

STATISTICAL REVIEW AND EVALUATION

Date: December 13th, 2007

FDA #:	STN 125251/0
SPONSOR:	Octapharma
PROPOSED USE:	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 treatment is ineffective or contraindicated. -----(b)(4)----- -----.
PRODUCT NAME:	WILATE: Human plasma-derived, stable, highly purified, double virus inactivated concentrate of freeze-dried active human coagulation FVIII and human VWF
BLA TITLE:	WILATE (Human coagulant factor VIII(FVIII) and human von Willebrand factor (VWF))
DOCUMENT REVIEWED:	Original BLA
FROM:	Jessica (Jeongsook) Kim, Ph.D. (HFM-219)
THROUGH:	Ghanshyam Gupta, Ph.D., Chief, Therapeutics Evaluation Branch, (HFM-219)

TO: Hon-Sum Ko (HFM-392)
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CC: Original STN 125251/0, HFM-99/DCC
HFM-219/ Shyam Gupta
HFM-215/Henry Hsu
HFM-210/Steve Anderson
HFM-215/Chronological File

JKim//STN 125251/0 Octapharma December-13-2007

Reference INDs: IND -(b)(4)-

BACKGROUND

This submission is a Biologic License Application for WILATE (Human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF)). In this submission, there were five VWD studies, namely, WIL-12, TMAE-105, TMAE-109, TMAE-104, and TMAE-106. The primary endpoints of those five studies were the PK parameters and the overall assessment of efficacy was defined as a secondary endpoint. At the filing meeting, the study WIL-12 (PK study) was considered as the pivotal study that will be used for the basis approval. The PK results will be reviewed and commented by Dr. Iftekhar Mahmood.

During the course of the review process, this reviewer was asked to summarize the efficacy analysis that needs to be comparable to the sponsor's efficacy summary statistics included in their package insert. Since the efficacy assessment was not appropriately entered in the sponsor's original data file, the sponsor's summary statistics for the efficacy endpoint (overall assessment of bleeding episodes by investigator) could not be reproduced using the original data file. This reviewer requested the sponsor to send a proper analysis data file. On August 10th, 2007, CBER received a revised/updated data set.

NOTE: Studies TMAE-104 and TMAE-106 were on-going studies at the time of the original BLA submission. These two studies were then completed and the study results were updated in a major amendment (Amendment #12 dated July 23rd, 2007) to this BLA.

The following tables (Tables 1 through 9) were produced using the updated data files (received on August 10th, 2007) to investigate the summary statistics of the efficacy assessments included in the sponsor's package insert. Since this submission failed to provide clear criteria for the efficacy assessment, this review includes the efficacy summary statistics based on the sponsor's criteria in the Part I of this review, as well as the efficacy summary statistics based on the FDA's recommend criteria and (By Dr. Hon-Sum Ko : Datafile named BLEEDALLc-fnl dated 11-26-2007) in Part II of the review.

List of Tables

	Table #	Title
Part I: based on the sponsor's criteria	Table A	Patients' distribution by study (Studies, TMAE-104, TMAE-105, TMAE-106, TMAE-109)
	Table B	Outcomes of bleeding episodes per study
	Table C	Number of bleeding episodes per subject by study
	Table D	Efficacy assessment in Bleeding Episodes by bleeding site
	Table E	Pediatric patients (age≤12) with number of bleeding episodes
	Table F	Efficacy assessment in Bleeding Episodes in Pediatric Population (≤12)
	Table G	------(b)(4)-----
Part II: based on FDA's criteria	Table H	Number of bleeding episodes per subject by study
	Table I	Number of successes per study and by bleeding site
	Table J	Efficacy assessment in Bleeding Episodes by bleeding site
	Table K	------(b)(4)-----
	Table L	------(b)(4)-----

NOTE: Tables **D**, **F**, and **G** are comparable to Tables 6, 8, and 9 in the sponsor's Package Insert.

Bleeding episodes (BLEEDALL data file)

	TMAE-104	TMAE-105	TMAE-106	TMAE-109
Subject ID	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	-(b)(6)-	-(b)(6)-	-(b)(6)-	-(b)(6)-
	Total (n=57)	27	12	12

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Table B “Outcomes” of bleeding episodes per study

Study	#of treatment	#of (no-outcome)	#of (Not recovered , Not Resolved)	#of(Recovered, Resolved)	#of (Recovering, Resolving)
104	2035	1021	1	990	23
105	158	158	0	0	0
106	96	39	0	32	25
109	290	172	0	115	3
Total	2579	1390	1	1137	51

NOTE: The variable “OUTCOMES” in the sponsor’s data file has four categories; “No outcome”, “Not recovered, Not resolved”, “Recovered, Resolved”, and” Recovering, Resolving”.

NOTE: “#of” indicates “The number of”.

Table C Number of bleeding episodes per subject by study

Study104		Study 105		Study 106		Study 109	
PATID	#of bleeding episode	PATID	#of bleeding episode	PATID	#of bleeding episode	PATID	#of bleeding episode
-(b)(6)-	46	-(b)(6)-	1	-(b)(6)-	44	-(b)(6)-	2
-(b)(6)-	54	-(b)(6)-	1	-(b)(6)-	2	-(b)(6)-	2
-(b)(6)-	43	-(b)(6)-	21	-(b)(6)-	3	-(b)(6)-	1
-(b)(6)-	2	-(b)(6)-	1	-(b)(6)-	9	-(b)(6)-	21
-(b)(6)-	46	-(b)(6)-	6	-(b)(6)-	1	-(b)(6)-	8
-(b)(6)-	8	-(b)(6)-	4			-(b)(6)-	9
-(b)(6)-	7	-(b)(6)-	9			-(b)(6)-	19
-(b)(6)-	67	-(b)(6)-	16			-(b)(6)-	5
-(b)(6)-	6	-(b)(6)-	2			-(b)(6)-	2
-(b)(6)-	4	-(b)(6)-	1			-(b)(6)-	12
-(b)(6)-	28	-(b)(6)-	7			-(b)(6)-	9
-(b)(6)-	3	-(b)(6)-	14			-(b)(6)-	2
-(b)(6)-	13					-(b)(6)-	2
-(b)(6)-	78					-(b)(6)-	2
-(b)(6)-	32					-(b)(6)-	3
-(b)(6)-	28					-(b)(6)-	19
-(b)(6)-	22						
-(b)(6)-	129						

-(b)(6)-	4						
-(b)(6)-	9						
-(b)(6)-	180						
-(b)(6)-	7						
-(b)(6)-	17						
-(b)(6)-	2						
-(b)(6)-	6						
-(b)(6)-	5						
-(b)(6)-	169						
N=27	N=1015	N=12	N=83	N=5	N=59	N=16	N=118

NOTE: Total number of episode = 1275 (1015 + 83 + 59 + 118)

Table D Efficacy assessment in Bleeding Episodes by bleeding site (BLEEDALL data file)

Predominant Site of Bleeds	# of Bleeding Episodes	Excellent/Good	Excellent/Good Efficacy (95% CI)
JOINT(S)	629	587	587/629=93.3% (91.1%, 95.2%)
EPISTAXIS	175	117	117/175=67.6% (59.4% , 73.8%)
GASTRO- INTESTINAL	145	112	112/145=77.2% (69.6% , 83.8%)
ORAL	57	37	37/57=64.9% (51.1% , 77.1%)
GYNAECOLOGIC	67	61	61/67=91.0% (81.5%, 96.6%)
OTHERS	202	195	195/202=96.5% (93.0%, 98.6%)
total	1275	1109	1109/1275=87.0% (85.0%, 88.8%)

Efficacy: Physician's rating at the last visit of each episode as either Excellent or Good

Pediatric population (BLEEDALL data file)

Table E Pediatric patients (age≤12) with number of bleeding episodes (n=212)

Patient ID	# of evaluated bleeding episodes	Patient ID	# of evaluated bleeding episodes
-(b)(6)-	46	-(b)(6)-	13
-(b)(6)-	46	-(b)(6)-	22
-(b)(6)-	67	-(b)(6)-	7
-(b)(6)-	6	-(b)(6)-	5

Table F Efficacy assessment in Bleeding Episodes in Pediatric Population (≤ 12)

Predominant Site of Bleeds	# of Bleeding Episodes	Excellent/Good	Excellent/Good Efficacy (95% CI)
JOINT(S)	132	130	130/132=98.5% (94.6%, 99.8%)
EPISTAXIS	31	29	29/31=94% (78.6%, 99.2%)
GI	1	1	1/1=100% (2.5%, 100%)
ORAL	26	24	24/26=92% (74.9%, 99.1%)
GYNAECOLOGIC	10	10	10/10=100% (69.2%, 100%)
OTHERS	12	12	12/12=100% (73.5%, 100%)
Total	212	206	206/212=97.1% (93.9%, 99.0%)

-----**(b)(4)**-----

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PART II. FDA's criteria in the evaluation of the clinical data in the submission

Data files BLEEDALLc-fnl and ---(b)(4)--- with Dr. Hon-Sum Ko's efficacy ratings/bleeding episodes were used to obtain the following tables.

Table H Number of bleeding episodes per subject by study

Study104		Study 105		Study 106		Study 109	
PATID	#of bleeding episode	PATID	#of bleeding episode	PATID	#of bleeding episode	PATID	#of bleeding episode
-(b)(6)-	45	-(b)(6)-	1	-(b)(6)-	38	-(b)(6)-	2
-(b)(6)-	51	-(b)(6)-	1	-(b)(6)-	3	-(b)(6)-	2
-(b)(6)-	42	-(b)(6)-	21	-(b)(6)-	3	-(b)(6)-	1
-(b)(6)-	2	-(b)(6)-	1	-(b)(6)-	9	-(b)(6)-	20
-(b)(6)-	42	-(b)(6)-	6	-(b)(6)-	1	-(b)(6)-	9
-(b)(6)-	8	-(b)(6)-	4			-(b)(6)-	11
-(b)(6)-	7	-(b)(6)-	9			-(b)(6)-	18
-(b)(6)-	66	-(b)(6)-	15			-(b)(6)-	5
-(b)(6)-	3	-(b)(6)-	3			-(b)(6)-	2
-(b)(6)-	5	-(b)(6)-	1			-(b)(6)-	12
-(b)(6)-	28	-(b)(6)-	7			-(b)(6)-	20
-(b)(6)-	3	-(b)(6)-	13			-(b)(6)-	2
-(b)(6)-	13					-(b)(6)-	2
-(b)(6)-	77					-(b)(6)-	2
-(b)(6)-	31					-(b)(6)-	3
-(b)(6)-	26					-(b)(6)-	25
-(b)(6)-	21						
-(b)(6)-	129						
-(b)(6)-	4						
-(b)(6)-	10						
-(b)(6)-	115						
-(b)(6)-	7						
-(b)(6)-	17						
-(b)(6)-	2						
-(b)(6)-	6						

-(b)(6)-	4						
-(b)(6)-	166						
N=27	N=930	N=12	N=82	N=5	N=54	N=16	N=136

NOTE: Total number of episode = 1202 (930 + 82 + 54 + 136)

Bold faced numbers: discrepancies between FDA and the sponsor

Table I Number of successes per study and by bleeding site

Study	Bleeding site	# of No-evaluation	# of Evaluation	#of successes
TMAE- 104	EPISTAXIS	148	130	88
	GASTRO-INTESTINAL	410	120	62
	GYNAECOLOGIC	40	33	25
	JOINT(S)	404	544	479
	ORAL	66	45	31
	OTHERS	37	59	52
	subtotal	1105	930	737
TMAE- 105	GASTRO-INTESTINAL	46	6	0
	JOINT(S)	16	16	13
	OTHERS	14	60	59
	subtotal	76	82	72
TMAE- 106	EPISTAXIS	0	3	3
	GYNAECOLOGIC	28	28	27
	JOINT(S)	10	9	7
	ORAL	0	2	2
	OTHERS	4	12	11
	subtotal	42	54	50
TMAE- 109	GASTRO-INTESTINAL	106	18	2
	JOINT(S)	25	45	42
	OTHERS	23	73	69
	subtotal	154	136	113
total	2579	1377	1202	972

Table J Overall efficacy by bleeding site

Predominant Site of Bleeds	# of treatment	# of Bleeding Episodes	#of successes	efficacy #of successes/#of episodes (95% CI)
JOINT(S)	1068	613	541	541/613=88% (85.5%, 90.7%)
EPISTAXIS	281	133	91	91/133=68% (59.8%, 76.2%)
GI	706	144	64	64/144=44% (36.2% , 53.0%)
ORAL	113	47	33	33/47=70% (55.1% , 82.7%)
GYNAECOLOGIC	129	61	52	52/61=85% (73.8%, 93.0%)
OTHERS	282	204	191	191/204=94% (89.4%, 96.6%)
Total	2579	1202	972	972/1202 = 81% (78.5%, 83.5%)

-----**(b)(4)**-----

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REVIEWER'S COMMENTS/QUESTIONS TO CBER

1. There were twelve subjects who were enrolled in the studies 105, 106, and 109 (three of the twelve were enrolled in the studies 105, 106, 109, and 104), which may raise selection bias issue in the efficacy evaluation.
2. In the BLEEDALL data file, there was a variable named "OUTCOM_C" that shows 1,137 recovered/resolved outcomes. However, the sponsor's efficacy assessment was done regardless of these outcomes. It is not clear how this variable, OUTCOM_C, was evaluated and used for the efficacy analysis (See the Table A).
3. Part I of this review was done using the sponsor's efficacy criteria (data file dated on August 10th 2007).
- 3-1. There were discrepancies between this reviewer's summary statistics and the sponsor's summary statistics for the bleeding episodes. The total number of bleeding episodes obtained by this reviewer using the August 10th data was 1257 and 1088 by the sponsor.
Note: There was a teleconference between the FDA and the sponsor to discuss this issue. However, this issue hasn't been resolved completely yet.
- 3-2. A lower 95% confidence limit of the overall efficacy for the bleeding episodes for the Epistaxis, the GI and the Oral site shows lower than 70%, which is the cutting value for the product to be considered as efficacious.
4. Part II of this review was done using the FDA's efficacy criteria.
- 4-1. A lower 95% confidence limit of the overall efficacy for the bleeding episodes for the GI and the Oral site shows lower than 70%, which is the cutting value for the product to be considered as efficacious.
- 4-2. -----(b)(4)-----

REVIEWER'S COMMENTS/QUESTIONS TO THE SPONSOR

1. There were twelve subjects who were enrolled in the studies 105, 106, and 109 (three of the twelve were enrolled in the studies 105, 106, 109, and 104), which may raise selection bias issue in the efficacy evaluation.
Please explain in detail under what condition those subjects were reenrolled.
2. There were twelve subjects who were enrolled in the studies 105, 106, and

109 (three of the twelve were enrolled in the studies 105, 106, 109, and 104), which may raise correlation issue among those subjects in the efficacy evaluation. Please comment.

3. In the BLEEDALL data file, there was a variable named “OUTCOM_C” that shows 1,137 recovered/resolved outcomes. However, your efficacy assessment was done regardless of these outcomes. It is not clear how this variable, OUTCOM_C, was evaluated and used for the efficacy analysis (See the Table 1). Please comment.
4. Part I of this review was done using the sponsor’s efficacy criteria (data file dated on August 10th 2007).
- 3-1. There were discrepancies between this reviewer’s summary statistics and your summary statistics for the bleeding episodes. The total number of bleeding episodes obtained by this reviewer using the August 10th data was 1257 and 1088 by you. Please comment.
- 3-2. A lower 95% confidence limit of the overall efficacy for the bleeding episodes for the Epistaxis, the GI and the Oral site shows lower than 70%, which is the cutting value for the product to be considered as efficacious. Please comment.
5. Part II of this review was done using the FDA’s efficacy criteria.
- 4-1. A lower 95% confidence limit of the overall efficacy for the bleeding episodes for the GI and the Oral site shows lower than 70%, which is the cutting value for the product to be considered as efficacious. Please comment.
- 4-2. -----(b)(4)-----

