36 ± 0.41	1.29 ± 1.42	1.17; 1.42	1.32	0.23 – 2.83

Source: Section 14.2.3, Tables 4 and 5

Conclusions: The results of the study indicated that inhibitor formation following the administration of Wilate would lead to approximately 50% decrease in Wilate concentrations in children. A more robust PK analysis such as measuring the area under the curve (AUC) may indicate that the magnitude of difference is even higher between children with and without inhibitor. Appearance of inhibitor warrants an appropriate dose adjustment in children.