

Memorandum on Clinical Section of BLA STN 125251

Date: January 25, 2007 **APPROVED**
By Hon-Sum Ko at 7:33 am, Jan 26, 2007

From: H. S. Ko, Medical Officer, Clinical Review Branch

To: Nancy Kirschbaum, Chair for BLA Committee

C.c.: **APPROVED**
By Toby A. Silverman at 3:54 pm, Jan 26, 2007
Toby Silverman, Chief of CRB
Franklin Stephenson, Project Manager for BLA STN 125251

Re: Filing comments

Description of the BLA Submission

This BLA is a paper submission of 60 volumes and includes two CDs: (a) draft labeling, and (b) electronic dataset in jmp files. It is in ICH Common Technical Document (CTD) format and was submitted on 12/12/06, received by FDA on 12/14/06. A separate volume requesting priority review of this application was submitted and received on the same dates.

As with ICH CTD submissions, this application has five modules. Modules 3 and 4 being information on product quality and nonclinical studies, they will be addressed by the CMC and P/T Reviewers, respectively. This Memorandum will address parts of Module 1 and 2 that are pertinent to clinical review, and Module 5, which contains the clinical data.

Module 1 includes the following which are relevant to clinical review:

- Financial disclosure/list of investigators (1.3.4)
- Draft labeling (1.14)

Module 2 includes the following clinical sections:

- Clinical overview (2.5)
- Clinical summary (2.7)

Module 5 consists of the clinical study reports, data from combined analyses, post-marketing safety updates, and references. It has 35 volumes, distributed as follows:

Information	Location
Summary of clinical studies (VWD and hemophilia A)	Volume 1
Biopharmaceutics studies	Volume 1
CSR for VWD studies	
• PK studies: TMAE-105/WIL-12/TMAE-106	Volume 1/Volumes 1-5/Volume 6
• Uncontrolled studies: TMAE-105 (completed)	Volumes 7-9
TMAE-109 (completed)	Volumes 10-12
TMAE-104 (ongoing)	Volumes 13-16
TMAE-106 (ongoing)	Volume 17
• Immunogenicity study: WIL-14 (ongoing)	Volume 17
CSR for Hemophilia A studies	
• Uncontrolled studies: TMAE-101 (completed)	Volumes 18-21
TMAE-102 (completed)	Volumes 22-24
TMAE-108 (completed)	Volumes 25-26
TMAE-110 (completed)	Volumes 27-29
TMAE-103 (ongoing)	Volumes 30
TMAE-111 (ongoing)	Volumes 30
Cross study analyses	
• VWD	Volume 31
• Hemophilia A	Volume 32
• PK comparison	Volume 33
Post-marketing reports – PSURs 01, 02, 03	Volume 33
References	Volumes 34-35

Priority Review Request is a one-volume submission with the Applicant's rationale and references. The arguments for this request are stated in the cover letter.

- WILATE is indicated in adult and pediatric patients for the treatment of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease (VWD), and in mild and moderate von Willebrand disease where use of DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment is ineffective or contraindicated. Besides this, WILATE is the first concentrate, which has been proven safe and effective in the (b)(4) (b)(4).
- WILATE is the first concentrate introducing double virus safety and high purity for patients with VWD. Double virus inactivation and a high purity represent new product features in the VWD-indication and thus provide a new safety level for VWD-patients, especially when compared to an earlier product Humate-P, which is of intermediate purity and with only one virus inactivation step.
- WILATE contains both functional VWF and FVIII in physiological amounts with similar and physiological pharmacokinetic properties, which can help to avoid over- or underdosing of FVIII or VWF. Besides double virus inactivation and high purity, these product attributes represent significant improvements, which make a major contribution to VWD patient care. The availability of WILATE will help secure the supply of VWF-concentrates also in the future, when the number of diagnosed and prophylactically-treated VWD patients will increase.
- Octapharma has submitted an Orphan drug application for WILATE in the indication inherited von Willebrand disease on November 16, 2006. Within the orphan designation application, clinical superiority of WILATE has been addressed and is also attached to this document.

Comment CBER's standard operating procedures specify that a biological product original or supplemental application will receive priority review if the product, if approved, "would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease." (SOPP 8405)

- The Applicant's first reason (prospective trials to demonstrate safety and efficacy) does not comport with SOPP 8405's criteria, which require significant improvement in safety or effectiveness, not simply improved study design.
- The CMC Reviewer and Chair of this BLA Committee, Dr. N. Kirschbaum, is of the opinion that there is an approved product which has yielded no reports of viral transmission since licensure in 1986, and so double viral inactivation is unlikely to further enhance safety. (b)(4), (b)(5) Thus, double viral inactivation may not be a viable rationale for claiming significant improvement.
- A case has not been made as to how the claimed functional VWF and FVIII in physiological amounts will enhance safety or effectiveness. Since the plasma VWF or FVIII levels may not necessarily be available at the time of dosing for bleeding episodes, product administration is generally based on certain preset criteria related to potency in IU of VWF:RCO. Although there is a theoretical risk of thromboembolic phenomenon due to elevated FVIII level, a correlation between FVIII and thrombosis in von Willebrand disease patients have not been established (communication from Nisha Jain).
- The "Statement of Clinical Superiority" has repeated these same arguments. Even though it is possible that the Applicant has developed an improved product in terms of purity and potential viral inactivation, it does not appear that they have demonstrated that this translates into significant improvement in safety or effectiveness.

In conclusion, Octapharma has not adequately supported the requirement for "a significant improvement in the safety or effectiveness" in the treatment of VWD in their request, and this priority review request should be denied.

Requested Indications and Recommended Dosing:

1. Indication(s) being sought

Under "Highlights of Prescribing Information", the proposed package insert has the following as Indications and Usage -

WILATE is a human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF) indicated for the control of bleeding in spontaneous (b)(4) situations in

- von Willebrand disease (VWD)

The Indications and Usage section in the proposed package insert (Section 1.1) says, under "Von Willebrand Disease (VWD)" -

- WILATE is indicated in adult and pediatric patients for the treatment (b)(4) of spontaneous and trauma-induced bleeding episodes in severe VWD, and in mild and moderate VWD where use of DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment is ineffective or contra-indicated. (b)(4)

(b)(4)

2. Recommended Dosing

Under "Highlights of Prescribing Information", the proposed package insert has the following Dosage and Administration recommendations -

- Minor hemorrhages: loading dose 20-40 IU/kg, maintenance dose 20-30 IU/kg every 12-24 hours;
- Major hemorrhages: loading dose (b)(4) IU/kg, maintenance dose 20(b)(4)IU/kg every 12-24 hours;
- (b)(4)

The dosage should be adjusted according to the extent and location of the bleeding (b)(4)
(b)(4) In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

The Dosage and Administration section in the proposed package Insert (Section 2) begins with: " Each vial of WILATE contains the labeled amount in International Units (IU) of factor VIII (FVIII) activity measured with the chromogenic assay (FVIII:C) and von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCO)", followed by more detailed elaborations of the dosing scheme (based on above) and administration methods.

Clinical Studies to Support Von Willebrand Disease Indication

Study ID & Title Product Batches Used & Strength (IU FVIII)	Population (N= patients in study; n=new individual)	Design/Dose Sites/Location Time frame	Efficacy Endpoints
Wil-12 , A prospective, randomized, controlled, open-labeled, two-arm cross-over study investigating the pharmacokinetic properties of WILATE and Humate-P® in subjects with inherited von Willebrand disease <u>Batches</u> 435 005 181 at 500 IU	Inherited VWD, any type n=22 8M/14F Ages 12-68; m=34	Phase 2, open, randomized, controlled, X-over, Safety-efficacy-PK study/ <u>≥40 IU VWF:RCO/</u> <u>kg iv bolus injection</u> 6-centers/US Jun 05 – Apr 06	<u>Primary</u> , <ul style="list-style-type: none"> • in vivo 1% of WILATE, calculated for FVIII:C, VWF:Ag, VWF:CB, VWF:RCO <u>Secondary</u> , <ul style="list-style-type: none"> • Other PK parameters • Incremental recovery of FVIII:C, VWF:RCO, VWF:Ag, & VWF:CB • multimeric patterns
YMAE-105 , Pharmacokinetic properties, safety and efficacy of WILATE in patients with inherited von Willebrand disease <u>Batches</u> 942 014 180 at 1000 IU 943 015 180 at 1000 IU 948 016 180 at 500 IU 948 018 180 at 500 IU	Inherited VWD, any type; not responding to DDAVP N=14; n=14 8M/6F Ages 13-64; m=36	Phase 2, open, uncontrolled, Safety-efficacy-PK study/ <u>1: 50 IU VWF:RCO/</u> <u>kg single iv injection</u> <u>2: ? dose regular iv</u> <u>injection or contin-</u> <u>uous infusion</u> <u>(surgery)</u> 2-centers/Poland & Bulgaria Dec 89 – Jul 00	<u>Primary</u> , <ul style="list-style-type: none"> • PK profile (AUC, AUC_{norm}, T_{1/2}, MRT, Vd, CL) for VWF:Ag, VWF:CB, VWF:RCO • plasma levels of FVIII:C <u>Secondary</u> , <ul style="list-style-type: none"> • PK profile (C_{max} & T_{max}) for VWF:Ag, VWF:CB, VWF:RCO, • recovery of FVIII:C, VWF:Ag, VWF:RCO • plasma levels of VWF:Ag, VWF:CB, VWF:RCO • bleeding time • multimeric pattern • Investigator overall efficacy

<p>TMAE-109. Clinical study to investigate efficacy and safety of human Factor VIII/VWF TMAE SEC in patients with inherited von Willebrand disease. Phase 2 study</p> <p><u>Batches</u> 007 002 180 at 500 IU 011 005 180 at 1000 IU 017 007 180 at 1000 IU 038 008 180 at 500 IU</p>	<p>Inherited VWD, any type; not responding to DDAVP</p> <p>N=16; n=5 10M/6F Ages 14-63; m=37</p>	<p>Phase 2, open, uncontrolled, Safety-efficacy study/ <u>? dose regular iv injection or continuous infusion (surgery)</u></p> <p>2-centers/Poland & Bulgaria</p> <p>Aug 00 – May 01</p>	<p><u>assessment</u></p> <p><u>Primary.</u></p> <ul style="list-style-type: none"> plasma levels of FVIII:C, VWF:Ag, VWF:RCO <p><u>Secondary.</u></p> <ul style="list-style-type: none"> bleeding time multimeric patterns Investigator overall efficacy assessment
<p>TMAE-104. International clinical study to investigate the safety and efficacy of WILATE in subjects with Inherited von Willebrand disease</p> <p><u>Batches</u> 23 batches including – 435 005 181 at 500 IU (as in WIL-12) & 5 other batches used in TMAE-106 (see below)</p>	<p>Inherited VWD, any type; not responding to DDAVP</p> <p>N=35; n=31 14M/21F Ages ≥6 - ≤85</p>	<p>Phase 3, open, uncontrolled, Safety-efficacy study/ <u>? dose regular iv injection or continuous infusion (surgery)</u></p> <p>Multicenter/Europe</p> <p>Started Q1 2002</p>	<p><u>Primary.</u></p> <ul style="list-style-type: none"> Plasma levels of FVIII:C, VWF:Ag, VWF:CB, VWF:RCO <p><u>Secondary.</u></p> <ul style="list-style-type: none"> bleeding time Investigator and/or patient overall efficacy assessment of overall clinical efficacy
<p>TMAE-106. Pharmacokinetic properties, safety and efficacy of human Factor VIII TMAE-SEC in patients with inherited von Willebrand disease. Phase II study</p> <p><u>Batches</u> 038 008 180 at 1000 IU* 204 001 181 at 500 IU* 249 010 181 at 500 IU* 318 001 181 at 1000 IU 337 005 180 at 500 IU* 435 006 181 at 500 IU* 450 008 181 at 1000 IU (* = batches also used in TMAE-104)</p>	<p>Inherited VWD, any type; not sufficiently responding to DDAVP</p> <p>n=13 3M/10F Ages ≥12 - ≤65</p>	<p>Phase 2, open, uncontrolled, Safety-efficacy-PK study/ <u>1: 50 IU VWF:RCO/kg single iv injection</u> <u>2: ? dose regular iv injection or continuous infusion (surgery)</u></p> <p>Multicenter/Germany</p> <p>Started Q1 2002</p>	<p><u>Primary.</u></p> <ul style="list-style-type: none"> PK profile (AUC, T_{1/2}, MRT, Vd_{ss}, CL) for VWF:Ag, VWF:CB, VWF:RCO plasma levels of FVIII:C <p><u>Secondary.</u></p> <ul style="list-style-type: none"> Incremental recovery of FVIII:C, VWF:RCO, VWF:Ag plasma levels of VWF:Ag, VWF:CB, VWF:RCO bleeding time closure time multimeric patterns Investigator overall efficacy assessment
<p>WIL-14. Clinical study to investigate the efficacy, safety and immunogenicity of Wilate in children < 6 years of age with inherited von Willebrand disease. A Phase 2 study</p> <p><u>Batches</u> [?]</p>	<p>Inherited VWD, any type; known or suspected to be inadequate for DDAVP treatment</p> <p>N=20 planned n=5 (enrolled) Age ≤6</p>	<p>Phase 2, open, uncontrolled, Safety-efficacy-Immunogenicity* study/ <u>? dose regular iv injection or continuous infusion (surgery)</u></p> <p>Multicenter/Germany & Poland</p> <p>Started Apr 2006</p>	<p><u>Primary.</u></p> <ul style="list-style-type: none"> Efficacy in b(4) treatment of bleeding episodes: no. of bleedings, amt of IMP reqd, no. exposures to stop bleeds, assessment of response to treatment of bleeding episodes Overall efficacy 4-point verbal rating scale <p>b(4)</p>

*Immunogenicity & safety evaluated by inhibitors vs VWF and FVIII, AEs, vital signs, lab parameters, viral safety

Discussion of Submitted Material for BLA STN 125251

1. The material is submitted in paper and appears to be legible and well organized, including the presentation of draft labeling with annotation. The proposed labeling is consistent with the newly required format for package inserts.

2. There are no adequate and well controlled trials to demonstrate safety and effectiveness. However, the indication sought concerns a rare disease for which conducting adequate and well controlled trials would not be easily achievable. The currently licensed product, Humate-P, was approved on the basis of retrospective analyses on data from patients who used the product.

3. Although the BLA contains -

(a) an open-label, randomized, controlled, cross-over study comparing WILATE with the licensed product, Humate-P, for PK properties,

(b) two completed, uncontrolled studies that enrolled small numbers of VWD patients (14 and 16 subjects, but only 19 individuals, as TMAE-109 has 11 out of 16 patients coming from TMAE-105), and

(c) two ongoing, uncontrolled studies that also enrolled small numbers of VWD patients not overlapping with those in previous studies (31 and 13 subjects), the Applicant has not specified which are the pivotal clinical trials intended to provide substantial evidence of efficacy for licensure. The data from actual clinical studies supporting the VWD indication are limited. However, as the comparative PK study between WILATE and the licensed product, Humate-P, is a controlled trial, and it uses objective criteria as endpoints (PK parameters), this should be considered the pivotal study to establish effectiveness in the treatment of VWD.

4. The requested indication for VWD includes b(4) treatment of bleeding episodes. b(4) As the clinical trials used patients that overlapped across studies, an accurate count of the number of patients exposed to WILATE under different situations (treatment of bleeding episodes, prophylaxis, surgical procedures) was requested from the applicant, who has provided the information in the following Table.

TMAE-105, 109, 104, and 106 together b(4)	VWD Type 1	VWD Type 2					VWD Type 3	Total
		A	B	M	N	NS*		
Treatment of bleeding episodes ONLY	6	1	1		1		3	12
Both b(4) treatment use, but NOT surgical use b(4)	1	3	2				12	18
		3					3	6
	3	2		1		1	5	12
			1					1
	1						6	7
					1		2	3
							1	1
Total	11	9	4	1	2	1	32	60

From this information, Wilate has been administered to 91 subjects (including 22 patients in the PK study in the U.S., WIL-12, 3 patients who only received product in the PK part of Study TMAE-106, and 6 in the ongoing immunogenicity study, WIL-14), with 921 bleeding episodes among the 60 patients in studies TMAE-105, 109, 104 and 106.

b(4) This database is comparable to that described in the label for Humate-P. There are a total of 11 type I, 17 type II and 32 type III VWD subjects enrolled in the four studies (60 individuals).

- For comparison, the Humate-P® package insert information states: "Humate-P® was administered to 97 subjects, in 530 treatment courses: 73 for surgery, 344 for treatment of bleeding and 20 for prophylaxis of bleeding. For 93 "other" uses, the majority involved dental procedures, diagnostic procedures, prophylaxis prior to a procedure, or a test dose."

It is noted that Humate-P is not labeled for prophylaxis of bleeding episodes or surgical procedures. Octapharma should be informed that licensure of WILATE for each of the requested indications will be based on the adequacy and quality of the data supporting each indication.

5. This BLA has not presented its approach with respect to the submission of required pediatric data under the PREA. Although pediatric data are available, the only presentation in an organized fashion for VWD is for patients aged 6 or under in the combined analyses section. It is noted that the indication being sought includes adults and pediatric patients.

6. Based on the above discussions and considering the requirements of SOPP 8404, this BLA is fileable, with comments to be conveyed to Octapharma.

7. As discussed above, priority review for this BLA is not recommended.

Comments to be Conveyed to Applicant

1. We consider the study for pharmacokinetic comparison between WILATE and Humate-P, the U.S. licensed product, in von Willebrand disease patients (Study WIL-12) as the pivotal controlled trial in this BLA, and the data from the uncontrolled trials in von Willebrand disease as supportive. Although at the present time, this BLA is fileable, licensure for each indication (treatment (b)(4) of spontaneous and trauma-induced bleeding episodes, (b)(4) will be based on the adequacy and quality of the data supporting each of those uses.

2. Your request for priority review does not comport with the requirements under SOPP 8405 and priority review is therefore not granted.

3. Please present your approach to fulfill the requirements for the submission of pediatric data under the Pediatric Research Equity Act. You would need to address use of your product in pediatric subpopulations by age. If waiver or deferral is to be requested for certain subpopulations, please provide your rationale.

4. To facilitate the clinical review, please provide electronic versions in Microsoft Word for Sections 2.5 and 2.7 of Module 2, as well as the following parts of clinical study reports on von Willebrand disease in Module 5:

- WIL-12 pp 1-125
- TMAE-105 pp 1-77
- TMAE-109 pp 1-63
- TMAE-104 pp 1-67
- TMAE-106 (protocol) pp 1-53

In addition, please provide Section 5.3.5.3.1 of Module 5 in adobe acrobat format.