



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION BLA

BLA/Supplement Number: 125251/0/31

Product Name: WILATE: Human plasma-derived, stable, highly purified, double virus inactivated concentrated of freeze-dried active human coagulation FVIII and human VWF

Indication(s): Treatment -----(b)(4)----- of spontaneous -----(b)(4)----- bleedings in patients with von Willebrand Disease (VWD)

Applicant: Octapharma

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Statistical Branch: CBER/OBE/DB/TEB (HFM-219)

Primary Statistical Reviewer: Shiowjen Lee, Ph.D.

Concurring Reviewer (1): Jessica Kim, Ph.D., Acting Team Leader
Therapeutic Evaluation Branch (HFM-219)

Concurring Reviewer (2): Ghanshyam Gupta, Ph.D., Chief
Therapeutic Evaluation Branch (HFM-219)

Medical Office/Division: CBER/OBRR/DH/CRB

Clinical Reviewer(s): Hon-Sum Ko, MD (HFM-392)

Project Manager: Pauline Cottrell (HFM-380)

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1. EXECUTIVE SUMMARY

Sponsor's current submission (STN125251/0/31) includes re-analyses of efficacy from open-labeled and uncontrolled studies TMAE-104, 105, 106 and 109. The FDA had determined in the CR letter (dated 1/8/2008) that results from studies TMAE-104, 105, 106 and 109 are not adequate to establish efficacy of WILATE due to design deficiencies. The FDA had recommended in the CR letter that the sponsor conducts appropriate studies with adequate design, taking into consideration of comments provided in the CR letter. The sponsor however elected not to conduct new studies. Instead, the sponsor re-evaluates each bleeding episodes --- (b)(4) --- according to FDA recommended criteria (dated 10/30/07). Results of the re-evaluation are submitted. This review memo summarizes the re-analyses and compares them to the FDA's results. The summary is:

- FDA's results for the efficacy of WILATE in treating bleeding episodes meet the specified criterion. The success rate in treating bleeding episode as a whole is 84.1% with a 95% confidence interval (81.8%, 86.2%). The lower bound 81.8% is greater than the criterion 70%.
- Sponsor's re-analyses and FDA's results are in agreement that the efficacy of WILATE meets the objective (i.e., lower 95% confidence limit > 70%) for treating bleeding episodes across multiple bleeding sites. The numbers of point estimates and the corresponding 95% confidence intervals however are not matched. The overall success rate is 78% with a 95% confidence interval of (75.8%, 80.4%) based on sponsor's re-analyses; while the success rate is 81% with a 95% confidence interval of (78.5%, 83.1%) based on FDA's results.
- For pediatric subjects 16 years and under, FDA's result of success rate in treating bleeding episode as a whole is 87.6% with a 95% confidence interval of (82.7%, 91.5%). The lower bound 82.7% is greater than the criterion 70%.
- ----- (b)(4) -----

It should be noted that the reason of different success rates and confidence intervals between FDA and the sponsor is due to different evaluation of each bleeding episode ---- (b)(4) --- (either success or failure) even though the sponsor was provided with FDA's evaluation criteria for efficacy rating (dated 10/30/2007). It is a clinical issue that the medical division should contact the sponsor to resolve the inconsistent evaluation of bleeding episodes ---- (b)(4) ----.

1.1 Conclusions and Recommendations

Efficacy data of WILATE derived from Studies TMAE-104, 105, 106 and 109 were submitted in the original Biologic License Application (BLA). The four studies were open-labeled and uncontrolled. Sponsor's results of re-evaluation (or re-analyses) and FDA's results are in agreement that the efficacy of WILATE meets the objective (> 70%) for treating bleeding episodes across multiple bleeding sites although the numbers of point estimates and the corresponding 95% confidence intervals are not matched. FDA's result of successfully treating bleeding episode as a whole meets the

objective (> 70%) for all subjects in the four studies combined and for pediatric subjects 16 years and younger, respectively. -----(b)(4)-----

1.2 Brief Overview of Clinical Studies

Results from five studies were submitted for the indication of Von Willebrand Disease (VWD) in the original Biologic License Application (BLA). They were studies WIL-12, TMAE-104, 105, 106 and 109. The primary endpoints of the five studies were PK parameters. The overall efficacy assessment was specified as secondary. Study WIL-12 was the pivotal for the basis of product approval. The other four studies that provided efficacy data of WILATE were open-labeled and uncontrolled. The FDA issued a CR letter on January 8, 2008 with the following key issues:

- The submitted PK data of Study WIL-12 generated by the previously used analytical method for ristocetin cofactor activity of VWF:RCo are non-interpretable. The FDA recommended that a sensitivity analytical method to measure the relevant concentration of VWF:RCo in plasma after WILATE infusion be developed.
- For establishing efficacy of WILATE, results from studies TMAE-104, 105, 106 and 109 are not adequate due to study design issues. The FDA recommended the sponsor to conduct appropriate studies with adequate design, taking into consideration comments provided in the CR letter.

To establish the efficacy of WILATE, sponsor's current submission (STN125251/0/31) includes results of re-evaluation of data from studies TMAE-104, 105, 106 and 109 based on FDA's recommended criteria for efficacy rating (10/30/2007).

1.3 Major Statistical Issues and Findings

Because of the study design issues, the FDA had recommended the sponsor to conduct appropriate studies with adequate design, taking into consideration of comments provided in the CR letter (dated 1/8/2008). The sponsor however elected not to conduct new studies. Instead, they submit results of re-evaluation of data from studies TMAE-104, 105, 106 and 109 according to FDA's recommended criteria (dated 10/30/2007).

This review memo provides a summary of the sponsor's re-analyses and comparisons to the FDA's results.

2. INTRODUCTION

2.1 Overview

The proposed product is WILATE (Human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF)). The seeking indication is the treatment ---(b)(4)--- of spontaneous -(b)(4)- ----- bleedings in patients with Von Willebrand Disease (VWD).

The original Biologic License Application (BLA) was submitted on 12/12/2006. Results from five studies were submitted for VWD indication. They were studies WIL-12, TMAE-104, 105, 106 and 109. The primary endpoints of the five studies were pharmacokinetic (PK) parameters. The overall

efficacy assessment was specified as secondary. Study WIL-12 was considered to be the pivotal for the basis of product approval. The primary PK reviewer for Study WIL-12 was Dr. Iftekhar Mahmood. The other four studies were open-labeled and uncontrolled. The efficacy assessment was reviewed by Dr. Hon-Sum Ko at OBRR and Dr. Jessica Kim at OBE.

The FDA issued a CR letter on January 8, 2008. The key issues included in the CR letter were:

- The submitted PK data of Study WIL-12 generated by the previously used analytical method for ristocetin cofactor activity of VWF:RCo are non-interpretable. The FDA recommended that a sensitivity analytical method to measure the relevant concentration of VWF:RCo in plasma after WILATE infusion be developed.
- For establishing efficacy of WILATE, results from studies TMAE-104, 105, 106 and 109 are not adequate due to study design issues. The FDA recommended the sponsor to conduct appropriate studies with adequate design, taking into consideration comments provided in the CR letter.

Sponsor's current submission (STN125251/0/31) includes responses to FDA's CR letter. To establish efficacy of WILATE in the indication of VWD, the sponsor states that they have re-evaluated data of studies TMAE-104, 105, 106 and 109 according to the FDA's recommended criteria which were conveyed to the sponsor on 10/30/2007. Results of the re-evaluation are included in the current submission. No new studies have been conducted.

2.2 Data Sources

Data sources include sponsor's submission (STN125251/0/31) and electronic SAS datasets in the Electronic Document Room (EDR); and FDA Clinical reviewer's electronic JMP datasets of ratings for bleeding episodes and surgeries.

3. STATISTICAL EVALUATION

Studies TMAE-104, 105, 106 and 109 were designed as open-labeled and uncontrolled. In addition to the inadequate design issues provided in FDA Clinical Review Memo (dated 12/6/2007), several subjects participated in at least two of studies TMAE-104, 105, 106 and 109. This raises an issue of patient selection bias. The FDA had recommended the sponsor to conduct appropriate studies with adequate design, taking into consideration comments provided in the CR letter to evaluate the efficacy of WILATE. However, the sponsor did not conduct any new studies.

It should be noted that in the original submission (STN125251/0) FDA (or Dr. Hon Sum Ko) had evaluated each bleeding episode -----(b)(4)----- to determine whether or not WILATE had successfully treated the condition. As a result, outcomes derived from FDA's evaluation were different from those of sponsor's results in STN125251/0. Sponsor had a t-con with the FDA (dated 10/25/07); and was provided with FDA's criteria of evaluation (dated 10/30/07). Sponsor re-evaluated data of bleeding episodes ----(b)(4)--- from the four studies based on FDA's criteria. Results of the re-evaluation are submitted as re-analyses in the current submission (STN125251/0/031).

This reviewer has been requested to summarize and compare efficacy with respect to successful treatment of bleeding episodes -----(b)(4)----- between the sponsor's re-

analyses and the FDA's results. The conclusion of the review memo will state only whether or not sponsor's re-analyses and FDA's results are in agreement disregard the clinical issues raised in the original BLA submission concerning the four studies.

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Results of four studies (TMAE-104, 105, 106 and 109) are included in the BLA to support the indication of VWD. The four studies were open-labeled and uncontrolled. Details about the design of the studies are stated in FDA Clinical Review Memo for STN125251/0.

The clinical efficacy of WILATE has been evaluated with respect to successful treatment of bleeding episodes -----(b)(4)-----. For each bleeding episode, an overall assessment of the clinical response to the treatment WILATE was done by the treating physician using a verbal rating scale (VRS) at the last visit; and was done by patient after each bleeding episode. The VRS scale is a 4-point scale with the following definitions:

None	Severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeds)
Moderate	Moderate bleeding or control of bleeding; required additional product.
Good	Slight oozing and adequate control of bleeding; did not require additional product.
Excellent	Haemostasis achieved; cessation of bleeding.

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

[
--(b)(4)--
]

Based on FDA Medical Review Memo (pages 33-35), the FDA used additional criteria to determine hemostatic efficacy due to the lack of clear definition of bleeding episodes and difficulties in applying the 4-point VRS in interpreting hemostatic efficacy. The criteria have been conveyed to the sponsor at a t-con (dated 10/25/07) and a fax (dated 10/30/2007). They are cited from Medical Review Memo whether an episode -----(b)(4)----- treated with WILATE is considered to be a success or a failure in the following:

1. Bleeding Episodes:

In addition to the 4-point subjective VRS scale used in the studies by the Investigator or patients to determine clinical efficacy, an arbitrary but more objective success/failure determination is to be based on additional factors. As a conservative approach, moderate and none scores in the 4-point

scale are regarded as failures, and excellent and good scores are subjected to more objective criteria to determine failure as follows:

- use of other products that contain VWF (not including whole blood)
 - inadequate hemostasis as shown by requiring unexplained blood transfusions
 - increase in dose without adequate justification or unexplained doses above that recommended in the protocol and proposed labeling.
 - number of infusions used -
 - Minor bleeds > 2 treatments (failure)
 - Moderate bleeds > 3 treatments (failure)
 - Severe bleeds > 4 treatments (failure)*
- *For severe bleeding, the site of bleeding will be taken into consideration, and each deviation from the 4-treatment cutoff must be justified.

Previously unrated episodes under the subjective 4-point scale are also assigned success/failure rating based on the above objective criteria.

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

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Totals of 41, 14, 14 and 16 subjects were included in studies TMAE-104, 105, 106, and 109, respectively, in sponsor's database (adsl.xpt located in EDR). The patient ID, gender and VWD type are tabulated in Table 1.

Of the subjects participated in the studies, totals of 27, 12, 5 and 16 subjects were included in bleeding episode database (adblettr.xpt in EDR) for studies TMAE-104, 105, 106 and 109, respectively. -----(b)(4)-----
----- for the respective study. The patient listings for bleeding episodes -----(b)(4)---- are summarized in Table 2.

As can be observed from Table 2, a total of 12 individuals (in bold) who had bleeding episodes participated in at least two of the studies; -----(b)(4)----- participated in two studies (TMAE-104 and 109). As a result, 45 different individuals contributed the database of bleeding episodes; -----(b)(4)-----.

Table 1: Subjects Participated in Studies TMAE-104, 105, 106 and 109

Study	Patient ID	Gender	VWD Type	Study	Patient ID	Gender	VWD Type
104 (n = 41)	-(b)(6)-	M	3	105 (n = 14)	-(b)(6)-	M	3
	-(b)(6)-	M	3		-(b)(6)-	M	3
	-(b)(6)-	M	3		-(b)(6)-	F	3
	-(b)(6)-	M	3		-(b)(6)-	F	2
	-(b)(6)-	F	3		-(b)(6)-	F	2
	-(b)(6)-	F	3		-(b)(6)-	M	2
	-(b)(6)-	F	3		-(b)(6)-	F	1
	-(b)(6)-	F	3		-(b)(6)-	F	1
	-(b)(6)-	F	3		-(b)(6)-	F	3
	-(b)(6)-	M	2		-(b)(6)-	M	3
	-(b)(6)-	F	3		-(b)(6)-	M	3
	-(b)(6)-	M	3		-(b)(6)-	M	3
	-(b)(6)-	M	2		-(b)(6)-	M	3
	-(b)(6)-	F	3		-(b)(6)-	M	3
	-(b)(6)-	F	3				
	-(b)(6)-	M	3				
	-(b)(6)-	M	3				
	-(b)(6)-	F	3				
	-(b)(6)-	F	3				
	-(b)(6)-	F	3				
	-(b)(6)-	F	1				
	-(b)(6)-	M	3				
	-(b)(6)-	F	3				
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	-(b)(6)-	M	2				
	-(b)(6)-	M	2				
	-(b)(6)-	F	3				
	-(b)(6)-	M	1				
	-(b)(6)-	M	3				
	-(b)(6)-	F	3				
	-(b)(6)-	F	2				
	-(b)(6)-	F	2				
Study	Patient ID	Gender	VWD Type	Study	Patient ID	Gender	VWD Type
106 (n = 14)	-(b)(6)-	M	2	109 (n = 16)	-(b)(6)-	M	3
	-(b)(6)-	F	2		-(b)(6)-	M	3
	-(b)(6)-	F	3		-(b)(6)-	M	3
	-(b)(6)-	F	3		-(b)(6)-	M	3
	-(b)(6)-	F	2		-(b)(6)-	M	3
	-(b)(6)-	M	2		-(b)(6)-	F	2
	-(b)(6)-	F	2		-(b)(6)-	M	3
	-(b)(6)-	M	2		-(b)(6)-	F	3
	-(b)(6)-	F	3		-(b)(6)-	F	2
	-(b)(6)-	F	3		-(b)(6)-	M	3
	-(b)(6)-	F	1		-(b)(6)-	F	1
	-(b)(6)-	M	2		-(b)(6)-	F	1
	-(b)(6)-	F	2		-(b)(6)-	M	1
	-(b)(6)-	F	1		-(b)(6)-	F	1
					-(b)(6)-	M	1
					-(b)(6)-	M	1

Source: Sponsor's electronic SAS database, adsl.xpt, in EDR (STN125251/0/31).

Table 2: Subjects Per Study Contributing to Bleeding Episodes -----(b)(4)-----

	Bleeding Episodes Database				----- (b)(4) -----			
Study	104	105	106	109	104	105	106	109
Patient 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)-	
	-(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	27	12	5	16	24	2	8	2
Source: FDA Medical Review Memo of STN125251/0; and sponsor database adsytrt.xpt in EDR. Patient IDs in bold participated in at least two studies within each of bleeding episodes database ----- (b)(4) ----- database.								

3.1.3 Statistical Methodologies

Point estimates and the corresponding 95% confidence limits were calculated for the proportion of successful treatment in bleeding episodes ----- (b)(4) ----- disregard the possible correlation of multiple treatments within the same individual. The following gives the overall success criteria for hemostatic efficacy FDA used which are cited from minutes of teleconference dated 10/25/2007:

A. Bleeding Episodes

- Apply a lower bound 95% C.I. of 70% for hemostasis success rate for treatment of bleeding episodes in an integrated analysis of the data from all four studies.

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

For dosage of WILATE used in treating bleeding episodes, descriptive statistics is used.

3.1.4 Results and Conclusions

The sponsor states that they have performed analyses of re-evaluation according to FDA's recommended criteria. Sponsor's re-analyses are summarized and compared to FDA's results.

It should be pointed out that two data files are used by the FDA to evaluate the efficacy of WILATE in treating bleeding episodes. This reviewer has been provided with the two JMP data files from Clinical Reviewer. The two data files are:

- A. BLEEDALLC-FNL.JMP (with 2579 rows of data): provides Clinical Reviewer's adjudication of each bleeding episode at bleeding sites involved. A bleeding episode could occur at multiple sites (e.g., oral and joints). Therefore, one rating (either Success or Failure) is assigned at each bleeding site involved per bleeding episode per subject per study. The data file also includes dosage of WILATE administered at each infusion.
- B. OVERALL USE-C.JMP (with 2452 rows of data): provides Clinical Reviewer's adjudication of each bleeding episode as a whole. Therefore, one rating (either Success or Failure) is assigned at each bleeding episode per subject per study.

The two data files serve different purposes. Data file A provides the success rate of WILATE treatment in treating bleedings by bleeding site. Data file B provides the overall efficacy of WILATE treatment in treating bleeding episodes for which one episode can be assigned with either success or failure regardless of the number of bleeding sites involved.

3.1.4.1 Efficacy in Treating Bleeding Episodes

Efficacy by Bleeding Site

Table A.1 of the Appendix summarizes the number of bleedings per subject by study according to FDA Dr. Hon-Sum Ko's efficacy ratings (i.e., data file A – BLEEDALLC-FNL.JMP) in the original BLA (STN125251/0); while Table A.2 of the Appendix gives a detailed summary of bleedings and the number of successful treatment with WILATE according to the sponsor's re-evaluation. It should be noted that a bleeding episode could occur at multiple sites (e.g., oral and joints) for a subject. Tables A.1-A.2 of the Appendix include multiple bleeding sites within each bleeding episode.

As a result, a total of 1202 bleedings ($= 930 + 82 + 54 + 136$ in Table A.1) are accounted for the efficacy assessment of WILATE in treating bleedings according to FDA's evaluation. On the other hand, sponsor's re-analyses gives a total of 1309 bleedings ($= 1024 + 86 + 60 + 139$ in Table A.2) for the efficacy assessment of WILATE.

Sponsor's re-analyses and FDA's results of overall successful treatment in bleeding episodes and results by bleeding site are presented in Table 3. The summary is:

- Though the numbers are not matched, both sponsor's re-analyses and FDA's results are in agreement that the lower bound of 95% confidence interval exceeds 70%.
 - The overall successful treatment rate in bleeding episodes across multiple bleeding sites is 78% with a 95% confidence interval of (75.8%, 80.4%) based on sponsor's re-analyses. The lower bound of 95% confidence interval 75.8% is greater than 70%.

- FDA's results give an overall success rate of 81% with a 95% confidence interval of (78.5%, 83.1%). The lower bound 78.5% is greater than 70%.
- There are similarities between sponsor's re-analyses and FDA's analyses in efficacy by bleeding site. The lower bounds of 95% confidence intervals for successful treatment rate in bleeding episodes are **below** 70% for bleeding sites of epistaxis, gastro-intestinal, and oral.

**Table 3: Efficacy in Treating Bleeding Episodes by Bleeding Site
Sponsor's Re-Analyses and FDA's Results**

Predominant Site of Bleeding	Sponsor's Re-Analyses			FDA's Results		
	No. of Bleedings	Successful Treatment	Success Rate (95% CI*)	No. of Bleedings	Successful Treatment	Success Rate (95% CI*)
Joint(s)	654	566	87% (83.7%, 89.1%)	613	541	88% (85.4%, 90.7%)
Epistaxis	175	110	63% (55.2%, 70.0%)	133	91	68% (59.8%, 76.2%)
Gastro-intestinal	149	62	42% (33.6%, 50.0%)	144	64	44% (36.2%, 53.0%)
Oral	57	35	61% (47.6%, 74.0%)	47	33	70% (55.1%, 82.7%)
Gynaecologic	67	57	85% (74.3%, 92.6%)	61	52	85% (73.8%, 93.0%)
Others	207	193	93% (88.9%, 96.3%)	204	191	94% (89.4%, 96.6%)
Total	1309	1023	78% (75.8%, 80.4%)	1202	972	81% (78.5%, 83.1%)
Source: Sponsor's re-analyses in STN125251/0/31; and FDA's results based on data file A (BLEEDALLC-FNL.JMP). *95% CI: 95% confidence intervals are exact Clopper-Pearson intervals.						

FDA's efficacy results of successful treatment in bleeding episodes by bleeding sites for each study and for different VWD types are presented in Tables A.3-A.4 of the Appendix, respectively. Sponsor's re-analyses report did not include this summary. The efficacy at bleeding site of gastro-intestinal, ranged from 0 to 51.7%, is particularly low as compared to results at other bleeding sites (Table A.3 of the Appendix).

The number of bleeding episodes was pre-dominated by patients who are VWD type 3 that accounts for 92% of bleedings (= 1108/1202, Table A.4 of the Appendix). As expected, the success rate and the corresponding 95% confidence interval for VWD type 3 patients are similar to the overall results. The success rate for VWD type 3 patients is 82% with a 95% confidence interval of (79.4%, 84.0%).

For successful treatment of bleeding episodes by bleeding site, the dosage of WILATE used (in IU/kg) in infusions is of interest. Table 4 gives a summary. A total of 1423 infusions of WILATE were administered across bleeding sites for those bleeding episodes that were considered to be successfully treated based on FDA's evaluation, with 971 initial infusions and 452 subsequent infusions. The total dosage administered to gastro-intestinal site appears to be larger on the average (40 IU/kg) with a wider standard deviation (20 IU/kg).

Table 4: Dosage (IU/kg) in Successful Episodes by Bleeding Site – FDA’s Results

Bleeding Site	All Doses considered		Initial Dose		Subsequent Doses	
	# of infusions	Dose Mean \pm sd (range)	# of infusions	Dose Mean \pm sd (range)	# of infusions	Dose Mean \pm sd (range)
Joint(s)	801	26 \pm 12 (7 - 69)	542	28 \pm 13 (7 - 69)	259	21 \pm 10 (7 - 60)
Epistaxis	132	24 \pm 11 (8 - 78)	91	25 \pm 10 (13 - 78)	41	22 \pm 14 (8 - 77)
Gastro-Intestinal	125	40 \pm 20 (9 - 76)	64	43 \pm 19 (9 - 76)	61	36 \pm 21 (9 - 76)
Oral	41	26 \pm 14 (8 - 80)	33	27 \pm 14 (10 - 80)	8	24 \pm 18 (8 - 60)
Gynecologic	87	27 \pm 14 (9 - 77)	52	28 \pm 17 (12 - 77)	35	26 \pm 9 (9 - 52)
Others	237	23 \pm 12 (10 - 95)	189	24 \pm 12 (12 - 95)	48	20 \pm 13 (10 - 95)
Source: Summary is based on FDA’s data file A – bleedallc-fnl.jmp (with 2579 rows of data).						

Efficacy Per Bleeding Episode

Efficacy of WILATE in treating bleeding episodes is summarized in this section. The summary is based on data file B, OVERALL USE-C.JMP (with 2452 rows of data). The data file provides Clinical Reviewer’s adjudication of each bleeding episode. One definite rating (either Success or Failure) is assigned to each bleeding episode per subject per study. Results of FDA’s evaluation by study are presented in Table 5. Details of bleeding episodes and successful treatment per subject by study are provided in Table A.5 of the Appendix.

Table 5: No. of Bleeding Episodes and Successes by Study – FDA’s Evaluation

Study	No. of Bleeding Episodes	No. of Successes (% of success rate)	95 % CI* for Success Rate
TMAE-104	799	665 (83.2%)	(80.5%, 85.8%)
TMAE-105	82	72 (87.8%)	(78.7%, 94.0%)
TMAE-106	53	49 (92.5%)	(81.8%, 97.9%)
TMAE-109	134	112 (83.6%)	(76.2%, 89.4%)
Total	1068	898 (84.1%)	(81.8%, 86.2%)
Source: Summary is based on data file, overall use-c.jmp, with 2452 rows of data listing.			
* The exact 95% confidence interval is calculated based on Clopper-Pearson’s method.			

The summary of Table 5 is:

- The lower bounds of 95% confidence intervals of success rate in treating bleeding episodes with WILATE are all greater than 70% for each study.
- The overall success rate is 84.1% with a 95% confidence interval of (81.8%, 86.2%). The lower bound of the confidence interval, 81.8%, is greater than the specified criterion 70%.

Efficacy in Treating Bleeding Episode for Pediatrics

A total of 8 and 10 individuals were pediatrics 12 years or younger and 16 years or younger, respectively. These individuals, VWD type, number of bleeding episodes and number of infusions administered are tabulated in Table 6. The summary is:

- The success rate in treating bleeding episodes for pediatrics 12 years and under is 86.6% with a 95% confidence interval of (81.0%, 91.1%). The lower bound 81.0% is greater than the criterion 70%.

- The success rate in treating bleeding episodes for pediatrics 16 years and under is 87.6% with a 95% confidence interval of (82.7%, 91.5%). The lower bound 82.7% is greater than the criterion 70%.

Table 6: Pediatric Individuals with Bleeding Episodes – FDA’s Evaluation

Study	Patient ID	VWD type	No. of Bleeding Episodes	No. of Episodes Successfully Treated	No. of Infusions
Pediatric of 12 Years and Younger					
104	-(b)(6)-	3	39	38	54
104	-(b)(6)-	3	45	44	57
104	-(b)(6)-	3	65	47	167
104	-(b)(6)-	3	7	7	7
104	-(b)(6)-	3	4	4	7
104	-(b)(6)-	3	21	19	33
104	-(b)(6)-	1	10	7	19
104	-(b)(6)-	2	3	2	10
Total			194	168	354
Overall Success			86.6% with 95% CI (81.0%, 91.1%)		
Pediatric of 16 Years and Younger					
104	-(b)(6)-	3	39	38	54
104	-(b)(6)-	3	45	44	57
104	-(b)(6)-	3	65	47	167
104	-(b)(6)-	3	7	7	7
104	-(b)(6)-	3	4	4	7
104	-(b)(6)-	3	21	19	33
104	-(b)(6)-	1	10	7	19
104	-(b)(6)-	2	3	2	10
105	-(b)(6)-	1	1	1	1
109			2	2	2
106	-(b)(6)-	3	37	34	74
Total			234	205	431
Overall Success			87.6% with 95% CI (82.7%, 91.5%)		
Source: Summary is based on FDA’s data file B – overall use-c.jmp, with 2452 rows of data listing.					

The dosage of WILATE administered in successfully treated episodes by bleeding site for pediatric subjects 16 years and under is summarized in Table 7.

Table 7: Dosages (IU/kg) in Successful Episodes for Pediatric ≤ 16 Years – FDA’s Results

Bleeding Site	All Doses considered		Initial Dose		Subsequent Doses	
	# of infusions	Dose Mean \pm sd (range)	# of infusions	Dose Mean \pm sd (range)	# of infusions	Dose Mean \pm sd (range)
Joint(s)	158	30 \pm 13 (12 - 69)	117	32 \pm 13 (14 - 69)	41	25 \pm 9 (12 - 52)
Epistaxis	30	27 \pm 14 (12 - 77)	25	25 \pm 10 (14 - 52)	5	37 \pm 25 (12 - 77)
Gastro-Intestinal	1	22 (N/A)	1	22 (N/A)	0	
Oral	23	25 \pm 8 (16 - 52)	21	24 \pm 8 (16 - 52)	2	25 \pm 13 (16 - 35)
Gynaecologic	58	27 \pm 13 (12 - 69)	33	27 \pm 16 (12 - 69)	25	26 \pm 8 (12 - 52)
Others	19	25 \pm 7 (16 - 37)	14	27 \pm 7 (19 - 37)	5	19 \pm 4 (16 - 26)
Source: Summary is based on FDA’s data file A – bleedallc-fnl.jmp (with 2579 rows of data).						

Two (2) pages determined to be non-releasable: (b)(4)

3.2 Evaluation of Safety

The clinical reviewer Dr. Hon-Sum Ko has provided in-depth review regarding the safety of WILATE in the original submission (STN125251/0).

3.3 Gender, Race, Age and Other Special/Subgroup Populations

As the product is designated as an orphan product, the study population is very limited. There were 45 different individuals in bleeding episodes database; and 34 different individuals in surgeries database. Subgroup results by patient demographic, and baseline characteristics are not performed. FDA's efficacy evaluation by VWD type are presented in Section 3.1.4 Results and Conclusions.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

Because of the study design issues, the FDA had recommended the sponsor to conduct appropriate studies with adequate design, taking into consideration of comments provided in the CR letter (dated 1/8/2008). The sponsor however elected not to conduct new studies.

It should be noted that in the original submission (STN125251/0) FDA (or Dr. Hon Sum Ko) had evaluated each bleeding episode ----- (b)(4) ----- to determine whether or not WILATE had successfully treated the condition. As a result, outcomes derived from FDA's evaluation were different from those of sponsor's results in STN125251/0. Sponsor had a t-con with the FDA (dated 10/25/07); and was provided with FDA's criteria of evaluation (dated 10/30/07). Sponsor re-evaluates data of bleeding episodes --- (b)(4) --- from the four studies based on FDA's criteria. Results of the re-evaluation are submitted as re-analyses in the current submission (STN125251/0/031). This review memo provides a summary of the sponsor's re-analyses and comparisons to the FDA's results.

4.2 Conclusions and Recommendations

Study WIL-12 is PK study and is the pivotal study for the basis of product approval. The efficacy data of WILATE are considered as the secondary and are derived from Studies TMAE-104, 105, 106 and 109 which were open-labeled and uncontrolled.

It is understood that study design issues have been raised in FDA Medical Review Memo and conveyed to the sponsor in the CR letter. The efficacy summary stated here is for the purpose of comparing sponsor's re-analyses and the FDA's results. Note that the key issue is different adjudication of each bleeding episode ---- (b)(4) ---- between the sponsor and the FDA. Different adjudication could be due to subtle views of each episode --- (b)(4) ---. Although the sponsor was provided a t-con discussion (dated 10/25/07) and a fax (dated 10/30/07) that describe the criteria FDA

used to evaluate each bleeding episode ----(b)(4)----, the outcome of re-evaluation does not result in identical results to FDA's.

The summary of sponsor's re-analyses and comparisons to FDA results is:

- FDA's results for the efficacy of WILATE in treating bleeding episodes meet the specified criterion. The success rate in treating bleeding episode as a whole is 84.1% with a 95% confidence interval (81.8%, 86.2%). The lower bound 81.8% is greater than the criterion 70%.
- Sponsor's re-analyses and FDA's results are in agreement that the efficacy of WILATE meets the objective (i.e., lower 95% confidence limit > 70%) for treating bleeding episodes across multiple bleeding sites. The numbers of point estimates and the corresponding 95% confidence intervals however are not matched. The overall success rate is 78% with a 95% confidence interval of (75.8%, 80.4%) based on sponsor's re-analyses; while the success rate is 81% with a 95% confidence interval of (78.5%, 83.1%) based on FDA's results.
- For pediatric subjects 16 years and under, FDA's result of success rate in treating bleeding episode as a whole is 87.6% with a 95% confidence interval of (82.7%, 91.5%). The lower bound 82.7% is greater than the criterion 70%.
- -----(b)(4)-----

It should be noted that the reason of different success rates and confidence intervals between FDA and the sponsor is due to different evaluation of each bleeding episode ---(b)(4)---- (either success or failure) even though the sponsor was provided with FDA's evaluation criteria for efficacy rating (dated 10/30/2007). It is a clinical issue that the medical division should contact the sponsor to resolve the inconsistent evaluation of bleeding episodes -----(b)(4)----.

APPENDICES

Table A.1: Number of Bleedings* Per Subject by Study – FDA’s Evaluation

Study 104		Study 105		Study 106		Study 109	
PATID	#of Bleedings	PATID	#of Bleedings	PATID	#of Bleedings	PATID	#of Bleedings
-(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
Source: FDA’s data file A – bleedallc-fnl.jmp (with 2579 rows of data). *A bleeding episode could occur at multiple sites (eg., oral and joints) for a subject. The numbers listed include multiple sites.							

**Table A.2: Number of Bleedings and Successes Per Subject by Study
Sponsor's Re-Evaluation**

Study 104			Study 105			Study 106			Study 109		
PATID	#of Bleeding	# of Success	PATID	#of Bleeding	# of Success	PATID	#of Bleeding	# of Success	PATID	#of Bleeding	# of Success
-(b)(6)-	46	46	-(b)(6)-	1	1	-(b)(6)-	44	42	-(b)(6)-	2	2
-(b)(6)-	54	16	-(b)(6)-	1	1	-(b)(6)-	3	2	-(b)(6)-	2	2
-(b)(6)-	43	36	-(b)(6)-	21	21	-(b)(6)-	3	3	-(b)(6)-	1	1
-(b)(6)-	2	1	-(b)(6)-	1	1	-(b)(6)-	9	9	-(b)(6)-	21	21
-(b)(6)-	46	46	-(b)(6)-	6	2	-(b)(6)-	1	1	-(b)(6)-	9	0
-(b)(6)-	8	6	-(b)(6)-	4	3				-(b)(6)-	11	10
-(b)(6)-	7	7	-(b)(6)-	10	8				-(b)(6)-	20	15
-(b)(6)-	69	51	-(b)(6)-	16	15				-(b)(6)-	5	3
-(b)(6)-	6	5	-(b)(6)-	3	2				-(b)(6)-	2	2
-(b)(6)-	5	3	-(b)(6)-	1	1				-(b)(6)-	12	11
-(b)(6)-	28	27	-(b)(6)-	7	7				-(b)(6)-	20	20
-(b)(6)-	3	1	-(b)(6)-	15	15				-(b)(6)-	2	2
-(b)(6)-	13	8							-(b)(6)-	2	2
-(b)(6)-	78	57							-(b)(6)-	2	2
-(b)(6)-	32	32							-(b)(6)-	3	3
-(b)(6)-	28	9							-(b)(6)-	25	24
-(b)(6)-	22	20									
-(b)(6)-	133	130									
-(b)(6)-	4	4									
-(b)(6)-	10	9									
-(b)(6)-	180	62									
-(b)(6)-	7	7									
-(b)(6)-	17	11									
-(b)(6)-	2	2									
-(b)(6)-	6	6									
-(b)(6)-	5	5									
-(b)(6)-	170	162									
n=27	N= 1024	769	n=12	N= 86	77	n=5	N= 60	57	n=16	N= 139	120
Source: Sponsor's electronic SAS dataset adbletrt.xpt and adblesum.xpt in EDR.											

**Table A.3: Efficacy in Bleedings per Study by Bleeding Site
FDA's Results**

Study	Bleeding site	No. of episodes*	No. of successes	Success Rate
104	Epistaxis	130	88	67.7%
	Gastro-Intestinal	120	62	51.7%
	Gynaecologic	33	25	75.8%
	Joint(s)	544	479	88.1%
	Oral	45	31	68.9%
	Others	59	52	88.1%
	Subtotal	930	737	79.2%
105	Gastro-Intestinal	6	0	0
	Joint(s)	16	13	81.3%
	Others	60	59	98.3%
	Subtotal	82	72	87.8%
106	Epistaxis	3	3	100%
	Gynecologic	28	27	96.4%
	Joint(s)	9	7	77.8%
	Oral	2	2	100%
	Others	12	11	91.7%
	Subtotal	54	50	92.6%
109	Gastro-Intestinal	18	2	11.1%
	Joint(s)	45	42	93.3%
	Others	73	69	94.5%
	Subtotal	136	113	83.1%
Total		1202	972	80.9%
Source: FDA's data file A – bleedallc-fnl.jmp (with 2579 rows of data). *An episode could occur at multiple sites (eg., oral and joints) for a subject.				

Table A.4: Efficacy in Bleedings by VWD Type – FDA's Results

VWD Type (Number of Individuals)	No. of Bleedings	No. of Successful Treatment	Success Rate	95% CI* of Success Rate
1 (n = 8)	29	24	83%	(64.2%, 94.2%)
2 (n = 12)	65	42	65%	(51.8%, 76.1%)
3 (n = 25)	1108	906	82%	(79.4%, 84.0%)
Total (n = 45)	1202	972	81%	(78.5%, 83.1%)
Source: FDA Clinical Review Memo of STN125251/0. * 95% CI: 95% confidence intervals are exact Clopper-Pearson intervals.				

Table A.5: Number of Bleeding Episodes* Per Subject by Study – FDA’s Evaluation

Study 104			Study 105			Study 106			Study 109		
PATID	#of Bleeding Episode	# of Success	PATID	#of Bleeding Episode	# of Success	PATID	#of Bleeding Episode	# of Success	PATID	#of Bleeding Episode	# of Success
-(b)(6)-	45	44	-(b)(6)-	1	1	-(b)(6)-	37	34	-(b)(6)-	2	2
-(b)(6)-	50	35	-(b)(6)-	1	1	-(b)(6)-	3	2	-(b)(6)-	2	2
-(b)(6)-	40	37	-(b)(6)-	21	21	-(b)(6)-	3	3	-(b)(6)-	1	1
-(b)(6)-	2	1	-(b)(6)-	1	1	-(b)(6)-	9	9	-(b)(6)-	20	20
-(b)(6)-	39	38	-(b)(6)-	6	0	-(b)(6)-	1	1	-(b)(6)-	9	0
-(b)(6)-	8	6	-(b)(6)-	4	3				-(b)(6)-	11	10
-(b)(6)-	7	7	-(b)(6)-	9	7				-(b)(6)-	17	9
-(b)(6)-	65	47	-(b)(6)-	15	15				-(b)(6)-	5	2
-(b)(6)-	3	2	-(b)(6)-	3	2				-(b)(6)-	2	2
-(b)(6)-	5	5	-(b)(6)-	1	1				-(b)(6)-	12	11
-(b)(6)-	28	28	-(b)(6)-	7	7				-(b)(6)-	20	20
-(b)(6)-	3	1	-(b)(6)-	13	13				-(b)(6)-	2	2
-(b)(6)-	10	7							-(b)(6)-	2	2
-(b)(6)-	73	47							-(b)(6)-	2	2
-(b)(6)-	30	30							-(b)(6)-	3	3
-(b)(6)-	24	6							-(b)(6)-	24	24
-(b)(6)-	21	19									
-(b)(6)-	113	109									
-(b)(6)-	4	4									
-(b)(6)-	10	6									
-(b)(6)-	38	15									
-(b)(6)-	7	7									
-(b)(6)-	17	11									
-(b)(6)-	2	2									
-(b)(6)-	6	6									
-(b)(6)-	4	4									
-(b)(6)-	145	141									
n=27	N= 799	665	n=12	N= 82	72	n=5	N= 53	49	n=16	N= 134	112
Source: FDA’s data file B - overall use-c.jmp, with 2452 rows of data listing. * Each bleeding episode is given a definite rating regardless of multiple bleeding sites.											

[--(b)(4)--]

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