



Clinical Review Memorandum

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Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

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**To:** To File (BLA STN 125251/0)

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by Koh at 7:22 pm, Dec 11, 2007

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**Applicant:** Octapharma Pharmazeutika

**Product:** WILATE (von Willebrand Factor/Factor VIII Concentrate (Human))

**Subject:** Review of Original BLA Submission

<u>Table of Contents</u>	<u>Page</u>
Executive Summary	2
Introductory Statement	10
Material Reviewed	11
Submission History	12
Indication(s) being Sought	13
Recommended Dosing in Labeling	13
Summary of Clinical Parts of BLA STN 125251 Submission	14
Comparison of the Protocols of TMAE-105, 109, 104, 106 and WIL-14	16
Clinical Studies to Support Von Willebrand Disease Indication	22
Review of Clinical Studies on von Willebrand Disease	22
I. WIL-12	22
II. TMAE-104	24
III. TMAE-105	44
IV. TMAE-109	54
V. TMAE-106	61
VI. WIL-14	70
Overview of Efficacy	71
Overview of Safety	89
Analysis of Risks and Benefits	96
Recommendations	97
CR Letter Comments	97
Appendices	104
I. Details of Patient Data in Wilete Studies	104
A. Study TMAE-104	104
B. Studies TMAE-105, -109, and -106	145
C. Follow-up on Subjects who Participated in More Than One VWD Study	145
D. Doses of Wilete (FVIII:C activity in IU/kg) (b)(4)	148
E. Efficacy Ratings by Patients/Investigators in VWD Bleeding Episodes with More Than One Infusion	150
II (b)(4)	158

### Executive Summary

This application by Octapharma is for the marketing of a new von Willebrand Factor/Antihemophilic Factor complex concentrate (Wilate) for von Willebrand disease (VWD) patients in the (b)(4) treatment of bleeding episodes. (b)(4)

In addition to a pharmacokinetics (PK) study (WIL-12), there are 4 clinical studies provided in this application to support the indication for von Willebrand disease (VWD): TMAE-105, -109, -104, and -106. (b)(4)

The clinical studies were designated by Octapharma as hypothesis-generating, using pharmacokinetic or recovery data as primary endpoints, and parameters for hemostatic efficacy in (b)(4) treatment of bleeding episodes. (b)(4)

The clinical protocols were not adequately designed to capture accurate data for evaluating hemostasis.

- The protocols do not provide definition for a "bleeding episode" or the scoring for the severity scale for bleeding episodes.

- (b)(4)
- Dosing of Wilate depended on the severity of a bleeding episode (b)(4). The dosing guidelines in the studies were based on FVIII:C activity and attainment of target FVIII:C levels, not VWF:RCO activity.
- The clinical endpoints are ill-defined, with the use of a 4-point verbal rating scale (excellent, good, moderate, and none).

Excluding the PK study, there were 70 individual subjects enrolled into the 4 clinical studies, but some subjects participated in 2 or 3 of these studies. There are 66 subjects in the database for clinical efficacy (type 1, 11, type 2, 21, type 3, 34), and 4 subjects who participated without efficacy data (PK or recovery only).

Because of the protocol deficiencies, this review has used arbitrary criteria combining the patient/investigator ratings for efficacy, use of other VWF-containing products, upward dose adjustment without proper justification, excessive blood loss, and unanticipated transfusions for the evaluation of success/failure of treatment. With this assessment, the data from the VWD studies can be summarized as follows:

### Bleeding Episodes

Bleeding "episodes" were adjudicated to be separated from each other by at least 3 days between Wilate infusions (at least 2 calendar days).

Overall efficacy by study			
Study ID	Bleeding Episodes	Successful Episodes	% successes (95% CI)
TMAE-104	931	763	82% (79%, 84%)
TMAE-105	82	73	89% (82%, 96%)
TMAE-106	54	50	93% (85%, 99.8%)

IMAE-109	136	115	85% (78%, 91%)
total	1203	1001	83% (81%, 85%)

The database contains bleeding episodes missing in treatment data, and this was attributed by Octapharma to either minor severity or unavailability of study product at the time of bleeding. Although the overall data for bleeding episode show a success rate of 83% (lower bound of 95% C.I. 81%), the rates for GI bleeding (39%) and oral bleeding (62%) are substantially lower, as shown below

Overall efficacy by bleeding site				
Predominant Site of Bleeds	# of treatment	# of Bleeding Episodes (n)	#of successes	Efficacy (95% CI)
JOINT(S) N=26, n=19 VWD1=1, VWD2=2, VWD3=16	1068	614	547	547/614=89.1% (86.4%, 91.4%)
EPISTAXIS N=20, n=20 VWD1=1, VWD2=3, VWD3=16	281	133	104	104/133=78.2% (70.2%, 84.9%)
GI N=14, n=10 VWD2=5, VWD3=5	706	144	68	68/144=47.2% (38.9%, 55.7%)
ORAL N=12, n=12 VWD1=1, VWD2=1, VWD3=10	113	47	36	36/47=76.6% (62.0%, 87.7%)
GYNAECOLOGIC N=9, n=9 VWD1=1, VWD3=8	129	61	52	52/61=85.3% (78.3%, 93.0%)
OTHERS N=40, n=28 VWD1=6, VWD2=5, VWD3=17	282	204	194	194/204=95.1% (91.2%, 97.6%)
Total N=60, n=45 VWD1=8, VWD2=12, VWD3=25	2579	1203	1001	1001/1203=83.2% (81.0.2%, 85.3%)

N=number of study subjects in the studies n=actual number of patients, as shown by the VWD type distribution below each

Dosing in the treatment of bleeding episodes for these studies were rarely monitored by plasma levels of VWF or FVIII. A pooled analysis of the dosing data and those for the successful cases can be made, but these must be viewed with caution because of the lack of guidance from plasma level information in the presence of active consumption of the coagulation factors during the bleeding episodes. In addition, the VWF:RCo levels performed in the Central Laboratory for recovery and PK are not reliable enough to support dosing recommendations.

The doses used for episodes evaluated as treated successfully can be summarized as follows:

Site of bleeding	Initial Dose (IU/kg FVIII:C)	Subsequent Doses (IU/kg FVIII:C)
	Mean + SD	Mean + SD
Joints	28 + 13	21 + 10
Epistaxis	25 + 10	22 + 14
GI bleeding	43 + 19	36 + 21
Oral bleeding	27 + 14	24 + 18
Gynecologic	28 + 17	26 + 9
Other*	24 + 12	20 + 13

\*muscle, hematoma, cutaneous, subcutaneous after trauma, and wounds

(b)(4)

(b)(4)

## Safety

Overview of Exposure to WILATE: VWD Studies

	Study ID				
	TMAE-104 N=41 (n=37)	TMAE-105 N=14 (n=14)	TMAE-106 N=14 (n=14)	TMAE-109 N=16 (n=5)	WIL-12 N=22 (n=22)
Dose of WILATE per kg BW	20-50 IU/kg	Phase I: 50 IU/kg Phase II: 20-50 IU/kg	Phase I: 50 IU/kg Phase II: 20-50 IU/kg	20-50 IU/kg	appr. 40 IU/kg
Total dose (IU) <sup>1</sup>	8,620,000	432,500	420,900	707,000	N/A
Total number of exposure days	4,917	202	206	343	22
Surgery, total dose (IU)	580,350 IU (n=45)*	128,000 IU (n=2)*	149,400 IU (n=13)*	55,000 IU (n=2)*	none

N (number of subjects in the study/analysis); n (number of new individuals)  
N/A not applicable \* No. of procedures \* Incl. surgical administrations

(b)(4)

There were 262 AEs reported in 63 subjects

- VWD studies. 231 AEs in 43 subjects

(b)(4)

In the VWD studies, 17 AEs in 9 subjects were regarded as probably or possibly related to Wilate treatment, i.e. dizziness (n=2), headache, dyspnea, abdominal discomfort, nausea, dysgeusia, vertigo, rash, urticaria (n=2), anemia, parvovirus B19 serology positive (n=4), and hypersensitivity. One subject was withdrawn from Study TMAE-106 because of one SAE (hypersensitivity), considered probably related to Wilate treatment. One subject in Study TMAE-104 experienced serious GI bleeding complications post-surgery, which ultimately resulted in death. One patient in Study TMAE-104 on Wilate prophylaxis for bleeding suffered from an episode of right atrial thrombus attributed by the Investigator to be due to Vascuport infection

(b)(4)

The VWD studies have not recorded inhibitor to VWF, whereas in the Hemophilia A studies, 7 of 29 previously untreated subjects (PUPs) in TMAE-103 developed inhibitor to FVIII (24%); this incidence is consistent with literature reports on inhibitor development in PUPs.

The plasma levels for FVIII:C were inadequately monitored in the VWD studies for bleeding episodes. Among 59 instances with post-dose levels available in the treatment of bleeding episodes, 10 of them showed levels above 150%.

There were no instances of confirmed viral seroconversion in Studies Wfl-12, TMAE-105 or -109. In TMAE-106 one subject showed seroconversion for B19, and in TMAE-104, 3 subjects seroconverted for B19. These conversions are believed to be due to lots previously manufactured before minipool testing for B19 was implemented. No subsequent seroconversion after minipool testing was implemented have been reported.

#### Analysis of Risks and Benefits

(b)(4)

- There is inadequate plasma level information in the presence of active consumption of the coagulation factors during bleeding episodes to support dosing recommendations for the treatment of such episodes. In addition, because of inherent dilution procedures in the assay that cannot distinguish values within serial

ranges of plasma levels, the VWF:RCo levels performed in the Central Laboratory for recovery and PK are not reliable enough to support dosing recommendations.

(b)(4)

Because of the potentially lower potency for VWF:RCo activity (see CMC Review), and the wide variability of the VWF:RCo to FVIII:C ratio, the use of Wilate may be associated with elevated FVIII:C plasma levels that predispose patients to thromboembolic complications. One case of right atrial thrombus occurred in a patient using Wilate for prophylaxis of bleeding episodes through a Vascuport catheter.

On the balance, this application has not presented sufficient evidence that the use of Wilate as recommended in proposed labeling provides benefits that outweigh the potential risks. Licensure for the proposed VWD indications is not recommended at this time.

#### Recommendations

- Approval of this BLA is not recommended at this time.
- The following comments should be conveyed in the CR letter to Octapharma:

1. The primary endpoints for the four VWD clinical studies supporting hemostatic efficacy (TMAE-105, -109, -104, and -106) are based on pharmacokinetic (PK) or recovery data. Please address the following issues pertaining to the plasma level data in support of your application:

a) The PK data in TMAE-104, -105, and -106 were generated by dosing based on VWF:RCo activity, whereas the clinical use of Wilate in these studies was based on FVIII:C activity. As the dosing recommendations in your proposed package insert use a VWF:RCo-based approach, please clarify how the disparate information on plasma levels may be combined to establish meaningful dosing guidelines.

b) As our testing of your Wilate conformance lots consistently yields potency values for VWF:RCo substantially lower than what is labeled, there are uncertainties in relating the PK data in the clinical studies to the VWF:RCo activity administered. Please clarify how the PK and plasma VWF:RCo level data in these studies may be appropriately evaluated in relation to the VWF:RCo activity administered in order to advise dosing.

c) Because of the difficulties in reading interval values in your VWF:RCo assay, the data generated from the Central Laboratory on VWF:RCo are not sufficiently reliable to support the clinical information on hemostatic efficacy in these studies. Please address the fact that without reliable data on the factor to be replaced, the efficacy of Wilate in the proposed indications cannot be established at this time.

d) The mean incremental recovery of VWF:RCo from these clinical studies (1.5 – 1.9%/IU/kg) is higher than that in the U.S. PK study (WIL-12) (1.1 – 1.2%/IU/kg). This difference may impact the calculation of doses to be administered. Please address this difference, especially in terms of the issues relating to VWF:RCo assay as discussed above.

e) As Wilate has lower levels of the highest molecular weight multimers of VWF present in normal plasma, please address the impact of this finding on the assaying of VWF:RCo activity in the plasma samples in the VWD clinical studies and its implications on dosing.

2. Please address the following comments pertaining to the proposed indications:

(b)(4)

b) For the treatment of bleeding episodes, although the clinical data may appear to suggest efficacy in an overall population, they do not demonstrate efficacy in oral and gastrointestinal bleeding. For those bleeding sites that may hold promise for efficacy with Wilate treatment, it is difficult to recommend dosing for the following reasons:

- The patients were dosed according to FVIII potency of the product. For a replacement therapy, it is appropriate to dose according to VWF strength of the product. Because of the variation in the ratio of

VWF:RCo to FVIII in the product lots for Wilate, and because of the width of allowed product potency, dosing by FVIII in these studies gives considerable uncertainties as to the amount of VWF actually received in each infusion.

ii. The data on VWF:RCo from the Central Laboratory are difficult to interpret due to readout from dilution curves that cannot provide accurate interval values. Any value obtained can be actually one dilution higher or one dilution lower in the actual VWF:RCo level. This renders supporting dosing recommendations with the plasma levels of VWF:RCo from the clinical data not possible.

iii. The above considerations are important since the doses used for bleeding episodes in the VWD studies on Wilate (and doses in the successfully treated episodes) appear to be lower than those observed in the literature and the label recommendations of the U.S.-licensed product for bleeding episodes in VWD.

iv. Even if one grants reliability of the VWF:RCo data, the VWF:RCo plasma levels attained after Wilate infusion in the treatment of bleeding episodes show a sizeable portion of these values not achieving a peak level of at least 50 IU/mL. Applying the doses used for the treatment of bleeding episodes of VWD patients in the clinical studies (which mirrors those in the proposed package insert) may result in under-dosing for the bleeding episodes.

v. Because our testing results on your conformance lots consistently show lower potency values for VWF:RCo than the labeled values, the ratio of the content of VWF:RCo to FVIII:C may be considerably lower than that claimed (1:1). This could lead to a need for upward dose adjustment. It is not clear whether higher doses based on VWF:RCo content might unduly elevate FVIII levels and predispose to thromboembolic phenomena. This narrow therapeutic window underscores the importance of thoroughly understanding the dosing relationship to plasma levels of FVIII and VWF in treating VWD patients with Wilate.

vi. There does not appear to be major differences between doses used in treating successful bleeding episodes and the doses used overall. When an attempt is made to relate the available peak plasma level achieved and the 4-point grading scale for hemostatic efficacy used by patients and investigators in bleeding episodes, no apparent relationship can be observed.

vii. Because of the above reasons, it is not possible to find a satisfactory way to recommend dosing for the treatment of bleeding episodes in labeling at this time. Please address these concerns in an adequately designed study so that proper dosing guidelines can be provided before this indication can be approved.

(b)(4)

d) With respect to dosing for the proposed indications:

- Please explain why the dosing recommendations in the proposed package insert are not consistent with those in the clinical studies, as:
  - The clinical studies use FVIII:C activity for dosing whereas labeling uses VWF:RCo activity
  - The proposed labeling recommendations include use of loading and maintenance doses, which were not in the protocols of the VWD trials
  - The distinction of "minor" and "major" bleeding episodes is different from the grading for bleeding severity in the VWD trials, which use scores of "minor", "moderate", and "severe"

ii. Please explain the following in the proposed package insert -

- the basis of the dosing intervals in the labeling recommendations
- the reasoning for higher doses for maintenance in major bleeding episodes (b)(4)

iii. Please also note that under "DOSAGE AND ADMINISTRATION" in the Highlights section of the package insert, there is no indication of the coagulation factor activity to be based upon for dosing (FVIII:C or VWF:RCO). This should be rectified

3. Please provide a cross-study analysis of subjects who participated in more than one VWD clinical study, to include, but not limited to the following analyses: changes in disease pattern, such as severity and location of bleeding, and changes in the pattern of product use, such as dosing, concomitant medications, prophylaxis vs treatment, etc.

4. Please provide the case report forms and all investigations including those in the hospital records for Patient Xan Center 5 in Study TMAE-104, during his serious adverse event of right atrial thrombus

(b)(4)

6. Please conduct appropriate studies with adequate design to acquire efficacy data in support of the indications sought, taking into consideration the comments below on the deficiencies in the VWD clinical studies of the current submission

a) The VWD clinical studies in this submission are listed as hypothesis-generating. Pivotal studies in support of an indication must be designed to support clearly stated hypothesis and contain measures to minimize bias and noncompliance for product use and evaluation. There should be prospectively defined criteria for success or failure.

b) Bleeding episodes were not clearly defined in the VWD studies of this submission. The number of infusions per episode and the duration of treatment within any episode are defined by the length of the "episode" arbitrarily assigned by the patient or investigator. Without an appropriate definition to be used consistently by all investigators and patients in all the studies, the number of infusions and duration of treatment are more prone to subject to bias

c) The 4-point VRS grading scale used by investigators and patients for clinical efficacy evaluation is vague and inadequately defined

i. It would be appropriate to have more refined language separately for bleeding episodes (b)(4). For instance, the definition of good includes the term "oozing" which would not be expected to occur with spontaneous or trauma-induced bleeding in soft tissue or joint. Bleeding into the joint would be classified according to swelling and pain, not visible oozing. In addition, the definitions should not include the term to be defined within them, e.g., the term "moderate" within the definition of moderate severity

(b)(4)

iii. The term "additional product" for the grades "good" and "moderate" can be misleading to patients and investigators. You have affirmed in previous communications that "additional product" refers to a non-Wile product. However, in Study WIL-14 (only protocol included in this submission), the term used instead of "additional product" is "additional injections of IMP (investigational medicinal product) or other styptic treatment." It is difficult to expect consistency in applying the current 4-point VRS without additional clarification to the patients and investigators, including -

- definition and criteria for using "additional product",
- a time-frame for use of the "additional product" and
- differences between hemostasis achieved (in excellent) in contrast to adequate control of bleeding (in good)

v. In contrast to the efficacy rating for each infusion, an overall assessment termed "outcome" was recorded for each bleeding episode in Studies TMAE-109, -104 and -106, with gradings of "recovered", "ongoing" and "unknown." This parameter is unclear, because in the absence of a definition for "bleeding episode", its duration may be adjusted to fit the outcome, hence making the terms "recovered" and "ongoing" rather circular, depending on how the "episode" has been recorded



d) The differentiation of bleeding episodes into "minor", "moderate" and "severe" is ill-defined. Please provide clearly the instructions given to patients to grade severity. In proposed labeling, bleeding episodes were divided into "minor" and "major" for the purpose of dosing. As the term "minor" may carry different meaning in the clinical trials vs that in proposed dosing recommendations of labeling, please address the potential confusion that may result from extrapolating the doses from clinical trials to labeling recommendations.

(b)(4)

g) The primary endpoint(s) for the VWD studies involve either PK or plasma level parameters. For the analysis of efficacy, the following comments pertain:

Please indicate in the protocol pre-specified criteria of success for the primary endpoint(s), regardless of their being clinical or surrogate laboratory parameters. This should be based on appropriate hypotheses testing. It will not be adequate to include multiple variables for analysis without stating how those parameters are to be used to establish success. If the primary endpoint is to be a composite parameter, please pre-specify any necessary steps for weighting of the variables involved.

(b)(4)

iii. Although the protocols in your VWD studies suggest analysis using an intent-to-treat approach, you have actually excluded subjects with major protocol violations in the actual analysis. Please ensure that analyses will be based on the intention to treat principle. Please also ensure that all subjects enrolled into the study have the diagnosis of VWD confirmed prior to entry, and the method for administration of Vilate standardized across study centers.

iv. Please specify in the protocol the analyses of efficacy as a function of dose administered and plasma levels of FVIII and VWF:RCO achieved in the subjects treated for each indication in order to establish the intended effect of the product, as well as the dosing recommendations for labeling.

h) In your submission, the VWD study protocols provided for the administration of product based on FVIII content, and only general dosing guidelines were provided, with emphasis on dependence on the clinical situation and individual calculations. Please note the following comments and recommendations:

i. As discussed above, the lack of definition for bleeding episode severity (minor, moderate, severe) (b)(4) the protocols makes interpretation of the dosing data difficult.

Please include in your study protocol appropriate instructions to investigators and study subjects in the grading of severity, taking into consideration the quantity and rapidity of blood loss, as well as the significance of the bleeding location.

(b)(4)

(b)(4)

iii. There have been no PK studies performed based on F-VIII dosing instead of using VWF:RCO. As VWF is the primary factor to be replaced in the treatment of VWD and proposed labeling is using VWF:RCO units/kg for dosing, please provide in your future studies dosing recommendations based on the VWF:RCO content of the product. This may also mitigate under-dosing arising from the wide variation in the ratio of VWF:RCO:FVIII:C in the product lots.

iv. In addition to information on dosing intervals, please include in your future VWD studies guidelines for repeating the use of the test product, as well as criteria for rescue products and blood transfusions. (b)(4)

(b)(4)

v. Most of the VWD study protocols in this submission provide target plasma levels of FVIII:C to be achieved (b)(4), but not for treatment of bleeding episodes. Your proposed labeling recommend monitoring with both FVIII:C and VWF:RCO plasma levels. Please state in your future studies instructions for monitoring, including target plasma levels of FVIII:C and VWF:RCO needed to achieve or maintain hemostasis, and prevent thromboembolic complications.

7. Please provide (a) the instructions for patients and investigators for using the tolerability assessment instrument in the form of a 4-point scale in your clinical studies on von Willebrand disease (b)(4) and (b) validation of this instrument. Please include in your future studies appropriate criteria for assignment into the grades of this scale.

8. You have an ongoing study with data collection in pediatric patients having VWD. In your response to this letter, please update your Pediatric Plan, and data pertaining to pediatric subjects for the proposed package insert, if such data become available.

### **Introductory Statement**

This is an original submission [STN 125251] to market WILATE (von Willebrand Factor/Factor VIII Concentrate (Human)) from: Octapharma Pharmazeutika at Wien, Austria

Von Willebrand factor (VWF) is a large multimeric glycoprotein with three biological functions:

- serving as a carrier for the pro-coagulant factor VIII and protects it from in vivo proteolysis,
- mediating platelet adhesion to sub-endothelium of the damaged blood vessel and
- mediating platelet aggregation among each other.

VWF circulates in blood as a series of multimers ranging in size from 500 to 20000 kDa. Only the largest multimers of VWF are active in platelet adhesion, while all multimers are apparently functional for FVIII binding.

VWF is synthesised by endothelial cells and megakaryocytes. The VWF gene encodes pre-pro-VWF consisting of a pre-peptide, a large 741 amino acid pro-peptide (which is cleaved off during intracellular processing) and the mature subunit of 2050 amino acids (VWF monomer). Each subunit of VWF monomer contains binding regions for FVIII coagulant activity (FVIII:C), for collagen and for platelet glycoproteins GPIb and GPIIb/IIIa. Dimers are formed by the creation of inter-subunit disulfide bonds at the C-terminal ends; multimerization occurs in the Golgi apparatus by formation of inter-subunit N-terminal disulfide bonds at the amino-terminal end. While a physiological (constitutive) secretion of VWF dominates in the healthy subject, acute-phase inducers, including pro-inflammatory cytokines, are known to promote acute release of VWF from stores.

### **Prevalence and classification of von Willebrand disease**

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, affecting both males and females. Population screening indicates that mildly deficient heterozygous persons with few or no symptoms represent ~1% of otherwise healthy persons. VWD is clinically a heterogeneous group of disease variants, each characterised by distinct quantitative or qualitative abnormalities in VWF, caused by widely heterogeneous mutations in the various domains of the VWF gene. The Subcommittee of the Scientific and Standardisation Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) on VWF endorsed a revised classification of VWD.

- Type 1 VWD: partial quantitative deficiency in VWF, which is qualitatively normal. Type 1 VWD is the most common form of VWD accounting for 70-80% of the patients.
- Type 2 VWD: qualitative deficiency of VWF, which is functionally abnormal. Type 2 VWD accounts for approximately 20% of the patients. Based upon the major mechanism by which the VWF function is impaired four major subcategories (2A, 2B, 2M, 2N) are recognised:
  - Type 2A VWD refers to qualitative variants with decreased platelet-dependent function that is associated with the absence of high molecular weight (HMW) VWF multimers.
  - Type 2B VWD refers to qualitative variants with increased affinity for platelet GPIIb that spontaneously bind VWF.
  - In type 2M variants, the platelet dependent function is decreased but this is not caused by the absence of HMW VWF multimers.

- Type 2N VWD refers to qualitative variants with markedly decreased affinity of VWF for factor VIII. Several other Type 2 variants have been described.
- Type 3 VWD accounts for 1-3% of cases of VWD, and patients have virtually complete deficiency of VWF in plasma and platelets and factor VIII:C levels are decreased to below 4% of normal.

### Treatment of patients with von Willebrand disease

Most patients with VWD have only mild symptoms and only require treatment in case of surgery or severe trauma.

Desmopressin acetate (DDAVP) is often the treatment of choice for mild to moderate type 1 VWD. DDAVP causes release of VWF from the endothelial cells resulting in an increased level of VWF and factor VIII:C in plasma. It may also be effective in the treatment of some patients with type 2A VWD, whereas it is not effective in type 3 VWD. In patients with type 2B VWD, DDAVP is considered contraindicated by most experts because of in vivo enhancement of platelet aggregation, risk of thrombosis, and exacerbation of pre-existing thrombocytopenia. The newly diagnosed patient with VWD, except for patients with type 2B and type 3 VWD, should be tested for his/her response to DDAVP to identify potential candidates for replacement therapy with a product containing VWF to control bleeding:

- Patients who do not respond adequately to DDAVP.
- Patients who display significant side effects to DDAVP, and
- Patients in whom DDAVP is contraindicated.

In addition, if repeated infusions of DDAVP are given, tachyphylaxis may develop in initially responsive patients, requiring VWF replacement therapy when adequate haemostasis has to be maintained for longer periods of time. Furthermore, in cases of severe bleedings, major and/or repeated surgery VWF-substitution in addition to DDAVP therapy is required.

Purified, viral inactivated, plasma derived VWF/FVIII products are most frequently used nowadays for VWF replacement therapy. The quantity of the ristocetin cofactor activity (VWF:RCo) in comparison to the factor VIII:C content varies by product. In addition, a purified plasma derived VWF product, almost depleted of FVIII, has been developed. In the future, recombinant VWF products might become available. Currently two plasma-derived products are available on the US market with VWD indications:

- Humate-P (CSL Behring): Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® is indicated (1) in adult patients for treatment and prevention of bleeding in hemophilia A (classical hemophilia). Humate-P® is also indicated in adult and pediatric patients with von Willebrand disease for (1) treatment of spontaneous and trauma-induced bleeding episodes and (2) prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where use of desmopressin is known or suspected to be inadequate. Controlled clinical trials to evaluate the safety and efficacy of prophylactic dosing with Humate-P® to prevent spontaneous bleeding have not been conducted in VWD subjects. Adequate data are not presently available on which to evaluate or to base dosing recommendations in this setting.
- Alphanate (Grifols): Antihemophilic Factor/von Willebrand Factor Complex (Human) Alphanate® is also indicated for surgical and/or invasive procedures in patients with von Willebrand Disease (VWD) in whom desmopressin (DDAVP®) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

Humate-P has a ratio of VWF:RCo activity/FVIII:C activity of approximately 2.5 and Alphanate a ratio of 0.4.

(b)(4)

(b)(4)

(b)(4) Wilate is of higher purity for VWF and FVIII in the protein content, as albumin is not added for stabilization. The role played by these properties in the activity assay for VWF (e.g., VWF:RCo) is unclear. Octapharma has suggested that the purity of Wilate results in finer platelet aggregation patterns which may give lower values in the automated VWF:RCo assay that requires reading by machine dependent on light transmission but not distinguishing aggregation patterns.

### Material Reviewed

This application has five modules in ICH CTD format. 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.

### Submission History

Octapharma submitted IND (b)(4) on 9/25/03 without a pre-IND meeting. At the time of IND (b)(4) submission, Octapharma expressed the intention to eventually market this product under two tradenames: WILDOCTIN for von Willebrand disease (VWD), (b)(4). The submission for IND (b)(4) was for the VWD indication only (WILDOCTIN). Previous human experience includes (b)(4) and 2 trials in VWD (TMAE-105 and -109). These were all uncontrolled, open studies. The two clinical trials with WILDOCTIN in VWD were as follows:

- "Pharmacokinetic properties, safety and efficacy of WILDOCTIN in patients with inherited von Willebrand Disease" (TMAE-105): 6-month study in Europe.
- "Clinical study to investigate efficacy and safety of human Factor VIII/vWF TMAE (b)(4) in patients with inherited von Willebrand disease" (TMAE-109): 6-month study in Europe

In the original submission of IND (b)(4), Octapharma proposed to study with a protocol (WIL-12), an open, uncontrolled, non-randomized trial consisting of two segments with potentially overlapping subjects:

- Segment I - to study the PK profile of WILDOCTIN in 20 patients with VWD
- Segment II - to evaluate the treatment effect of WILDOCTIN in 40-60 patients with VWD who are undergoing surgery or having bleeding episodes.

This IND was placed on clinical hold<sup>1</sup>, but in Amendment 4 submitted 6/24/04, Octapharma agreed to study pharmacokinetics of WILDOCTIN in WIL-12, and revised the protocol, removing segment II, which pertain to use of the product to treat VWD. The IND was subsequently removed from clinical hold. In June 2004, Octapharma notified FDA that the product name was changed to WILATE.

In the mean time, Octapharma continued pursuing its European studies and obtained approval for marketing in Germany in 2005, Brazil, Switzerland, and Canada in 2006.

On 3/14/06 Octapharma submitted Amendment 19 to IND (b)(4) asking for input on statistical analysis for the PK study WIL-12. Comments from Dr. I. Mahmood was conveyed to the Sponsor by the RPM.

On 5/5/06, Octapharma submitted Amendment 20 to IND (b)(4) requesting a meeting to discuss the PK data from the WIL-12 study, and the potential filing of a BLA based on WIL-12 and European data. This meeting was denied by FDA on the basis that discussions on the data might incur a BLA-type of review in order to provide meaningful answers. Nevertheless, Octapharma could submit BLA at its own risk.

On 12/14/06, Octapharma submitted BLA STN 125251, which was filed on 2/7/07. Octapharma did not get priority review for this submission, [but was granted orphan drug indication by OPD.]

<sup>1</sup> Clinical Hold items from FDA:

- Segment I and Segment II of the protocol should be conducted sequentially, with pharmacokinetic data obtained from different disease types for VWD in Segment I used to support dosing in Segment II. We recommend that the two segments be separated into different studies. We also recommend that you discuss the design of the treatment (b)(4) study (Segment II), including the endpoints for efficacy, with the FDA when you have completed the pharmacokinetics data collection study (Segment I), so that dosing in the second segment may be better individualized.
- We recommend that you compare the pharmacokinetics of WILDOCTIN with currently marketed product in the U.S., using the same parameters you intend to support dosing in Segment II of this study. To adequately characterize the pharmacokinetics of WILDOCTIN, please obtain evaluable data in at least 5 subjects in each VWD type. The blood sampling times for PK analysis should ideally cover 5 elimination half-lives. If this is difficult for some VWD patients, a rationale should be provided for shorter sampling periods, e.g., at least 3 half-lives.
- We recommend that you provide details, including timeliness for clinical use, of the assays for vWF which you intend to use in the study, especially the vWF RCoF assay to be used in Segment II for monitoring and dosing patients (b)(4).
- It may be necessary for you to demonstrate the contribution of F-VIII in your product to efficacy, e.g., for patients with type 3 von Willebrand disease. Please also clarify your purpose for setting specifications for this ingredient, as well as the lack of specification for the ratio F-VIII/vWF.
- As a safety issue, we recommend that you study the immunogenicity of your product, with respect to both F-VIII and vWF, and have such testing incorporated into the protocol at appropriately defined time points.

On 7/23/07, Octapharma submitted study reports of two clinical trials, TMAE-104 and -106, together with revised integrated summaries of efficacy and safety. This was considered a major amendment, extending the clock to 1/13/08.

### 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 (b)(4) of bleeding in spontaneous (b)(4) 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)

### 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) 60 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). 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:

Usually, about 20 to 60 IU VWF RCo /kg body weight (BW) are given to achieve adequate hemostasis every 12 to 24 hours. The dosage should be adjusted according to the extent and location of the bleeding (b)(4). In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

### Recommended Dose Schedule:

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of hemorrhages is provided in Table 1. (b)(4) The careful control of replacement therapy is especially important in (b)(4) or life-threatening hemorrhages.

Table 1 Guide to WILATE Dosing for Treatment of Hemorrhages

Type of VWD	Severity of Hemorrhage	Dosage (IU VWF:RCO /kg BW)
Any Type	minor (e.g. mild forms of epistaxis, oral bleeding, menorrhagia)	loading dose 20-40 IU/kg, maintenance dose 20-30 IU/kg every 12-24 hours
	major (e.g. GI bleeding, muscle bleeding, hemarthrosis, severe refractory epistaxis)	loading dose (b)(4) 60 IU/kg maintenance dose 20 (b)(4) IU/kg every 12-24 hours

Repeat doses are administered for as long as needed based upon repeat monitoring of appropriate clinical and laboratory measures.

(b)(4)

Although dose can be estimated by the guidelines above, it is highly recommended that whenever possible appropriate laboratory tests should be performed on the patient's plasma at suitable intervals to assure that adequate FVIII:C and VWF:RCO levels have been reached and are maintained.

### **Important CMC and PK Issues with Clinical Implications**

#### **1. CMC issues.** Several CMC issues impact the dosing recommendations for Wilate:

- Wilate's content of VWF and FVIII is formulated to be at a ratio close to 1:1. However, there is a range in this ratio from as low as 0.7 to as high as 1.5.
- Testing of Wilate conformance lots by Don Lebel in the Division of Hematology showed that the potency of Wilate in VWF:RCO activity is consistently lower than the labeled potency, at times close to 30% lower.
- The manual assay for VWF:RCO activity in human plasma conducted at the Central Laboratory for the clinical studies used dilutions not sufficiently refined to provide accurate interval values of VWF:RCO. This renders the plasma level data on VWF:RCO activity difficult to interpret.

#### **2. PK issues.** The PK Reviewer, Dr. Iftexhar Mahmood, has the following letter-ready comments to Octapharma:

- Of the three assays used in PK studies the VWF:RCO is the most relevant functional assay. The pharmacokinetic data (plasma concentrations vs time data) of Wilate generated by the current analytical method are not interpretable. It appears that the analytical method is not sensitive enough to appropriately detect Wilate concentrations (VWF:RCO) in blood or plasma. According to the sponsor, the method is somewhat 'coarse' and the results are limited to one of a discrete series of possible concentrations, 1%, 5%, 12%, 24%, and 35%, etc. The end result of this analytical method is that following administration to VWD patients measured plasma concentrations of VWF:RCO and VWF:CB remain unchanged in many subjects during multiple sampling at different time points. Since these concentrations may not be accurate, the PK parameters generated from these concentrations versus time data may also be inaccurate. Although not a functional assay and therefore not suitable for approval of a PK study, the VWF measured by the antigen assay results in a PK profile showing more acceptable changes of concentration over time. Thus, the PK parameters determined from the VWF:RCO and VWF:CB assays are unreliable and can not be used in the package insert for dosing recommendations. Therefore, the US FDA recommends that the sponsor develop a sensitive analytical method to measure the relevant concentrations of Wilate in blood or plasma and then conduct a PK study of Wilate with a suitable sample size.
- Even though the FVIII:C dose of Wilate is more than twice the dose of Humate-P, the AUC of FVIII:C for Humate-P is higher than the AUC of Wilate in all VWD type patients. This result suggests that Wilate VWF is less able to stabilize and/or induce release of endogenous FVIII. Please comment.
- Two types of half-lives (terminal and average) have been described as PK parameters for Wilate and Humate-P. Please describe the method of calculation of average half-life and its significance. Is average half-life more relevant or meaningful than the terminal half-life?

### **Summary of Clinical Part of BLA STN 125251 Submission**

This BLA is a paper submission of 60 volumes in the ICH Common Technical Document (CTD) format. It was submitted on 12/12/06 and received by FDA on 12/14/06. The application is in 5 modules. This review will cover portions of Module 5 related to clinical protocols for Human Coagulation Factor VIII/von Willebrand Factor (Wilate).

Module 5 contains 35 volumes that include several clinical study reports, data from combined analyses, post marketing safety updates (PSURs), and references.

Table 1: Information	Location
Summary of clinical studies (VWD) (b)(4)	Volume 1
Biopharmaceutics studies	Volume 1
CSR for VWD studies	
• PK studies: TMAE-105/WIL-12/TMAE-106	Vol 1/Vol. 1-6/Vol. 6
• Uncontrolled studies: TMAE-105 (completed) TMAE-109 (completed) TMAE-104 (ongoing) TMAE-106 (ongoing)	Volumes 7-9 Volumes 10-12 Volumes 13-16 Volume 17
• Immunogenicity study: WIL-14 (ongoing)	Volume 17
(b)(4)	
Cross study analyses:	
• vWD	Volume 31
• (b)(4)	Volume 32
• PK comparison	Volume 33
Post-marketing reports – PSURs 01, 02, 03	Volume 33
References	Volumes 34-35

Studies TMAE-104 and -106 were ongoing at the time of BLA submission. Since then the studies have been completed and Clinical Study Reports written. Octapharma has submitted a major amendment of 15 volumes in July 2007 with the final study reports of these two studies, and revised pooled data analysis.

In addition, WIL-14, an immunogenicity study in pediatric subjects, also collects safety and efficacy data. It is ongoing and no data or report from this study has been submitted.

The following table summarizes the 5 clinical protocols for evaluation of efficacy/safety of Wilate for VWD (TMAE-105, -109, -104, -106, and WIL-14).

### Comparison of the Protocols of TMAE-105, 109, 104, 106, and WIL-14.

Study ID & Title	TMAE-105. Pharmacokinetic properties, safety and efficacy of WILACTIN in patients with inherited von Willebrand disease	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	TMAE-104. International clinical study to investigate the safety and efficacy of WILATE in subjects with inherited von Willebrand disease	TMAE-106. Pharmacokinetic properties, safety and efficacy of human Factor VIII TMAE- $\alpha_1$ in patients with inherited von Willebrand disease, Phase II study	WIL 14 Clinical study to investigate the efficacy, safety, and immunogenicity of WILATE in children <6 years of age with inherited von Willebrand Disease, Phase II study (from Dr. T. Silverman)
Selection Criteria	<p><b>INCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Defined inherited vWD, types 1 to 3</li> <li>Age &gt; 12 and &lt; 65 years.</li> <li>HIV-1/2 negative.</li> <li>Known to the study centre</li> <li>Patients resistant to DDAVP treatment.</li> <li>Freely given written informed consent.</li> </ul> <p><b>EXCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Present or past inhibitor activity.</li> <li>Administration of other plasma derived or blood products or DDAVP 15 days before study entry.</li> <li>Administration of acetylsalicylic acid 7 days before study</li> </ul>	<p><b>INCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Defined inherited vWD types 1, 2 and 3</li> <li>Age <math>\geq</math> 12 and <math>\leq</math> 65 years</li> <li>Anti-HIV-1/2 negative.</li> <li>Known to the study centre.</li> <li>Patients resistant to DDAVP treatment</li> <li>Freely given written informed consent</li> </ul> <p><b>EXCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Present or past inhibitor activity.</li> <li>Administration of other p-d or blood product 72 hours before treatment.</li> <li>Administration of DDAVP 15 days before treatment.</li> <li>Administration of acetylsalicylic acid 7 days before treatment.</li> </ul>	<p><b>INCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Defined inherited vWD, types 1 to 3</li> <li>Age &gt; 6 and &lt; 35 years</li> <li>Subjects not sufficiently responding to DDAVP treatment.</li> <li>Freely given written informed consent.</li> </ul> <p><b>EXCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Administration of other plasma derived or blood product within 72 hours prior to treatment.</li> <li>Administration of DDAVP within 15 days prior to treatment.</li> <li>Administration of acetylsalicylic acid</li> </ul>	<p><b>INCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Classified inherited vWD, types 1 to 3</li> <li>Age &gt; 18 and &lt; 65 years.</li> <li>Immunocompetent patients (if HIV positive: CD4 always <math>\geq</math> 400/<math>\mu</math>L in the past).</li> <li>Known to the study centre.</li> <li>Patients not responding to DDAVP treatment, confirmed by a test, if appropriate.</li> <li>Freely given written informed consent.</li> </ul> <p><b>EXCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>Present or past inhibitor activity.</li> <li>Administration of other plasma derived or blood products or DDAVP 15 days before study entry.</li> <li>Administration of acetylsalicylic acid 7 days prior to study entry.</li> </ul>	<p><b>INCLUSION CRITERIA</b></p> <ol style="list-style-type: none"> <li>Defined vWD of any type</li> <li>&lt; 6 at study adm.</li> <li>HIV-1/2 negative</li> <li>DDAVP Rx known or suspected to be inadequate, insufficient or contraindicated</li> <li>Expected minimum 5 exposure days to within 1 yr of observation</li> <li>Informed consent</li> </ol> <p><b>EXCLUSION CRITERIA</b></p> <ol style="list-style-type: none"> <li>known past or present inhibitor to VWF or FVIII</li> <li>Acquired vWD</li> <li>Any hematological disorder other than vWD</li> <li>Use of blood/plasma product: 5 days before first Wilate injection</li> <li>Use of DDAVP 5 days before study entry</li> <li>ASA within 14 days before Rx</li> </ol>



	<ul style="list-style-type: none"> <li>entry.</li> <li>Known history of intolerance versus plasma derived or blood products.</li> <li>Symptomatic infection.</li> <li>Severe liver or kidney disease (ALT x 5 &gt; normal value, creatinine &gt; 120 <math>\mu</math>mol/l).</li> <li>Participation in another clinical study currently or during the past 4 weeks.</li> <li>Pregnancy or lactating women.</li> </ul>	<ul style="list-style-type: none"> <li>History of intolerance to blood or blood products.</li> <li>Symptomatic infection.</li> <li>Severe liver or kidney disease (ALT x 5 &gt; normal value, creatinine &gt; 120 <math>\mu</math>mol/l).</li> <li>Participation in another clinical study currently or during the past 4 weeks (except 105).</li> <li>Pregnancy or lactating women.</li> </ul>	<ul style="list-style-type: none"> <li>within 7 days prior to treatment.</li> <li>Known history of intolerance versus plasma derived or blood products.</li> <li>Symptomatic infection.</li> <li>Severe liver or kidney disease (ALT 5x &gt; normal value, creatinine &gt; 120 <math>\mu</math>mol/l).</li> <li>Participation in another clinical study (ongoing or within the previous four weeks).</li> <li>Pregnant or lactating women.</li> </ul>	<ul style="list-style-type: none"> <li>Known history of intolerance versus plasma derived or blood products.</li> <li>Symptomatic infection.</li> <li>Severe liver or kidney disease (ALAT x 5 &gt; normal value, creatinine &gt; 120 <math>\mu</math>mol/l).</li> <li>Participation in another clinical study currently or during the past four weeks.</li> <li>Pregnancy or lactating women.</li> </ul>	<p>7. Known history of intolerance to plasma derived or blood products</p> <p>8. Participation in another study within 4 weeks</p>
<b>Efficacy Endpoints</b>	<p><u>Primary</u></p> <ul style="list-style-type: none"> <li>PK profile (AUC, AUC<sub>0-12</sub>, T<sub>1/2</sub>, MRT, Vd, CL) for VWF:Ag, VWF:CB, VWF:RCO</li> <li>plasma levels of FVIII:C</li> </ul> <p><u>Secondary</u></p> <ul style="list-style-type: none"> <li>PK profile (C<sub>max</sub> &amp; T<sub>max</sub>) for VWF:Ag, VWF:CB, VWF:RCO,</li> <li>recovery of FVIII:C.</li> </ul>	<p><u>Primary</u></p> <ul style="list-style-type: none"> <li>plasma levels of FVIII:C, VWF:Ag, VWF:RCO</li> </ul> <p><u>Secondary</u></p> <ul style="list-style-type: none"> <li>bleeding time</li> <li>multimeric patterns</li> <li>Investigator overall efficacy assessment</li> </ul>	<p><u>Primary</u></p> <ul style="list-style-type: none"> <li>Plasma levels of FVIII:C, VWF:Ag, VWF:CB, VWF:RCO</li> </ul> <p>During a subject's <u>first</u> treatment with WILATE, plasma levels of FVIII:C, VWF:RCO, VWF:Ag and VWF:CB were to be determined at baseline and 0.5, 1, 3 hours, and optionally at 6 and 12 hours after treatment. For subsequent infusions, the parameters were monitored as often as was considered necessary by the treating physician.</p> <p><u>Secondary</u></p> <ul style="list-style-type: none"> <li>bleeding time</li> <li>investigator and/or patient overall efficacy assessment of overall</li> </ul>	<p><u>Primary</u></p> <ul style="list-style-type: none"> <li>PK profile (AUC, T<sub>1/2</sub>, MRT, Vd<sub>ss</sub>, CL) for VWF:Ag, VWF:CB, VWF:RCO</li> <li>plasma levels of FVIII:C</li> </ul> <p><u>At least one pre- and one post-administration sample</u> for plasma levels of FVIII:C, VWF:RCO, and VWF:Ag were to be taken. In addition, a pre- and 1 hr post-infusion sample for HMW multimers was to be taken.</p> <p><u>Secondary</u></p> <ul style="list-style-type: none"> <li>Incremental recovery of FVIII:C, VWF:RCO, VWF:Ag</li> <li>plasma levels of</li> </ul>	<p>Prior to first infusion of product, baseline plasma levels of FVIII:C, VWF:RCO, VWF:Ag, and VWF:CB</p> <p>Primary</p> <p>A. Efficacy treatment or bleeding episodes</p>

	<p>VWF:Ag, VWF:RC<sub>5</sub></p> <ul style="list-style-type: none"> <li>plasma levels of VWF:Ag, VWF:CB, VWF:RC<sub>5</sub></li> <li>bleeding time</li> <li>multimeric pattern</li> <li>Investigator overall efficacy assessment</li> </ul>		clinical efficacy	<p>VWF:Ag, VWF:CB, VWF:RC<sub>5</sub></p> <ul style="list-style-type: none"> <li>bleeding time</li> <li>closure time</li> <li>multimeric patterns</li> <li>Investigator overall efficacy assessment</li> </ul>	<p>B. Efficacy in surgery Secondary:</p> <p>(b)(6)</p> <p>2. Immunogenicity</p> <p>3. Safety parameters</p>
<u>Details on Dosing</u>	<p>Phase I. A dose of about 50 IU VWF:RC<sub>5</sub> / kg BW of WILATE was to be administered for the PK investigations. As no product should be discarded, the amount to be administered was to be rounded up or down.</p> <p>Phase II. The number of administrations and the actual dose for treating spontaneous bleedings</p> <p>(b)(6) depended on the clinical situation of the patient, i.e. the severity of the bleeding or the</p> <p>Single administrations or multiple doses were appropriate. Guidance only</p> <p>Spontaneous or post-traumatic bleeding: ~ 20 to 50 IU FVIII C / kg BW once daily or every other day</p> <p>(b)(6)</p>	<p>The number of infusions and actual dose in spontaneous bleedings</p> <p>(b)(6) depended on the clinical situation of the patient, e.g. the severity of the bleeding, and the (b)(6) Single or multiple administrations could be given. Guidance only</p> <ul style="list-style-type: none"> <li>For spontaneous or post-traumatic bleeding: about 20-50 IU FVIII C/kg BW were to be given once daily or every other day.</li> </ul> <p>(b)(6)</p>	<p>The dose for spontaneous bleeding, (b)(6) was dependant upon the clinical situation, and calculated individually.</p> <p>The usual range is between 20 to 50 IU VWF:RC<sub>5</sub>/FVIII C / kg BW given as a single dose or repeatedly</p> <ul style="list-style-type: none"> <li>Spontaneous or post-traumatic bleeding: ~ 20-50 IU FVIII C/kg BW once daily or every other day is normally sufficient.</li> </ul> <p>(b)(6)</p>	<p>Phase I. A dose of 50 IU VWF:RC<sub>5</sub> / kg BW of Wilate was administered for the PK investigations. As no product should be discarded, the amount to be administered will be rounded up or down according to the table below</p> <p>Phase II. The number of administrations and the actual dose for treating spontaneous bleeding episodes</p> <p>(b)(6) depend on the clinical situation of the patient, e.g. the severity of the bleeding episode.</p> <p>(b)(6)</p> <p><u>Treatment Duration</u></p> <p>For PK (Phase I), the dose FVIII TMAE (b)(6) will be injected IV at a speed of 2-3 ml per minute at a single occasion.</p> <p>For bleeding episodes (b)(6) the intended dose is given as a single dose or as multiple doses over a few days, depending on the</p>	<p><u>Recovery</u></p> <p>In vivo recovery- 50 IU/kg (analyte not specified) BW</p> <p><u>Bleeding Episodes</u></p> <p>20-50 IU FVIII C/kg BW once daily or every other day</p> <p>(b)(6)</p>

until healing was complete given once daily or every other day

clinical situation.

(b)(4)  
[Original protocol [5.4.2] says no home treatment, only at site.]  
Patients were allowed to treat their spontaneous bleeding episodes at home. In phase II they were provided with a sufficient amount of trial medication. The recording of these self-injections had to include the date, dose, batch and reason for injection. This was to be done by the patients on the respective form of the CRF or in a patient diary. If the patient received an injection as treatment for a bleeding episode he/she

(b)(4)  
As patients usually treat bleeding episodes at home they were provided with a sufficient amount of trial medication. The recording of these self-injections had to include the date, dose, batch and reason for injection. This was to be done by the patients on the respective form of the CRF or in a patient diary. If the patient received an injection as treatment for a bleeding episode he/she was asked to document the site and severity of the bleeding and his subjective impression of efficacy [5.4.2].

(b)(4)  
Subjects with VWD treat spontaneous bleeding episodes at home. Subjects were provided with adequate supplies of trial medication to permit home treatment. Each subject was required to keep records of treatment episodes and to visit the clinic at least every 3 months and at study termination. If the patient will receive an injection as treatment for a bleeding episode he will be asked to document the site and severity of the bleeding and his subjective impression of efficacy and tolerability [5.4.2].

(b)(4)  
Phase II: Patients usually treat their spontaneous bleeding episodes at home, provided with required amount of trial medication until the next visit. The recording of self-injections will include the date, dose, batch and reason for injection. If the patient will receive an injection as treatment for a bleeding episode he will be asked to document the site and severity of the bleeding and his subjective impression of efficacy [5.4.2].

(b)(4)

<p>was asked to document the site and severity of the bleeding and his subjective impression of efficacy</p>				
<p><b>Details on Clinical efficacy evaluation</b></p> <p>An overall assessment of the clinical response will be done by the treating physician using a VRS (none - moderate - good - excellent) after each treatment episode using the following definitions:</p> <ul style="list-style-type: none"> <li>• none: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeds);</li> <li>• moderate: moderate bleeding or control of bleeding, required additional product;</li> <li>• good: slight oozing and adequate control of bleeding, did not require additional product;</li> <li>• excellent: haemostasis achieved, cessation of bleeding.</li> </ul> <p>P 9 of protocol: Schedule of events table shows efficacy evaluation by investigator is at last visit only, not really after each episode</p>	<p>Overall efficacy assessment by treating physician uses verbal rating scale (VRS) after each treatment episode at the last visit as follows</p> <p>none: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeds);</p> <p>moderate: moderate bleeding or control of bleeding, required additional product</p> <p>good: slight oozing and adequate control of bleeding; did not require additional product</p> <p>excellent: haemostasis achieved, bleeding cessation</p> <p>P 17 of protocol: Schedule of events table shows efficacy evaluation by investigator is at last visit only, i.e., last visit related to the episode?</p>	<p>An assessment of the clinical response will be done by the treating physician and/or the subject using a verbal rating scale (VRS) none - moderate - good - excellent after each treatment episode using the following definitions:</p> <ul style="list-style-type: none"> <li>• none: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeds);</li> <li>• moderate: moderate bleeding or control of bleeding, required additional product;</li> <li>• good: slight oozing and adequate control of bleeding, did not require additional product;</li> <li>• excellent: haemostasis achieved, cessation of bleeding.</li> </ul> <p>P 17 of protocol: Schedule of events table shows efficacy evaluation by investigator is at last visit only, i.e., last visit related to the episode?</p>	<p>Overall assessment of the clinical response will be done by the treating physician using a VRS after each treatment episode using the following definitions:</p> <ul style="list-style-type: none"> <li>• none: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeding episodes);</li> <li>• moderate: moderate bleeding, or control of bleeding, required additional product;</li> <li>• good: slight oozing and adequate control of bleeding episode, did not require additional product;</li> <li>• excellent: haemostasis achieved, cessation of bleeding episode.</li> </ul> <p>Schedule of Event table shows Investigator VRS is at last visit not necessarily after each episode.</p>	<p>For each bleeding episode, efficacy using a 4-point VRS with details of all treatments and bleedings recorded</p> <p>1. None: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeds); require additional injection of product or other symptomatic treatment</p> <p>2. Moderate: moderate bleeding or control of bleeding required additional test product or other symptomatic treatment</p> <p>3. Good: Slight oozing and adequate control of bleeding, did not require additional test product or other symptomatic treatment</p> <p>4. Excellent: haemostasis achieved, cessation of bleeding</p> <p>At end of study period</p>

Assessment of overall response. Overall response to treatment was assessed by Investigator and subject at the end of the study on a VRS i.e. as none, moderate, good, excellent.	Overall efficacy assessment by MD and parents of patient.
	(b)(4)

## Clinical Studies to Support Von Willebrand Disease Indication

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

TMAE-105. Pharmacokinetic properties, safety and efficacy of WILACTIN in patients with inherited von Willebrand disease

TMAE-109. Clinical study to investigate efficacy and safety of human Factor VIII/WWF TMAE (b)(4) in patients with inherited von Willebrand disease. Phase 2 study

TMAE-104. International clinical study to investigate the safety and efficacy of WILATE in subjects with inherited von Willebrand disease

TMAE-106. Pharmacokinetic properties, safety and efficacy of human Factor VIII TMAE (b)(4) in patients with inherited von Willebrand disease, Phase II study

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

(b)(4)

## Review of Clinical Studies on von Willebrand Disease

**I. 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**

This is a safety and pharmacokinetics (PK) study. For PK data, reference is made to the reviews by Drs. T. Silverman and I. Mahmood. For further discussions on PK, see Overview of Efficacy section.

### Safety Data

A total of 21 subjects received both study injections, Wilate and Humate-P®, separated by at least seven days. Subject (b)(6) (VWD Type 3) received only one study injection, Period 1 treatment (Wilate), and not Period 2 treatment (Humate-P®).

Number of Subjects/Dose of Study Product		
Total Dose* (IU VWF:RC <sub>0</sub> )	Wilate	Humate-P®
1500 – 1999	1	0
2000 – 2499	3	3
2500 – 2999	10	8
3000 – 3499	1	2
3500 – 3999	2	4
4000 – 4499	4	2
4500 – 4999	0	1
5000 – 5499	0	0
5500 – 5999	1	1

There were no deaths or serious adverse events observed in this study.

Ten (45%) subjects experienced at least one adverse event (AE) while on study, total 28 AEs; 14 were considered mild, 12 moderate, and 2 severe. Subject (b)(6) experienced the two severe adverse events reported (urinary tract infection and nephroillithiasis); both events resolved and were not considered related to study treatment by the investigator. The same subject (b)(6) reported experiencing a metallic taste at the start of injection (Wilate) which lasted approximately five minutes; this event was considered

possibly related to study treatment by the investigator (indicated in a follow-up report). No serious adverse events were reported.

Listing of Subjects with Adverse Events				
Subject/ VWD Type	Adverse Event (Preferred Term)	Severity	Relationship to Treatment*	Outcome
Type 2A	Headache	Mild	None	Resolved
Type 3	Arthralgia, right ankle	Mild	None	Resolved
Type 3	Headache	Mild	None	Resolved
Type 1	Headache, bilateral temporal	Mild	None	Resolved
	Fatigue	Mild	None	Resolved
	Muscle twitching, near eyelid	Mild	None	Resolved
	Dizziness	Mild	None	Resolved
	Alanine aminotransferase increased	Mild	Unlikely	Resolved
	Aspartate aminotransferase increased	Mild	Unlikely	Resolved
	Contusion, elbow	Mild	None	Resolved
	Back pain, bilateral lower	Moderate	None	Resolved
Type 2A	Dysgeusia, metallic taste at start of Wilate injection	Mild	Possible	Resolved
(b)(6)	Fatigue	Moderate	None	Resolved
	Shoulder pain, left	Moderate	None	Resolved
	Joint manipulation, under anesthesia	Moderate	None	Resolved
	Shoulder pain, due to manipulation	Moderate	None	Resolved
	Muscle spasms	Moderate	None	Unresolved
	Panic attack	Moderate	None	Unresolved
	Vomiting psychogenic	Moderate	None	Resolved
	Nephrolithiasis (1 <sup>st</sup> episode)	Severe	None	Resolved
	Nephrolithiasis (2 <sup>nd</sup> episode)	Moderate	None	Resolved
	Urinary tract infection	Severe	None	Resolved
Type 1	Sjogren's syndrome	Mild	None	Resolved
	Migraine	Moderate	None	Resolved
Type 2B	Back pain	Moderate	None	Resolved
Type 3	Psoriasis	Mild	None	Unresolved
Type 2A	Laceration, caused by nail	Mild	None	Resolved
Type 2A	Arthralgia, right knee	Moderate	None	Unresolved

\* As assessed by the investigator.

Bleeding episodes occurring in the study have not been included as AEs. One episode of nose bleed for subject (b)(6) occurred two weeks before infusion of any study medication. The subjects reported seven episodes of bleeding during the study; three of these episodes were considered minor and four were considered moderate; 4 occurred in the nose, 2 in the urinary tract, and 1 in the ankle.

Bleeding Episodes During Study				
Subject/ VWD Type	Time of Bleed	Bleed Site	Severity	Treatment
Type 1	2 days after Period 1 inj (Wilate)	Nose	Moderate	Simulast <sup>®</sup> Spray
Type 3	3 days after Period 2 inj (Wilate)	Right ankle	Minor	None
Type 2A	33 days after Period 2 inj (Humate-P <sup>®</sup> )	Urinary tract	Moderate	Humate-P <sup>®</sup>
(b)(6)	49 days after Period 2 inj (Humate-P <sup>®</sup> )	Urinary tract	Moderate	Humate-P <sup>®</sup>
	2 days after Period 2 inj (Wilate)	Nose	Minor	None
Type 2B	5 days after Period 2 inj (Wilate)	Nose	Moderate	Humate-P <sup>®</sup>
Type 2A	13 days after Period 2 inj (Humate-P <sup>®</sup> )	Nose	Minor	None

One subject (b)(6) VWD Type 1) had increases in ALT (pre-injection 1 = 34 U/L, post-injection 1 = 51 U/L) and AST (pre-injection 1 = 25 U/L, post-injection 1 = 83 U/L).

The viral marker status of each subject was documented at screening. Most subjects who were non-reactive or reactive for a viral marker test at baseline (pre-injection/Period1) maintained this pattern throughout the follow-up period (4-8 weeks). Subjects were reactive for the following markers at baseline and remained reactive throughout the study: parvovirus B19 IgG (18 subjects); HBs (15 subjects); HAV-IgG (9 subjects); HCV (7 subjects); HBc (5 subjects); and) HIV 1/2 (1 subject); 3 subjects had apparent changes in serology

Subjects with Change from Baseline Viral Markers During the Study				
Subject	Viral Marker	Baseline Pre-Injection/ Period 1	Pre-Injection/ Period 2	Follow-up Weeks 4-8
Type 2M	Anti-HBs	non-reactive	non-reactive	reactive
(b)(6) Type 2B	Anti-HBc	reactive	non-reactive	non-reactive
Type 3	Anti-HAV IgG	non-reactive	non-reactive	reactive

- Subject (b)(6) (VWD Type 2M) had a history of hepatitis B and reported being immunized for both hepatitis A and B in 1999. The subject was non-reactive for anti-HBs at Pre-injection 1 and Pre-injection 2, and then was reactive at follow-up. A medical interpretation from the laboratory that performed the virology, indicated that the positive test was borderline reactive.
- Subject (b)(6) VWD (Type 2B) was reactive for anti-HBc at Pre-injection 1, and then was non-reactive on Pre-injection 2 and Weeks 4-8. A medical interpretation from the laboratory that performed the virology, indicated that the reactive tests yielded results that were close to the antibody cutoff used in this test, and therefore the results were interpreted as reactive.
- Subject (b)(6) (VWD Type 3) had a history of hepatitis A and reported being immunized for hepatitis A in the past (date unknown). The subject's sample from Pre-injection 1 was non-reactive for anti-HAV IgG on two separate runs. The Pre-injection 2 sample also was non-reactive. At the Weeks 4-8 visits, the subject's sample was analyzed twice with reactive results. With each sampling, the results were close to the antibody cutoff value making it difficult to make a statement as to whether or not antibody was present.

**Comment** Subject (b)(6) and (b)(6) had histories of hepatitis (B and A respectively), while Subject (b)(6) had borderline reactivity for anti-HBc at baseline, but not at subsequent testing. These cannot be considered to be true seroconversions for HBV or HAV.

## II. TMAE-104. International clinical study to investigate the safety and efficacy of WILATE in subjects with inherited von Willebrand disease

This is the largest study and its protocol is similar to the other three studies that contain efficacy and safety data. This study is therefore discussed first here.

### INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

#### Investigators and Study Centres:

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 Dr. Gerard Dolan, Queen's Medical Centre, Nottingham, UK  
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## STUDY OBJECTIVES

PRIMARY OBJECTIVES to confirm the efficacy of WILATE using surrogate markers, i.e. the plasma levels before and after administration of the following factors:

- Factor VIII coagulant activity (FVIII:C)
- von Willebrand Factor Ristocetin Co-factor Activity (VWF:RCO)
- von Willebrand Factor Antigen (VWF:Ag)
- von Willebrand Factor Collagen Binding Activity (VWF:CB)

## SECONDARY OBJECTIVES

- To establish a pharmacokinetic (PK) profile of WILATE in approximately 10 subjects
- to measure the correction of bleeding time (BT)
- to assess the overall efficacy of WILATE
- to assess the clinical safety and tolerability of WILATE

## INVESTIGATIONAL PLAN

### OVERALL STUDY DESIGN AND PLAN

International, multicentre, prospective, non-randomised, non-controlled, open-labelled phase 3 study for the assessment of efficacy and safety of WILATE. It was intended that at least 50 subjects would be treated with single or multiple doses of WILATE, depending on the needs of the subjects and the recommendations of the treating physician. The study was completed after > 5 years and after a total of 41 subjects had been enrolled because the data collected were considered by Octapharma to be sufficient to meet regulatory requirements.

The dose of WILATE to be administered during the study to treat cases of spontaneous bleeding, for surgery or for prophylactic treatment were dependent on the clinical situation, and therefore calculated individually. The usual range was 20 to 50 IU VWF:RCO/FVIII:C/kg given as single dose or repeatedly.

During a subject's first treatment with WILATE, plasma levels of FVIII:C, VWF:RCO, VWF:Ag and VWF:CB were to be determined at baseline and 30 minutes, 1 hour, 3 hours, and optionally at 6 and 12 hours after treatment. If subsequent infusions of WILATE were given, the coagulation parameters were to be monitored as often as was considered necessary by the treating physician.

Comment The plasma sampling for coagulation factor levels was not consistently performed. Octapharma indicated that as the patients used Wilate for home treatment, checking plasma samples would be difficult. However, even the sampling for first treatment was inconsistent in TMAE-104.

An assessment of the correction of the BT was to be optionally performed once during the study using the Ivy method, which involves measuring the length of time required for a standardised cut to stop bleeding. The cut was made with an automatic, spring-loaded blade device and blotted every 30 seconds with filter paper until it stopped bleeding completely. Assessment of BT was to be made at baseline and 30 minutes, 1, 3, 6 and 12 hours after WILATE infusion. If the BT had returned to baseline by 3 hours, further assessments were not required.

Subjects were provided with adequate supplies of trial medication to permit home treatment. Each **subject was required to keep records of treatment episodes and to visit the clinic at least every 3 months and at study termination.**

As determined by protocol amendment I, approximately 10 subjects were to have full PK evaluation for AUC,  $1/\lambda$ , MRT,  $V_{dss}$ ,  $Cl$ ,  $C_{max}$ ,  $T_{max}$  in FVIII:C, VWF:RCO, VWF:Ag and VWF:CB. For the PK assessment, a dose of ~50 IU VWF:RCO per kg BW was administered and the incremental recovery was to be calculated for FVIII:C, VWF:RCO, VWF:Ag and VWF:CB using the actual potency of the WILATE batch as reference.

For future testing of immunogenicity, blood samples were stored at -70°C. Inhibitors against FVIII and VWF were to be assessed at baseline, every 3 months, at study completion and additionally in suspicion of inhibitor development. Inhibitors against FVIII would be determined using the <sup>(b)(4)</sup> assay. There is no standardised method for determination of inhibitors to VWF, and <sup>(b)(4)</sup> was planned.

All subjects were to be monitored for adverse events (AEs) throughout the study. Subjective assessments of tolerability and of efficacy were to be made by the subject or the investigator after each infusion. An overall assessment of safety and efficacy was to be made by both after their last study treatment.

Subjects were to be screened for viral markers for HAV, HBV, HCV, HIV and parvovirus B19 at baseline. All parameters negative at baseline were retested every 3 months during the study and at study completion.

#### FLOWCHART OF STUDY EVENTS

##### Study Flowchart

##### Study Flowchart

Assessments to be performed at first WILATE treatment (repetitions optional)

Assessments	↓ Injection(s)						Further optional treatment	After last treatment
	before first treatment	30'	1h	3h	6h	12h		
Plasma Levels*	x	x	x	x	(x)	(x)	x1	
Bleeding Time	x	x	x	x	(x)	(x)	x1	
Efficacy Assessment**						x	after each injection	
Tolerability Assessment**						x	after each injection	
Adverse Events		x	x	x	x	x	x	x
Viral Safety	x						every 3 months	x2
Overall Efficacy and Safety Assessment**								x

\* FVIII C, VWF Ag, VWF:CB and VWF:RCO

\*\* subjects' and/or physicians' assessment

(x) optional assessments

x1 = repetition of assessments as frequently as necessary

x2 = Parvovirus B19: 7 – 14 days after last WILATE treatment, HIV, HAV, HBV, HCV: 4 – 8 weeks after last WILATE treatment

For the PK assessments, a dose of approximately 50 IU VWF:RCO/kg BW of WILATE was to be administered. Table 2 summarises the procedures to be performed for the subjects undergoing PK evaluation.

#### Pharmacokinetic Evaluation

Time Point	Parameter					Tolerability Assessment
	FVIII C	VWF:RCO	VWF:Ag	VWF:CB	ACTs	
Baseline	X	X	X	X	X	
15 min*	X	X	X	X	X	
30 min	X	X	X	X	X	
45 min*	X	X	X	X	X	
1 h	X	X	X	X	X	
3 h	X	X	X	X	X	
6 h	X	X	X	X	X	
9 h	X	X	X	X	X	
12 h	X	X	X	X	X	
24 h	X	X	X	X	X	
48 h	X	X	X	X	X	X†
72 h*	X	X	X	X	X	X†
96 h*	X	X	X	X	X	X†

\* Optional time points

† Tolerability assessment should be performed after last sampling time point, which could be at 48, 72 or 96 hours.

**Comment** The design of the study is similar to that of TMAE-105, 109 and 100 (see above in the comparison Table under "Summary of Clinical Part of BIA 125251 Submission"). The design of these studies was based on the recommendations of the CPMP Guideline for plasma-derived factor VIII C and factor IX C products. At the time that the studies were designed, no specific guideline existed for VWF concentrates. In November 2005, a guideline for the clinical investigation of human plasma-derived VWF products was accepted by CPMP, and the recommendations are shown below.

CPMP Recommendations. Clinical trials with plasma-derived VWF products: new products		
TRIAL SUBJECTS	INVESTIGATION	PARAMETERS
12 patients with severe VWD (baseline VWF:RCO < 5-20 %, F	1 Pharmacokinetics	VWF:RCO, VWF:Ag, VWF:CB and FVIII C Incremental recovery, half-life, AUC, clearance and

VIII < 20%) without inhibitors and not actively bleeding, including at least 6 type 3 VWD <sup>1</sup> Age > 12 years		mean residence time. Multimeric sizing analysis Note: for VWF products depleted of FVIII C, incremental recovery of FVIII C cannot be determined. However, FVIII C levels should still be monitored
Retesting of type 3 VWD patients after at least 6 months.	2. Safety	Blood pressure, heart rate, temperature, respiratory rate and adverse events
20 patients suffering from severe VWD, including preferably all patients from the PK study. Age > 12 years Followed for 1 year.	1. Clinical efficacy 2. Immunogenicity 3. Safety	Response documented in all bleeding episodes VWF and FVIII consumption <sup>2</sup> Inhibitor titre <sup>3</sup> Adverse events.
At least 15 surgical procedures (10 major)	(b)(4) 2. Safety	(b)(4) VWF and FVIII consumption <sup>1</sup> Adverse events. Thrombogenicity (for products containing FVIII).
At least 10 bleeding episodes (5 major mucosal)	1. Clinical efficacy 2. Safety (b)(4)	Response documented in all bleeding episodes VWF and FVIII consumption <sup>2</sup> Adverse events.
A minimum of 5 type 3 VWD patients followed for 1 year	2. Immunogenicity 3. Safety	(b)(4) Adverse events.
Open multicentre trial in 8 children (< 6 years) to be started after results of 1 year of exposure in 10 patients > 12 years have become available	1. Pharmacokinetics 2. Clinical efficacy	Similar to adults. Recovery study in type 3 VWD patients after 6 months Physician's assessment of response in treatment of major bleeds (b)(4) VWF and FVIII consumption <sup>2</sup>
Continue until 1 year of treatment	3. Immunogenicity 4. Safety	Inhibitor titre <sup>3</sup> Adverse events.
Post-marketing study	1. Clinical efficacy 2. Immunogenicity 3. Safety	Protocol should be provided.

1) Due to the rarity of hereditary type 3 VWD (prevalence between 0.55 to 6.0 per million) applicants might encounter difficulties to enrol 6 patients with type 3 VWD. In this case the competent authority should be contacted. 2) VWF and FVIII consumption number of infusions (IU/kg per event (on-demand) (b)(4) 3) Inhibitor titre at baseline, every 3 months until end of observation period of 1 year, and also if there is suspicion of inhibitor development.

Differences between guideline recommendations and the conduct of TMAE-104 include: (1) The CPMP guideline recommends all patients entering into clinical trials be vaccinated against hepatitis A and B (unless protective antibodies are present resulting from a previously experienced infection), and evidence of immunization should be present at baseline. Past immunization for hepatitis A or B was not an entry criterion for TMAE-104. (2) The guideline recommends for PK studies, sampling for VWF:RCO, VWF:Ag, VWF:CB, and FVIII:C be taken before infusion of 80 VWF:RCO IU/kg of the product, but in TMAE-104, the dose used was ~50 VWF:RCO IU/kg. (3) Not all subjects with type 3 disease having PK evaluation at baseline had repeat after at least 6 months; 6 subjects had repeat PK. However, TMAE-104 did include enough type 3 subjects followed for 1 year in the prevention (16) and treatment (21) of bleeding episodes.

## SELECTION OF STUDY POPULATION

### INCLUSION CRITERIA

- Defined inherited VWD, types 1 to 3
- Age > 6 and < 65 years
- Subjects not sufficiently responding to DDAVP treatment
- Freely given written informed consent

### EXCLUSION CRITERIA

- Administration of other plasma derived or blood product within 72 hours prior to treatment
- Administration of DDAVP within 15 days prior to treatment
- Administration of acetylsalicylic acid within 7 days prior to treatment
- Known history of intolerance versus plasma derived or blood products
- Symptomatic infection

- Severe liver or kidney disease (ALAT 5x > normal value, creatinine > 120 µmol/l)
- Participation in another clinical study (ongoing or within the previous four weeks)
- Pregnant or lactating women

#### TREATMENT ADMINISTERED

The following dose regimens were recommended as guidance:

- Spontaneous or post-traumatic bleeding: a dose of approximately 20-50 IU FVIII:C/kg BW given once daily or every other day is normally sufficient.

(b)(4)

#### Comments

(b)(4)

(b)(4)

WILATE was to be injected IV at a speed of 2-3 mL per minute, using aseptic technique. At the end of the infusion, the injection line was to be flushed with 0.9 % sodium chloride. It could also be administered by continuous infusion. WILATE was supplied for this study in vials containing either 500 or 1000 IU of FVIII:C. Prior to administration, the WILATE solution was warmed to room or body temperature and used immediately after dissolution, unused solution was discarded. Solutions which are cloudy or have deposits were discarded.

Twenty eight batches of WILATE were used in the study:

Batch #	Size (IU)	Expiry Date	Batch #	Size (IU)	Expiry Date
036008181	1000	06/2002	337005181	500	03/2006
204001181	500	10/2002	338006181	500	02/2006
217003181	500	04/2004	340008181	1000	03/2006
219004181	500	02/2003	405001181	500	06/2006
227005181	500	05/2004	424002181	500	11/2006
224006181	500	06/2004	435004181	1000	02/2007
238007181	500	09/2004	435005181	500	07/2006
242008181	500	09/2004	436006181	500	08/2006
248009181	500	10/2004	441007181	1000	09/2006
249010181	500	11/2004	450008181	1000	11/2006
251012181	500	05/2005	505001181	1000	12/2006
322002181	500	04/2005	540012181	500	09/2007
324003181	500	05/2005	541013181	500	09/2007
335004181	1000	01/2006	542015181	1000	09/2007

#### PRIOR AND CONCOMITANT THERAPY

**Prior Treatment.** In patients who underwent PK and/or recovery investigations, the administration of other plasma derived or blood products within 72 hours before treatment with WILATE was not permitted and DDAVP could not be administered within 15 days before treatment. Subjects must not have received acetylsalicylic acid within 7 days prior to starting treatment with WILATE.

**Permitted Concomitant Therapy.** Concomitant administration of therapies not interfering with the primary objectives was permitted.

**Forbidden Concomitant Therapy.** Concomitant administration of DDAVP might be required in emergency situations. However, in principle, the administration of DDAVP had to be avoided during the course of the study. Acetylsalicylic acid was forbidden. The reconstituted product was not to be mixed with other drugs and no VWF/FVIII preparations other than WILATE were to be given (except in emergency situations). Administration of other blood products had to be avoided if possible. For home-treatment, the subject had to document concomitant medications in the treatment diary.

## EFFICACY AND SAFETY MEASUREMENTS

### Efficacy measurements

a) Coagulation Parameters. Efficacy was assessed at the first infusion of WILATE by measuring plasma levels of FVIII:C, VWF:RCO, VWF:Ag and VWF:CB at baseline and 30 minutes, 1 and 3 hours after infusion. Additional samples could optionally be taken after 6 and 12 hours. Further assessments were made as frequently as necessary.

For PK assessment, the incremental recovery was calculated for FVIII:C, VWF:RCO and VWF:Ag.

b) Bleeding time. It was planned that the correction of BT should be measured once during the whole treatment phase of the study, using the Ivy method. BT was to be measured before treatment (baseline), and at 30 minutes, 1, 3, 6, and 12 hours after infusion. BT tests later than 3 hours after injection were not required if the bleeding time had returned to baseline. If an additional dose of WILATE was administered during the evaluation period, no further assessments of BT were required.

c) Assessment of spontaneous bleeding episodes. All spontaneous bleeding episodes were documented by indicating the site of bleeding, the severity and the details of treatment administered. A subjective assessment of efficacy and tolerability was also recorded.

Comment The grading of severity of bleeding episodes is not clear in the protocol. In the data provided, bleeding episodes are graded as minor, moderate and severe. However, these are subjective designations by patient, and no clear instructions have been documented.

(b)(4)

e) Efficacy assessment of treatment episodes. An assessment of the clinical response was done by the treating physician and/or the subject, using a verbal rating scale (VRS: none - moderate - good - excellent) after each treatment episode using 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.

Comment The grading VRS grading is by patient for each bleeding episode. These are subjective designations by patient, and no clear instructions have been documented. When asked specifically, Octapharma indicated that "additional product" refers to a non-Wilate product, but documentation for this instruction to patients is also lacking.

The counting of bleeding episodes is not clearly defined. When asked specifically, Octapharma stated that in earlier studies, the episodes were not defined, but for later studies such as TMAE-104, bleeding separated by 2 calendar days are counted as separate episodes.

(b)(4)

f) Assessment of overall response. Overall response to treatment was assessed by investigator and subject at the end of the study on a VRS i.e. as "none", "moderate", "good", "excellent" (see above)

### Safety measurements

a) Tolerability and other safety aspects. AEs were documented by the investigator on the CRF. The subject was asked to answer 'Yes' or 'No' to the question "Did you experience any inconvenience since the administration?" The answer, together with further details about any reported or observed AE, was to be recorded in CRF. The evaluation of AEs was according to generally accepted criteria for severity (mild, moderate, severe) and causality (probably, possible, unlikely, unrelated), and the definition of serious AEs (SAEs) was consistent with the U.S. regulations. At the end of the study, subjects and investigators were both required to assess the overall tolerability on a 4-point scale (unsatisfactory - satisfactory - good - very good).

b) Viral Safety. Subjects were tested for serological markers for the following viruses at baseline, before the first injection of WILATE: HIV, HAV, HBV, HCV, and parvovirus B19. If a positive result was obtained at entry, it was not necessary to repeat assessment during study. However, pretreatment samples from each subject were to be taken and stored at -70 °C for future testing if required.

All viral markers that were found to be negative at baseline were to be re-tested every 3 months throughout the study. A final viral screen was performed at study end; samples were taken at 7-14 days after last WILATE treatment for parvovirus B19, and at 4 to 8 weeks after last treatment for HIV, HAV, HBV and HCV.

**Comment** Safety evaluation appears to be adequate for AEs. However, the tolerability assessment for the infusions and overall tolerability assessment at the end of study by patients and Investigators uses a 4-point scale that is poorly defined for the gradings. This instrument is not adequate as a stand alone tool. The 3-monthly viral safety evaluations appear to be adequate.

#### STATISTICAL AND ANALYTICAL PLANS

For the PK analysis, the following parameters were calculated with two sided 95% confidence intervals, using the computer program Topfit, version 2.1: AUC, ( $t_{1/2}$ ), MRT, Vdss CI, C<sub>max</sub> and T<sub>max</sub>. Descriptive statistical procedures were applied to the analysis of all data recorded in the CRF. Standard summary statistics were calculated. Categorical data were presented in frequency tables.

Population for Efficacy Analysis: intention-to-treat, i.e. all subjects in the study who were treated with WILATE. However, exclusion from the primary analysis of subjects with major protocol violations (e.g. other coagulation disorder than VWD) was permitted.

AEs were coded according to MedDRA (Version 9.0) and grouped by primary system organ class. Laboratory parameters were analysed using shift tables and scatter graphs. AEs were categorised according to intensity, duration, frequency and time of occurrence.

Any viral seroconversions were presented in a frequency table. Only subjects with negative baseline values were evaluated for seroconversion.

#### AMENDMENTS TO THE PROTOCOL

Amendments	Date	Countries Valid	Subject
Amendment I	14-Nov-2001	All	Inclusion of PK assessment in >10 subjects.
Amendment II	12-Mar-2002	Portugal, Sweden	New insurance company providing cover for study in countries for which this amendment was applicable.
Amendment III	07-May-2003	Finland	Reduction in volume of blood to be collected from children for FVIII:C, VWF:RCO, VWF:Ag and VWF:CB, at request of Finnish ethics committee. Different collector tubes.
Amendment IV	08-Oct-2003	Austria	Regular pregnancy tests for females.
Amendment V	12-Jul-2006	Germany	Inclusion of a study centre in Germany.
Amendment VI	16-Oct-2006	All	Including testing for VIII & VWF antibodies to

#### STUDY SUBJECTS

##### DISPOSITION OF SUBJECTS

A total of 41 subjects were enrolled. One subject (Centre 1) Subject removed from Poland to the UK and switched from centre 1 to an additional centre (centre 15) in the UK.

Number of Subjects per Study Part	
Study Part	Number of Subjects
Pharmacokinetics	9
Treatment of bleeding episodes (efficacy evaluation)	29
Surgery	24

Ten subjects failed to complete the study.

Ctr Subject	Study Part	Reason(s) for withdrawal
1	Efficacy (b)(4)	multi-organ failure ultimately resulting in death.
1	Efficacy	At subject's request, protocol violation, insufficient therapeutic response;
1	(b)(6) Efficacy	(b)(4) postponed until after completion of study.
6	Efficacy	Insufficient therapeutic response.

6	Efficacy	Insufficient therapeutic response
7	Surgery	Insufficient therapeutic response
8	Efficacy	At subjects request; insufficient therapeutic response, withdrawn by investigator
9	Efficacy	At subjects request
10	Surgery	Insufficient therapeutic response
13	Efficacy	At subjects request

Three subjects were found to have been enrolled into the study despite failing to meet the inclusion/exclusion criteria.

- Subject in Centre 11 was 5 years of age not meeting the required age range (6 to 85).
- Subject in Centre 16 did not meet the inclusion criterion of having defined, inherited VWD, types 1 to 3. On further investigation he was found to have acquired VWD with a Type II phenotype.
- Subject in Centre 1 was treated with other p-c or blood products within 72 hours prior to treatment, but the inclusion of this subject was approved by the sponsor prior to enrollment.

#### DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The total study population consisted of 18 males (44%) and 23 females (56%). This included a subset of 8 paediatric subjects of less than 12 years, of which 3 were male and 5 female. Age, height and weight at baseline for the total study population are shown below:

Parameter	Mean	Standard Deviation	Median	Range
Age	36.2	21.1	39.0	5.0-73.0
Height (cm)	161.2	18.4	163.0	110.0-187.0
Weight (Kg)	63.7	21.4	68.0	19.0-106.0

In the paediatric subset, one subject (12.5%) had Type 1 VWD, one subject (12.5%, Subject 1 in Centre 17) had Type 2 VWD and the remaining 6 subjects (75%) had Type 3 VWD.

#### Gender, Blood Group Previous Exposure Days and Bleeding Time at Baseline by VWD Type

VWD Type	Type 1 (N=3)	Type 2* (N=11)	Type 3 (N=27)	Total (N=41)
Gender				
Male	1 (33%)	6 (55%)	11 (41%)	18 (44%)
Female	2 (67%)	5 (45%)	16 (59%)	23 (56%)
Blood Group				
Group A	0 (0%)	3 (27%)	8 (30%)	11 (27%)
Group B	0 (0%)	2 (18%)	7 (26%)	9 (22%)
Group AB	1 (33%)	1 (9%)	1 (4%)	3 (7%)
Group O	2 (67%)	5 (45%)	11 (41%)	18 (44%)
Exposure Days at Entry				
Unknown	0 (0%)	1 (9%)	0 (0%)	1 (2%)
<20	3 (100%)	2 (18%)	2 (7%)	7 (17%)
20 - 150	0 (0%)	4 (36%)	7 (26%)	11 (27%)
>150	0 (0%)	4 (36%)	18 (67%)	22 (54%)
Bleeding Time/baseline				
Unknown	3 (100%)	6 (55%)	7 (26%)	16 (39%)
< 30 min	0 (0%)	3 (27%)	2 (7%)	5 (12%)
≥ 30 min	0 (0%)	2 (18%)	18 (67%)	20 (49%)

\*Of the 11 subjects with Type 2 VWD, 6 were categorised as Type 2A, 3 as Type 2B and 1 as Type 2M. No further diagnosis was specified for one subject

#### EFFICACY EVALUATION

##### Plasma Level Data of FVIII:C, VWF:RCO, VWF:Ag and VWF:CB

Plasma level data on FVIII:C, VWF:RCO, VWF:Ag and VWF:CB were usually from central laboratory, although some local lab values have been available for the surgical cases. Values obtained for recoveries of VWF:RCO, VWF:Ag and FVIII:C, other than from PK analyses or surgery are summarized below.

Mean Recoveries\* of VWF:RCO, VWF:Ag and FVIII

VWD Type	VWF:RCO (U/mL)	VWF:Ag (U/mL)	FVIII chromo <sup>a</sup> (%)	FVIII <sup>b</sup> (%)
Type 1, N=3	0.69	2.12	1.91	1.68
Type 2, N=8	0.96	1.52	1.79	1.49
Type 3, N=21	1.27	1.65	1.91	1.98
All Types, N=32	1.14	1.66	1.88	1.83

<sup>a</sup>based on nominal potency of Wilate; <sup>a</sup>=FVIII:C by chromogenic assay; <sup>b</sup>=FVIII:C by one-stage clotting assay

The PK data evaluation is conducted by Dr. Iftikhar Mahmood. See Dr. Mahmood's review for details.

This study also compared the PK data in a portion of subjects (N=9) at baseline and 6 months after initiation of Wilate therapy.

#### PK Parameters and Recovery for VWF:RCO and FVIII:C at Baseline and 6-Months

Parameter (unit)	VWF:RCO		FVIII:C <sup>chromo</sup>	
	Baseline visit	6-month visit	Baseline visit	6-month visit
C <sub>max</sub> (%)	95	95	105	96
C <sub>max, nom</sub> (%/IU/kg)	1.5 (1.9)	1.5 (1.9)	1.77 (1.78)	1.68 (1.75)
AUC (% * h)	1,761	1,622	1,963	1,513
AUC <sub>nom</sub> (% * h/IU/kg)	29 (37)	26 (33)	34 (34)	25 (26)
MRT (h)	26.80	22.16	25.11	23.85
Clearance (ml/h/kg)	3.6 (2.7)	3.9 (3.0)	2.9 (2.9)	4.1 (3.9)
Distribution volume (ml/kg)	0.86 (0.69)	0.93 (0.75)	0.68 (0.67)	0.77 (0.72)
t <sub>1/2</sub> (h)	18.96	15.75	16.84	16.35
Recovery (%/IU/kg)	1.47 (1.85)	1.41 (1.75)	1.72 (1.76)	1.61 (1.67)

FVIII:C chromo = FVIII coagulation activity measured with the chromogenic method;

FVIII:C = FVIII coagulation activity measured by the one-stage clotting assay

The following shows the data in 6 VWD type 3 subjects on half-life and recovery.

#### Median Half-Life and Recovery in VWD Type 3 Subjects undergoing Repeat PK Analysis

VWD Type	Parameter	Time of PK Analysis	Half-life (h)	Recovery (%/IU/kg) nominal (actual)
Type 3 N=6	VWF RCo (IU/ml)	Baseline	18.96	1.47 (1.85)
		> 6M	15.75	1.41 (1.75)
	VWF Ag (IU/ml)	Baseline	9.44	1.35 (-)
		> 6M	9.66	1.63 (-)
	VWF CB (IU/ml)	Baseline	12.46	- (-)
		> 6M	13.42	(-)
	FVIII:C <sup>chromo</sup> (%)	Baseline	16.84	1.72 (1.76)
		> 6M	16.35	1.61 (1.67)
	FVIII:C	Baseline	24.21	1.76 (1.80)
		> 6M	18.57	1.67 (1.74)

BL = baseline, 6mo = after at least 6-month follow-up treatment with WILATE; RCo = VWF:RCO, FVIII Chr = FVIII coagulation activity measured with the chromogenic method, FVIII:C = FVIII coagulation activity measured by the one-stage clotting assay

The comparison between baseline and 6-month data suggests stable pharmacokinetics and recovery upon 6-month treatment with Wilate. Without antibody data, the study of PK and recovery alone is not adequate to support lack of immunogenicity.

**Comment** The PK Reviewer, Dr. Iftikhar Mahmood, has reservations on the data on VWF RCo because of assay problems. However, he has also agreed that (a) the results indicate that there was no difference in PK parameters between single and multiple dosing in patients with VWD type 3, and (b) compared to patients with VWD type 3, the half-life of VWF:RCO and FVIII:C<sup>chromo</sup> was almost 1.5 times longer in patients with VWD type 2. See Overview of Efficacy section for further discussions.

#### Bleeding Time

Assessment of BT correction pre and post injection was performed on one or more occasions for 26 out of the 41 subjects (63%). 15 out of 26 (58%) were found to be responders on at least one occasion, defined as subjects who showed a reduction in BT at any time point after baseline (See section "Overview



of Efficacy" for details and an analysis relating bleeding time data to infusion efficacy rating for bleeding episodes)

#### Treatment of Bleeding Episodes

According to the dataset, there were 1015 unique bleeding "episodes" for which at least one infusion was given. However, only 1014 of them were attributed under "treatment", as one "episode" and its infusion (Patient 1 in Center 14, first infusion) was grouped under "prophylaxis". The bleeding sites for these 1014 "episodes" are provided below:

- GYN 36
- Oral/nasal 224
- Other (hematuria, wound, etc) 28
- Joint 565
- GI 122
- Muscle/soft tissue 39

In addition, there were 140 bleeding "episodes" not treated with investigational product, making a total of 1155 "episodes". Octapharma explained that these were mostly minor bleeds recorded but not requiring treatment, but some patients might have used other products at a time of shortage of their product.

Most of the bleeding "episodes" were treated with one (581 episodes) or two (239 episodes) infusions.

Distribution of infusions by type of bleeding by VWD Type						
VWD Type	Joint	Oral/nasal	GI	Muscle/soft tissue	Gynecologic	"Other"
Type 1	0	18	0	1	3	0
Type 2	0	15	95	5	0	0
Type 3	937	352	435	59	70	45
Total	937	365	530	65	73	45

Because of the lack of clear definition of bleeding episodes and difficulties in applying the 4-point verbal rating scale in interpreting hemostatic efficacy, this review has used additional criteria to determine hemostatic efficacy. The methodology has been conveyed to Octapharma on October 30, 2007, and summarized as follows:

Bleeding episodes are separated from each other as distinct episodes when there is an interval of 2 or more calendar days without replacement therapy with Wilate. In addition to the 4-point subjective verbal rating scale (VRS) used in the studies by the Investigator or patient 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 will be regarded as failures, and excellent and good scores will be 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 -
  - o Minor bleeds > 2 treatments (failure)
  - o Moderate bleeds > 3 treatments (failure)
  - o 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 will also be assigned success/failure rating based on the above objective criteria.

Based on the above, the results in Wilate treatment of bleeding episodes can be shown as follows.

TMAE-104 BE Categories by Site				
	Site of bleeding	#Episodes	#Successfully treated Episodes	% Success
1	Joints	544	480	88
2	Epistaxis	130	88	68
3	GI bleeding	120	62	52
4	Oral bleeding	45	31	69
5	Gynecologic	33	25	76

6	Other*	59	52	88
	Total	931**	738	79

\*muscle, hematoma, cutaneous, subcutaneous after trauma, and wounds. \*\*there were 139 episodes, usually minor, that were not treated with Wilate. Octapharm, also noting there were 3 severe GI bleeding episodes not treated due to unavailability of Wilate.

Results of Treatment in TMAE-104 BE by VWD Type				
VWD Type	1	2	3	Total
N (# subjects)	2	6	19	27
#Episodes	15	34	882	931
Successfully treated Episodes	10	27	701	738
% Success	67	79	79	79

The doses used for the infusions can be summarized as follows:

Doses Used in TMAE-104		
Site of bleeding	Initial Dose (IU/kg FVIII:C) Mean + SD	Subsequent Doses (IU/kg FVIII:C) Mean + SD
Joints	28 + 12	25 + 12
Epistaxis	24 + 9	22 + 11
GI bleeding	41 + 18	34 + 17
Oral bleeding	25 + 12	23 + 10
Gynecologic	33 + 16	31 + 14
Other*	25 + 8	23 + 8

\*muscle, hematoma, cutaneous, subcutaneous after trauma, and wounds

These doses were administered without support from plasma levels, as the patients were given the product for home treatment. Only two patients (Center 5<sub>(b)(6)</sub> and Center 3<sub>(b)(6)</sub>) had FVIII and VWF levels studied because the recovery investigation happened to be at the time of bleeding (see below). It would be difficult to advise dosing based simply on the doses used without corresponding plasma level data on VWF or FVIII to confirm adequacy of replacement at a time of active consumption of the coagulation factors.

Center 3 <sub>(b)(6)</sub> (VWD Type 1)	FVIII one-stage (%)	VWF:RC <sub>Co</sub> (%)
03 JUN 2004/ 11:55	13.8	63
03 JUN 2004/ 12:00	injection of 1500 IU (23 IU/kg)	
03 JUN 2004/ 12:30	57.7	95
03 JUN 2004/ 13:00	57.2	95
03 JUN 2004/ 15:00	68.4	95
04 JUN 2004/ 13:00	74.0	63
Time unspecified	injection of 1500 IU (23 IU/kg)	
04 JUN 2004/ 13:30	107.4	95
04 JUN 2004/ 14:00	107.4	95
Center 5 <sub>(b)(6)</sub> (VWD Type 3)	FVIII one stage (%)	VWF:RC <sub>Co</sub> (%)
05 OCT 2006 / 13:00	1.9	1
05 OCT 2006 / 13:25	injection of 1500 IU (60 IU / kg BW)	
05 OCT 2006 / 14:00	84.0	42
05 OCT 2006 / 14:30	83.8	42
05 OCT 2006 / 16:30	60.9	28

See Appendix 1 for details of each individual patient's treatment of bleeding episodes, including narrative and plasma levels of FVIII and VWF:RC<sub>Co</sub>, if available.

Pages 35 through 50 redacted for the following reasons:  
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(b)(4)

(b)(4)

SAFETY EVALUATION

**Number of Infusions and Exposure Days\* to WILATE (N=41)**

Reason for Administration	Number of Infusions of WILATE administered	Number of WILATE Exposure Days
Treatment of Bleeding	1,916	1,772
Surgical Procedures	250	189
Prophylaxis	2,974	2911
Study Related Administration (PK/recovery)	45	45
Total	5,185	4,917

\*Exposure days ('treatment days') are days when an actual Wilate infusion was administered. Each exposure day might include one or more infusions.

**Comment** Octapharma contends that some single infusions have been counted as >1 due to the use of different lot batches and thus went into the record under >1 entry, and that 'treatment days' would more accurately present Wilate administration than the number of infusions. However, since it is not possible to tell whether two entries in the same day represent a single infusion using different batches or not because the infusion times for bleeding episodes are neither in the CRF nor in the database, both counting methods leave uncertainties that cannot be easily overcome.

**AE Frequency**

MedDRA PRIMARY SOC	PREFERRED TERM	No. of Subjects (%)	No. of Events
Blood and Lymphatic System Disorders	Anaemia	5 (12.2)	10
Gastrointestinal Disorders	Gastrointestinal haemorrhage	5 (12.2)	30
Infections and Infestations	Pharyngitis	9 (22.0)	18
	Nasopharyngitis	4 (9.8)	10
General and Administration Site Conditions	Pyrexia	3 (7.3)	6
Nervous System Disorders	Headache	3 (7.3)	4
Parvovirus B19 seroconversion	Parvovirus B19 serology positive	3 (7.3)	3

**AEs Considered to be Related to Treatment**

Centre/ Subject	Event Description	Serious Yes/No	Intensity	Resolved Yes/No	Causality
1-	Wheals after infusion	No	Mild	No	Probable
1- (b)(6)	Headache	No	Moderate	Yes	Possible
	Abdominal discomfort	No	Moderate	Yes	Possible
	Breathlessness	No	Moderate	Yes	Possible
6-	Dizziness	No	Mild	Yes	Possible
	Nausea	No	Mild	Yes	Possible
	Vertigo	No	Mild	Yes	Possible
	Anaemia	No	Moderate	No	Possible
	Dizziness	No	Mild	Yes	Possible
	Exanthema in the face	No	Mild	Yes	Possible
11-	Parvovirus B19 seroconversion	Yes	Mild	Yes	Possible
11-(b)(6)	Parvovirus B19 seroconversion	Yes	Mild	No	Possible
17-	Parvovirus B19 seroconversion	Yes	Mild	No	Probable

**Narratives of SAEs and Death**

**Centre 1, Subject No. (b)(6)**

See above under major surgery narrative.

**Centre 1, Subject No. (b)(6)**

This male subject was included into the study on 27-Feb-2002 at the age of 49, and had VWD type 3 and angiodysplasia of the duodenum, with many episodes of GI bleeding before. He developed melaena on 29-Mar-2002 and was hospitalized on 31-Mar-2002. The event was rated as severe SAE. He was treated with WILATE, blood transfusion and tranexamic acid and recovered. Within the next two years he experienced several episodes of GI bleeding and epistaxis which were all rated as severe and were treated with WILATE, blood transfusions, tranexamic acid and omeprazole.

**Centre 1, Subject No. (b)(6)**

This female was included into the study on 01-Mar-2002, aged 20, and had VWD type 3. She suffered from GI bleeding, epistaxis and joint bleeding and was treated with WILATE prophylactically and on demand. On 21-Mar-2002 she experienced GI bleeding and hematemesis due to gastric ulcer. She was treated with WILATE, blood transfusion, omeprazole and tranexamic acid and was admitted to the Surgical Department for gastroscopy. The event was rated as a severe SAE. It resolved on 23-Mar-2002. The subject was hospitalised again on 12-Apr-2002 due to a GI bleeding episode and during a gastroscopy, an angiodysplasia of duodenum was discovered. She was treated with WILATE and tranexamic acid. The event was not related to WILATE treatment and was rated as a severe SAE. The subject recovered and was discharged on 19-Apr-2002. Between December 2002 and January 2005 she experienced three GI bleedings with melæna, which were all unrelated to WILATE treatment and were rated as severe SAEs as they resulted in hospitalization. She was treated with WILATE, blood transfusion and tranexamic acid and the events were resolved.

**Centre 5, Subject No. (b)(6)**

This male subject was included into the study on 14-Jan-2003 at the age of 9, and had VWD type 3. On 20-Jan-2003 he underwent a tooth extraction and received 500 IU of WILATE. The subject required hospitalization two weeks later for oral bleeding, and was treated with WILATE, Exacyl, Tachocomb, Hemofer, folic acid, vitamin B6 and blood transfusions. Despite WILATE infusions, hospitalization was prolonged due to recurrent oral hemorrhage until 23-Feb-2003. The event was rated as severe SAE. Because of lack of efficacy the event was rated as probably related to WILATE treatment. The subject was further treated prophylactically and on demand with WILATE and developed a Vascuport infection with a thrombus in the right atrium on 11-July-2004. The subject was hospitalized on 13-July-2004, recovered and was discharged on 22-July-2004. This event was rated as moderate and unrelated to WILATE treatment.

**Comment** The patient was using Wilate for prophylaxis with doses of 500 to 1000 units (11.8 to 23.5 IU/kg) in July 2004. Although the thrombus could have been related to Vascuport infection, it is also possible that plasma level for FVIII had been too high due to Wilate administration. Since no plasma levels are available for confirmation, this SAE underscores the importance of monitoring when Wilate is used.

From 24-Nov-2005 the subject suffered from recurrent knee joint bleedings and was hospitalized on 14-Dec-2005. The intensity of the event was rated as severe and the event itself was rated as unrelated to WILATE treatment. The subject was treated with WILATE and Ibuprofen and was discharged on 22-Dec-2005. On 21-Jan-2006 the subject was hospitalized again due to synovitis of the right knee. Blood culture, morphology and sonography were performed. He was treated with WILATE and prednisone and was discharged from hospital on 17-Feb-2006. The intensity of the event was rated as moderate. The event was assessed as not related to WILATE treatment. The subject had further knee bleedings in November 2006 and January 2007, treated with WILATE and Ibuprofen. An infection of the Vascuport occurred on 26-Aug-2006. The subject was hospitalized and treated with Zinnat, Nystatine and Amikin. He was discharged on 01-Sep-2006. The intensity of the event was rated as mild and the event itself was assessed as not related to WILATE treatment.

**Centre 5, Subject No. (b)(6)**

This female subject was included into study on 15-May-2003 at the age of 11 with VWD type 3 and was treated with WILATE for surgical procedures (tooth extractions), and prophylactically. On 17-Dec-2004 she developed an epidemic parotitis and lymphocytic meningitis. She was hospitalized until 29-Dec-2004. The event was rated as severe SAE and was successfully treated with Penicillin, Decadron, Mannitol, Luminal, Bactrim and Ketonal.

**Centre 6, Subject No. (b)(6)**

This female was included into the study on 25-Feb-2004 at the age of 64 with VWD type 2A and liver cirrhosis due to chronic hepatitis C infection. She was treated with WILATE prophylactically and on demand. On 20-Mar-2004 she was hospitalized due to GI bleeding. From 23-Mar-2004 she received a daily dose of 1000-2000 IU WILATE (12.5-25 IU/kg BW) until 26-Mar-2004 and the bleeding was stopped. The GI bleeding was rated as severe SAE.

**Centre 7, Subject No. (b)(6)**

This male subject gave informed consent for study participation on 19-Dec-2003 and was included into the study on 30-Jan-2006 at the age of 65 with VWD type 2B. He had a long history of GI bleeding. On 08-Feb-2006 and 09-Mar-2006 he was hospitalized for one to two days due to poor general condition.

caused by GI bleeding, resulting in low haemoglobin. He received packed red blood cells. On 14-Mar-2006 the patient was hospitalized again for capsular endoscopy of small intestine. Three 2-3mm large angiodysplasias were found in duodenum. He was treated locally with argon plasma coagulation and received WILATE. He was discharged from hospital on 28-Mar-2006.

#### Centre 9, Subject No. (b)(6)

This female was included into the study on 13-Jul-2004 at the age of 73 with VWD type 2A and chronic obstructive pulmonary disease (COPD) and was treated with WILATE prophylactically due to GI bleeding. On 13-Oct-2004 she developed an exacerbation of COPD and was hospitalized on 15-Oct-2004. She was treated with steroids, antibiotics, inhalation of ipratropium bromide and beclomethasone. Throughout the admission there was intermittent melena treated with WILATE (2000-3000 IU). The subject was discharged from hospital on 10-Nov-2004. The event was rated as severe SAE.

#### Centre 11, Subject No. (b)(6)

This 7-year old girl with VWD type 3 was included into the study on 25-Mar-2004. She received a prophylactic dose of 500 IU of WILATE via Port-a-Cath® (implantable venous access system) and developed bleeding from the device on 02-Oct-2004. Two further doses of 500 IU were needed to stop the hemorrhage and the subject fully recovered on the same day and was discharged on 03-Oct-2004. Due to the required hospitalisation, the event was classified as serious. The intensity of the event was rated as severe. The subject was negative for parvovirus B19 IgG and IgM at baseline and positive for both markers at 3 months but did not develop any clinical symptoms. The follow-up investigations showed that the WILATE batch concerned (No. 248 009 181) was B19 PCR positive. This batch was produced and released before the B19 PCR testing of the pool became part of the batch release. This subject was hospitalized again on 27-Jul-2006 for one day, because she fell and needed several stitches to a scratch between the lips and nose. The subject was on holiday and it was not possible to supply WILATE on short notice. She received Haemate, Cyclokapren and Panadol for bleeding and pain. The intensity of the event was rated as mild.

#### Centre 11, Subject No. (b)(6)

This 5 year old boy with Type 1 VWD entered the study in May 2004. Between 06-May-2004 and 18-Feb-2007 he received a total of 69,500 IU of WILATE, mainly on a prophylactic basis. The subject was negative for parvovirus B19 IgG and IgM at baseline. Testing at 3-monthly intervals showed that he remained negative until 04-May-2006 when the result for B19 IgG was positive although IgM remained negative. All subsequent tests for B19 IgG were positive. The subject did not develop clinical symptoms and the Investigator did not report the sero-conversion as an adverse event. The subject was receiving treatment with WILATE batch 436006181, a batch produced and released before the B19 PCR testing of the pool became part of the batch release.

#### Centre 16, Subject No. (b)(6)

This female subject was included into the study on 31-May-2005 at the age of 60 with VWD type 2A. She was hospitalized on 30-May-2005 due to planned ERCP on 31-May-2005. After this surgical procedure an acute pancreatitis occurred. The subject received a total amount of 12,000 IU of WILATE (pre and post surgery) and was treated with analgesia and antibiotics. She was discharged from hospital on 06-Jun-2005.

#### Centre 17, Subject No. (b)(6)

This 10-year old girl suffering from VWD type 2A was included into the study on 23-Mar-2006. The subject had a history of approximately 40 bleeds per year. She received a dose of 1,000 IU of WILATE 3 times a week from 23-Mar-2006 (batch no. 505001181). The subject was negative for parvovirus B19 IgG and IgM at baseline and positive for both markers on 04-Jul-2006. She did not develop clinical symptoms.

#### Viral Seroconversion

Centre/ Subject	Viral Marker	Baseline Date/Result	First Changed Status Date/Result	Comments
1- (b)(6)	HAV-Ab	02-Jan-2002 Negative	06-Jan-2004 Limit	This borderline result was followed by 15 subsequent negative results.
1	HAV-Ab	27-Feb-2002 Negative	09-July-2002 Positive	The subject was vaccinated against HAV on 07-Jul-2000. The negative result from the screening sample is

1-	Parvovirus B19 IgM	27-Feb-2002	30-Jan-2003	believed to be false
1-	HAV-Ab	23-Mar-2004	01-Jun-2004	Subject was B19 IgG positive from baseline.
		Negative	Positive	A second HAV (b)(4) test of a sample obtained on 01-Jun-2004 and an (b)(4) test of a sample obtained on 17-Jan-2006 revealed negative results. The (b)(4) result on 01-Jun-2006 is assumed to be a false positive.
5-	HAV-Ab	16-Dec-2002	24-Jun-2003	Vaccinated against HAV on 14 Mar 2003.
5-	HAV-Ab	15-Jan-2003	13-Oct-2003	Vaccinated against HAV on 11 Jul 2003.
5-	HAV-Ab	15-May-2003	14-Aug-2003	Vaccinated against HAV on 16 May 2003.
9-	Parvovirus B19 IgG	13-Jul-2004	13-Oct-2004	Baseline sample was borderline positive.
11	Parvovirus B19 IgG	25-Mar-2004	17-Jun-2004	Seroconversion for parvovirus B19.
11	HAV-Ab	06-May-2004	12-Jan-2006	Vaccinated against HAV on 29-Sep-2005.
11	Parvovirus B19 IgG	06-May-2004	04-May-2006	Seroconversion for parvovirus B19.
17	Parvovirus B19 IgG	23-Mar-2006	04-Jul-2006	Seroconversion for parvovirus B19.

**Comment** Three cases of seroconversion for B19 has occurred during this study.

### III. TMAE-105. Pharmacokinetic properties, safety and efficacy of WILACTIN in patients with inherited von Willebrand disease

#### INVESTIGATORS

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#### STUDY OBJECTIVE(S)

**Primary.** To assess the PK profile (AUC<sub>0-1</sub>, AUC<sub>0-t</sub> norm, AUC<sub>0-∞</sub>, AUC<sub>0-∞</sub> norm, t<sub>1/2</sub>, MRT, V<sub>dss</sub> and CL) for vWF:RCoF, vWF:Ag and vWF:CBA and FVIII C plasma levels as surrogate markers of efficacy.

**Secondary.** To measure C<sub>max</sub> and t<sub>max</sub> for vWF:RCoF, vWF:Ag and vWF:CBA. In addition:

- The assessment of recovery for FVIII:C, vWF:RCoF and vWF:Ag, calculated from the declared potency of the respective drug.
- The assessment of the correction of bleeding time (BT).
- The influence of WILATE administration on plasma levels of vWF:Ag, vWF:RCoF, and vWF:CBA.
- The assessment of the multimeric pattern.
- The assessment of the overall efficacy.
- The assessment of the clinical safety and tolerability of WILATE.

#### INVESTIGATIONAL PLAN

##### Overall Study Design and Plan

This study was a prospective, non-randomised, non controlled, open-labelled, multicentre phase II study with 2 phases, i.e. a PK phase (phase I) and a treatment phase (phase II). In total, 12 patients with inherited and defined vWD were to be enrolled for the PK assessments (phase I). For the assessment of efficacy, a total of at least 10 treatment episodes were to be documented in phase II of the study.

Patients had to give their written informed consent and had to meet the inclusion criteria of the study. Baseline measurements were to be performed for all relevant parameters.



The clinical phase of the study was to be 6 months, i.e. recruitment had to be stopped after this period. For the PK assessments, a dose of about 50 IU vWF:RCoF / kg BW of WILATE was to be administered to the patients

The dose to be administered in case of spontaneous bleedings or prophylactic treatment depended on the clinical situation and was to be calculated individually. The expected range was between 20 to 50 IU vWF:RCoF/FVIII:C/kg BW of WILATE given as a single or multiple dose.

Find in Table 1 and Table 2 all study related procedures to be performed during phase I and phase II of the study.

#### Overview of Study Events in phase I

Parameter	Details	Concerned	Pre-dose	15'	30'	45'	1h	3h	6h	9h	12h	24h	48h	72h
Pharmacokinetics	AUC, AUC <sub>0-12h</sub> , t1/2, MRT, Vdss, CL <sub>GMR</sub> , t <sub>max</sub>	vWF:RCoF, vWF Ag, vWF:CBA	x	x	x	x	x	x	x	x	x	x	x	x
Recovery	from peak levels	vWF:RCoF, vWF Ag, FVIII:C	x	x	x	x	x	x	x	x	x	x		
Multimers			x				x							
Bleeding time	(b)(4)		x		x		(x)	(x)	(x)		(x)			
Vital signs	HR, BP, RR, temperature		x	x			x							
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x
Laboratory	haematology (haemoglobin, haematocrit, platelets, RBC, WBC), clinical chemistry (bilirubin, creatinine) and serum electrolytes (calcium, chloride, sodium)		x								x			
	isoagglutinins		x				x							
	Viral safety		x											
Tolerability assessment	investigator & patient (VRS)													x

#### Overview of Study Events in phase II

Parameter	Details	Concerned	before	d0	d1	d2	d3	d4	d5	...	last
Plasma levels		FVIII:C, vWF Ag, vWF:RCoF	x	x	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>		
Multimers			x	x							
Bleeding time	(b)(4)		x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>		
Efficacy assessment	Investigator (VRS)										x
Vital signs	HR, BP, RR, temp		x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>		
Adverse events			x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>		x
Laboratory	haematology (haemoglobin, haematocrit, platelets, RBC, WBC), clinical chemistry (ALT, bilirubin, creatinine) serum electrolytes (calcium, chloride, sodium) and coagulation parameters (aPTT, P1)		x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>		
	isoagglutinins		x	x							
	viral safety		x								
Tolerability assessment	investigator & patient (VRS)										x

d = Day, x<sup>1</sup> = as frequently as necessary, x<sup>2</sup> = only in case of further administration; \* = anti-HAV and anti-parvovirus B19 were to be assessed at baseline and 7-14 days (parvovirus B19) and/or 4-8 weeks (HAV) after the last treatment

#### Inclusion Criteria

- Defined inherited vWD, types 1 to 3
- Age > 12 and < 65 years

- HIV 1/2 negative.
- Known to the study centre
- Patients resistant to DDAVP treatment
- Freely given written informed consent

#### Exclusion Criteria

- Present or past inhibitor activity
- Administration of other plasma derived or blood products or DDAVP 15 days before study entry.
- Administration of acetylsalicylic acid 7 days before study entry
- Known history of intolerance versus plasma derived or blood products
- Symptomatic infection.
- Severe liver or kidney disease (ALT x 5 > normal value, creatinine > 120 µmol/l).
- Participation in another clinical study currently or during the past 4 weeks.
- Pregnancy or lactating women

#### Treatments

Phase I: A dose of ~ 50 IU vWF:RCof / kg BW of WILATE was to be administered for the PK investigations. As no product should be discarded, the amount to be administered was to be rounded up or down according to the following Table.

Patient's Weight	Dose if only 1000 IU vials were available	Patient's Weight	Dose if 500 IU and 1000 IU vials were available
< 50 kg	2000 IU	< 55 kg	2500 IU
50 – 69 kg	3000 IU	55 – 64 kg	3000 IU
70 – 89 kg	4000 IU	65 – 74 kg	3500 IU
		75 – 84 kg	4000 IU
		85 – 94 kg	4500 IU
> 89 kg	5000 IU	95 – 104 kg	5000 IU
		> 104 kg	5500 IU

Phase II: The number of administrations and actual dose for treating spontaneous bleedings (b)(4) depended on the clinical situation of the patient, i.e. the severity of the bleeding (b)(4). Single administrations or multiple doses were appropriate. The following dose regimes were provided as a guidance only:

(b)(4)

- spontaneous or post-traumatic bleeding: about 20 to 50 IU FVIII:C / kg BW, once daily or every other day.

(b)(4)

The dose of WILATE should be in accordance with the needs of the patients.

- Prior treatment: A wash-out period of at least 15 days before study entry was required. During this period the administration of plasma derived or blood products or DDAVP was to be avoided. Administration of acetylsalicylic acid (aspirin) was also forbidden for 7 days before any administration of WILATE
- Permitted Concomitant Therapy: Concomitant administration of therapies not interfering with the primary objectives of the study was permitted
- Forbidden Concomitant Therapy: Concomitant administration of DDAVP could be required in emergency situations. Patients with DDAVP treatment required in emergency situations were to be excluded from efficacy analysis. In principle, the administration of DDAVP was to be avoided during the course of the study. Acetylsalicylic acid and other FVIII preparations were forbidden (except in emergency situations), and administration of other blood products was to be avoided, if possible.

Patients were allowed to treat bleeding episodes at home. In phase II they were provided with a sufficient amount of trial medication. The recording of these self-injections included the date, dose, batch and reason for injection. This was to be done by the patients on the respective form of the CRF or in a patient:

diary. If the patient received an injection as treatment for a bleeding episode he/she was to document the site and severity of the bleeding and his subjective impression of efficacy. The investigator had to explain to the patients the use of the treatment forms or diaries. He had to emphasize the necessity of carefully recording the treatments and bleeding episodes. For each follow up visit at the centre, the patients were to bring all their forms to the centre. When the patients received injections (treatment of bleeding episodes, surgery) at the study centre, the physician had to record those infusions directly into the original CRF.

## Efficacy and Safety Variables

### Efficacy measurements

#### Pharmacokinetic profile

PK profile was evaluated after application of approximately 50 IU WILATE per kg body weight. Primary PK parameters (AUC, AUC<sub>norm</sub>, t<sub>1/2</sub>, MRT, V<sub>dss</sub> and CL) and secondary PK parameters (C<sub>max</sub>, t<sub>max</sub>) were to be calculated from plasma concentrations of vWF:RCoF, vWF:Ag and vWF:CBA determined before and 0.25, 0.5, 0.75, 1, 3, 6, 9, 12, 24, 48 and 72 hours after administration of WILATE according to non-compartmental methods using the computer program <sup>(B)M</sup>. Before the PK analysis a validation example was evaluated to confirm the operational qualification of the data system.

#### PK calculations

The maximal plasma concentration (C<sub>max</sub>) and the time of the peak plasma concentration (t<sub>max</sub>) was taken directly from the plasma concentration-time curve

The area under the plasma concentration-time curve (AUC<sub>0-t</sub>) was to be calculated from the measured data points until the time of last quantifiable concentration by the linear trapezoidal rule (The data points available are joined by straight lines resulting in trapezoidal segments for the calculation).

The area under the plasma concentration-time curve (AUC<sub>0-∞</sub>) was to be calculated by the trapezoidal rule and extrapolated to infinity based on the last quantified time point according to the following formula:

$$AUC_{0-\infty} \approx C_{last} / \beta$$

where C<sub>last</sub> denotes the last quantified data point and β denotes the terminal elimination rate constant.

The resulting AUC<sub>0-∞</sub> was then to be calculated according to the formula:

$$AUC_{0-\infty} = AUC_{0-t} + AUC_{last}$$

Only in case of a concentration value equal to zero, an approximation of the last data point was to be used for extrapolation to infinity.

The residual area was to be calculated to prove that the extrapolated part of the curve does not exceed 20 % of the AUC<sub>0-∞</sub>. They were to be determined by the following equation:

$$[(AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty}] \times 100\%$$

The terminal half-life (t<sub>1/2</sub>) was to be estimated from the slope of the linear regression of the semi-logarithmic plot of the terminal phase of the plasma concentration curve represented by the last 5 data points. An assumption was that the terminal elimination phase is reached within sampling period

#### Log-Linear Regression Analysis (t<sub>1/2</sub>)

Based on individual data pairs (x, log(y)) the negative slope of the regression line was to be estimated based on selected data pairs. The resulting value β is the terminal elimination rate constant, the terminal half life was to be calculated from β according to the following formula.

$$t_{1/2} = (\ln(2)) / \beta = 0.69315 / \beta$$

According to the study protocol all plasma samples which were below detection limit were to be set to zero.

#### Incremental Recovery

Incremental recovery was to be evaluated in the course of the PK evaluations for FVIII:C, vWF:RCoF and vWF:Ag levels before administration and from the maximum concentrations (peak levels) in the first 24 hours post-infusion samples

The actual blood sampling time points were allowed to vary within a range of +/- 1 minute until 1 hour after injection or within a range of +/- 15 minutes between the 3 and the 12 hour sampling points when compared to planned blood sampling time points. Between 12 and 72 hours the actual blood sampling time points were allowed to scatter within a range of +/- 2 hours.

For the calculation of recovery, the declared potency of the respective drug was considered as reference. The following formula was used for computation of the incremental recovery:

recovery =  $(C_{max} - C_0) \cdot (\text{body weight}) / \text{dose}$ , units given in kg/dL

#### Bleeding time (BT)

BT was to be measured according to Ivy using the (b)(4) device (b)(4). During the PK phase BT was to be measured at baseline and 30 minutes after injection. Further measurements (e.g. 1 hour, 3 hours, 6 hours and 12 hours) after injection were optional and were only to be performed after approval of the responsible physician. The BT was to be measured until the baseline result was reached again.

During the treatment phase the BT was to be measured only in case of surgery once daily as long as the patient received WILATE. In case a patient's BT was already assessed in phase I of the trial, BT measurements were not to be repeated.

#### Multimers

For each treatment episode at study site the multimeric pattern was to be evaluated from samples taken before and 1 hour post infusion.

#### Clinical efficacy

An overall assessment of the clinical response was to be done by the treating physician using a 4-point verbal rating scale (VRS) (none – moderate – good – excellent) after the last WILATE administration.

#### Plasma levels

During phase II, plasma levels of FVIII:C, vWF:Ag and vWF RCoF were to be measured as frequently as necessary.

#### Safety measurements

Viral Safety. The following viral markers were determined at baseline before the first injection of WILATE, anti-HAV and anti-parvovirus B19. In case of a confirmed positive result at study entry, it was not necessary to repeat the virology measurement in course of the study. However, pre-treatment samples were to be taken from each patient and stored at - 70 °C for future testing.

From patients who were negative or borderline at study entry with respect to antibodies to parvovirus B19 (IgG, IgM) or HAV (IgG, IgM) or in case baseline values were not known at that time point, additional heparin plasma samples were to be taken 7 to 14 days (regarding parvovirus B19) and/or 4 to 8 weeks (regarding HAV) after the last administration of WILATE.

These samples were to be frozen at - 70 °C and were to be checked in case of a change in these viral markers during the study.

Laboratory parameters. Clinical safety was to be assessed by monitoring laboratory parameters: hematology (hematocrit, hemoglobin, platelet count, red blood count and white blood count), clinical chemistry (bilirubin, creatinine), electrolytes (calcium, chloride, sodium) and isoagglutinins. During phase I, hematology, clinical chemistry and serum electrolytes were measured before and 12 hours after WILATE administration. During phase II of the study, these parameters were determined before injection and on each further treatment day of the observed treatment episode. During both phases, isoagglutinins were assessed before and 1 hour after WILATE administration.

Tolerability and other safety aspects. During the whole study period any adverse event (AE) was to be documented. Reported or observed AE was to be recorded in CRF. During both phases, immediate tolerability was assessed by monitoring vital signs, i.e. heart rate, body temperature, blood pressure and respiratory rate, before and 15 minutes and 1 hour after the injection of WILATE.

Patients and investigators also had to assess the overall tolerability on a 4-point VRS (unsatisfactory – satisfactory – good – very good).

#### Statistical Methods and Determination of Sample Size

Descriptive statistical procedures were to be applied to the analysis of data, i.e. frequency distributions or contingency tables for categorical variables and characteristics of the sampling distribution for metrically scaled variables (arithmetic mean, standard deviation, median, extremes and quartiles)

#### Concentrations of FVIII/vWF complex and efficacy analysis

The PK parameters were calculated according to non-compartmental methods using standard formulas. The individual concentrations and the PK characteristics were to be listed and described by arithmetic and geometric mean, arithmetic and geometric standard deviation, coefficient of variation, geometric coefficient of variation, median, extremes and quartiles. Two-sided 95 % confidence intervals were to be calculated for the geometric means of the concentrations and the PK parameters of WILATE. The distribution of tmax was to be described by median, minimum and maximum.

Mean concentration versus time profiles were to be presented graphically on a linear as well as on a semi-logarithmic scale. These plots present geometric means together with the corresponding 95 % confidence limits. Additionally, individual plasma concentration vs time profiles were to be presented for all patients and for each patient separately. These plots were also presented on a linear as well as on a semi-logarithmic scale.

All calculations were presented firstly for the total study population and then for subgroups corresponding to the different types of vWD separately

Individual plasma concentrations of FVIII:C, vWF RCoF and vWF:Ag, determined during phase II of the study, were also to be listed and described by arithmetic and geometric mean, arithmetic and geometric standard deviation, coefficient of variation, geometric coefficient of variation, median, extremes and quartiles. Two-sided 95 % confidence intervals were to be calculated for the geometric means of the concentrations. Individual plasma concentration versus time profiles were to be presented for all patients and for each patient separately.

Individual data on bleeding time and multimer results were to be listed and described by arithmetic mean and standard deviation, median, extremes and quartiles. Changes in BT after study drug administration were to be analysed by determination of differences to baseline. The correction of bleeding time compared with the individual plasma concentrations of FVIII/vWF complex after WILATE injection was to be presented also graphically. Due to multimer analysis the multimer decomposition in large, intermediate and small multimers was graphically presented in bar charts and results of patient's plasma was compared with normal plasma at all time points

For analysis of efficacy, in a separate Statistical Analysis Plan, it is stated that frequency tables on the efficacy ratings of treatments in bleeding episodes and surgeries would be provided as well as summary statistics on the amount of WILATE used in tables and summary listings

#### Safety analysis of Adverse Events

AEs were to be recorded with intensity, duration, frequency and time of occurrence. The number of patients complaining of AEs were to be displayed by decreasing frequency sorting of their occurrence, grouped by body system according to the recommendations of the WHO.

#### Viral seroconversions

Only patients with negative baseline values were to be used for evaluation of seroconversions. A frequency table was planned to be produced in case of seroconversions

#### Laboratory results and vital signs

Changes in laboratory parameters and vital signs were to be analysed by determination of differences detected after WILATE treatment compared to baseline. They were to be tabulated using shift tables and plotted in scatter graphs.

#### Determination of Sample Size

For vWD no specific guideline exists but the proposed number of 12 patients is proposed to be sufficient for this type of disease.

#### Changes in the Conduct of the Study or Planned Analyses

In protocol amendment I (November 15, 1999) some major changes were made. First, the method for the assessment of BT and therefore the time points for the determination of BT were changed. Instead of using the (b)(4) technique it was decided to use the (b)(4) because it does not cause any scars and it's use is nearly painless. Therefore, BT could be measured more frequently than originally planned. It was originally planned to assess the BT 2 times during the PK phase. Due to the change of the method it was acceptable to measure more frequently. A maximum of 6 BT tests could take place (no further tests were necessary when the patient's baseline result was reached, again).

Secondly, patients could be treated at home. This change was made due to the fact that patients who lived far away from the study site could not travel in case of acute bleeding episodes. For immediate treatment study drug had to be available at home.

Furthermore, one sample time point (haematology, 1 hour after WILATE injection) was considered as unnecessary and was therefore deleted.

Other minor changes were also part of protocol amendment I. Patients who participated in the PK phase of the study (phase I) and were treated in phase II again, had to keep the same patient number throughout the whole study period. Originally it was planned to allocate a different patient number to an individual patient who participated in phase II.

Furthermore, the confirmation for a patient's resistance to DDAVP treatment was only required for patients with vWD type 1 and type 2a.

In addition, the characteristics of WILATE were amended. The vWF:Ag/FVIII:C ratio of the product was to be ~1.0 (instead of ~0.9) and the vWF:RCoF/FVIII:C ratio of the product was to be also ~1.0 (instead of ~0.8).

(b)(4)

Protocol amendment II (November 24, 1999), valid for Poland, presented the same items as listed in protocol amendment I, valid for Bulgaria. Additionally, blood sampling time points were amended. Due to administrative reasons blood samples taken 15 minutes, 45 minutes and 72 hours after the first injection were optional for the study centre.

## STUDY SUBJECTS

### Disposition of Subjects

In total, 13 patients were enrolled into the PK phase (phase I) of the study. The first WILATE injection was on December 14, 1999.

Patient nos. 1 to 8 (n=8) were enrolled at the National Centre of Haematology & Transfusiology in Sofia, Bulgaria. All 8 patients completed phase I of the study and were enrolled into phase II. Patient nos. 11 to 16 (n=6) were enrolled at the Institute of Haematology & Blood Transfusion in Warsaw, Poland, for PK assessments. In 5 patients PK assessments were performed, 4 of them were treated for bleeding episodes in phase II of the trial and in 1 of them a surgical procedure was documented. Furthermore, 1 additional patient was enrolled for a surgical procedure only.

Disposition of patients

Pat ID	vWD type	Participation			Study site
		PK	E	S	
(b)(6)	3	+	+		Bulgaria
	3	+	+		Bulgaria
	3	+	+		Bulgaria
	2A	+	+		Bulgaria
	2A	+	+		Bulgaria
	2A	+	+		Bulgaria
	1	+	+		Bulgaria
	1	+	+		Bulgaria

(b)(6)	3	+			Poland
	3	+	+		Poland
	3	+	+		Poland
	3	+		+	Poland
	3	+	+		Poland
	3	+	+		Poland

PK = phase I; E = bleeding episode; S = surgery

#### Protocol Deviations

PK investigations were performed in patient no. (b)(6) who experienced an acute bleeding episode 10 days before WILATE injection. This bleeding episode was treated with another FVIII concentrate 8 days before the PK assessments. However, this was not considered to have an impact on the PK parameters of this patient.

Deviations in the actual blood sampling time points exceeding the allowed range are shown in the following table. These deviations had no impact on the study results as the actual time points were taken for PK calculations.

Deviations from blood sampling schedule, phase I

Patient no.	Time point (h)	Scheduled time after injection	Actual time after injection
(b)(6)	1	09:49 – 09:51	09:52
	0.25	09:06 – 09:10	09:07
	1	09:53 – 09:55	09:52
	0.25	09:16 – 09:18	09:20
	0.75	09:46 – 09:48	09:49

#### EFFICACY EVALUATION

PK Evaluation See reviews by Drs. I. Mahmood and T. Silverman.

##### Bleeding time

In 12 out of 14 patients, a BT of >24 minutes was recorded at baseline.

- For Patient (b)(6) (VWD type 1) a BT of 8 minutes was recorded at baseline and for Patient (b)(6) (VWD type 2) it was 6 minutes. These 2 cases were considered as "normal" and no further measurements were done.
- For 5 patients (nos. (b)(6), (b)(6), (b)(6), (b)(6), (b)(6)), all of VWD type 3, no change in BT was observed. This includes 2 patients (nos. (b)(6), (b)(6)) who had (b)(4) and in whom BT was measured after 75 min (Pat. no. (b)(6)) and 100 min (Pat. no. (b)(6)) respectively. The non-response in BT in patient no. (b)(6) was explained in the study report by her lower dose (43.5 IU/kg BW). In addition,  $t_{max}$  for VWF:RCof was 45 min (15 min after BT testing) and a level of > 0.5 IU/ml for VWF:RCof was only obtained from 45 to 60 min after infusion. For the remaining 3 patients no obvious explanation exists. It was suggested that the time point for measuring BT was too early after WILATE administration, but no further measurements were made after 30 min when no change was observed.

##### Multimers

During the PK phase and the treatment phase, the multimeric pattern was evaluated from samples taken before and 1 hour post infusion. The multimeric structure of patient's plasma was always compared with normal plasma (NP). The study report shows the multimeric pattern of 8 patients before and 1 hour after treatment with WILATE. For the remaining patients nos. 11 to 16 a visual presentation could not be done because pre- and post-infusion samples were analysed not in parallel but at separate runs. After WILATE injection multimers were usually present, with a relatively low portion of the largest HMW multimers, however, this is in accordance with the characteristics of the product.

- Patient (b)(6) with VWD type 3 and baseline FVIII C of 36% showed all multimers present at baseline with a relatively low portion of the largest multimers. No triplet structure was detectable.
- Patient (b)(6) (VWD type 3), whose multimeric pattern was documented (b)(4) all multimers were present at baseline but with a relatively low portion of the largest multimers.
- Patients of VWD type 2 (patient nos. (b)(6), (b)(6)) had multimers visible before injection, but the large multimers were absent. The intermediate multimers were also absent for patient no. (b)(6) at baseline.

After WILATE administration the percentage of HMW multimers increased with a relatively low portion of the largest multimers

#### Treatment of Bleeding Episodes

Using the analysis methodology as in TMAE-104, the results in Wilate treatment of bleeding episodes can be shown as follows for TMAE-105.

TMAE-105 BE Categories by Site				
	Site of bleeding	#Episodes	#Successfully treated Episodes	% Success
(b)(6)	Joints	16	13	81
	GI bleeding	6	1	17
	Other*	60	59	98
	Total	82	73	89

\*The database has classified non-joint or GI bleedings as "other"

Results of Treatment in TMAE-105 BE by VWD Type				
VWD Type	1	2	3	Total
N (# subjects)	2	3	7	12
#Episodes	2	8	72	82
Successfully treated Episodes	2	2	69	73
% Success	100	25	96	89

Because of the more limited sizes of the cells in analyzing dosage used in the treatment of bleeding episodes, analysis will be made with pooled data from all four VWD studies.

(b)(4)

#### **SAFETY EVALUATION**

##### Extent of Exposure

The following tables provide an overview on the extent of exposure in the different phases of the study. In total, 202 exposure days were documented in 14 patients.

##### Extent of exposure in phase I (n=13)

Pat ID	BW	Total dose (IU)	Dose/kg BW (IU)
(b)(6)	75.0	4,000	53.3
	80.0	4,000	50.0
	69.0	3,000	43.5
	63.0	3,000	47.6
	86.0	4,000	45.4
	72.0	4,000	55.6
	51.0	3,000	55.6



	60.0	3,000	50.0
	53.0	2,500	47.2
(b)(6)	104.0	5,000	48.1
	85.0	4,000	47.1
	76.0	4,000	52.6
	70.0	3,500	50.0
		47,000	

#### Extent of exposure in phase II (n=12) (without surgery)

Pat. ID	vWD type	Exposure days	Total dose (IU)	Range (IU/kg BW)
	3	22	43,000	27.8 - 40.0
	3	21	23,000	12.5 - 37.5
	3	7	24,000	43.5 - 58.0
	2A	64	160,000	31.7 - 63.5
	2A	1	3,000	34.1
(b)(6)	2A	1	3,000	41.7
	1	1	2,000	37.0
	1	1	2,000	33.3
	3	17	27,000	8.7 - 24.0
	3	28	36,000	11.8 - 23.5
	3	7	9,500	13.2 - 26.3
	3	7	17,000	33.9 - 35.7
		177	351,500	

#### Extent of exposure in phase II, surgical procedures (n=2)

Pat. No	Dose FVIII/vWF (IU)			Exposure days
	Pre-OP	Post-OP	Total	
	2,000	2,000	4,000	1
(b)(6)	4,000	26,000	30,000	11

#### Brief Summary of Adverse Events

##### No. of AEs in total and sorted by patient and body system

Body system	Adverse event (WHO-coded)	
BODY AS A WHOLE		
	Back pain	Pat. no. (Moderate)
CASTRO-INTESTINAL		(b)(6)
	Melena	Pat. no. (moderate)

In patient (b)(6) who suffered from GI bleeds, melena was observed at 5 occasions during the total study period

- In phase I (PK), it occurred 40 hours after product administration, lasting for 4 days and was of moderate intensity. The patient was already hospitalized because of the PK investigations, i.e. 2 days before onset of the event.
- During phase II, mild melaena occurred 10 days after study drug administration, lasting for 2 days. The patient was again hospitalized for 7 days. Two days after discharge from hospital, melaena occurred again with moderate intensity and was resolved 9 days after onset. For this event, the patient was hospitalized for 14 days. The 4th episode of moderate melaena, accompanied by back pain occurred 14 days after study drug administration, requiring hospitalization. A retroperitoneal soft tissue bleeding as a potential cause for the low back pain was said to be excluded by sonography. An X-ray showed signs of spondyloarthritis. The last episode of moderate melaena occurred 86 days after treatment.

In all instances the events were treated with red cell concentrates, and judged as not related to the study drug administration. The study report emphasizes that the patient had been suffering from GI bleeds at 2x/week previously.

#### Analysis of Adverse Events

Because of the low number of events, no further analysis was performed.

#### Deaths, other Serious Adverse Events and other Significant Adverse Events

No deaths occurred during the study. Patient no. 16 was hospitalised because of GI bleeding for 5 times, which is classified as an SAE.

#### Clinical Laboratory Evaluation

Hematology and clinical chemistry parameters were evaluated in both phases of the study. There were no unexpected findings with respect to clinical laboratory values.

#### Viral Safety

For anti-HAV, 7 patients were negative for such antibodies at study entry and 7 were positive.

For anti-parvovirus B19, 7 patients tested negative at baseline and the remaining 7 were positive.

No viral seroconversion was observed during the study period.

### **IV. TMAE-109. Clinical study to investigate efficacy and safety of human Factor VIII/VWF TMAE<sup>(b)(4)</sup> in patients with inherited von Willebrand disease. Phase 2 study**

#### **INVESTIGATORS**

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Prof. T. Lissitchkov, MD, Ph.D. of National Centre of Haematology & Transfusiology, Sofia, Bulgaria

#### **STUDY OBJECTIVE(S)**

Primary. To assess the efficacy of WILATE using surrogate markers, using plasma levels for FVIII:C, vWF:Ag, and vWF RCoF.

Secondary. To measure the correction of BT, and assess WILATE's

- multimeric pattern
- overall efficacy
- clinical safety and tolerability.

#### **INVESTIGATIONAL PLAN**

Overall Design. This follow-up study to TMAE-105 was a prospective, non-randomised, non-controlled, open-labelled, multi-centre, phase 2 trial. The dose to be administered was chosen in accordance with the indication and the clinical situation and calculated individually. The expected range was between 20 and 50 IU/kg BW of WILATE, given as single or multiple doses.

<sup>(b)(4)</sup> Patients usually treated bleeding episodes at home, and were given a sufficient amount of trial medication at study entry. After 3 and 6 months control visits were planned.

**Study Flowchart**

Parameter	Details	Time to injection								
		before	30'	1h	3h	6h	12h	day post	last	Follow-up
Plasma levels	FVIII:C, vWF:Ag, vWF RCoF	x	x	x	x			xx <sup>1</sup>		
Multimers		x	x	x	x					
Bleeding time	To be measured only once during treatment phase	x	x	x	x	x	x	xx <sup>1</sup>		
Efficacy assessment	Investigator (VRS)								x <sup>1</sup>	
Vital signs	HR, BP, RR, temp	x					x	x <sup>1</sup>		
Adverse events		x	x	x	x	x	x	x <sup>1</sup>	x	
Laboratory	Hematology (haemoglobin, haematocrit, platelets, RBC, WBC, bilirubin)	x				x			x	
	Clinical chemistry (ALT, creatinine, serum electrolytes)	x				x			x	
	Viral safety (anti-HAV and Parvovirus B19)*	x								x
Tolerability assessment	Investigator & patient (VRS)								x	

<sup>1</sup> days after treatment

<sup>†</sup> as frequently as necessary

§ just in case of further demonstrations

Plasma levels of FVIII C, vWF Ag and vWF:RCoF were measured at baseline and 30 minutes, 1 and 3 hours after infusion. Further measurements were performed as frequently as necessary

Correction of the bleeding time (BT) was measured once: before treatment (baseline), and 30 minutes, 1, 3, 6, and 12 hours after infusion. Some tests could have been omitted if the values returned to baseline during measurement period. On subsequent days, BT was measured as frequently as necessary.

Multimeric pattern was evaluated from samples taken before and 30 minutes, 1 and 3 hours post infusion.

Overall efficacy assessment by treating physician used verbal rating scale (VRS) after each treatment episode at the last visit as follows:

none	moderate	good	excellent
severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeds)	moderate bleeding or control of bleeding; required additional product	slight oozing and adequate control of bleeding; did not require additional product	haemostasis achieved, bleeding cessation

Clinical tolerability was assessed by monitoring vital signs, hematological (hemoglobin, bilirubin, full blood cell count, hematocrit), and chemistry (ALAT, creatinine, electrolytes) parameters and by monitoring AEs. Overall assessment of tolerability by the treating physician and the patient also uses a VRS (unsatisfactory - satisfactory - good - very good).

Viral safety was investigated in patients negative for viral markers at study entry by measuring anti-HAV (4 to 8 weeks after the last administration), and anti-Parvovirus B19 (7 to 14 days after the last administration of WILATE).

**Comment** This study was initiated as a follow-up study to obtain more data on the plasma level characteristics of the investigational product. For the vWF indication no specific guideline existed; the design of this study follows as close as possible to the requirements set up in the CPMP Guideline for plasma derived Factor VIII:C and Factor IX C products.

#### STUDY POPULATION

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"><li>• Defined inherited vWD types 1, 2 and 3</li><li>• Age <math>\geq 12</math> and <math>\leq 65</math> years</li><li>• Anti HIV-1/2 negative</li><li>• Known to the study centre</li><li>• Patients resistant to DDAVP treatment</li><li>• Freely given written informed consent</li></ul>	<ul style="list-style-type: none"><li>• Present or past inhibitor activity.</li><li>• Administration of other p-d or blood product 72 hours before treatment</li><li>• Administration of DDAVP 15 days before treatment.</li><li>• Administration of acetylsalicylic acid 7 days before treatment</li><li>• History of intolerance to p-d or blood products</li><li>• Symptomatic infection.</li></ul>

#### TREATMENTS

The number of infusions and actual dose in spontaneous bleedings or for surgical procedures depended on the clinical situation of the patient, e.g. the severity of the bleeding, and the type of surgery. Single or multiple administrations could be given. The following dose regimens were provided as a guidance only

(b)(4)

For spontaneous or post-traumatic bleeding, about 20-50 IU FVIII C/kg BW were to be given once daily or every other day

The preparation, supplied as powder, was dissolved in its solvent using a double-ended needle. The reconstitution time should have been  $\leq 10$  minutes at room temperature. Prior to injection, the solution was warmed up to room or body temperature, and used immediately after dissolution. Unused solution was discarded. Usually, the solution is clear or slightly opalescent, solutions which were cloudy or had deposits were discarded. Doses of WILATE were given as IV injections at a speed of 2-3 ml/min or as

continuous infusion (b)(4)  
flushed with 0.9 % sodium chloride

At the end of administration, the injection line had to be

#### CONCOMITANT THERAPY

- During treatment with WILATE concomitant administration of therapies not interfering with the primary objectives of the study was permitted. Administration of DDAVP was to be avoided during study, but if DDAVP was required in emergency situations, the patients with DDAVP treatment required in emergency situations were to be excluded from efficacy analysis.
- No FVIII/vWF preparations other than WILATE should be given (except in emergency situations), and administration of other blood products should be avoided, if possible.
- The reconstituted WILATE product should not be mixed with other drugs.

Because of home treatment, the patients recorded self-injections including the date, dose, batch and reason for injection on the respective form of the CRF or in a patient diary. For treatment of a bleeding episode the patient documented the site and severity of bleeding and subjective impression of efficacy. Investigators explained to patients the use of the treatment forms or diaries, emphasizing the need of carefully recording any substitutions and bleeding episodes.

There were 2 control visits in any case: 3 and 6 months after study entry. For each visit at the centre, patients were to bring all their forms to the centre.

#### EFFICACY AND SAFETY MEASUREMENTS

##### Efficacy measurements

- Plasma levels. Plasma levels of FVIII C, vWF Ag, and vWF:RCoF were to be determined at baseline and 30 minutes, 1 and 3 hours after treatment. Further assessments were to be made as frequently as necessary.
- Bleeding Time. The correction of BT was to be measured once during the treatment phase of the study, using the (b)(4). BT was measured before treatment (baseline), and 30 minutes, 1, 3, 6, and 12 hours after infusion. Some of the tests were omitted if values had been normalized within the measurement period.
- Multimers. The multimeric pattern was evaluated from samples taken before and 30 minutes, 1 and 3 hours post infusion to show the presence of high molecular weight (HMW) vWF multimers.
- Assessment of spontaneous bleeding episodes. All spontaneous bleeding episodes were documented by indicating the site of bleeding, the severity and the actual treatment dose.

(b)(4)

- Assessment of overall response. Response to treatment was assessed on a VRS, i.e. as "none", "moderate", "good", or "excellent". This assessment was done by the treating physician.

##### Safety measurements

Viral Safety. Anti-HAV and anti-Parvovirus B19 were measured at baseline prior to the first injection of product. If a result at study entry is confirmed positive, no further measurements during the study period were performed for the subject. From subjects tested negative or borderline at study entry with respect to antibodies to parvovirus B19 (IgG, IgM) or HAV (IgG, IgM), or in case baseline values were not known at this stage, additional heparin plasma samples were to be taken 7 to 14 days (anti-parvovirus B 19) and/or 4 to 8 weeks (anti-HAV) after the first administration of WILATE. All samples were kept frozen at -70 °C and, if applicable, were (re-)tested in case of a change in these viral markers during study.

Tolerability and other safety aspects. During the whole study period, AEs were documented on CRF. In addition:

- Immediate tolerability was assessed with vital signs: heart rate, body temperature, blood pressure and respiratory rate, prior to, 15 min and 1 hour after injection of WILATE.
- Patients and investigators assessed the overall tolerability on a 4-point VRS (unsatisfactory - satisfactory - good - very good)
- Hematological and clinical chemistry parameters were tested at the local laboratory.

#### STATISTICAL AND ANALYTICAL PLAN

Descriptive statistical procedures were applied to data analysis. Individual plasma concentrations of FVIII:C, vWF Ag and vWF RCoF were listed and described by arithmetic and geometric mean, arithmetic

and geometric standard deviation, coefficient of variation, geometric coefficient of variation, median, extremes and quantiles. Two-sided 95 % confidence intervals were calculated for the geometric means of the concentrations. Individual plasma concentration-vs-time profiles were presented for all patients and for each patient separately

The primary efficacy variables were plasma levels of FVIII:C, vWF:Ag and vWF:RCof prior to and in response to the treatment with WILATF were chosen.

For multimer analysis, the multimer decomposition in large, intermediate and small multimers was graphically presented in bar charts, and patient's plasma was compared with normal plasma at all time points.

Similar to TMAE-105, for analysis of efficacy it is stated in a separate Statistical Analysis Plan that frequency tables on the efficacy ratings of treatments in bleeding episodes (b)(4) would be provided, as well as summary statistics on the amount of WILATE used in tables and summary listings.

AEs were recorded with intensity, duration, frequency and time of occurrence. The number of patients complaining of AEs were to be displayed by decreasing frequency sorting of their occurrence. Only patients with negative baseline values were to be used for evaluation of viral seroconversions.

As there were no specific guidelines at the time of this study, the proposed number of >10 treatments was regarded as sufficient to for this type of follow-up study.

## STUDY SUBJECTS

All 16 patients enrolled completed the study

Pat. ID	vWD type	Study site	Pat. ID	vWD type	Study site	Pat. ID	vWD type	Study site
	3	Warsaw		2A	Sofia		1	Sofia
	3	Warsaw		3	Sofia		1	Sofia
(b)(6)	3	Warsaw	(b)(6)	3	Sofia	(b)(6)	1	Sofia
	3	Warsaw		2A	Sofia		1	Sofia
	3	Warsaw		3	Sofia		1	Sofia
							1	Sofia

## DATA SETS ANALYSED

All data from the 16 study patients were available for efficacy evaluation, with:

- 263 exposure days for 117 acute haemorrhages (in 16 patients),
- 51 (b)(4) (in 5 patients), and
- 2 (b)(4) (in 2 patients)

## DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

There were 11 patients from the previous study TMAE-105, and 5 more patients were included in TMAE-109, making 16.

Parameter	Mean $\pm$ s.d.	Median (Range)
Age (years)	37.06 $\pm$ 15.65	34.50 (14.00 – 63.00)
Height (cm)	170.75 $\pm$ 8.74	171.00 (159.00 – 183.00)
Weight (kg)	71.88 $\pm$ 12.86	70.00 (55.00 – 104.00)

- Sex: 10 patients were male, 6 patients were female.
- Blood groups: 8 patients had blood group O, 3 group A, 4 group B, and 1 group AB.
- Previous exposure days to FVIII/vWF containing products: median 150 days (range 0 – 1,000).
- VWD types: 6 of type 1, 2 of type 2A and 8 of type 3.
- General physical condition at study entry: considered to be "good" for all patients

Pat. ID	Age/sex	BC	Bleeding frequency	Exposure days	vWD type
	24m	B	3 / month	1,000	3
	47m	O	20 / year	500	3
(b)(6)	41m	O	2 / month	500	3
	23m	B	4 / month	800	3

	45m	O	2 / month	600	3
	62f	O	2 / month	700	2A
	19m	A	10 / year	120	3
	28f	A	5 / month	260	3
	54f	O	1 / month	170	2A
(b)(6)	24m	A	5 / month	180	3
	14f	O	3 / year	30	1
	32f	B	1 / month	2	1
	26m	O	1 / month	0	1
	54f	O	1 / month	1	1
	63m	AB	4 / year	15	1
	37m	B	2 / year	15	1

Baseline plasma concentrations, BT and multimeric pattern:

Pat ID	VWD type	BT (min)	FVIII:C (%)	vWF:Ag (IU/ml)	vWF:RCof (IU/ml)	Multimeric pattern
(b)(6)	3	>30.0	1.10	< 0.05	< 0.01	none visible
	3	>30.0	1.50	< 0.05	0.01	none visible
	3	>30.0	1.00	< 0.05	< 0.01	none visible
	3	>30.0	2.00	< 0.05	< 0.01	none visible
	3	>30.0	3.30	< 0.05	< 0.01	none visible
	2A	>26.0*	149.50	1.09	0.65	HMW missing, relative loss of others, TS aberrant
	3	>30.0*	2.80	< 0.05	0.03	none visible, only faint band 1 multimer 5
	3	>26.5*	2.00	< 0.05	< 0.01	none visible
	2A	6.0*	38.40	0.31	0.14	HMW missing, relative loss of others, TS aberrant
	3	>24.5*	16.40	0.06	0.07	only faint bands HMW visible
	1	8.0*	23.20	0.13	0.07	all present, TS aberrant
	1	>26.5*	30.70	0.19	0.07	all present but relative loss of HMW, TS aberrant
	1	3.5	65.30	0.44	0.43	"almost" normal, weak bands of LMW and IMW
	1	4.5	126.30	0.98	0.65	"almost" normal, weak bands of LMW and IMW
	1	4.0	129.8	1.10	1.42	"almost" normal, weak bands of LMW and IMW
	1	4.5	57.4	1.08	0.95	"almost" normal, weak bands of LMW and IMW

IMW (HMW, LMW) = high (intermediate, low) molecular weight; TS = triplet structure; \*data from TMAE-105 study

As discussed above, 11 patients had been in study TMAE-105. In 4 patients, a different FVIII/vWF preparation had been administered during the last 6 months before study start. All had resistance to DDAVP treatment.

Six patients used blood-derived concomitant medication during study:

- (b)(6) human factor VIII
- concentrated RBC, cryoprecipitate, and another FVIII/vWF preparation (Immunate)
- (b)(6) cryoprecipitate at several occasions
- (b)(6) concentrated RBC.

## EFFICACY EVALUATION

### Plasma Level Data

The following Table is a summary of the plasma concentrations of FVIII:C, VWF:AG and VWF:RCoF.

#### GEOMETRIC MEAN VALUES (SD) OF FVIII:C, VWF:AG AND VWF:RCoF

Time (h)	FVIII:C (%)	VWF:Ag (IU/mL)	VWF:RCoF (IU/mL)
All patients n = 15			
Baseline	12.16 (6.41)	- (-)	- (-)
0.50	60.22 (1.79)	0.72 (2.21)	0.60 (1.93)
1.00	76.37 (1.77)	0.69 (2.23)	0.58 (1.94)
3.00	72.28 (1.78)	0.55 (2.44)	0.46 (2.20)
Day 1 (N=11)	69.26 (1.64)	0.41 (2.70)	0.26 (3.27)
VWD type 1, n=6			
Baseline	58.66 (2.00)	0.49 (2.60)	0.35 (3.70)
0.50	113.98 (1.35)	1.23 (1.61)	0.95 (1.93)
1.00	106.22 (1.31)	1.19 (1.60)	0.95 (1.73)
3.00	90.84 (1.36)	0.99 (1.73)	0.74 (1.92)
Day 1	75.02 (1.69)	0.63 (2.19)	0.47 (2.85)

VWD type 2A, n=2			
Baseline	15.77 (2.61)	0.58 (2.43)	0.30 (2.96)
0.50	142.90 (1.74)	0.59 (1.66)	0.65 (1.00)
1.00	143.87 (1.81)	0.59 (1.72)	0.79 (1.33)
3.00	133.56 (2.05)	0.56 (1.77)	0.65 (1.78)
Day 1	87.81 (2.13)	0.74 (2.29)	0.30 (2.96)
VWD type 3, n=8			
Baseline	2.37 (2.42)	- (-)	- (-)
0.50	53.35 (1.51)	0.41 (1.91)	0.41 (1.69)
1.00	50.90 (1.55)	0.38 (1.86)	0.37 (1.65)
3.00	49.02 (1.57)	0.29 (1.92)	0.30 (2.08)
Day 1 (N=3)	1.18 (1.80)	0.12 (1.05)	0.07 (1.00)

The most homogenous group is shown in the VWD type 3 patients, who have extremely low or unmeasurable vWF. The results for vWD types 1 and 2 are biased by endogenous VWF of the patients, and the results for these types of patients are more variable.

#### Bleeding Time

Bleeding time was measured in 9 patients. Some patients participated in TMAE-105, and the Investigators were allowed to decide whether the assessment should be repeated, or whether the results from the previous study should be transferred to the study at hand. The results presented are based on the whole study population (n=16).

- For 6 patients (5 type 1 patients, 1 type 2A patient) a normal BT was measured at baseline (<8 minutes). No further measurements have been performed in these patients.
- In 10 patients, baseline BT of >24 min was recorded. For 5 patients no change in BT was observed.

#### Mullimers

The multimeric structure of patient's plasma was compared with normal plasma (NP). After study product injection, multimers were usually present, with a relatively low portion of the largest HMW multimers. This is in accordance with the characteristics of the product. However, for patients (b)(6) it was shown that all multimers of normal plasma are present with an almost normal distribution of all multimers. The triplet structure was also normal.

#### Treatment of Bleeding Episodes

Using the analysis methodology as in TMAE-104, the results in Wifale treatment of bleeding episodes can be shown as follows for TMAE-109.

TMAE-109 BE Categories by Site				
(b)(6)	Site of bleeding	#Episodes	#Successfully treated Episodes	% Success
	Joints	45	42	93
	GI bleeding	18	4	22
	Other*	73	69	95
	Total	136	115	85

\* The database has classified non-joint or GI bleedings as "other".

Results of Treatment in TMAE-109 BE by VWD Type				
VWD Type	1	2	3	Total
N (# subjects)	6	2	8	16
#Episodes	12	10	114	136
Successfully treated Episodes	12	1	102	115
% Success	100	10	90	85

Because of the more limited sizes of the cells in analyzing dosage used in the treatment of bleeding episodes, analysis will be made with pooled data from all four VWD studies.

(b)(4)

(b)(4)

## SAFETY EVALUATION

### Extent of Exposure

The following Table provides an overview on the extent of product exposure during the study. In total, 343 exposure days were documented in 16 patients

Pat. ID	BW	Reason for treatment*	Total dose (IU)	Exposure Days	Average Dose/Exposure Day/kg BW (IU)
(b)(4)	70	B, P	79,000	27	41.8
	66	B, P, S	71,000	36	29.9
	76	B, P	34,000	20	22.4
	85	B, P	62,000	46	15.9
	104	B, S	125,000	67	17.9
	58	B, P	255,500	93	47.4
	76	B, P	22,000	16	18.1
	69	B, P	9,000	4	32.6
	88	B, P	2,000	1	22.7
	80	B, P	22,500	21	13.4
	55	B	4,000	2	36.4
	61	B	5,000	2	41.0
	57	B	4,000	2	35.1
	65	B	4,000	2	30.8
	70	B	4,000	2	28.6
	70	B	4,000	2	28.6

\* B = bleeding episodes, P = prophylaxis, S = surgery

### Brief Summary of Adverse Events

In total, 5 patients reported 25 AEs, none of which were considered related to study drug.

Body System	AE (Coded)	Frequency	Patient No./ Intensity
GASTRO-INTESTINAL SYSTEM	Hemorrhagic Gastritis	1	/ moderate
	GI Hemorrhage	9	/ moderate – severe (b)(4) / moderate
	Measles	8	/ mild - moderate - severe
PLATELET, BLEEDING, CLOTTING	Epistaxis	2	(b)(4) / moderate (b)(4) / moderate
RED BLOOD CELL	Anaemia	2	/ moderate – severe (b)(4) / moderate
RESPIRATORY SYSTEM	Pharyngitis	1	/ mild
URINARY SYSTEM	Renal Calculus	1	/ mild
	Renal Pain	1	/ mild

No deaths occurred during the study. SAEs reported because of patients' hospitalizations are detailed below. None of the SAEs were assessed as related to study treatment, but to underlying disease. All patients who were hospitalized recovered and were discharged before the study was completed.

- Patient no. 80 reported 3 GI bleedings in the study. From the patient's history frequent GI bleedings are known. The patient had from vWD type 3 and angiodysplasia of duodenum. Two events were assessed as "severe", one event as "moderate". All GI bleedings required hospitalization. In parallel with the second GI bleeding, an anaemia was detected (starting with "moderate" intensity, continued as "severe" and did not disappear until study was completed). The patient also reported "moderate" epistaxis and "mild" pharyngitis during study. From both events the patient recovered. All events were assessed as not related to the WILATE treatment, but – except the pharyngitis – to the underlying



VWD, and were therefore treated with increased doses of WILATE, or alternative VWF-containing products. Immunate was used during the first GI bleeding, as the patient did not have sufficient amount of study drug available when the bleeding started.

- Patient no. 10 also reported 6 GI bleedings during study. From the patient's history frequent GI bleedings are known. The events were all assessed as "moderate". Only the last GI bleedings required hospitalization, the previous ones were treated by the patient at home. All GI bleedings (except the 2nd, which was treated with cryoprecipitate, caused by missing study drug at patient's home) were treated with increased doses of WILATE. In parallel with the start of the 5<sup>th</sup> GI bleeding, a "moderate" anemia was detected. The anemia did not disappear until the study was completed. From this patient a "moderate" hemorrhagic gastritis (confirmed by presence of helicobacter pylori) was reported. The patient recovered from this event. All events were assessed as not related to the WILATE treatment, but – except the hemorrhagic gastritis – to the underlying VWD.
- In patient no. 11 who suffered from GI bleeds, melena was observed at 8 occasions during study. From the patient's history, frequent GI bleedings were known. They were most probably related to angiodysplasia of the small intestine. First, it occurred three days after patient's inclusion into the study, before any study drug has been given. The event recurred in nearly monthly intervals. Hospitalization was required in all cases, even if the intensity was assessed as "mild" in three cases. The melena was 1 time assessed as "sever", 4 times assessed as "moderate", and 3 times assessed as "mild", while the patient always recovered after increased doses of WILATE. All these events were judged as not being related to the study drug.
- Patient no. 12 suffered from epistaxis during the study. The patient was hospitalized for 10 days, and received WILATE and RBC concentrates. The event started while the patient was asleep. There was no trauma or other predisposing reason. The event was assessed as moderate, and not related to the study drug. The patient recovered.
- Patient no. 13 reported renal calculus and renal pain. Both events were assessed as mild. As the patient did not receive WILATE prior to the event, the relationship was assessed as "not related". The patient recovered after 1 week.

#### Clinical Laboratory

There were no unexpected findings with respect to hematology or clinical chemistry values.

Viral safety was documented by determining anti-HAV and anti-parvovirus B19. In case of negative or borderline values at baseline, the tests were repeated in course of the study and after the last injection of WILATE (7 to 14 days after administration for anti-parvovirus B19 and 4 to 8 weeks for anti-HAV).

- Of the total study population (n=16), 6 patients were negative for anti-HAV at study start and remained negative until the follow-up.
- With respect to anti-parvovirus B19, 2 patients were positive at baseline, 1 patient had a borderline result. After the completion of the study, 3 patients were measured as positive. The baseline sample giving borderline result and the follow-up sample of the same patient were checked by the central laboratory, and the previous results were confirmed. The patient was considered to be probably infected by parvovirus B19 shortly before he has been included into the study. It is also noted that the patient received the same study drug batch as other patients who remained anti-virus B19 negative throughout the study period.

No confirmed viral seroconversion was observed during the study period.

### **V. TMAE-106. Pharmacokinetic properties, safety and efficacy of human Factor VIII TMAE- (b)(4) in patients with inherited von Willebrand disease, Phase II study**

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## STUDY OBJECTIVE(S)

**Primary** To assess the efficacy of WILATE using as surrogate markers the PK profile from:

- plasma levels of FVIII:C before and after administration

**Secondary** To assess the incremental recovery from:

- plasma levels of VWF:RCO, VWF:Ag, and VWF:CB;
- correction of bleeding time (BT)
- closure time (CT)
- to assess the multicentric pattern.
- to assess the overall efficacy and tolerability of WILATE.

## INVESTIGATIONAL PLAN

**Overall design** Prospective, non-randomised, uncontrolled, open-labelled, multicentre phase 2 study with two phases, a PK phase (Phase I), and a treatment phase (Phase II). Between 12 to 30 subjects with inherited and classified vWD were to be enrolled for PK assessments (Phase I). For the assessment of efficacy in Phase II, at least 10 treatment episodes were to be documented. Subjects in Phase II were permitted to have participated in the PK program (Phase I), but other subjects requiring therapy could also be enrolled.

Baseline measurements were performed for all study parameters. For PK assessments, a WILATE dose of ~50 IU VWF:RCO/kg BW was to be administered. For the treatment of spontaneous bleeding episodes or (b)(4) the dose was dependant on the clinical situation and to be calculated individually, with the expected range between 20 to 50 IU WILATE/kg BW given as a single or multiple dose

The following flow chart provides an overview of the study related procedures and the time points:

PHARMACOKINETICS (Phase I)		baseline	15'	30'	45'	1h	3h	6h	9h	12h	24h	48h	72h	FU
PK parameters: AUC, t <sub>1/2</sub> , MRT, Vdss, C <sub>1</sub> , C <sub>max</sub> , t <sub>max</sub>	VWF:RCO, VWF:Ag, VWF:CB	x	x	x	x	x	x	x	x	x	x	x	x	
Incremental recovery from peak levels	VWF:RCO, FVIII:C, VWF:Ag	x	x	x	x	x	x	x	x	x	x			
Multimers		x				x								
Bleeding time	(b)(4)	x		x		x	x	x		x				
Closure time	PFA-100	x		x		x	x	x		x				
Vital signs	HR, BP, RR, temp	x	x			x								
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	
Laboratory	RBC, WBC, PC, haemoglobin, HCT, bilirubin	x								x				
	Creatinine, electrolytes, sodium, calcium, chloride, isoagglutinins	x								x				
	Viral safety (anti-parvovirus B19, anti-HAV)	x												x
Tolerability assessment	Investigator & subject (VRS)												x	

TREATMENT (PHASE II)		before	d0	d1	d2	d3	d4	d5	...	last	follow-up
Plasma levels	FVIII:C, VWF:Ag, VWF:RCO, VWF:CB	x	x	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>	x <sup>1</sup>			
Multimers		x	x <sup>1</sup>								
Bleeding time	(b)(4)	x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>			
Closure time	PFA-100	x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>			
Efficacy assessment	Investigator (VRS)									x	
Vital signs	HR, BP, RR, temp	x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>			

Adverse events		x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>		x	
Laboratory	RBC, WBC, PC, haemoglobin, HCT, bilirubin	x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>			
	Creatinine, electrolytes (sodium, calcium, chloride)	x	x	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>	x <sup>2</sup>			
	Isoagglutinins	x	x								
	Viral safety (anti-parvovirus B19, anti-HAV)	x <sup>1</sup>									x
Tolerability assessment	Investigator & subject (VRS)									x	

d = day, x1 = as frequently as necessary, x2 = if additional doses given, x3 = 1 hour post infusion, x4 = if no PK baseline result is available

## SELECTION OF STUDY POPULATION

### Inclusion Criteria

- Defined, inherited vWD, types 1 to 3
- Age > 12 and < 65 years
- Immunocompetent subjects (if HIV positive: CD4 always previously >400/l L).
- Known to the study centre
- Subjects not responding sufficiently to DDAVP treatment, confirmed by a test, if appropriate
- Freely given written informed consent.

### Exclusion Criteria

- Present or past inhibitor activity
- Administration of other plasma derived or blood products or DDAVP 15 days prior to study entry
- Administration of acetylsalicylic acid within 7 days prior to study entry
- Known history of intolerance to plasma derived or blood products.
- Symptomatic infection
- Severe liver or kidney disease (ALAT x 5 > normal value, creatinine > 120 µmol/l)
- Participation in another clinical study (ongoing or during the previous four weeks).
- Pregnancy or lactation in women
- For inclusion in the PK phase, an acute bleeding episode within the previous 15 days.

### Treatments

**Phase I:** A dose of ~50 IU VWF:RCO/kg BW of WILATE was to be administered intravenously at a speed of 2-3 ml/min for PK investigations. Since it was not intended that any product be discarded, the amount administered was rounded up or down as shown below:

Subjects Weight	Total dose	Subjects Weight	Total dose
< 50 kg	if only 1000 IU vials available	< 55 kg	if 500 IU and 1000 IU vials available
	2000 IU		
50 – 69 kg	3000 IU	55 – 64 kg	2500 IU
		65 – 74 kg	3000 IU
70 – 89 kg	4000 IU	75 – 84 kg	3500 IU
		85 – 94 kg	4000 IU
> 89 kg	5000 IU	95 – 104 kg	4500 IU
		> 104 kg	5000 IU
			5500 IU

**Phase II:** The number of treatments and dose administered to treat spontaneous bleeding episodes, (b)(4) depend upon the clinical situation of the subject, e.g. the severity of the bleeding episode. (b)(4) Single or multiple doses (bolus injections or continuous infusions) were to be administered as appropriate. Continuous infusion (e.g. for peri-operative treatment) was allowed.

### CONCOMITANT THERAPY

**Prior Treatment:** For subjects who underwent PK and/or recovery investigations, the administration of other plasma derived or blood products within 72 hours before treatment with WILATE was not permitted and DDAVP could not be administered within 15 days before treatment. Treatment with acetylsalicylic acid within 7 days prior to starting treatment with WILATE was not allowed.

**Permitted Concomitant Therapy:** Therapies not interfering with the primary objectives of the study was permitted. Details of any concomitant medication were recorded in the CRF.

Forbidden Concomitant Therapy. DDAVP was to be avoided during study but could be administered in emergency if required. Such subjects were to be excluded from efficacy analysis. The concomitant administration of acetylsalicylic acid (aspirin) was forbidden. No FVIII/VWF preparations other than WILATF were allowed (except in emergency). Administration of other blood products was to be avoided.

Each investigator maintained a drug-dispensing log detailing the dates and quantities of investigational product dispensed to each subject

Assessment of Treatment Compliance. Subjects normally treated themselves at home, and were provided with sufficient trial medication for self-administration. They maintained a treatment record either on the appropriate form of the CRF or in a separate treatment diary. Each time treatment was administered, the subject would document the date, dose, batch and reason for injection, the site and severity of the bleeding and a subjective impression of efficacy and tolerability. The use of the treatment forms or diaries was explained to the subject by the investigator, who emphasized the importance of carefully recording the required information. Each subject who participated in the efficacy and safety analysis of the study was required to visit the investigational centre every 3 months after study entry and at study termination. The subjects were asked to bring all their treatment records to the centre at each visit.

If subjects received treatment at the study centre, the investigator recorded the details directly into the original CRF

## EFFICACY AND SAFETY MEASUREMENTS

### Efficacy Measurements

PK profile. PK-parameters after application of ~50 IU/kg of Wilate were to be computed according to non-compartmental methods, using the computer program (b)(4) AUC,  $t_{1/2}$ , MRT,  $V_{dss}$  and CI (primary parameters), and  $C_{max}$  and  $T_{max}$  (secondary parameters). The computations of dose-related quantities were based on the nominal potency of the factor components contained in the trial medication and, additionally, on the actual potency of the used batches.

Comment Although not specified, it would appear that PK parameters of FVIII and VWF levels were to be computed with the (b)(4) program.

Incremental Recovery. Incremental recovery was calculated from FVIII:C, VWF:RCO, and VWF:Ag levels at baseline and from peak levels in the first 24 hr-post-infusion samples with the formula: recovery =  $(C_{max} - C_0) \times BW / \text{dose}$ . For the calculation of recovery, the declared potency of the drug was to be the reference.

Bleeding time. The correction of BT was to be measured using the (b)(4). During the PK phase, BT was to be measured at baseline, and 0.5, 1, 3, 6 and 12 hrs after injection (or until BT had returned to baseline). During the treatment phase, in subjects undergoing surgery, the BT was to be measured once daily for as long as the subject continued to receive WILATE.

Closure time. During the PK phase the CT was to be measured at baseline, and 0.5, 1, 3, 6 and 12 hrs after injection using the (b)(4). During the treatment phase, in subjects undergoing surgery, the CT was recommended to be measured once daily for as long as the subject continued to receive WILATE.

Multimers. The multimeric pattern of VWF was to be evaluated from samples taken before and 1 hour post infusion

Clinical Efficacy. Assessment of clinical response was to be made by the treating physician using a verbal rating scale (VRS) (none-moderate-good-excellent) after each treatment episode using the following definitions.

- none: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeding episodes);
- moderate: moderate bleeding, or control of bleeding required additional product;
- good: slight oozing and adequate control of bleeding episode; did not require additional product;
- excellent: haemostasis achieved, cessation of bleeding episode

**Plasma levels.** During Phase II of the study, plasma levels of FVIII:C, VWF:Ag and VWF:RCO were to be measured as frequently as necessary

The primary efficacy variables were the plasma levels of FVIII:C, VWF:RCO, VWF:Ag and VWF:CB, prior to and in response to treatment with WILATE. The assays for FVIII:C, VWF:Ag, VWF:RCO and VWF:CB<sup>2</sup> were performed by a central lab.

#### Safety Measurements

**Tolerability and Adverse Events.** During both phases of the study, immediate tolerability was assessed by monitoring vital signs, hematological (hemoglobin, bilirubin, full blood cell count, hematocrit) and other laboratory parameters (creatinine, electrolytes, isoagglutinins), as well as by monitoring the nature and frequency of AEs. An overall assessment of tolerability was to be performed by both the treating physician and the subject using a VRS (unsatisfactory - satisfactory - good - very good).

**Viral Safety.** Antibodies against hepatitis A virus (HAV) and parvovirus B19 were measured at baseline, before the first injection of WILATE. If confirmed positive at study entry, it was not necessary to repeat testing during study. However, pre-treatment samples were to be taken from each subject and stored at <-70°C for future testing. If the test were negative or borderline at study entry with respect to IgG or IgM antibodies, or if baseline values were not yet known, additional heparin plasma samples were to be taken 7 days (for parvovirus B19) or 14 days and/or 4 to 8 weeks (for HAV) after the last administration of WILATE.

#### STATISTICAL AND ANALYTICAL PLANS

Descriptive statistical methods were used to analyze the data. PK, efficacy, and safety analyses were based on all subjects treated (intention-to-treat approach). Per-protocol analysis was also to be performed. The statistical evaluation was performed by using the SAS® software package version 9.1

**Sample Size.** At the time that the protocol for this study was designed, there was no specific guideline available for studies with VWF products. The sample size was based on the CPMP Guidance on the Clinical Investigation of Plasma Derived Factor VIII and IX Products (CPMP/BPWG/198/95) which recommends that half-life and recovery of FVIII concentrates are measured in at least 12 subjects. CPMP subsequently published the Guideline on the Clinical Investigation of Human Plasma Derived von Willebrand Factor Products (CPMP/BPWG/220/02), which recommends that a PK trial should be performed in at least 12 subjects suffering from severe VWD (defined as baseline VWF:RCO <15-20%) and that at least 6 out of the 12 subjects should be suffering from hereditary type 3 VWD for separate analysis.

For analysis of efficacy in a separate Statistical Analysis Plan, it is stated that frequency tables on the efficacy ratings of treatments in bleeding episodes (b)(4) would be provided, as well as summary statistics on the amount of WILATE used in tables and summary listings. In addition, different bleeding sites on the same date would be counted as different bleeding episodes. The submitted Statistical Analysis Plan is dated 12/1/06

#### Amendments to Protocol

Three amendments were made to the final protocol dated 11/15/99.

Amendment #/Date	Subject
Amendment I February 15, 2000	<ul style="list-style-type: none"> <li>Addition of a study site in Leipzig</li> <li>Clarification of laboratory instructions for preparation of plasma and serum samples</li> <li>Revision to subject information and informed consent documentation</li> </ul>
Amendment II September 27, 2000	<ul style="list-style-type: none"> <li>Addition of 0.1% polysorbate 80 to the diluent used to reconstitute WILATE</li> <li>Deletion of the study centre in Leipzig</li> </ul>
Amendment III July 09, 2003	<ul style="list-style-type: none"> <li>Amendment of the number of subjects for inclusion into the PK phase from 12 to between 12 and 30</li> </ul>

<sup>2</sup> FVIII:C was measured by both the chromogenic substrate method using a kit from (b)(4) and the (b)(4) assay using a kit from (b)(4). VWF:Ag was determined with an (b)(4) system using the (b)(4) expressed in IU VWF:Ag/mL. One IU VWF:Ag/mL corresponds to a VWF concentration of 10 µg/mL VWF. Laboratory (b)(4) (b)(4) VWF:RCO activity was determined by (b)(4) and expressed in IU VWF:RCO/mL. VWF:CB was assessed using an (b)(4) system (b)(4) expressed in IU VWF:CB/mL.

Amendment #/Date	Subject
	<ul style="list-style-type: none"> <li>Clarification of duration of study</li> <li>Increase in the number of study centres</li> <li>Change in the minimum age specified in the inclusion criteria from 18 years to 12 years</li> <li>Change to the inclusion criterion to state that subjects should be showing insufficient response to DDAVP (rather than not responding to DDAVP)</li> <li>Procedures for safety reporting were modified</li> <li>The number of the insurance policy for the study was changed</li> </ul>

## STUDY SUBJECTS

### Disposition of Subjects

A total of 14 subjects were enrolled into the study in 8 investigational sites in Germany.

Study Part	Subjects in study part	Subjects Evaluable
Pharmacokinetics	10	7
Treatment of bleeding episodes	6	5
Surgery	8	8

### Participants in each Study Part and Status of Participation

Centre	Subject	PK	Efficacy	Surgery	Safety
1		X	X		X
1		X	X	X	X
1		X	X <sup>†</sup>		X
1		X <sup>†</sup>			X
2				X	X
2				X	X
3		X <sup>†</sup>		X	X
3	(b)(6)	X <sup>†</sup>			X
4		X	X		X
4		X	X	X	X
5		X		X	X
6				X	X
11		X	X		X
15				X	X
<b>Totals</b>		<b>10</b>	<b>6</b>	<b>8</b>	<b>14</b>

<sup>†</sup> Excluded from analysis

- Blood samples taken from Subject (b)(6) from Centre 3 (b)(6) during the PK phase of the study were not frozen.
- Blood samples taken from Subject (b)(6) from Centre 3 (b)(6) during the PK phase of the study were not stored.
- Subject (b)(6) from Centre 1 (b)(6) did not receive WILATE during the efficacy phase of the study and is thus not included in the efficacy evaluation
- Subject (b)(6) from Centre 1 (b)(6) discontinued the PK phase of the study due to an AE

### Protocol Deviations

Two subjects were accepted to be enrolled into the study despite failing to meet eligibility criteria.

- Subject (b)(6) from Centre 2 (b)(6) was 77 years of age (age criteria  $\geq 12$  and  $\leq 65$  years)
- Subject (b)(6) from Centre 5 (b)(6) was enrolled despite being known to have a history of intolerance to plasma-derived or blood products (previous anaphylactic reaction following Haemate treatment).
- VWF multimer analysis was performed for only 3 out of 14 subjects in the study
- BF and CT were not performed as scheduled in protocol for surgical subjects.

### Demographic and Other Baseline Characteristics

Parameter	Mean	Standard Deviation	Median	Range
Age	39.1	18.5	35.5	16 - 77
Height (cm)	166.9	11.4	166.0	147 - 185
Weight (kg)	72.2	15.4	69.5	42 - 95

### Gender, Blood Group and Previous Exposure Days by VWD Type

VWD Type	Type 1 (N=2)	Type 2 (N=8)	Type 3 (N=4)	Total (N=14)
Gender				
Male	0 (0%)	4 (50%)	0 (0%)	4 (28.6%)
Female	2 (100%)	4 (50%)	4 (100%)	10 (71.4%)
Blood Group				

Group A	0 (0%)	2 (25%)	3 (75%)	5 (35.7%)
Group B	0 (0%)	0 (0%)	1 (25%)	1 (7.1%)
Group AB	0 (0%)	1 (12.5%)	0 (0%)	1 (7.1%)
Group O	2 (100%)	5 (62.5%)	0 (0%)	7 (50%)
Exposure Days at Entry*				
<20	1 (50%)	0 (75%)	0 (0%)	7 (50%)
20 - 150	1 (50%)	0 (0%)	2 (50%)	3 (21.4%)
>150	0 (0%)	2 (25%)	2 (50%)	4 (28.6%)

\*Number of previous exposure days ranged from none to 1,000 with a median of 22.5

#### Levels of VWF:RCo and FVIII:C, Bleeding Time and Frequency of Bleeding at Study Entry

VWD Type	Parameter	N	Units	Mean	SD	Range
Type 1	VWF:RCo	2	%	58.5	0.7	58 - 59
	FVIII:C	2	%	101.5	33.2	78.0 - 125.0
	Bleeding Time	1	min	6.2	-	6.2 - 6.2
	Bleeding Frequency	1	n/month	0.3	-	0.3 - 0.3
Type 2	VWF:RCo	8	%	51.1	32.5	12 - 111
	FVIII:C	7	%	50.0	36.5	6.0 - 105.0
	Bleeding Time	3	min	8.9	5.3	5.3 - 15.0
	Bleeding Frequency	8	n/month	1.3	2.8	0.0 - 8.0
Type 3	VWF:RCo	4	%	3.8	2.5	0 - 5
	FVIII:C	4	%	4.1	2.5	1.4 - 7.0
	Bleeding Time	2	min	15.0	0.0	15 - 15
	Bleeding Frequency	4	n/month	2.3	2.6	0.2 - 6.0
All Types	VWF:RCo	14	%	38.6	33.2	0 - 111
	FVIII:C	13	%	43.8	43.2	1.4 - 125.0
	Bleeding Time	6	min	10.5	5.0	5.3 - 15.0
	Bleeding Frequency	13	n/month	1.5	2.6	0.0 - 8.0

There were 6 subjects (43%) known to have been vaccinated against HAV at entry and 10 (71%) against hepatitis B virus (HBV). For history of viral infections, 4 subjects (29%) had previously been infected with HAV and 2 (14%) with HCV; none had a prior history of infection with HBV or HIV. Antibodies to parvovirus B19 were detected in 7 subjects (50%) at baseline with one additional subject (7%) having a test result on the borderline of positivity (central laboratory).

There were 6 of 14 subjects (43%) recorded as having locations with a higher bleeding tendency, while all (100%) were reported to be in good general physical condition at entry; 11 out of 14 (79%) had taken concomitant medication during the 30 days prior to study entry and/or during the study.

#### EFFICACY EVALUATION

PK Evaluation See reviews by Drs. I. Mahmood and T. Silverman.

#### Bleeding Time Correction

Assessment of the correction of BT pre- and post-injection was performed for 4 out of 10 subjects who were recruited into Phase 1 of the study for PK evaluation: 3 out of the 4 subjects tested were found to be responders, defined as subjects who showed a reduction in BT at any time point after baseline

#### Correction of Bleeding Time in Subjects Enrolled in Phase I of the Study: Individual

Center/subject	VWD Type	Pre-Treatment BT (min:sec)	Shortest Post-Treatment BT (min:sec)	Responder?
1-	2	5:15	2:30	Yes
1-	W	15:00	6:00	Yes
1-	3	>15:00	>15:00	No
1-	3	>15:00	ND	NA
3 (b)(6)	2	ND	ND	NA
3-	2	ND	ND	NA
4-	3	ND	ND	NA
4-	3	ND	ND	NA
5-	1	6:10	4:30	Yes
11 (b)(6)	2	ND	ND	NA

ND = Not done, NA = Not Applicable

# Bleeding Episodes

Using the analysis methodology as in TMAE-104, the results in Wlate treatment of bleeding episodes can be shown as follows for TMAE 106

TMAE-106 BE Categories by Site				
	Site of bleeding	#Episodes	#Successfully treated Episodes	% Success
1	Joints	9	7	78
2	Epistaxis	3	3	100
4	Oral	2	2	100
5	Gynecologic	28	27	96
6	Other*	12	11	92
	Total	54	50	93

\*The database has classified muscle bleeds and cut thumb as "other"

Results of Treatment in TMAE-106 BE by VWD Type				
VWD Type	1	2	3	Total
N (# subjects)	0	3	2	5
#Episodes	0	13	41	54
Successfully treated Episodes	0	2	38	50
% Success	-	92	93	93

Because of the more limited sizes of the cells in analyzing dosage used in the treatment of bleeding episodes, analysis will be made with pooled data from all four VWD studies

(b)(4)



## SAFETY EVALUATION

### Extent of Exposure

Reason for Administration	Number of Infusions of WILATE administered	Number of WILATE Exposure Days
Treatment of Bleeding	93	72
Surgical Procedures	66	42
Prophylaxis	88	81
Study Related Administration	9	9
Total	256	204

### Adverse Events

#### Treatment Emergent Adverse Events by MedDRA Coded Term

MedDRA PRIMARY SOC	PREFERRED TERM	No. of Subjects (%)	No. of Events
Any Class	Any Event	5 (35.7)	7
Infections and Infestations	Upper Respiratory Tract Infection	1 (7.1)	1
Immune System Disorders	Hypersensitivity	1 (7.1)	1
	Transplant Rejection	1 (7.1)	1
Vascular Disorders	Haematoma	1 (7.1)	1
Gastrointestinal Disorders	Abdominal Pain	1 (7.1)	1
Skin and Subcutaneous Tissue Disorders	Urticaria	1 (7.1)	1
Investigations	Parvovirus B19 Serology Positive	1 (7.1)	1

#### Adverse Events Possibly or Probably Related to Treatment with WILATE

Centre/ Subject	Event Description	Serious Yes/No	Intensity	Resolved Yes/No	Causality
1-	Hypersensitivity	No	Moderate	Yes	Probable
5 (b)(6)	Parvovirus B19 serology +ve	Yes	Mild	No	Probable
5-	Urticaria	No	Mild	Yes	Probable

**Serious Adverse Events** There were no deaths reported in this study. Two SAEs are described below:

#### Centre 5 Subject N01004

This 60-year old female, who was included into the study on 23-Nov-2004 had VWD type 1. She received 3500 IU WILATE on 24-Nov-2004 for PK assessment. Two months later she was admitted to hospital for arthroscopy and surgical reconstruction of left shoulder rotator cuff which was performed on 24-Jan-2005. She received 417.9 IU/kg (in total 28,000 IU) of WILATE. The intervention was uncomplicated without excessive bleeding. Recovery was good. When the subject was tested for parvovirus B19 before the operation, the sample was found to be positive for IgG and IgM and in the PCR test. The subject did not develop any clinical symptoms.

	Baseline sample 23-Nov-2004	Pre-operative sample 24-Jan-2005	Follow-up sample 11-Feb-2005
--	--------------------------------	-------------------------------------	---------------------------------

Anti-PV B19 IgG (EIA)	Negative	Positive	Positive
Anti-PV B19 IgM	Negative	Positive	Positive
PCR	Negative	Positive	Positive

**Comment** The batch the subject received (337005181) was produced and released before (b)(4) testing of mini-pools for parvovirus B19 became routine. The subject did not receive other blood or plasma products during the study period.

**Centre 15, Subject No. (b)(4)**

This 51-year old female (VWD type 1) had suffered from breast cancer 4 years earlier and was admitted to hospital for autologous tissue transplantation to reconstruct her ablated breast. Surgery was performed on 07-Feb-2005. In the late evening of the same day, the patient had to be re-operated because of suspected moderate post-operative bleeding or a hematoma. However, the tissue transplant was rejected and the patient had to undergo another surgical procedure on 11-Feb-2005. Due to the prolongation of the hospital stay, the event was classified as serious.

**Clinical Laboratory**

Hematology and clinical chemistry results obtained from local laboratories showed low hematocrit, hemoglobin and red blood cells as the most commonly reported abnormalities, as might be expected in a cohort of subjects with a bleeding disorder.

Six out of the 14 subjects (42.9%) had a history of previous infection with at least one virus type studied. The most common was HAV, with which 4 (28.6%) had previously been infected. Two subjects (14.3%) had been infected with HCV. Baseline data on vaccination status were recorded for all subjects; 6 (42.9%) were known to have been vaccinated against HAV and 10 (71.4%) against HBV.

Laboratory data on tests for antibodies to parvovirus B19 and HAV are available for 10 subjects (71.4%).

Changes from baseline with respect to parvovirus B-19 IgG status were seen for 2 subjects:

- Subject 1 (b)(4) had a test result for parvovirus B19 IgG in March 2002 that was borderline positive. A re-test in May 2005 gave a positive result.
- Subject 5 (b)(4) tested negative for parvovirus B19 IgG in November 2004 but positive in January 2005.

Subject 1 (b)(4) was not considered to have undergone seroconversion. Seroconversion of Subject 5-1 was assessed as probably related to treatment with WILATE. The subject did not develop clinical symptoms. No changes in serological status were seen with respect to HAV-Ab.

**VI. 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**

The study report and data of WIL-14 are not included in this submission. The protocol has been submitted. A comparison with TMAE-104, -105, -109, and -106 has been presented in the Section "Summary of Clinical Parts of BLA STN 125251 Submission".

(b)(4)

(b)(4)

### Overview of Efficacy

This application is for the indication of von Willebrand disease.

(b)(4)

(b)(4)

This discussion is confined to the VWD indication.

There are four clinical studies (TMAE-104, 105, 106, 109) and one PK study (WIL-12) to support the VWD indication.

The PK data have been reviewed by Drs. I. Mahmood and T. Silverman. In summary, the assay for VWF:RCo has been a manual assay, and the data obtained for this parameter in Octapharma's Central Laboratory are deemed not reliable to support labeling and advise dosing.

(b)(6)

As noted above, there are major deficiencies in the study protocols for VWD. These can be summarized as follows:

#### Summary of Protocol Deficiencies in TMAE-104, 105, 109, 106, and WIL-14 for Evaluation of Efficacy

There are the following problems in evaluating clinical efficacy in these studies:

(1) The grading of severity of bleeding episodes is not clear in the protocol. In the data collected, bleeding episodes are graded as minor, moderate and severe. However, these are subjective designations by patient, and no clear instructions have been documented.

(b)(4)

(3) The VRS grading of excellent-good-moderate-none is by patient for each bleeding episode. These are subjective designations, and no clear instructions have been documented. When asked specifically, Octapharma indicated that "additional product" in the grading explanation refers to a non-Wilate product, but instructions for this to patients is also lacking.

(4) The counting of bleeding episodes is not clearly defined. When asked specifically, Octapharma stated that in earlier studies the episodes were not defined, but for later studies such as TMAE-104 bleeding separated by 7 calendar days have been counted as separate episodes. An interesting point in the statistical analysis plan for TMAE-106 is that it is stated that bleeding at different sites on the same date would be counted as different bleeding episodes. It appears that this has been similarly counted in the other studies even though it has not been explicitly stated.

(b)(4)

(6) The dosing in TMAE-106 "depends upon the clinical situation" and is not clearly specified in the protocol as in the other three studies. Without specific dosing guidelines, it is difficult to judge whether the administration of study product was as anticipated or exceeding what might have been usually adequate for hemostasis.

Dr. T. Silverman has also reviewed the clinical protocols and given her comments in her memo [see Dr. Silverman's draft review of 9/17/07].

#### Subjects in Wlate Studies on VWD

The number of subjects in each study has been presented above in the discussions on the studies. This can be summarized as follows:

Study	Center	PI ID	PI initial	Birthdate	Sex	VWD type
105	1	(b)(6)	(b)(6)	(b)(6)	1	3
105	1				1	3
105	1				2	3
105	1				2	2B
105	1				2	2B
105	1				1	2A
105	1				2	1
105	1				2	1
105	2				2	3
105	2				1	3
105	2				1	3
105	2				1	3
105	2				1	3
105	2				1	3
105	2				1	3
Study	Center	PI ID	PI initial	Birthdate	Sex	VWD type
109	1	(b)(6)	(b)(6)	(b)(6)	1	3
109	1				1	3
109	1				1	3
109	1				1	3
109	1				1	3
109	2				2	2A
109	2				1	3
109	2				2	3
109	2				2	2A
109	2				1	3
109	2				2	1
109	2				2	1
109	2				1	1
109	2				2	1
109	2				2	1
Study	Center	PI ID	PI initial	Birthdate	Sex	VWD type
104	1	(b)(6)	(b)(6)	(b)(6)	1	3
104	1				1	3
104	1				1	3
104	1				1	3
104	1				2	3
104	1				2	3

104	
104	1
104	1
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104	5
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104	5
104	5
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104	6
104	6
104	7
104	7
104	7
104	8
104	9
104	9
104	10
104	11
104	11
104	13
104	14
104	16
104	17

(b)(6)

2	3
2	3
2	3
1	2
2	3
2	3
1	2A
2	3
2	3
1	3
1	3
2	3
2	3
2	3
2	3
1	3
2	III
1	III
2	III
1	III
2	2A
2	3
1	2B
1	2D
2	1
2	2A
2	2A
1	2A
1	2M
2	3
1	1
1	III
2	3
2	2A
2	2A

moderate

Study	Center	PIID	PI initial	Birthdate	Sex	VWD type
103	1				1	2N
105	1				2	2N
105	1				2	III
106	1				2	III
103	2				2	2A
105	2				1	2A
105	3				2	2A
106	3				1	IIA
106	4				2	III
106	4				2	III
106	5				2	1
106	6				1	2A
106	11				2	2A
106	15				2	1

Sex - 1= male, 2 = female.

(b)(6)

(b)(6)

Patients in Bleeding Episode Database			
Study	Ctr	Pt	PtID
104			
104			
104			
104			
104			
104			
104			
104			
104			
104			
104			
104			
104			
104			

(b)(6)

104	5		
104	5		
104	6		
104	6		
104	7		
104	7		
104	8		
104	9		
104	11		
104	11		
104	13		
104	14		
104	17		
105	1		
105	1		
105	1		
105	1		
105	1		
105	1		
105	1		
105	1		
105	2		
105	2		
105	2	(b)(6)	
105	2		
105	1		
106	1		
106	4		(b)(4)
106	4		
106	11		
109	1		
109	1		
109	1		
109	1		
109	2		
109	2		
109	2		
109	2		
109	2		
109	2		
109	2		
109	2		
109	2		
109	2		
109	2		
109	2		

Total of 60 subjects; 45 individuals.

The following patients participated in 2 studies:

(b)(6)

(b)(6)

(b)(6) (in red)

The following participated in 3 studies.

(b)(6) (in blue)

These two databases account for 66 individuals. There are 4 additional subjects who were not in these two databases, making a total of 70 individuals.

- Study 106: (b)(6) was withdrawn for AE
- Study 106: patients (b)(6) and (b)(6) were dosed only for PK and so were not present in the datafiles for bleeding or surgery.
- Study 104 patient (b)(6) had sampling for recovery before (b)(4), and yet the surgery was postponed till after study completion; so her information was in neither the bleeding nor the (b)(4) datafiles.

These 4 cases account for the missing subjects in the bleeding and (b)(4) datafiles, but they do have data in other files of the dataset.

In addition, there are bleeding episodes with no treatment data. These are primarily found in TMAE-104. Octapharma states that these episodes were either so mild that treatment was not required, or they were not treated with Wilate at a time of product shortage.

For subjects who had participation in more than one VWD study, their information from the case report forms have been extracted and shown in Appendix IC: "Follow-up on Subjects who Participated in More Than One VWD Study".

### Bleeding Time Evaluations

Bleeding Time Correction in VWD Studies										
"Responders"					"Non-Responders"					
Study	Clr	PI	PtID	BT correction	Study	Clr	PI	PtID	BT	
104	1			>30 min → 4.5 min	104	1			>30 min	
104	1			>30 min → 6.27 min	104	1			>30 min	
104	1			>30 min → 8.33 min	104	1			>30 min	
104	1			>30 min → 18.5 min	104	1			>30 min	
104	1			>30 min → 15.8 min	104	5			No baseline**	
104	1			>11.5 min → 5.3 min	104	6			>15 min	
104	5			50 min → 45 min	104	6			>15 min	
104	5			33 min → 10 min						
104	5			>40 min → 33 min	105	2			>30 min	
104	7			>30 min → 15.33 min	105	2		(b)(6)	>30 min	
104	17			>20 min → 18.5 min	105	2			>30 min	
105	1			>30 min → 9 min	106	1			>15 min**	
105	1			>24.5 min → 10.5 min						
105	1		(b)(6)	>26 min → 7 min	109	1			>30 min	
105	1			>26 min → 6.5 min	109	1			>30 min	
105	1			>26.5 min → 5.5 min	109	1			>30 min	
105	2			>30 min → 7.5 min	109	1			>30 min	
					109	2			>26.5 min	
106	1			5.25 min → 2.5 min						
106	1			15 min → 6 min						
106	5			6.2 min → 4.6 min***						
109	2			>30 min → 8.5 min						
109	2			>26 min → 7 min						
109	2			>30 min → 9 min						
109	2			>24.5 min → 10.5 min						
109	2			>26.5 min → 5.5 min						

\*Responder/non responder status was defined by any correction of baseline bleeding time after administration of Wilate

\*\*Baseline not recorded, 1 hr post-injection BT of 18.5 min; \*\*\*patients without bleeding episode data

Applying the success criteria for bleeding episode treatment (see TMAE-104) the hemostatic efficacy of Wilate in the treatment of hemorrhages for bleeding-time "responders" and "non-responders" can be shown as follows:

Treatment of Bleeding Episodes with Wilate in Bleeding-Time Responders and Non-Responders		
	Responder's Bleeding Episodes	Non-Responder's Bleeding Episodes
Success	596 (89%) [95% C.I. 86.73%, 91.45%]	202 (77%) [95% C.I. 71.41%, 81.63%]
Failure	73 (11%) [95% C.I. 8.55%, 13.27%]	62 (23%) [95% C.I. 18.37%, 28.59%]
Total	669	264

**Comment** It appears that bleeding-time responders tend to have better success in the treatment of bleeding episodes with Wilate (95% C.I. do not overlap). However, as shown in the Table below, there

are responders who had no successful episode, and non-responders who had 100% successful episodes. Since the "episodes" were not necessarily treated with the same dose as that administered for testing bleeding time, and the plasma levels of FVIII C or VWF:RCO activity might vary at different times in different episodes, such an analysis would only be useful under standardized conditions.

Details of Successes in the Treatment of Bleeding Episodes in Bleeding Time Responders and Non-Responders							
	Bleeding Time Responders				Bleeding Time Non-Responders		
	Total Episodes	Successful Episdoes	Rate		Total Episodes	Successful Epicsodes	Rate
(b)(6)	45	44	98%	(b)(6)	2	1	50%
	3	3	100%		42	41	98%
	51	35	67%		5	5	100%
	42	39	93%		15	13	87%
	66	48	73%		104	65	63%
	3	2	67%		31	31	100%
	28	28	100%		26	8	31%
	3	2	67%		3	2	67%
	41	41	100%		7	7	100%
	1	1	100%		4	4	100%
	15	0	0		25	25	100%
	5	2	60%				
	27	26	96%				
	129	125	97%				
	7	7	100%				
	17	11	65%				
	1	1	100%				
	6	6	100%				
		179	175		98%		
Total	669	596	89%	Total	264	202	77%

#### Efficacy of Wilate in the Treatment of Bleeding Episodes

For bleeding episodes, the protocols (b)(4) treatment of the episodes. However, the study designs have deficiencies that make adequate analysis difficult, including the lack of definition of bleeding episodes, vagueness of the efficacy rating scale, and dosing without plasma level guidance. Octapharma has attributed these to their desire to simulate actual home use situations by patients. The lack of accurate baseline information and the wide variation of doses used for prevention also make analysis for efficacy difficult. The use of Wilate for prevention of bleeding episodes will not be further discussed, as no information is provided in the protocols for proper design in the evaluation of efficacy for the prophylaxis indication. Moreover, the proposed package insert also has no information to guide dosing for prevention of bleeding episodes. This suggests that the request for this indication has not been properly supported.

A pooled analysis of the bleeding episode data has been conducted by the Statistical Reviewer, Dr. J. Kim, and is shown in the following Tables. The success criteria are those described above (see discussion under TMAE-104)

Overall efficacy by study			
Study ID	Bleeding Episodes	Successful Episodes	% successes (95% CI)
TMAE-104	931	763	82% (79%, 84%)
TMAE-105	82	73	89% (82%, 96%)
TMAE-106	54	50	93% (85%, 99.8%)
TMAE-109	136	115	85% (78%, 91%)



total	1203	1001	83% (81%, 85%)
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#### Overall efficacy by bleeding site

Predominant Site of Bleeds	# of treatment	# of Bleeding Episodes (n)	# of successes	Efficacy (95% CI)
JOINT(S) N=26, n=19 VWD1=1, VWD2=2, VWD3=16	1068	614	547	547/614=89.1% (86.4%, 91.4%)
EPISTAXIS N=20, n=20 VWD1=1, VWD2=3, VWD3=16	281	133	104	104/133=78.2% (70.2%, 84.9%)
GI N=14, n=10 VWD2=5, VWD3=5	706	144	68	68/144=47.2% (38.9%, 55.7%)
ORAL N=12, n=12 VWD1=1, VWD2=1, VWD3=10	113	47	36	36/47=76.6% (62.0%, 87.7%)
GYNAECOLOGIC N=9, n=9 VWD1=1, VWD3=8	129	61	52	52/61=85.3% (78.3%, 93.0%)
OTHERS N=40, n=28 VWD1=6, VWD2=5, VWD3=17	282	204	194	194/204=95.1% (91.2%, 97.6%)
Total N=60, n=45 VWD1=8, VWD2=12, VWD3=25	2579	1203	1001	1001/1203=83.2% (81.0.2%, 85.3%)

N=number of study subjects in the studies. n=actual number of patients, as shown by the VWD type distribution below each.

#### Comments

1. Although the overall data for bleeding episode show a success rate of 83% (lower bound of 95% C.I. 81%), the rates for GI bleeding (39%) and oral bleeding (62%) are substantially lower. Since the "episodes" in the database provided had duplications for infusions due to bleeding at multiple sites, it was necessary to remove these duplications so that the multiple-site bleedings could be counted as one episode. In so doing, one can obtain an overall success rate, but no longer accurately determine the rates for bleedings at specific sites. The total number of "episodes" is then reduced to 1067, with 898 successfully treated with Wilate (84%).

2. The lower success rate associated with treatment of GI bleeding may be related to the fact that such bleeding could be associated with anatomical lesions, e.g., angiodysplasia, duodenal ulcer, etc., that require intervention other than medical therapy. If this were the case, even adjusting the plasma levels of the coagulation factors to normal would not be sufficient to stop bleeding. The presence of gastrointestinal angiodysplastic lesions in von Willebrand disease patients has been well documented.

#### Analysis of Bleeding Episodes by VWD Type

Bleeding Episodes: Success Rate by VWD Type			
VWD Type	Success Episodes	Failure Episodes	Success Rate
1 (N=8)	24	5	24/29 = 83%
2 (N=12)	42	23	42/65 = 65%
3 (N=25)	906	202	906/1108 = 82%

N = number of subjects

Breakdown of Doses used for Wilate Infusions in Bleeding Episodes by VWD Type		
	Initial Dose	Subsequent Doses
VWD Type 1 (N=8)	(n=26)	(n=3)
Mean $\pm$ SD	29 $\pm$ 7	23 $\pm$ 0.1
Median	29	23
VWD Type 2 (N=12)	(n=65)	(n=198)
Mean $\pm$ SD	37 $\pm$ 16	39 $\pm$ 15
Median	29	35
VWD Type 3 (N=25)	(n=982)	(n=1180)
Mean $\pm$ SD	28 $\pm$ 14	24 $\pm$ 14

Median	24	20
N = number of subjects, n = infusion numbers		

**Comment** It would appear that VWD Type 2 patients used higher doses of Wilate than Type 1 and Type 3 patients. The following Table shows the bleeding sites observed in the VWD studies.

Breakdown of Bleeding Episodes by VWD Type			
	VWD Type 1	VWD Type 2	VWD Type 3
Joints	1 (3%) [N=1]	2 (3%) [N=2]	610 (55%) [N=16]
Epistaxis	10 (34%) [N=1]	10 (15%) [N=3]	113 (10%) [N=16]
GI	0 [N=0]	37 (57%) [N=5]	107 (10%) [N=5]
Oral	2 (7%) [N=1]	1 (2%) [N=1]	44 (4%) [N=10]
Gynecologic	2 (7%) [N=1]	0 [N=0]	59 (5%) [N=8]
Other	14 (48%) [N=5]	15 (23%) [N=5]	175 (16%) [N=17]
Total	29 (100%) [N=8]	65 (100%) [N=12]	1108 (100%) [N=25]
N = number of subjects			

This suggests that the higher doses used in VWD Type 2 patients might have been related to the GI bleeding which is experienced much more commonly in this group of patients (42% of patients, 57% of episodes). It may also be noted that a small number of patients with multiple episodes of bleeding at certain bleeding sites can skew the picture. For instance, over half of the episodes (37, or 57%) for type 2 patients were from the GI bleeding of 5 subjects, whereas in type 3, there were more GI bleeding episodes (107) in the same number of patients (5), and yet this was only of 10% total because of the large number of episodes in other sites.

Dosing in the treatment of bleeding episodes for these studies were not monitored by plasma levels of VWF or FVIII. A pooled analysis of the dosing data and those for the successful cases can be made, but these must be viewed with caution because of the lack of guidance from plasma level information in the presence of active consumption of the coagulation factors during the bleeding episodes. In addition, the VWF:RCO levels performed in the Central Laboratory for recovery and PK are not reliable enough to support dosing recommendations.

The doses used for the infusions can be summarized as follows:

Site of bleeding	Initial Dose (IU/kg FVIII:C) Mean ± SD	Subsequent Doses (IU/kg FVIII:C) Mean ± SD
Joints	28 ± 12	20 ± 9
Epistaxis	24 ± 9	21 ± 12
GI bleeding	41 ± 18	34 ± 16
Oral bleeding	25 ± 12	22 ± 9
Gynecologic	28 ± 16	27 ± 10
Other*	24 ± 12	23 ± 15

\*muscle, hematuria, cutaneous, subcutaneous after trauma, and wounds

The doses used for episodes evaluated as treated successfully and unsuccessfully by the arbitrary criteria in this review can be summarized as follows:

Site of bleeding	Initial Dose (IU/kg FVIII:C) Mean ± SD	Subsequent Doses (IU/kg FVIII:C) Mean ± SD
<b>Successfully Treated episodes</b>		
Joints	28 ± 13	21 ± 10
Epistaxis	25 ± 10	22 ± 14
GI bleeding	43 ± 19	36 ± 21
Oral bleeding	27 ± 14	24 ± 18
Gynecologic	28 ± 17	26 ± 9
Other*	24 ± 12	20 ± 13
<b>Unsuccessfully Treated episodes</b>		
Joints	22 ± 8	19 ± 9
Epistaxis	21 ± 8	21 ± 11

GI bleeding	40 ± 17	34 ± 15
Oral bleeding	21 ± 6	24 ± 18
Gynecologic	29 ± 14	28 ± 11
Other*	27 ± 15	28 ± 16
*muscle, hematoma, cutaneous, subcutaneous after trauma and wounds		

**Comment** The successfully treated episodes often involved higher doses. However, the gynecologic and "other" sites apparently were treated with higher doses in the unsuccessfully treated episodes

In some of the bleeding episodes plasma levels of coagulation factors have been taken for monitoring purposes. These can be summarized as follows:

**Plasma Levels of FVIII and VWF:RCO in Treatment of Bleeding Episode in VWD Studies**

Study	Ctr	Pt	Date	Time	Batch #	Dose IU/kg	Bleed Site	FVIII* Level	U	VWFRCo Level	U	E**
105	1		06/01/2000		9480181801	3000	40	"Other"				1
105	1		06/01/2000	09:02				3.2	%	0.06	IU/ML	
105	1		06/01/2000	10:08				106.4	%	0.36	IU/ML	
105	1		06/05/2000		9480181801	3000	38	"Other"				1
105	1		06/05/2000	10:40				14.8	%	0.02	IU/ML	
105	1		06/05/2000	11:48				94.5	%	0.36	IU/ML	
105	1		06/14/2000		9480181801	3000	44	"Other"				1
105	1		06/14/2000	09:20				2.8	%	0.02	IU/ML	
105	1		06/14/2000	10:25				136.6	%	0.36	IU/ML	
105	1		01/15/2000		9420141801	2000	32	GI				2
105	1		01/15/2000	09:06						0.35	IU/ML	
105	1		02/01/2000		9420141801	3000	48	GI				2
105	1		02/01/2000	10:50				86.5	%	0.24	IU/ML	
105	1		02/01/2000	12:00				117.7	%	0.81	IU/ML	
105	1		02/02/2000		9420141801	2000	32	GI				2
105	1		02/02/2000	11:40				121.2	%	0.54	IU/ML	
105	1		02/03/2000		9420141801	2000	32	GI				1
105	1		02/03/2000	11:30				118	%	0.54	IU/ML	
105	1		02/04/2000		9420141801	2000	32	GI				1
105	1		02/04/2000	11:30				121.6	%	0.54	IU/ML	
105	1		02/11/2000		9420141801	3000	48	GI				1
105	1		02/11/2000	11:05				102.5	%	0.27	IU/ML	
105	1		02/11/2000	12:15				146.9	%	0.54	IU/ML	
105	1		02/18/2000		9420141501	2000	32	GI				1
105	1	(b)(6)	02/22/2000	13:00				95.5	%	0.36	IU/ML	
105	1		02/22/2000	14:05				199.5	%	0.81	IU/ML	
105	1		03/08/2000		9420141801	3000	48	GI				2
105	1		03/08/2000	09:15				151.3	%	0.81	IU/ML	
105	1		03/08/2000	10:15				238.3	%	0.81	IU/ML	
105	1		03/09/2000		9420141801	2000	32	GI				2
105	1		03/09/2000	10:40				250	%	0.81	IU/ML	
105	1		03/10/2000		9420141801	4000	64	GI				2
105	1		03/10/2000	11:05				219.8	%	0.81	IU/ML	
105	1		05/05/2000		9480181801	3000	34	"Other"				1
105	1		05/05/2000	09:20				41.7	%	0.12	IU/ML	
105	1		05/05/2000	10:28				139.7	%	0.54	IU/ML	
105	1		05/08/2000		9480181801	3000	42	"Other"				1
105	1		05/08/2000	10:25				29.5	%	0.06	IU/ML	
105	1		05/08/2000	11:30				110	%	0.56	IU/ML	
105	1		05/02/2000		9480181801	2000	37	"Other"				1
105	1		05/02/2000	11:10				27.9	%	0.06	IU/ML	
105	1		05/02/2000	12:15				105.1	%	0.54	IU/ML	
105	1		05/02/2000		9480181801	2000	33	"Other"				1
105	1		05/02/2000	10:50				34	%	0.12	IU/ML	
105	1		05/02/2000	11:55				97.8	%	0.54	IU/ML	
105	2		05/16/2000		9480181801	2000	24	Joint				1
105	2		05/16/2000	12:00				0.2	%	0.06	IU/ML	
105	2		05/16/2000	13:30				48	%	0.56	IU/ML	

105	2	07/12/2000	10:48	9480151801	2000	25	Joint	0.9	%	0.31	IU/ML	1
105	2	07/12/2000	12:00					31.4	%	0.28	IU/ML	
109	1	08/02/2000		0110351801	3000	43	Joint					1
109	1	08/02/2000	09:42					1.1	%	0.01	IU/ML	
109	1	08/02/2000	10:24					54.9	%	0.65	IU/ML	
109	1	08/02/2000	10:54					52.8	%	0.43	IU/ML	
109	1	08/02/2000	12:54					51.3	%	0.43	IU/ML	
109	1	08/08/2000		0110351801	3000	46	"Other"					1
109	1	08/08/2000	11:42					1.5	%	0.01	IU/ML	
109	1	08/08/2000	12:24					75.3	%	0.65	IU/ML	
109	1	08/08/2000	12:54					69.6	%	0.65	IU/ML	
109	1	08/08/2000	14:54					65.1	%	0.43	IU/ML	
109	1	02/06/2001	09:00					1.9	%	0.01	IU/ML	
109	1	02/06/2001	10:20					143.2	%	0.95	IU/ML	
109	1	08/14/2000		0110051801	1000	13	Joint					1
109	1	08/14/2000	09:13						%	0.01	IU/ML	
109	1	08/14/2000	09:51					25.1	%	0.14	IU/ML	
109	1	08/14/2000	10:21					24.1	%	0.14	IU/ML	
109	1	08/14/2000	12:21					22	%	0.07	IU/ML	
109	1	08/14/2000		0110051801	2000	24	Joint					1
109	1	08/14/2000	07:34					2	%	0.01	IU/ML	
109	1	08/14/2000	08:16					50.4	%	0.43	IU/ML	
109	1	08/14/2000	08:46					47.7	%	0.29	IU/ML	
109	1	08/14/2000	10:46					42	%	0.29	IU/ML	
109	1	08/14/2000		0110051801	1000	10	Joint					1
109	1	08/14/2000		0110051801	3000	29	Joint					3
109	1	08/14/2000	10:29					3.3	%	0.01	IU/ML	
109	1	08/14/2000	11:12					28.1	%	0.29	IU/ML	
109	1	08/14/2000	11:42					28.4	%	0.29	IU/ML	
109	1	08/14/2000	13:42					30.3	%	0.14	IU/ML	
109	1	01/14/2001		0170071801	1000	10	GI					1
109	1	01/15/2001	07:30					48	%	0.07	IU/ML	
109	1	01/16/2001	09:25					107	%	0.63	IU/ML	
109	1	01/17/2001	07:40					64.8	%	0.28	IU/ML	
109	1	01/18/2001	07:40					107.6	%	0.28	IU/ML	
109	1	01/19/2001	07:30					119.1	%	0.43	IU/ML	
109	1	01/20/2001	08:00					112.9	%	0.28	IU/ML	
109	1	01/21/2001	08:30					88.4	%	0.14	IU/ML	
109	1	01/22/2001	07:30					59.9	%	0.28	IU/ML	
109	1	01/24/2001	07:30					51.5	%	0.05	IU/ML	
109	2	11/20/2000		0170071801	3000	52	GI					1
109	2	11/20/2000	09:52					149.5	%	0.65	IU/ML	
109	2	11/20/2000	10:32					21.4	%	0.65	IU/ML	
109	2	11/20/2000	11:06					218.8	%	0.97	IU/ML	
109	2	11/20/2000	13:00					221.6	%	0.97	IU/ML	
109	2	11/21/2000		0170071801	3000	52	GI					1
109	2	11/21/2000	08:15					150	%	0.65	IU/ML	
109	2	02/20/2001		0380081801	2000	26	"Other"					1
109	2	02/20/2001	09:10					2.8	%	0.03	IU/ML	
109	2	02/20/2001	09:50					60.5	%	0.42	IU/ML	
109	2	02/20/2001	10:20					52.5	%	0.42	IU/ML	
109	2	02/20/2001	12:20					52.2	%	0.42	IU/ML	
109	2	02/21/2001	10:15					49.9	%	0.07	IU/ML	
109	2	12/06/2000		0170071801	3000	44	"Other"					1
109	2	12/06/2000	09:35					2	%	0.01	IU/ML	
109	2	12/06/2000	10:10					90.3	%	0.65	IU/ML	
109	2	12/06/2000	10:40					79.4	%	0.65	IU/ML	
109	2	12/06/2000	12:40					71.1	%	0.42	IU/ML	
109	2	12/07/2000	10:30					42.9	%	0.07	IU/ML	
109	2	09/20/2000		0170071801	2000	23	"Other"					1
109	2	09/20/2000	09:30					38.4	%	0.14	IU/ML	
109	2	09/20/2000	10:07					96.6	%	0.65	IU/ML	
109	2	09/20/2000	10:36					94.6	%	0.65	IU/ML	

109	2	09/20/2000	12:40					80.5	%	0.43	IU/ML	
109	2	09/21/2000	09:30					51.4	%	0.14	IU/ML	
109	2	02/19/2001		0070021801	2500	31	"Other"					1
109	2	02/19/2001	09:08					16.4	%	0.07	IU/ML	
109	2	02/19/2001	10:00					81.4	%	0.42	IU/ML	
109	2	02/19/2001	10:28					75.7	%	0.42	IU/ML	
109	2	02/19/2001	12:30					79.4	%	0.63	IU/ML	
109	2	02/20/2001	09:55					59.8	%	0.07	IU/ML	
109	2	09/12/2000		0170071801	2000	36	"Other"					1
109	2	09/12/2000	11:05					23.2	%	0.07	IU/ML	
109	2	09/12/2000	11:45					85.8	%	0.43	IU/ML	
109	2	09/12/2000	12:11					81.3	%	0.65	IU/ML	
109	2	09/12/2000	14:12					76.8	%	0.43	IU/ML	
109	2	09/13/2000	09:30					40.1	%	0.14	IU/ML	
109	2	11/20/2000		0170071801	2000	36	"Other"					1
109	2	09/12/2000		0170071801	2000	33	"Other"					1
109	2	09/12/2000	11:00					30.7	%	0.07	IU/ML	
109	2	09/12/2000	11:35					75.3	%	0.43	IU/ML	
109	2	09/12/2000	12:05					71.6	%	0.43	IU/ML	
109	2	09/12/2000	14:05					63.1	%	0.29	IU/ML	
109	2	09/13/2000	09:10					43.4	%	0.14	IU/ML	
109	2	10/10/2000		0170071801	3000	49	"Other"					1
109	2	10/10/2000		0170071801	2000	35	"Other"					1
109	2	10/10/2000	09:35					65.3	%	0.43	IU/ML	
109	2	10/10/2000	10:13					120.8	%	0.97	IU/ML	
109	2	10/10/2000	10:43					115.2	%	0.97	IU/ML	
109	2	10/10/2000	12:43					114.1	%	0.65	IU/ML	
109	2	10/11/2000	09:35					74.7	%	0.43	IU/ML	
109	2	10/10/2000		0170071801	2000	31	"Other"					1
109	2	10/10/2000	09:30					126.3	%	0.65	IU/ML	
109	2	10/10/2000	10:06					141.9	%	1.46	IU/ML	
109	2	10/10/2000	10:38					136.5	%	0.97	IU/ML	
109	2	10/10/2000	12:38					131.9	%	0.97	IU/ML	
109	2	10/11/2000	09:24					124.3	%	0.65	IU/ML	
109	2	11/27/2000		0170071801	2000	29	"Other"					1
109	2	11/27/2000	12:08					120.8	%	1.42	IU/ML	
109	2	11/27/2000	12:45					166.7	%	2	IU/ML	
109	2	11/27/2000	13:15					136.9	%	2	IU/ML	
109	2	11/27/2000	15:15					134.4	%	1.42	IU/ML	
109	2	11/28/2000	07:45					144	%	1.42	IU/ML	
109	2	11/27/2000		0170071801	2000	29	"Other"					1
109	2	11/27/2000	12:15					57.4	%	0.95	IU/ML	
109	2	11/27/2000	12:55					118.8	%	1.42	IU/ML	
109	2	11/27/2000	13:25					114.6	%	1.42	IU/ML	
109	2	11/27/2000	15:26					95.1	%	1.42	IU/ML	
109	2	11/28/2000	08:00					76.6	%	1.42	IU/ML	
104	1	09/14/2004		3380061812	4000	36	GI					1
104	1	09/15/2004	08:00					114	%	63	%	
104	1	09/16/2004	08:00					141	%	95	%	
104	1	09/17/2004						94.2	%	42	%	
104	1	09/18/2004		3380061812	2000	19	GI					4
104	1	09/18/2004		3380061812	2000	19	GI					4
104	1	09/18/2004	09:00					111.2	%	42	%	
104	1	09/19/2004		3380061812	2000	19	GI					3
104	1	09/19/2004		3380061812	2000	19	GI					4
104	1	09/20/2004						139	%	95	%	
104	1	09/21/2004	08:00					162.6	%	142	%	
104	1	09/22/2004	08:00					153.4	%	142	%	
104	1	09/23/2004	08:00					160.2	%	95	%	
104	1	09/24/2004	08:00					107.2	%	95	%	
104	1	09/25/2004	08:00					91.5	%	95	%	
104	1	09/27/2004		3380061812	3000	28	GI					1
104	1	09/27/2004		3380061812	1000	9	GI					2
104	1	09/27/2004	08:00					83.5	%	63	%	

104	1	09/28/2004	08:00						158	%	95	%	
104	1	09/29/2004	08:00						129.8	%	42	%	
104	1	09/30/2004	08:00						87.5	%	28	%	
104	1	10/01/2004	08:00						82.5	%	28	%	
104	1	10/04/2004	08:00						67.6	%	28	%	
104	1	02/02/2005		4350051813	2000	19	GI						3
104	1	02/02/2005		4350051813	3000	28	GI						3
104	1	02/02/2005	08:00						152.6	%	95	%	
104	1	02/03/2005		4350051813	3000	28	G						3
104	1	02/03/2005		4350051813	4000	38	GI						3
104	1	02/03/2005	08:00							%	63	%	
104	1	02/04/2005		4350051813	4000	38	GI						3
104	1	02/04/2005		4350051813	4000	38	GI						3
104	1	02/04/2005	08:00							%	142	%	
104	1	02/05/2005		4350051813	4000	38	GI						3
104	1	02/05/2005		4350051813	4000	38	GI						3
104	1	02/05/2005	08:00							%	142	%	
104	1	02/07/2005		4350051813	4000	38	GI						2
104	1	02/07/2005		4350051813	4000	38	GI						2
104	1	02/07/2005	08:00							%	142	%	
104	1	02/08/2005		4350051813	4000	38	GI						2
104	1	02/08/2005		4350051813	4000	38	GI						2
104	1	02/08/2005	08:00							%	142	%	
104	1	02/09/2005	08:00							%	142	%	
104	1	02/10/2005	08:00							%	142	%	
104	1	02/11/2005	08:00							%	95	%	
104	1	02/14/2005	08:00							%	63	%	
104	1	03/15/2005		3220021811	4000	38	GI						2
104	1	03/15/2005		3220021811	4000	38	GI						3
104	1	03/15/2005	08:00						79.2	%	63	%	
104	1	03/16/2005	08:00						103.4	%	95	%	
104	1	03/17/2005	08:00						117.8	%	95	%	
104	1	03/18/2005	08:00						122	%	63	%	
104	1	03/22/2005	08:00						95.6	%	63	%	
104	1	03/30/2005	08:00						81.4	%	28	%	
104	1	03/31/2005	08:00						93.8	%	42	%	
104	1	04/01/2005	08:00						106.2	%	42	%	
104	1	04/04/2005		4350051813	2000	19	GI						4
104	1	04/04/2005		4350051813	2000	19	GI						4
104	1	04/04/2005	08:00						103.4	%	42	%	
104	1	04/05/2005		4350051813	2000	19	GI						4
104	1	04/05/2005		4350051813	2000	19	GI						4
104	1	04/05/2005	08:00						97.2	%	42	%	
104	1	04/06/2005		4350051813	2000	19	GI						4
104	1	04/06/2005		4350051813	2000	19	GI						4
104	1	04/06/2005	08:00						112.8	%	63	%	
104	1	04/07/2005		4350051813	2000	19	GI						4
104	1	04/07/2005		4350051813	2000	19	GI						4
104	1	04/07/2005	08:00						102.4	%	63	%	
104	1	04/09/2005		4350051813	2000	19	GI						4
104	1	04/09/2005		4350051813	2000	19	GI						4
104	1	04/09/2005	08:00						127.4	%	42	%	
104	1	04/11/2005		4350051813	4000	38	GI						4
104	1	04/11/2005		4350051813	4000	38	G						4
104	1	04/11/2005	08:00						94.8	%	63	%	
104	1	04/12/2005		4350051813	4000	38	GI						4
104	1	04/12/2005		4350051813	4000	38	GI						4
104	1	04/12/2005	08:00						93.8	%	95	%	
104	1	04/13/2005		4350051813	4000	38	GI						4
104	1	04/13/2005		4350051813	4000	38	GI						4
104	1	04/13/2005	08:00						109	%	95	%	
104	1	04/14/2005		4350051813	4000	38	GI						4
104	1	04/14/2005		4350051813	4000	38	GI						4
104	1	04/14/2005	08:00						121	%	95	%	
104	1	04/15/2005		4350051813	4000	38	GI						4

104	1	04/15/2005		4350051813	4000	38	GI					4
104	1	04/15/2005	08:00					25.2	%	95	%	
104	1	04/17/2005		4350051813	4000	38	GI					4
104	1	04/17/2005		4350051813	4000	38	GI					4
104	1	04/18/2005	08:00					155	%	142	%	
104	1	04/19/2005	08:30					46.6	%	95	%	
104	1	03/30/2006		5050011811	3000	52	Joint					1
104	1	03/30/2006	07:15					16	%	7	%	
104	3	06/03/2004		4050011811	1500	23	Gynec					3
104	3	06/03/2004	11:55					13.8	%	63	%	
104	3	06/03/2004	12:30					57.7	%	95	%	
104	3	06/03/2004	13:00					57.2	%	95	%	
104	3	06/03/2004	14:00					68.4	%	95	%	
104	3	06/04/2004		4050011811	1500	23	Gynec					2
104	3	06/04/2004	13:00					74	%	63	%	
104	3	06/04/2004	13:00					107.4	%	95	%	
104	3	06/04/2004	14:00					107.4	%	95	%	
104	5	04/12/2003		2380071811	500	16	"Other"					1
104	5	04/14/2003	11:00					6.4	%	28	%	
104	5	11/27/2006		5400121817	1000	19	Joint					1
104	5	11/27/2006	11:30					1	%	1	%	
104	5	10/05/2006		5400121817	1500	61	Joint					1
104	5	10/05/2006	13:00					1.9	%	1	%	
104	5	10/05/2006	14:00					84	%	42	%	
104	5	10/05/2006	14:30					83.8	%	42	%	
104	5	10/05/2006	16:30					60.9	%	28	%	

No plasma level data in TMAE-106. Patient's dosing by FVIII:C IU/kg. Data from Central Laboratory only.

\*FVIII plasma level values by chromogenic assay for TMAE-105, 106, and 109, and by one-stage assay for TMAE-104.

\*\*E=Investigator or Patient rating of hemostatic efficacy of the infusion.

In the above Table, only FVIII:C and VWF:RCO levels are provided, as these are the most relevant levels for the clinician in the use of an AHF/VWF product. Each set of plasma level data is preceded by the information of the infusion used to treat the bleeding episode.

#### Comments

1. TMAE-105, -109, and -106 had mandatory plasma level data collection requirements for bleeding episodes at study site in the case report forms, but the collection of these data have not been consistent. In TMAE-105, there are plasma levels taken pre- and post- infusion for one infusion in most patients during a bleeding episode. For TMAE-109, there are recovery data during one episode for the non-surgical cases. TMAE-106 was primarily a PK study, and the PK data were not to be collected in patients while in a bleeding episodes. TMAE-104 had no plasma level requirements for bleeding episodes, and two subjects had recovery studies while they were having bleeding episodes (Subject (b)(6) on 6/3/04 and 6/4/04; Subject (b)(6) on 10/5/06). However, even in this study, plasma level determinations did take place for some other bleeding episodes, especially for the GI bleedings in Subject (b)(6).

2. The patients were dosed according to FVIII potency of the product. In the U.S., the usual practice is to dose according to VWF strength in the product. Because of the looseness of the product lot specifications with respect to the ratio of VWF:RCO/FVIII, and because of the width of allowed product potency (b)(4) dosing by FVIII in these studies gives considerable uncertainties as to the amount of VWF actually received in each infusion.

3. The assay for VWF:RCO in the Central Laboratory was a manual assay using stepwise dilutions, and the data obtained in this laboratory have been problematic due to readout from dilution curves that cannot provide accurate interval values. This renders interpretation of the plasma levels of VWF:RCO in relation to dosing difficult.

4. The above considerations are important since the doses used for bleeding episodes in the VWD studies on Wilate (and doses in the successfully treated episodes) appear to be lower than those observed in the literature and in the Humate-P label recommendations.

#### Doses in Literature Reports for the Treatment of VWD Bleeding Episodes

Reference	N	Uses	Loading Dose (IU/kg)*
Gill et al 2003	53	Bleeding events	67*
Lillierap 2002	344/73	Bleeding events	55.3*
Lubetsky et al 1999	3/9	Bleeding events/surgery	39.5**

\*median \*\*mean

#### Recommendations for Humate-P Use in the Treatment of VWD Bleeding Episodes (Current label)

VWD	Hemorrhage	Dose (IU VWF:RCO/kg BW)
Type 1 Mild, if desmopressin is inappropriate (BL VWF:RCO typically >30%)	<ul style="list-style-type: none"> <li>Major (e.g., severe or refractory epistaxis, GI bleeding, CNS trauma or traumatic hemorrhage)</li> </ul>	Loading dose 40-60 IU/kg, then 40-50 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCO >50%; then 40-50 IU/kg daily for a total of up to 7 days of treatment.
Moderate or severe (BL VWF:RCO typically <30%)	<ul style="list-style-type: none"> <li>Minor (e.g., epistaxis, oral bleeding, menorrhagia)</li> <li>Major (e.g., severe or refractory epistaxis, GI bleeding, CNS trauma, hemarthrosis or traumatic hemorrhage)</li> </ul>	40-50 IU/kg (1 or 2 doses)  Loading dose 50-75 IU/kg, then 40-60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCO >50%; then 40-60 IU/kg daily for a total of up to 7 days of treatment. FVIII:C levels should be monitored and maintained according to the guidelines for hemophilia A therapy, Table 9
Type 2 and Type 3	<ul style="list-style-type: none"> <li>Minor (clinical indications above)</li> <li>Major (clinical indications above)</li> </ul>	40-50 IU/kg (1 or 2 doses)  Loading dose 60-80 IU/kg, then 40-60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCO >50%; then 40-60 IU/kg daily for a total of up to 7 days of treatment. FVIII:C levels should be monitored and maintained according to the guidelines for hemophilia A therapy, Table 9.

5. Upon analysis of the VWF:RCO plasma levels attained after Wilate infusion in the treatment of bleeding episodes, 19 out of 64 sets of plasma levels (30%) did not show achieving a peak target level of at least 50 IU/mL. Because of inherent problems of the VWF:RCO assay performed for these studies in the Central laboratory, the reliability of any estimate about achieving a particular target level is uncertain. However, it appears likely that with the doses used (which mirrors those in the proposed package insert), a fair size of the target population may be under-dosed in the treatment of bleeding episodes.

6. The product contains a higher proportion of FVIII than that in one product marketed for von Willebrand disease indications in the U.S. (Humate-P), but lower than that in another (Alphanate). However, because of the potential need for upward dose adjustment as a result of lower potency than that labeled (see above), it is not clear whether higher doses based on VWF:RCO content might unduly elevate FVIII levels and predispose to thromboembolic phenomena, especially in non-type 3 VWD patients. On analyzing the Table shown above, there are 59 sets of data for recovery or monitoring during bleeding episodes in which both FVIII and VWF:RCO levels are available, and out of these there are 10 sets where FVIII levels are over 150% (10/59=17%). This narrow therapeutic window underscores the importance of thoroughly understanding the dosing relationship to plasma levels of FVIII and VWF in treating VWD patients with Wilate.

7. Although one can derive doses from those used in the successful episodes, there does not appear to be any major difference between those used in the successful episodes and the overall doses. Because of the nature of the "outcome" data for the bleeding episodes in these studies (recovered, ongoing,



unknown), relationship between plasma levels and outcome are not practical, as they do not inform the treatment effect of any particular infusion. Each infusion is rated by patient or Investigator with the 4-point VRS scale, but as discussed previously, the scale is vague and can be confusing to the subject in the absence of detailed grading instructions (Octapharma stated that details are not available). An attempt to relate the available peak plasma level achieved with the 4-point efficacy grading scale in bleeding episodes does not show a trend in observed peak plasma levels related to the grading:

	Excellent (N=29)	Good (N=15)	Moderate (N=7)	Poor (N=13)
FVIII C (%)	92 ± 47	162 ± 52	85 ± 54	116 ± 20
VWF:RCO (IU/mL)	0.63 ± 0.42	0.79 ± 0.31	0.94 ± 0.40	0.79 ± 0.36

N = # of episodes with data; data as mean ± S.D

It is also possible that the treatment effect may be more dependent on other parameters such as the location of bleeding, severity of bleeding and use of concomitant medications rather than plasma levels alone.

8. Because of the above reasons, this Reviewer cannot find a satisfactory way to recommend dosing for the treatment of bleeding episodes in labeling. All these concerns must be addressed in an adequately designed study so that proper dosing guidelines can be provided before this indication can be approved.

Long-Term Treatment of Bleeding Episodes with Wilate. Because patients could be enrolled into more than one study for the study of VWD treatment, some of the subjects had Wilate administered for bleeding episodes for at least one year. The following Table lists the 21 subjects treated for bleeding episodes for one year or longer:

Subjects Follow-Up over 1 Year with Wilate Treatment of Bleeding Episodes		
PtID	1 <sup>st</sup> infusion	Last infusion
(b)(6)	12/19/2002	08/18/2006
	03/14/2002	12/04/2006
	06/01/2003	01/08/2007
	07/20/2003	01/25/2007
	06/18/2004	11/13/2006
	01/21/2003	01/08/2007
	06/21/2005	01/09/2007
	08/14/2002	05/20/2005
	01/07/2000	02/19/2001
	01/16/2000	02/18/2001
	12/17/2004	12/08/2006
	03/17/2000	04/17/2005
	12/23/2004	01/27/2007
	08/08/2000	12/04/2003
	01/02/2000	02/20/2001
	05/14/2004	01/03/2007
	06/24/2000	01/24/2007
	04/18/2005	06/01/2006
	03/01/2004	09/23/2006
	07/31/2005	12/31/2006
	04/04/2000	01/22/2007

The long-term follow-up information of the subjects with information across the VWD studies as captured in the case report forms is presented in Appendix C (12 subjects). It does not appear that changes in bleeding severity or management in bleeding were observed. This may not be unexpected for patients treated with Wilate on-demand for bleeding episodes rather than using it for prevention of such episodes. The efficacy ratings for the infusions and initial dosing for bleeding episodes with more than one infusion are shown in Appendix E.

Follow-up of Efficacy Ratings in Bleeding Episodes in VWD Patients. Because of the vagueness of the efficacy rating scale for the distinction between grades (e.g., excellent

refers to cessation of bleeding and good to adequate control of bleeding), an evaluation of the efficacy ratings for infusions in episodes with more than one administration of Wilate was also conducted with the Table in Appendix IE, "Efficacy Ratings by Patients/Investigators in VWD Bleeding Episodes with More Than One Infusion" to see how ratings varied within individual subjects and episodes.

**Comment** It appears that the general trend for the efficacy ratings of the infusions was from a less efficacious rating to one that is more efficacious, i.e., from none to moderate, to good, and to excellent. Reversals of this trend are also observed, but the overall direction was towards a better rating in the end. Thus, the last rating for infusions in an episode might be biased towards a better outcome. The distinction between "good" and "excellent" is not well defined (adequate control of bleeding vs cessation of bleeding), but the infusions were generally rated in the direction from "good" towards "excellent" as time progressed. The last rating is therefore not representative of an average of the ratings for individual infusions. Rather, it often is the best rating in the series within an "episode."

(b)(4)

(084)

Use in Pediatric Population

The clinical studies on VWD had included pediatric subjects for bleeding episodes and surgery.

#### Bleeding Episodes

Patients aged 16 or younger						
Study	Center	Patient	Patient ID	VWD Types	Episodes	Infusions
104	1	(b)(6)		3	42	54
104	5			3	45	57
104	5			3	66	167
104	5			3	7	7
104	5			3	4	7
104	11			3	21	33
104	11			1	13	19
104	17			2	3	10
109	2			1		
105	1				3	3
106	4				3	
Total					242	431

Patients aged 12 or younger						
Study	Center	Patient	Patient ID	VWD Types	Episodes	Infusions
104	1	(b)(6)		3	42	54
104	5			3	45	57
104	5			3	66	167
104	5			3	7	7
104	5			3	4	7
104	11			3	21	33
104	11			1	13	19
104	17			2	3	10
				Total	201	354

Using the criteria for success and failure discussed previously (see Section on TMAE-104), and using age 16 as cut-off for pediatric population), there were 211 bleeding episodes treated successfully with Wilate (211/242=87%). With age 12 as cut-off, there were 173 episodes successfully treated (173/201=86%)

(b)(4)

## Overview of Safety

The overall safety profile of Wilate in the clinical studies can be summarized as follows:

### VWD

The incidence of adverse events in the VWD studies is presented below.

Incidence of Adverse Events: VWD Studies

	TMAE-104 N=11; n=37	TMAE-105 N=14; n=14	TMAE-106 N=14; n=14	TMAE-109 N=16; n=5	WIL-12 N=22; n=22	All Studies N=85; n=70
Total # AEs	165	6	7	25	28	231
# of subjects with an AE	25	1	5	5	10	43
# treatment related* AEs in # of subjects	13 in 6	0	3 in 2	0	1 in 1	17 in 8
# subjects withdrawn for AE	0	0	1	0	0	1

Seventeen (17) adverse drug reactions (ADRs) with a possible or probable causal relationship to WILATE treatment have been observed in 9 subjects, details are given as follows:

Drug Related Adverse Events: VWD Studies

Subject ID	Study	Reaction (coded)	Serious?	Severity, Outcome
(b)(6)	TMAE-104	headache	no	moderate, R/R
		abdominal discomfort	no	moderate, R/R
		dyspnoea	no	moderate, R/R
	TMAE-104	parvovirus B19 serology positive	yes	mild, NR/NR
		dizziness (2 occurrences)	no	mild, R/R
	TMAE-104	vertigo	no	mild, R/R
		nausea	no	mild, R/R
		anemia	no	moderate, NR/NR
		rash	no	mild, R/R
		parvovirus B19 serology positive	yes*	mild, NR/NR
	TMAE-104	parvovirus B19 serology positive	yes	mild, NR/NR
		urticaria	no	mild, NR/NR
	TMAE-106	urticaria	no	mild, R/R
	TMAE-106	parvovirus B19 serology positive	yes	mild, NR/NR
		hypersensitivity	no	moderate, R/R
	WIL-12	cysgeusia	no	mild, R/R

R/R recovered, resolved; NR/NR, not recovered, not resolved

In Study TMAE-106, one subject was withdrawn from the study because of an AE. This 22-year old female subject developed a moderate allergic type of reaction during the first injection of WILATE. After the administration of approx. 750 IU of WILATE, the injection had to be stopped. The subject received dimenhydrone (4mg) and recovered

(b)(4)

(b)(4)

#### Exposure to the Drug

The total population for the safety analysis consists of 160 individual subjects recruited into 9 completed studies conducted with WILATE 5 in VWD subjects (n=92) (b)(4) and the following Table summarizes the overall study population.

Overall Study Population (n=160):			Study Allocation	
Study ID	Status	Study Period	No. of subjects	No. of individuals
VWD studies				
TMAE-104	Completed	Jan 2002 – Mar 2007	41	37
TMAE-105	Completed	Dec 1999 – Jul 2000	14	14
TMAE-106	Completed	Mar 2002 – Jul 2006	14	14
TMAE-109	Completed	Aug 2000 – May 2001	16	5
WIL-12	Completed	Jun 2005 – April 2006	22	22
SUB-TOTAL			107	92

(b)(4)

A total of 53 different batches of WILATE have been used in the 9 studies included in this application and 2 strengths (500 IU FVIII or 1,000 IU FVIII).

**Overview of Exposure to WILATE: VWD Studies**

	Study ID				
	TMAE-104 N=41 (n=37)	TMAE-105 N=14 (n=14)	TMAE-106 N=14 (n=14)	TMAE-109 N=16 (n=5)	WIL-12 N=22 (n=22)
Dose of WILATE per kg BW	20-50 IU/kg	Phase I: 50 IU/kg Phase II: 20-50 IU/kg	Phase I: 50 IU/kg Phase II: 20-50 IU/kg	20-50 IU/kg	appr. 40 IU/kg
Dosing interval	Once daily or every other day depending on clinical situation; single or multiple doses.	Phase I: Single dose, treatment day (PK). Phase II: Single dose, ≥1 treatment day, depending on clinical situation.	Phase I: Single dose, treatment day (PK). Phase II: Single dose, ≥1 treatment day, depending on clinical situation.	Once daily or every other day depending on clinical situation; single or multiple doses.	One single dose
Total dose (IU) <sup>1</sup>	8,620,000	432,500	420,900	707,000	N/A
Total number of exposure days	4,917	202	206	343	22
Surgery, total dose (IU)	580,350 IU (n=45)*	128,000 IU (n=2)*	149,400 IU (n=10)*	55,000 IU (n=2)*	none

N (number of subjects in the study/analysis), n (number of new individuals).  
N/A not applicable \* No. of procedures <sup>1</sup> Incl. surgical administrations

(b)(4)

For VWD, 38 different batches have been used in the 5 VWD studies, with about 10.2 million IU of WILATE administered. In the 4 efficacy studies, exposure to the product was for a longer period, in total 5,654 exposure days have been documented to date in these studies

## Adverse Events



During surgery the haemostatic effect of WILATE was assessed as very good. However, post-operatively, hypotension developed caused by intra-abdominal bleeds and the subject had to undergo a re-operation the same evening. The bleeding episode was then stopped. The next day, some of the subject's laboratory parameters deteriorated: INR was > 5 and fibrinogen was 1.0 g/L. FVIII levels were within the normal range. However, the subject's condition worsened: he developed renal failure and controlled respiration was employed. On (b)(6) the subject died, his death being unrelated to WILATE treatment.

**Withdrawals.** The following Table shows the patient withdrawals and reasoning in the VWD clinical studies.

Study	Center	Subject (Sex, Age at entry)	Date of Withdrawal	Reason(s) of Withdrawal
TMAE-104	1	M, 47)	20-Apr-2005	consequence of SAE (Death)
	1	M, 49)	6-Apr-2004	at subjects request; insufficient therapeutic response, protocol violation
	1	(F, 23)	31-Jan-2007	other reason (planned surgical procedure postponed until after completion of study)
	6	F, 64)	19-May-2004	insufficient therapeutic response
		F, 47)	16-Aug-2004	insufficient therapeutic response
	7	F, 65)	25-Apr-2005	insufficient therapeutic response
	8	F, 39)	12-Sep-2005	at subjects request, insufficient therapeutic response, withdrawn by investigator
	9	F, 73)	14-Jan-2005	at subjects request
	10	M, 58)	10-Feb-2005	insufficient therapeutic response
	13	M, 40)	19-Dec-2006	at subjects request
TMAE-106	1	F, 22)	2-Mar-2004	adverse event (allergic reaction)

**Other Serious Adverse Events.** The following Table summarizes the incidence of serious adverse events (SAEs) by body system. In total, 80 serious adverse events have been reported in 21 individual subjects: 51 of these SAEs were VWD related GI bleeds. Four cases (parvovirus B19 serology positive) were regarded as possibly related to WILATE treatment.

**Frequency of Serious Adverse Events, by System Organ Class**

Meddra Primary System Organ Class	Meddra Preferred Term	No. Of Events
Any Class	Any Event	80
Infections And Infestations	Any Event	3
	Catheter Related Infection*	2
	Parotitis	1
Blood And Lymphatic System Disorders	Any Event	1
	Anaemia	1
Immune System Disorders	Any Event	1
	Transplant Rejection	1
Nervous System Disorders	Any Event	1
	Syncope	1
Respiratory, Thoracic And Mediastinal Disorders	Any Event	6
	Epistaxis	6
Gastrointestinal Disorders	Any Event	51
	Gastrointestinal Hemorrhage	34
	Melaena	14
	Duodenal Ulcer Hemorrhage	1
	Mouth Hemorrhage	1
	Pancreatitis Acute	1
Musculoskeletal And Connective Tissue Disorders	Any Event	5
	Hemarthrosis	2
	Back Pain	1
	Synovitis	1
Renal And Urinary Disorders	Any Event	2
	Hematuria	2
General Disorders And Administration Site Conditions	Any Event	3
	Catheter Site Hemorrhage	1
	Chest Pain	1
	Multi-Organ Failure	1
Investigations	Any Event*	5
	Parvovirus B19 Serology Positive	4

Meddra Primary System Organ Class	Meddra Preferred Term	No. Of Events
	Hepatitis A Antibody Positive	1
Injury, Poisoning And Procedural Complications	Any Event	1
	Scratch	1
Surgical And Medical Procedures	Any Event	1
	Tooth Extraction	1

\*Catheter related infection refers to a patient using Vascuport for infusion of Wilate in prevention of bleeding episodes who developed infection of the catheter and development right atrial thrombus (Study 104 Patient 2 of Center 5). See section on TMAE-104 for details.

#### Other Significant Adverse Events

Two non-serious adverse events were considered as clinically significant:

- TMAE-106, Subject No. 10106/Center 1: dropout due to allergic reaction
- WIL-12, Subject No. 10112/Center 5: increased liver transaminases

#### TMAE-106, Subject No. 10106/Center 1

This case concerns a 22 year-old female subject suffering from type 3 VWD who was enrolled in Study TMAE-106 on 02-Mar-2004. The same day, she received WILATE treatment and developed a moderate allergic reaction characterized by flushing and feeling unwell immediately after the start of the infusion. The infusion was stopped, blood pressure was checked (but was normal) and after treatment with antihistamins (cimetidine 4mg orally), the subject fully recovered after 5-10 minutes. The event was classified as non-serious but the subject was withdrawn from the study.

#### WIL-12, Subject No. 10112/Center 5

This 39-year old male subject (VWD type 1) had increases in ALAT (pre-injection 1: 34 U/L, post-injection 1: 51 U/L) and ASAT (pre-injection 1: 25 U/L, post-injection 1: 83 U/L). The investigator reported these laboratory changes as adverse events, however, considered these increases unlikely related to the WILATE study treatment

#### Clinical Laboratory Evaluations

Standard clinical laboratory evaluations were performed in all the studies. There were no particular safety issues raised for any laboratory parameters in any of the studies. In all studies, several subjects had hematological parameters (hemoglobin, haematocrit, platelets, RBC and WBC) outside normal ranges. However, levels below the lower limit of normal are common in subjects with bleeding disorders. Therefore, these abnormal values were not regarded to represent a safety issue associated with WILATE. Liver transaminase levels were of particular interest as markers for viral safety and are discussed in the following section

#### Viral Safety

**A. VWD Studies.** Viral safety was documented by determining anti-HAV and anti-parvovirus B19 (all studies) and in addition, in the ongoing Study TMAE-104 only, by determining anti-HIV, and viral markers for HBV and HCV. In case of negative or borderline values at baseline, the tests were repeated during the study and after the last injection of WILATE (7 to 14 days after administration for anti-parvovirus B19 and 4 to 8 weeks for anti-HAV). For those subjects in TMAE-105 continuing with WILATE in Study TMAE-109, no follow-up sample was drawn at study end.

**Study TMAE-105.** Out of the total study population (n=14), 7 subjects were negative for anti-HAV at study entry and 7 were positive. With respect to anti-parvovirus B19 again 7 subjects tested negative at baseline and the remaining 7 were positive. No viral seroconversion was observed during the study period. Values for ALAT were within the normal range for all subjects

**Study TMAE-109.** Out of the total study population (n=16), 6 subjects were negative for anti-HAV at study entry and remained negative until the follow-up. With respect to anti-parvovirus B19, 2 subjects were positive at baseline and 1 subject had a borderline result. After the completion of the study, these 3 subjects were measured as positive. The borderline result of the subject measured at baseline, and the follow-up sample were checked by the central laboratory, and confirmed the previous results. The subject was probably infected by parvovirus B19 shortly before he was included in the study. Furthermore, it should be mentioned that this subject had received the same batch of the study drug as other subjects, who had remained anti-parvovirus B19 negative throughout the study period. No confirmed viral seroconversion was observed during the study period. There were no concerns regarding liver test results in any subjects in this study

Study TMAE-104. Baseline data on viral serology were recorded for all 41 subjects. Of these, 2 (4.9%) were positive for antibodies to HIV, 18 (43.9%) had antibodies to HBc, 21 (51.2%) were positive for HCV antibodies, 24 (58.5%) were positive for HAV antibodies and 37 (90.2%) were positive for IgG antibodies to parvovirus B19. An additional subject was borderline for IgG antibodies to parvovirus B19. Changes from baseline negative results were seen for 4 subjects with respect to parvovirus B-19 IgG status and 2 for parvovirus B-19 IgM status.

- Subject from Centre 1 was parvovirus B19-IgM negative at baseline but positive at 3 months. All subsequent samples were negative for parvovirus B19-IgM. However, the result for parvovirus B19-IgG was positive at baseline, showing that the subject had previously been exposed to parvovirus B19 and was immune. The subject did not develop any clinical symptoms of a recent PV B19 infection.
- Subject from Centre 9 had a borderline positive result for parvovirus B19 IgG at baseline followed by a positive result at 3 months. IgM values were negative at both timepoints indicating that the subject did not have a recent infection and it thus seems likely that the subject was already immune to parvovirus B19 at baseline. This subject did not develop any clinical symptoms of a recent PV B19 infection.
- Subject from Centre 11 was negative for parvovirus B19 IgG and IgM at baseline and positive for both markers at 3 months. The subject did not develop any clinical symptoms. The follow-up investigations showed that the concerned WILATE batch (No. 248 009 181) was B19 positive. This batch was produced and released before the B19 testing of the pool became part of the batch release. However, subject from the same centre who received the same WILATE batch did not develop any antibodies against PV B19.
- Subject from Centre 11 was negative for parvovirus B19 IgG and IgM at baseline and was tested at 3-monthly intervals and remained negative until 2 years after inclusion in the study when a positive result was recorded for B19 IgG although IgM remained negative. All subsequent samples tested positive for B19 IgG and negative for IgM.
- Subject from Centre 17 was negative for parvovirus B19 IgG and IgM at baseline but positive for IgG at 3 months. IgM remained negative.

Seven subjects showed a change from negative to positive with respect to HAV-Ab. In two cases this appears to have been due to a false positive result. For subject in centre 1 a single borderline result was obtained at 2 years, followed by six subsequent negative results. The most likely explanation is therefore that the result was false positive. For subject in centre 1, a negative baseline result was followed by a positive result 3 months later. However, two subsequent tests gave negative results and it is thus assumed that the single positive result was a false positive. All other seroconversions for HAV were a result of vaccination. The changes in viral serology are summarised below:

Changes in Viral Serology in Study TMAE-104

Centre/ Subject	Viral Marker	Baseline Date/Result	First Changed Status Date/Result	Comments
1	HAV-Ab	02-Jan-2002 Negative	06-Jan-2004 Limit	This borderline result was followed by 6 subsequent negative results
1	HAV-Ab	27-Feb-2002 Negative	09-July-2002 Positive	The subject was vaccinated against HAV on 07-Jul-2000. Thus the negative result from the screening sample is false.
1	Parvovirus B19 IgM	22-Oct-2002 Negative	30-Jan-2003 Positive	Subject was B19 IgG positive at baseline
1 (b)(6)	HAV-Ab	23-Mar-2004 Negative	01-Jun-2004 Positive	A second HAV RNA test of a sample obtained on 01-Jun-2004 and an test of a sample obtained on 17-Jan-2006 revealed negative results. Thus the result on 01-Jun-2006 is assumed to be a false positive.
5	HAV-Ab	16-Dec-2002 Negative	24-Jun-2003 Positive	Vaccinated against HAV on 14 Mar 2003
5	HAV-Ab	15-Jan-2003	13-Oct-2003	Vaccinated against HAV on 11 Jul

		Negative	Positive	2003.
5	HAV-Ab	15-May-2003 Negative	14-Aug-2003 Positive	Vaccinated against HAV on 16 May 2003.
9 (b)(6)	Parvovirus B19 IgG	13-Jul-2004 Limit	13-Oct-2004 Positive	Baseline sample was borderline positive.
11-	Parvovirus B19 IgG	25-Mar-2004 Negative	17-Jun-2004 Positive	Seroconversion for parvovirus B19.
11-	HAV-Ab	06-May-2004 Negative	12-Jan-2006 Positive	Vaccinated against HAV on 29-Sep-2005.
11- (b)(6)	Parvovirus B19 IgG	06-May-2004 Negative	04-May-2006 Positive	Seroconversion for parvovirus B19.
17-	Parvovirus B19 IgG	23-Mar-2006 Negative	04-Jul-2006 Positive	Seroconversion for parvovirus B19.

**Study TMAE-106.** In a 60-year old subject a parvovirus B19 seroconversion was observed. The subject did not develop any clinical symptoms. The batch was produced and released before the parvovirus B19 (b)(4) testing of the mini-pools became routine.

(b)(4) [See Dr. N. Jain's review]

Immunogenicity [See Dr. N. Jain's review]

C. Periodic Safety Update Reports [See Dr. N. Jain's review]

Comment

Dr. Jain's review comments that Octapharma should provide (1) listings of raw data of inhibitor titers for each subject enrolled in Studies TMAE-101 and -108, (2) the number of exposure days for each subject in those studies in tabular format, as well as (3) criteria used in tolerability assessment with the 4-point scale in the (b)(4) studies. The inhibitor information has been provided by Octapharma in a submission dated 10/10/07. Information on tolerability criteria has not been submitted, and will be part of the comments to be conveyed.

Analysis of Risks and Benefits

(b)(4)

- The use of Wilate for prevention of bleeding episodes was not evaluated with accurate baseline documentation or breakthrough bleeding episodes per unit time after starting Wilate.
- There is inadequate plasma level information in the presence of active consumption of the coagulation factors during bleeding episodes to support dosing recommendations for the treatment of such episodes. In addition, because of inherent dilution procedures in the assay that cannot distinguish values within serial ranges of plasma levels, the VWF:Co levels performed in the Central Laboratory for recovery and PK are not reliable enough to support dosing recommendations.

(b)(4)

Because of the potentially lower potency for VWF:RCo activity (see CMC Review), and the wide variability of the VWF:RCo to FVIII:C ratio, the use of Wilate may be associated with elevated FVIII:C plasma levels that predispose patients to

thromboembolic complications. One case of right atrial thrombus occurred in a patient using Wilate for prophylaxis of bleeding episodes through a Vascuport catheter.

On the balance, this application has not presented sufficient evidence that the use of Wilate as recommended in proposed labeling provides benefits that outweigh the potential risks. Licensure for the proposed VWD indications is not recommended at this time.

### Recommendations

1. Approval of this BLA is not recommended at this time, because

- There is inadequate plasma level information in the presence of active consumption of the coagulation factors during bleeding episodes to provide guidance on dosing recommendations for such episodes. In addition, the VWF:Co levels performed in the Central Laboratory for recovery and PK are not reliable enough to support dosing recommendations.
- Due to higher Factor VIII content in this product, the risks of thromboembolic adverse events have to be balanced with the potential benefits from appropriate dosing regimens in VWD patients who can produce Factor VIII, but this risk-benefit evaluation cannot be made from available information.

2. A CR Letter should be issued to Octapharma with comments as elaborated in the following section.

### CR Letter Comments

1. The primary endpoints for the four VWD clinical studies supporting hemostatic efficacy (TMAE-105, -109, -104, and -106) are based on pharmacokinetic (PK) or recovery data. Please address the following issues pertaining to the plasma level data in support of your application:

a) The PK data in TMAE-104, -105, and -106 were generated by dosing based on VWF:RCo activity, whereas the clinical use of Wilate in these studies was based on FVIII:C activity. As the dosing recommendations in your proposed package insert use a VWF:RCo-based approach, Please clarify how the disparate information on plasma levels may be combined to establish meaningful dosing guidelines.

b) As our testing of your Wilate conformance lots consistently yields potency values for VWF:RCo substantially lower than what is labeled, there are uncertainties in relating the PK data in the clinical studies to the VWF:RCo activity administered. Please clarify how the PK and plasma VWF:RCo level data in these studies may be appropriately evaluated in relation to the VWF:RCo activity administered in order to advise dosing.

c) Because of the difficulties in reading interval values in your VWF:RCo assay, the data generated from the Central Laboratory on VWF:RCo are not sufficiently reliable to support the clinical information on hemostatic efficacy in these studies. Please address the fact that without reliable data on the factor to be replaced, the efficacy of Wilate in the proposed indications cannot be established at this time.

d) The mean incremental recovery of VWF:RCo from these clinical studies (1.5 – 1.9%/IU/kg) is higher than that in the U.S. PK study (WIL-12) (1.1 – 1.2 %/IU/kg). This difference may impact the calculation of doses to be administered. Please address this difference, especially in terms of the issues relating to VWF:RCo assay as discussed above.

e) As Wilate has lower levels of the highest molecular weight multimers of VWF present in normal plasma, please address the impact of this finding on the assaying of VWF:RCo activity in the plasma samples in the VWD clinical studies, and its implications on dosing.

2. Please address the following comments pertaining to the proposed indications:



b) For the treatment of bleeding episodes, although the clinical data may appear to suggest efficacy in an overall population, they do not demonstrate efficacy in oral and gastrointestinal bleeding. For those bleeding sites that may hold promise for efficacy with Wilate treatment, it is difficult to recommend dosing for the following reasons:

- i. The patients were dosed according to FVIII potency of the product. For a replacement therapy, it is appropriate to dose according to VWF strength of the product. Because of the variation in the ratio of VWF:RCo to FVIII in the product lots for Wilate, and because of the width of allowed product potency, dosing by FVIII in these studies gives considerable uncertainties as to the amount of VWF actually received in each infusion.
- ii. The data on VWF:RCo from the Central Laboratory are difficult to interpret due to readout from dilution curves that cannot provide accurate interval values. Any value obtained can be actually one dilution higher or one dilution lower in the actual VWF:RCo level. This renders supporting dosing recommendations with the plasma levels of VWF:RCo from the clinical data not possible.
- iii. The above considerations are important since the doses used for bleeding episodes in the VWD studies on Wilate (and doses in the successfully treated episodes) appear to be lower than those observed in the literature and the label recommendations of the U.S.-licensed product for bleeding episodes in VWD.
- iv. Even if one grants reliability of the VWF:RCo data, the VWF:RCo plasma levels attained after Wilate infusion in the treatment of bleeding episodes show a sizeable portion of these values not achieving a peak level of at least 50 IU/mL. Applying the doses used for the treatment of bleeding episodes of VWD patients in the clinical studies (which mirrors those in the proposed package insert) may result in under-dosing for the bleeding episodes.

v. Because our testing results on your conformance lots consistently show lower potency values for VWF:RCO than the labeled values, the ratio of the content of VWF:RCO to FVIII:C may be considerably lower than that claimed (1:1). This could lead to a need for upward dose adjustment. It is not clear whether higher doses based on VWF:RCO content might unduly elevate FVIII levels and predispose to thromboembolic phenomena. This narrow therapeutic window underscores the importance of thoroughly understanding the dosing relationship to plasma levels of FVIII and VWF in treating VWD patients with Wilate.

vi. There does not appear to be major differences between doses used in treating successful bleeding episodes and the doses used overall. When an attempt is made to relate the available peak plasma level achieved and the 4-point grading scale for hemostatic efficacy used by patients and Investigators in bleeding episodes, no apparent relationship can be observed.

vii. Because of the above reasons, it is not possible to find a satisfactory way to recommend dosing for the treatment of bleeding episodes in labeling at this time. Please address these concerns in an adequately designed study so that proper dosing guidelines can be provided before this indication can be approved.

(b)(4)

d) With respect to dosing for the proposed indications:

i. Please explain why the dosing recommendations in the proposed package insert are not consistent with those in the clinical studies, as -

- The clinical studies use FVIII:C activity for dosing whereas labeling uses VWF:RCO activity.
- The proposed labeling recommendations include use of loading and maintenance doses, which were not in the protocols of the VWD trials.
- The distinction of "minor" and "major" bleeding episodes is different from the grading for bleeding severity in the VWD trials, which use scores of "minor", "moderate", and "severe".

ii. Please explain the following in the proposed package insert -

- the basis of the dosing intervals in the labeling recommendations,
- 
- (b)(4)

iii. Please also note that under "DOSAGE AND ADMINISTRATION" in the Highlights section of the package insert, there is no indication of the coagulation factor activity to be based upon for dosing (FVIII:C or VWF:RCO). This should be rectified.

3. Please provide a cross-study analysis of subjects who participated in more than one VWD clinical study, to include, but not limited to the following analyses: changes in disease pattern, such as severity and location of bleeding, and changes in the pattern of product use, such as dosing, concomitant medications, prophylaxis vs treatment, etc.

4. Please provide the case report forms and all investigations including those in the hospital records for Patient (b)(4) in Center 5 in Study TMAE-104, during his serious adverse event of right atrial thrombus.

(b)(4)

6. Please conduct appropriate studies with adequate design to acquire efficacy data in support of the indications sought, taking into consideration the comments below on the deficiencies in the VWD clinical studies of the current submission.

a) The VWD clinical studies in this submission are listed as hypothesis-generating. Pivotal studies in support of an indication must be designed to support clearly stated hypothesis and contain measures to minimize bias and noncompliance for product use and evaluation. There should be prospectively defined criteria for success or failure.

b) Bleeding episodes were not clearly defined in the VWD studies of this submission. The number of infusions per episode and the duration of treatment within any episode are defined by the length of the "episode" arbitrarily assigned by the patient or investigator. Without an appropriate definition to be used consistently by all



Investigators and patients in all the studies, the number of infusions and duration of treatment are more prone to subject to bias

c) The 4-point VRS grading scale used by Investigators and patients for clinical efficacy evaluation is vague and inadequately defined.

i. It would be appropriate to have more refined language separately for bleeding episodes and for surgery. For instance, the definition of good includes the term "oozing" which would not be expected to occur with spontaneous or trauma-induced bleeding in soft tissue or joint. Bleeding into the joint would be classified according to swelling and pain, not visible oozing. In addition, the definitions should not include the term to be defined within them, e.g., the term "moderate" within the definition of moderate severity.

(b)(4)

iii. The term "additional product" for the grades "good" and "moderate" can be misleading to patients and Investigators. You have affirmed in previous communications that "additional product" refers to a non-Wilate product. However, in Study WIL-14 (only protocol included in this submission), the term used instead of "additional product" is "additional injections of IMP (investigational medicinal product) or other styptic treatment." It is difficult to expect consistency in applying the current 4-point VRS without additional clarification to the patients and Investigators, including –

- definition and criteria for using "additional product",
- a time-frame for use of the "additional product", and
- differences between "hemostasis achieved" (in excellent) in contrast to "adequate control of bleeding" (in good).

iv. In contrast to the efficacy rating for each infusion, an overall assessment termed "outcome" was recorded for each bleeding episode in Studies TMAE-109, -104 and -106, with gradings of "recovered", "ongoing" and "unknown." This parameter is unclear, because in the absence of a definition for "bleeding episode", its duration may be adjusted to fit the outcome, hence making the terms "recovered" and "ongoing" rather circular, depending on how the "episode" has been recorded.

d) The differentiation of bleeding episodes into "minor", "moderate" and "severe" is ill-defined. Please provide clearly the instructions given to patients to grade severity. In proposed labeling, bleeding episodes were divided into "minor" and "major" for the purpose of dosing. As the term "minor" may carry different meaning in the clinical trials vs that in proposed dosing recommendations of labeling, please address the potential confusion that may result from extrapolating the doses from clinical trials to labeling recommendations.

(b)(4)

(b)(4)

g) The primary endpoint(s) for the VWD studies involve either PK or plasma level parameters. For the analysis of efficacy, the following comments pertain:

i. Please indicate in the protocol pre-specified criteria of success for the primary endpoint(s), regardless of their being clinical or surrogate laboratory parameter(s). This should be based on appropriate hypotheses testing. It will not be adequate to include multiple variables for analysis without stating how those parameters are to be used to establish success. If the primary endpoint is to be a composite parameter, please pre-specify any necessary steps for weighting of the variables involved.

(b)(4)

iii. Although the protocols in your VWD studies suggest analysis using an intent-to-treat approach, you have actually excluded subjects with major protocol violations in the actual analysis. Please ensure that analyses will be based on the intention to treat principle. Please also ensure that all subjects enrolled into the study have the diagnosis of VWD confirmed prior to entry, and the method for administration of Wilate standardized across study centers.

iv. Please specify in the protocol the analyses of efficacy as a function of dose administered and plasma levels of FVIII and VWF:RCO achieved in the subjects treated for each indication in order to establish the intended effect of the product, as well as the dosing recommendations for labeling.

h) In your submission, the VWD study protocols provided for the administration of product based on FVIII content, and only general dosing guidelines were provide, with emphasis on dependence on the clinical situation and individual calculations. Please note the following comments and recommendations:

i. As discussed above, the lack of definition for bleeding episode severity (minor, moderate, severe) (b)(4) in the protocols makes interpretation of the dosing data difficult. Please include in your study protocol appropriate instructions to Investigators and study subjects in the

grading of severity, taking into consideration the quantity and rapidity of blood loss, as well as the significance of the bleeding location, and provide your plan for categorizing surgeries into "minor" and "major".

(b)(4)

iii. There have been no PK studies performed based on FVIII dosing instead of using VWF:RCo. As VWF is the primary factor to be replaced in the treatment of VWD, and proposed labeling is using VWF:RCo units/kg for dosing, please provide in your future studies dosing recommendations based on the VWF:RCo content of the product. This may also mitigate under-dosing arising from the wide variation in the ratio of VWF:RCoF : FVIII:C in the product lots.

iv. In addition to information on dosing intervals, please include in your future VWD studies guidelines for repeating the use of the test product, as well as criteria for rescue products and blood transfusions.

(b)(4)

(b)(4)

v. Most of the VWD study protocols in this submission provide target plasma levels of FVIII:C (b)(4) but not for treatment of bleeding episodes. Your proposed labeling recommend monitoring with both FVIII:C and VWF:RCo plasma levels. Please state in your future studies instructions for monitoring, including target plasma levels of FVIII:C and VWF:RCoF needed to achieve or maintain hemostasis, and prevent thromboembolic complications.

7. Please provide (a) the instructions for patients and Investigators for using the tolerability assessment instrument in the form of a 4-point scale in your clinical studies on von Willebrand disease (b)(4) and (b) validation of this instrument. Please include in your future studies appropriate criteria for assignment into the grades of this scale.

8. You have an ongoing study with data collection in pediatric patients having VWD. In your response to this letter, please update your Pediatric Plan, and data pertaining to pediatric subjects for the proposed package insert, if such data become available

## Appendices

### I. Details of Patient Data in Wilate Studies on Von Willebrand Disease

#### A. Study TMAE-104

The following provides details on individual patients in bleeding episodes from the datasets:

Abbreviations used in the Tables below are as follows: S=severity of bleeding (1=minor, 2=moderate, 3=severe), R=last rating of efficacy by patient or Investigator (1=excellent, 2=good, 3=moderate, 4=none) for the treatment "episode", F8-1=FVIII:C level pre-infusion, VF-1=VWF:RCo level pre-infusion, F8-2=FVIII:C level post-infusion, VF-2=VWF:RCo level post-infusion (all levels given as %), TA=tranexamic acid, cyclo or cyklo=cyclokapron, RBC=red blood cells, WB=whole blood. Cryoppt=cryoprecipitate, EACA=aminocaproic acid

Episode numbers and infusion numbers are not given in the Table. The last rating of efficacy (R) indicates the row showing the last infusion in any given "episode" as provided in the database (see review memo comments on definition of bleeding episode and readjudication).

TMAE-104: Bleeding Episode by Individual Patient: Ctr 1 - P1006										
01/08/2002 Patient underwent dental extraction. 04/23/2003 Patient came for planned visit a few days too late due to Easter holidays.										
11/08/2006 2nd PK analysis needed 5000 IU 11/10/2006 2000 IU for home treatment, 12/05/2006: 20x1000 IU for home treatment,										
01/15/2007 20x1000 IU for home treatment.										
VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VF -1	F8 -2	VF -2	Concomitant Medications
3	1	Ankle	01/13/2002	11.8	1					TA
3	1	Ankle	01/18/2002	11.8	1					TA
3	2	Muscle, right	01/23/2002	11.8						
3	2	Muscle, right	01/24/2002	11.8	1					
3	1	Ankle, right	01/30/2002	11.8	1					
3	2	Joint, left	02/03/2002	11.8	2					
3	1	Muscle, left	02/08/2002	11.8	1					
3	1	Ankle, left	02/10/2002	23.5	1					
3	2	Joint, right	02/14/2002	11.8						
3	2	Joint, right	02/15/2002	23.5						
3	2	Joint, right	02/16/2002	23.5	1					
3	1	Muscle, right	03/14/2002	11.8	1					
3	1	Muscle, right	03/26/2002	11.8	1					
3	1	Ankle, left	04/16/2002	23.5						
3	1	Joint, right knee	04/16/2002	23.5						
3	1	Ankle, left ankle	04/17/2002	11.8	1					
3	1	Joint, right knee	04/17/2002	11.8	1					
3	2	Joint, left hip	04/22/2002	23.5						
3	2	Joint, left hip	04/23/2002	23.5						
3	2	Joint, left hip	04/24/2002	11.8	1					
3	1	Joint, right knee	05/14/2002	11.8						
3	1	Joint, right knee	05/15/2002	11.8	1					
3	1	Joint, right elbow	05/24/2002	11.8						
3	1	Joint, right elbow	05/25/2002	11.8	1					
3	1	Ankle, left ankle	06/01/2002	23.5	1					
3	1	Ankle, left ankle	06/05/2002	11.8	1					
3	1	Joint, right knee	06/17/2002	11.8						
3	1	Joint, right knee	06/19/2002	11.8	1					
3	1	Joint, left hip	06/24/2002	23.5						
3	1	Joint, left hip	06/25/2002	23.5	1					















3	2	Epistaxis	02/01/2002	18.9						IA		
3	2	Epistaxis	02/02/2002	18.9						TA		
3	2	Epistaxis	02/03/2002	9.4	2					TA		
3	2	Gastrointestinal	03/15/2002	18.9								
3	2	Gastrointestinal	03/16/2002	9.4								
3	2	Gastrointestinal	03/17/2002	9.4								
3	2	Gastrointestinal	03/18/2002	9.4	2							
3	1	Ankle, right	04/29/2002	18.9	2							
3	1	Epistaxis	05/10/2002	18.9	2					IA		
3	2	Epistaxis	05/18/2002	18.9						IA		
3	2	Epistaxis	05/19/2002	9.4	2					IA		
3	2	Ankle, right	06/05/2002	18.9								
3	2	Ankle, right	06/06/2002	18.9								
3	2	Ankle, right	06/07/2002	9.4	1							
3	2	Gastrointestinal	06/19/2002	28.3						ETAMSILATE		
3	2	Gastrointestinal	06/20/2002	18.9						ETAMSILATE		
3	2	Gastrointestinal	06/21/2002	9.4	2					ETAMSILATE		
3	2	Joint, left knee	07/14/2002	18.9								
3	2	Joint, left knee	07/16/2002	18.9								
3	2	Joint, left knee	07/17/2002	9.4	2							
3	1	Epistaxis	07/23/2002	18.9	2					TA		
3	2	Gastrointestinal	07/31/2002	18.9								
3	2	Gastrointestinal	08/01/2002	18.9								
3	2	Gastrointestinal	08/02/2002	9.4								
3	2	Gastrointestinal	08/03/2002	9.4								
3	2	Gastrointestinal	08/04/2002	9.4	2							
3	1	Ankle, left	08/18/2002	18.9								
3	1	Ankle, left	08/19/2002	9.4	2							
3	2	Gastrointestinal	09/20/2002	18.9								
3	2	Gastrointestinal	09/21/2002	9.4								
3	2	Gastrointestinal	09/22/2002	9.4	2							
3	2	Gastrointestinal	09/26/2002	18.9								
3	2	Gastrointestinal	09/27/2002	9.4								
3	2	Gastrointestinal	09/28/2002	9.4	2							
3	2	Gastrointestinal	10/20/2002	14.2								
3	2	Gastrointestinal	10/20/2002	14.2								
3	2	Gastrointestinal	10/21/2002	9.4								
3	2	Gastrointestinal	10/22/2002	9.4								
3	2	Gastrointestinal	10/23/2002	9.4	2							
3	1	Ankle	10/29/2002	18.9								
3	1	Ankle	10/30/2002	9.4	1							
3	-	Epistaxis	11/06/2002	18.9	1					TA		
3	-	Epistaxis	11/10/2002	18.9	1					TA		
3	2	Gastrointestinal	12/02/2002	28.3						TA		
3	2	Gastrointestinal	12/03/2002	18.9						TA		
3	2	Gastrointestinal	12/04/2002	9.4						TA		
3	2	Gastrointestinal	12/05/2002	9.4						IA		
3	3	Gastrointestinal	12/10/2002	37.7	3					TA		
3	3	Epistaxis	12/12/2002	28.3						TA		
3	3	Epistaxis	12/13/2002	28.3						TA		
3	3	Epistaxis	12/14/2002	28.3						TA		
3	3	Epistaxis	12/15/2002	28.3						TA		
3	3	Epistaxis	12/16/2002	28.3						IA		
3	3	Gastrointestinal	12/18/2002	23.6						IA		
3	3	Gastrointestinal	12/19/2002	37.7						WB	TA	
3	3	Gastrointestinal	12/20/2002	28.3						WB	IA	
3	3	Gastrointestinal	12/21/2002	28.3						WB	TA	
3	3	Gastrointestinal	12/22/2002	28.3						WB	TA	
3	3	Gastrointestinal	12/23/2002	28.3						WB	TA	
3	3	Gastrointestinal	12/24/2002	28.3						WB	TA	
3	3	Gastrointestinal	12/25/2002	28.3						WB	TA	
3	3	Gastrointestinal	12/26/2002	28.3						WB	IA	
3	3	Gastrointestinal	12/27/2002	28.3						WB	IA	
3	3	Gastrointestinal	12/28/2002	28.3						WB	IA	
3	3	Gastrointestinal	12/29/2002	28.3						WB	IA	
3	3	Gastrointestinal	12/30/2002	37.7						WB	IA	
3	3	Gastrointestinal	12/31/2002	37.7						WB	TA	
3	2	Gastrointestinal	01/01/2003	37.7						WB	TA	
3	3	Gastrointestinal	01/02/2003	28.3						WB	TA	
3	3	Gastrointestinal	01/03/2003	23.6						WB	TA	
3	3	Gastrointestinal	01/04/2003	23.6						WB	TA	
3	3	Gastrointestinal	01/05/2003	23.6						WB	TA	

3	3	Gastrointestinal	01/08/2003	28.3						WB	TA	
3	3	Gastrointestinal	01/17/2003	28.3						WB	TA	
3	3	Gastrointestinal	01/29/2003	18.9						CRYOPPT	TA	
3	3	Gastrointestinal	01/29/2003	18.9	3					CRYOPPT	TA	
3	2	Epistaxis	01/24/2003	18.9								
3	2	Epistaxis	01/25/2003	9.4	2							
3	2	Ankle	01/31/2003	18.9								
3	2	Ankle	02/01/2003	18.9								
3	2	Ankle	02/02/2003	18.9								
3	2	Ankle	02/03/2003	9.4	2							
3	3	Gastrointestinal	02/14/2003	28.3								
3	3	Gastrointestinal	02/15/2003	28.3								
3	3	Gastrointestinal	02/16/2003	28.3								
3	3	Gastrointestinal	02/17/2003	9.4	2							
3	2	Epistaxis	04/25/2003	18.9						TA		
3	2	Epistaxis	04/26/2003	9.4	2					TA		
3	2	Ankle, right	05/08/2003	28.3								
3	2	Ankle, right	05/09/2003	18.9								
3	2	Ankle, right	05/10/2003	18.9	1							
3	2	Joint, left elbow	05/21/2003	18.9								
3	2	Joint, left elbow	05/22/2003	18.9	1							
3	2	Epistaxis	06/02/2003	18.9						TA		
3	2	Epistaxis	06/03/2003	18.9	1					TA		
3	2	Epistaxis	06/07/2003	18.9						TA		
3	2	Epistaxis	06/08/2003	18.9	1					TA		
3	2	Ankle, right	06/20/2003	18.9								
3	2	Ankle, right	06/21/2003	9.4								
3	2	Joint, right knee	07/06/2003	18.9								
3	2	Joint, right knee	07/07/2003	9.4	2							
3	2	Epistaxis	07/11/2003	18.9								
3	2	Epistaxis	07/12/2003	9.4	2							
3	2	Epistaxis	07/23/2003	18.9						TA		
3	2	Epistaxis	07/24/2003	18.9	1					TA		
3	2	Gastrointestinal	08/03/2003	18.9						TA		
3	2	Gastrointestinal	08/04/2003	18.9						TA		
3	2	Gastrointestinal	08/05/2003	9.4	1							
3	2	Joint, left knee	08/11/2003	18.9								
3	2	Joint, left knee	08/12/2003	18.9								
3	2	Joint, left knee	08/13/2003	18.9								
3	2	Joint, left knee	08/14/2003	9.4	1							
3	2	Epistaxis	08/21/2003	18.9								
3	2	Epistaxis	08/22/2003	9.4	1							
3	2	Epistaxis	08/30/2003	18.9								
3	2	Epistaxis	08/31/2003	9.4	1							
3	3	Gastrointestinal	09/06/2003	28.3						TA		
3	3	Gastrointestinal	09/09/2003	18.9						TA		
3	3	Gastrointestinal	09/10/2003	18.9						TA		
3	3	Gastrointestinal	09/11/2003	9.4						TA		
3	3	Gastrointestinal	09/12/2003	9.4	1					TA		
3	2	Epistaxis	09/21/2003	18.9								
3	2	Epistaxis	09/22/2003	9.4	1							
3	1	Epistaxis	10/19/2003	18.9	2							
3	3	Gastrointestinal	10/23/2003	37.7						TA		
3	3	Gastrointestinal	10/24/2003	28.3						TA		
3	3	Gastrointestinal	10/25/2003	28.3						TA		
3	3	Gastrointestinal	10/26/2003	28.3						TA		
3	3	Gastrointestinal	10/27/2003	18.9						TA		
3	3	Gastrointestinal	10/28/2003	18.9						TA		
3	3	Gastrointestinal	10/29/2003	9.4	2					TA		
3	1	Epistaxis	10/31/2003	28.3	1							
3	3	Gastrointestinal	11/02/2003	37.7								
3	3	Gastrointestinal	11/03/2003	28.3	4					TA		
3	3	Gastrointestinal	11/09/2003	9.4						WB	CRYOPPT	TA
3	3	Gastrointestinal	11/10/2003	37.7						WB	CRYOPPT	TA
3	3	Gastrointestinal	11/11/2003	18.9	4					WB	CRYOPPT	TA
3	3	Gastrointestinal	11/17/2003	18.9						WB	CRYOPPT	TA
3	3	Gastrointestinal	11/18/2003	18.9						CRYOPPT	TA	
3	3	Gastrointestinal	11/19/2003	9.4						CRYOPPT	TA	
3	3	Gastrointestinal	11/20/2003	18.9						TA		
3	3	Gastrointestinal	11/21/2003	9.4	2					TA		

3	1	Epistaxis	11/30/2003	28.3	1						TA	
3	1	Ankle, right	12/05/2003	18.9								
3	1	Ankle, right	12/07/2003	9.4	1							
3	3	Gastrointestinal	12/21/2003	37.7								
3	3	Gastrointestinal	12/22/2003	28.3								
3	3	Gastrointestinal	12/23/2003	28.3								
3	3	Gastrointestinal	12/24/2003	28.3	2							
3	1	Epistaxis	01/11/2004	28.3	1							
3	2	Epistaxis	01/18/2004	28.3								
3	2	Epistaxis	01/19/2004	9.4								
3	2	Epistaxis	01/19/2004	18.9	1							
3	2	Ankle	01/25/2004	28.3								
3	2	Ankle	01/27/2004	9.4								
3	2	Ankle	01/28/2004	9.4	1							
3	3	Epistaxis	02/13/2004	18.9								
3	3	Epistaxis	02/14/2004	18.9	1							
3	2	Epistaxis	02/18/2004	28.3								
3	2	Epistaxis	02/19/2004	18.9	1							
3	3	Gastrointestinal	02/27/2004	37.7								
3	3	Gastrointestinal	02/28/2004	28.3								
3	3	Gastrointestinal	02/29/2004	28.3								
3	3	Gastrointestinal	03/01/2004	28.3	4							
3	3	Gastrointestinal	03/16/2004	28.3								
3	3	Gastrointestinal	03/17/2004	28.3								
3	3	Gastrointestinal	03/17/2004	28.3								
3	3	Gastrointestinal	03/18/2004	18.9								
3	3	Gastrointestinal	03/18/2004	28.3	4							
3	3	Gastrointestinal	03/22/2004	37.7							TA	
3	3	Gastrointestinal	03/23/2004	37.7							TA	
3	3	Gastrointestinal	03/23/2004	37.7							TA	
3	3	Gastrointestinal	03/24/2004	28.3							TA	
3	3	Gastrointestinal	03/24/2004	28.3							TA	
3	3	Gastrointestinal	03/25/2004	28.3							TA	
3	3	Gastrointestinal	03/25/2004	28.3							TA	
3	3	Gastrointestinal	03/26/2004	18.9							TA	
3	3	Gastrointestinal	03/26/2004	18.9							TA	
3	3	Gastrointestinal	03/27/2004	18.9							TA	
3	3	Gastrointestinal	03/27/2004	18.9							TA	
3	3	Gastrointestinal	03/28/2004	18.9							TA	
3	3	Gastrointestinal	03/28/2004	18.9							TA	
3	3	Gastrointestinal	03/29/2004	18.9							TA	
3	3	Gastrointestinal	03/29/2004	18.9							TA	
3	3	Gastrointestinal	03/30/2004	28.3	1						TA	
3	3	Gastrointestinal, melena	04/28/2004	37.7							TA	
3	3	Gastrointestinal, melena	04/29/2004	37.7							TA	
3	3	Gastrointestinal, melena	04/29/2004	37.7							TA	
3	3	Gastrointestinal, melena	04/30/2004	37.7							TA	
3	3	Gastrointestinal, melena	04/30/2004	37.7							TA	
3	3	Gastrointestinal, melena	05/01/2004	37.7							TA	
3	3	Gastrointestinal, melena	05/01/2004	37.7							TA	
3	3	Gastrointestinal, melena	05/02/2004	37.7							TA	
3	3	Gastrointestinal, melena	05/02/2004	37.7	2						TA	
3	2	Ankle, right	05/06/2004	28.3								
3	2	Ankle, right	05/07/2004	28.3	2							
3	3	Gastrointestinal, melena	07/20/2004	37.7							TA	
3	3	Gastrointestinal melena	07/20/2004	37.7							TA	
3	3	Gastrointestinal melena	07/21/2004	37.7							TA	
3	3	Gastrointestinal melena	07/21/2004	37.7							TA	
3	3	Gastrointestinal melena	07/22/2004	37.7							TA	

3	3	Gastrointestinal, melena	07/22/2004	28.3	1						TA	
3	3	Gastrointestinal, melena	08/15/2004	37.7								
3	3	Gastrointestinal, melena	08/16/2004	37.7								
3	3	Gastrointestinal, melena	08/16/2004	37.7								
3	3	Gastrointestinal, melena	08/17/2004	37.7								
3	3	Gastrointestinal, melena	08/17/2004	37.7	1							
3	3	Gastrointestinal, melena	09/07/2004	37.7							ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/08/2004	37.7							ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/08/2004	37.7							ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/09/2004	37.7							ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/09/2004	37.7							ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/10/2004	37.7							ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/10/2004	37.7							ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/11/2004	18.9	4						ETAMSILATE	TA
3	3	Gastrointestinal, melena	09/14/2004	37.7	1							
			09/15/2004					114	63			
			09/16/2004					141	95			
3	3	Gastrointestinal, melena	09/17/2004	18.9								
3	3	Gastrointestinal, melena	09/17/2004	9.4								
			09/17/2004					94.2	42			
3	3	Gastrointestinal, melena	09/18/2004	18.9								
3	3	Gastrointestinal, melena	09/18/2004	18.9								
			09/18/2004					111.2	42			
3	2	Gastrointestinal, melena	09/19/2004	18.9								
3	3	Gastrointestinal, melena	09/19/2004	18.9	3							
			09/20/2004					139	95			
			09/21/2004					162.6	142			
			09/22/2004					153.4	142			
			09/23/2004					160.2	95			
			09/24/2004					107.2	95			
			09/25/2004					91.5	95			
3	3	Gastrointestinal, melena	09/27/2004	28.3								
3	3	Gastrointestinal, melena	09/27/2004	9.4	2							
			09/27/2004					82.5	63			
			09/28/2004					158	95			
			09/29/2004					129.8	42			
			09/30/2004					67.5	28			
			10/01/2004					82.5	28			
			10/04/2004					67.5	28			
2	1	Ankle, right	10/20/2004	18.9								
3	1	Ankle, right	10/21/2004	18.9	1							
3	1	Ankle, right	11/15/2004	28.3	1							
3	1	Epistaxis	11/18/2004	28.3								
3	1	Epistaxis	11/19/2004	18.9	1							
3	3	Gastrointestinal	12/27/2004	28.3							ETAMSILATE	TA
3	3	Gastrointestinal	12/27/2004	28.3							ETAMSILATE	TA
3	3	Gastrointestinal	12/28/2004	28.3							ETAMSILATE	TA
3	3	Gastrointestinal	12/29/2004	28.3							ETAMSILATE	TA
3	3	Gastrointestinal	12/29/2004	28.3							ETAMSILATE	TA
3	3	Gastrointestinal	12/29/2004	28.3							ETAMSILATE	TA

3	3	Gastrointestinal	12/30/2004	18.9						ETAMSILATE	TA	
3	3	Gastrointestinal	12/30/2004	18.9	1					ETAMSILATE	TA	
3	3	Gastrointestinal	01/17/2005	47.2								
3	3	Gastrointestinal	01/17/2005	47.2								
3	3	Gastrointestinal	01/18/2005	37.7								
3	3	Gastrointestinal	01/18/2005	37.7								
3	3	Gastrointestinal	01/19/2005	37.7								
3	3	Gastrointestinal	01/19/2005	37.7	1							
3	3	Gastrointestinal	01/27/2005	37.7						TA		
3	3	Gastrointestinal	01/27/2005	47.2						TA		
3	3	Gastrointestinal	01/28/2005	37.7						TA		
3	3	Gastrointestinal	01/28/2005	37.7						TA		
3	3	Gastrointestinal	01/29/2005	37.7						TA		
3	3	Gastrointestinal	01/29/2005	37.7						TA		
3	3	Gastrointestinal	01/30/2005	37.7						TA		
3	3	Gastrointestinal	01/30/2005	37.7						TA		
3	3	Gastrointestinal	01/31/2005	14.2						TA		
3	3	Gastrointestinal	01/31/2005	37.7						TA		
3	3	Gastrointestinal	01/31/2005	9.4						TA		
3	3	Gastrointestinal	02/01/2005	47.2						WB	ETAMSILATE	IA x 2
3	3	Gastrointestinal	02/01/2005	47.2						WB	ETAMSILATE	IA x 2
3	3	Gastrointestinal	02/02/2005	28.3						WB	ETAMSILATE	IA
3	3	Gastrointestinal	02/02/2005	18.9						WB	ETAMSILATE	IA
			02/02/2005				152.6	95				
3	3	Gastrointestinal	02/03/2005	37.7						WB	ETAMSILATE	IA
3	3	Gastrointestinal	02/03/2005	28.3						WB	ETAMSILATE	IA
			02/03/2005					63				
3	3	Gastrointestinal	02/04/2005	37.7						WB	ETAMSILATE	IA
3	3	Gastrointestinal	02/04/2005	37.7						WB	ETAMSILATE	IA
			02/04/2005					142				
3	3	Gastrointestinal	02/05/2005	37.7						WB	ETAMSILATE	TA
3	3	Gastrointestinal	02/05/2005	37.7						WB	ETAMSILATE	TA
			02/05/2005					142				
3	3	Gastrointestinal	02/06/2005	37.7						WB	ETAMSILATE	TA
3	3	Gastrointestinal	02/06/2005	37.7						WB	ETAMSILATE	TA
3	3	Gastrointestinal	02/07/2005	37.7						WB	ETAMSILATE	IA
3	3	Gastrointestinal	02/07/2005	37.7						WB	ETAMSILATE	TA
			02/07/2005					142				
3	3	Gastrointestinal	02/08/2005	37.7						WB	ETAMSILATE	TA
3	3	Gastrointestinal	02/08/2005	37.7	2					WB	ETAMSILATE	IA
			02/08/2005									
			02/09/2005									
			02/10/2005									
			02/11/2005									
			02/14/2005									
3	3	Gastrointestinal	02/17/2005	47.2								
3	3	Gastrointestinal	02/18/2005	47.2								
3	3	Gastrointestinal	02/18/2005	47.2								
3	3	Gastrointestinal	02/19/2005	47.2								
3	3	Gastrointestinal	02/19/2005	47.2								
3	3	Gastrointestinal	02/20/2005	37.7								
3	3	Gastrointestinal	02/20/2005	37.7	1							
3	3	Gastrointestinal	03/03/2005	47.2								
3	3	Gastrointestinal	03/04/2005	28.3	4					CRYOPPI		
3	3	Gastrointestinal	03/14/2005	9.4						WB	TA	
3	3	Gastrointestinal	03/14/2005	37.7						WB	TA	
3	3	Gastrointestinal	03/14/2005	28.3						WB	TA	
3	3	Gastrointestinal	03/15/2005	37.7						WB	TA	
3	3	Gastrointestinal	03/15/2005	37.7	3					WB	TA	
			03/15/2005					79.2	63			
			03/16/2005					103.4	95			
			03/17/2005					117.8	95			
			03/18/2005					122	63			
			03/22/2005					95.6	63			
			03/23/2005					81.4	28			
			03/31/2005					93.8	42			
			04/01/2005					106.2	42			
3	3	Gastrointestinal	04/03/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/03/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/04/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/04/2005	18.9						WB	TA	
			04/04/2005					103.4	42			

3	3	Gastrointestinal	04/05/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/05/2005	18.9						WB	TA	
			04/05/2005				97.2	42				
3	3	Gastrointestinal	04/06/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/06/2005	18.9						WB	TA	
			04/06/2005				112.8	63				
3	3	Gastrointestinal	04/07/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/07/2005	18.9						WB	TA	
			04/07/2005				102.4	63				
3	3	Gastrointestinal	04/08/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/08/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/09/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/09/2005	18.9						WB	TA	
			04/09/2005				127.4	42				
3	3	Gastrointestinal	04/10/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/10/2005	18.9						WB	TA	
3	3	Gastrointestinal	04/11/2005	37.7						WB	TA	
3	3	Gastrointestinal	04/11/2005	37.7						WB	TA	
			04/11/2005				94.8	63				
3	3	Gastrointestinal	04/12/2005	37.7						WB	TA	
3	3	Gastrointestinal	04/12/2005	37.7	4					WB	TA	
			04/12/2005				93.8	95				
3	3	Gastrointestinal	04/13/2005	37.7						WB	TA	TA
3	3	Gastrointestinal	04/13/2005	37.7						WB	TA	TA
			04/13/2005				109	95				
			04/14/2005				121	95				
3	3	Gastrointestinal	04/14/2005	37.7						TA		
3	3	Gastrointestinal	04/14/2005	37.7						TA		
3	3	Gastrointestinal	04/15/2005	37.7						WB	TA	
3	3	Gastrointestinal	04/15/2005	37.7						WB	TA	
			04/15/2005				125.2	95				
3	3	Gastrointestinal	04/16/2005	37.7						TA		
3	3	Gastrointestinal	04/16/2005	37.7						TA		
3	3	Gastrointestinal	04/17/2005	37.7						TA		
3	3	Gastrointestinal	04/17/2005	37.7	4					TA		
			04/18/2005				155	142				
			04/19/2005				45.6	95				

1MAE-104: Bleeding Episode by Individual Patient: Ctr 1 - PL (b)(8)

04/19/2002 Adverse event - not serious - bronchitis acuta. All data one may find in AE's form. A/E not related to study drug administration. On Feb. 9th patient stated to take ursodeoxycholic acid (750 mg/day) for "hepatoprotection" (prophylaxis) as prescribed by patient's physician. 07/03/2002 Patient took for three days rofecoxib (pain killer due to pain in elbow. 06/18/2003 Patient has come earlier for visit no 06 (18 months) because he's going abroad. 05/20/2006 Patient moved to the UK with his remaining wife. Study completion visit filled in without detailed patient information.

VWD type	S	Bleeding Site	Date	Dose (U/kg)	R	F-8 -1	VF-1	F8 -2	VF -2	Concomitant Medications
3	1	Joint, elbow	02/11/2002	42.9	1					
3	2	Joint, elbow	03/05/2002	42.9						
3	2	Joint, elbow	03/08/2002	42.9						
3	2	Joint, elbow	03/09/2002	28.6						
3	2	Joint, elbow	03/14/2002	42.9						
3	2	Joint, elbow	03/18/2002	42.9	1					
3	1	Joint, elbow	04/02/2002	42.9	1					
3	1	Muscle	05/19/2002	42.9	1					
3	1	Muscle	08/27/2002	42.9	1					
3	1	Muscle	09/10/2002	35.7	1					
3	1	Muscle	09/29/2002	42.9	1					
3	2	Ankle	10/12/2002	42.9						
3	2	Ankle	10/14/2002	28.6						
3	2	Ankle	10/15/2002	35.7	2					
3	2	Ankle	10/26/2002	42.9						
3	2	Ankle	10/27/2002	21.4						
3	2	Ankle	10/30/2002	21.4						
3	2	Ankle	10/31/2002	28.6	2					
3	1	Ankle	11/03/2002	35.7	1					
3	1	Muscle	11/03/2002	35.7	1					
3	1	Joint, left elbow	12/05/2002	14.3						
3	1	Joint, left elbow	12/05/2002	7.1						
3	1	Joint, left elbow	12/07/2002	14.3	1					
3	1	Joint, right elbow	12/10/2002	7.1						









3	5	Gastrointestinal	06/04/2002	39.5	2					WB	KOATE	
3	2	Epistaxis	06/21/2002	26.3	1					TA		
3	1	Epistaxis	07/09/2002	19.7						ETAMSILATE		
3	1	Epistaxis	07/11/2002	39.5	2							
3	3	Gastrointestinal	07/12/2002	39.5								
3	3	Gastrointestinal	07/13/2002	39.5						WB	TA	
3	3	Gastrointestinal	07/14/2002	39.5						TA		
3	3	Gastrointestinal	07/15/2002	39.5						TA		
3	3	Gastrointestinal	07/16/2002	39.5						TA		
3	3	Gastrointestinal	07/17/2002	39.5						TA		
3	3	Gastrointestinal	07/18/2002	13.2	2					TA		
3	3	Gastrointestinal	07/31/2002	26.3						WB	TA	
3	3	Gastrointestinal	08/01/2002	26.3						WB	TA	
3	3	Gastrointestinal	08/02/2002	13.2						WB	TA	
3	3	Gastrointestinal	08/03/2002	13.2						WB	CRYOPPT	TA
3	3	Gastrointestinal	08/04/2002	13.2						WB	TA	
3	3	Gastrointestinal	08/05/2002	13.2						WB	TA	
3	3	Gastrointestinal	08/06/2002	13.2						WB	TA	
3	3	Gastrointestinal	08/08/2002	13.2	2					WB	TA	
3	2	Gastrointestinal	08/13/2002	26.3						WB	TA	
3	2	Gastrointestinal	08/14/2002	26.3						WB	TA	
3	2	Gastrointestinal	08/15/2002	13.2						TA		
3	2	Gastrointestinal	08/16/2002	13.2	2					TA		
3	3	Gastrointestinal	08/19/2002	26.3						TA		
3	3	Gastrointestinal	08/20/2002	26.3						TA		
3	3	Gastrointestinal	08/21/2002	26.3						TA		
3	3	Gastrointestinal	08/22/2002	26.3						TA		
3	3	Gastrointestinal	08/23/2002	26.3	2					TA		
3	3	Gastrointestinal	08/29/2002	39.5						ETAMSILATE	TA	
3	3	Gastrointestinal	08/30/2002	39.5						ETAMSILATE	TA	
3	3	Gastrointestinal	08/31/2002	26.3						ETAMSILATE	TA	
3	3	Gastrointestinal	09/01/2002	26.3						ETAMSILATE	TA	
3	3	Gastrointestinal	09/02/2002	26.3	2					ETAMSILATE	TA	
3	2	Epistaxis	10/07/2002	26.3								
3	2	Epistaxis	10/08/2002	13.2								
3	2	Epistaxis	10/09/2002	13.2	2							
3	3	Gastrointestinal	12/21/2002	26.3								
3	3	Gastrointestinal	12/22/2002	39.5						WB, ETAMSILATE, FVIII, TA, KOATE		
3	3	Gastrointestinal	12/23/2002	39.5						WB, ETAMSILATE, FVIII, TA, KOATE		
3	3	Gastrointestinal	12/24/2002	39.5						ETAMSILATE	FVIII, TA	KOATE
3	3	Gastrointestinal	12/25/2002	19.7						ETAMSILATE	FVIII, TA	KOATE
3	3	Gastrointestinal	12/26/2002	19.7						ETAMSILATE	FVIII, TA	KOATE
3	3	Gastrointestinal	12/27/2002	19.7						ETAMSILATE	FVIII, TA	KOATE
3	3	Gastrointestinal	12/28/2002	19.7						ETAMSILATE	FVIII, TA	KOATE
3	3	Gastrointestinal	12/29/2002	19.7						ETAMSILATE	FVIII, TA	KOATE
3	3	Gastrointestinal	12/30/2002	13.2						ETAMSILATE	FVIII, TA	KOATE
3	3	Gastrointestinal	12/31/2002	6.6	3					ETAMSILATE	FVIII, TA	KOATE
3	1	Epistaxis	01/30/2003	26.3	3							
3	2	Echymosis	02/10/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/11/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/12/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/13/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/14/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/15/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/16/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/17/2003	26.3						ETAMSILATE		
3	3	Echymosis	02/18/2003	26.3	3					ETAMSILATE		
3	1	Epistaxis	02/24/2003	19.7	1					TA		
3	1	Epistaxis	02/26/2003	26.3	1					TA		
3	2	Epistaxis	03/14/2003	32.9						TA		
3	2	Epistaxis	03/16/2003	32.9						TA		
3	2	Epistaxis	03/18/2003	32.9	2							
3	3	Epistaxis	03/22/2003	39.5								
3	3	Epistaxis	03/28/2003	65.8								
3	3	Epistaxis	03/29/2003	39.5								
3	3	Epistaxis	03/30/2003	19.7	3							
3	2	Epistaxis	03/31/2003	39.5						ETAMSILATE	TA	
3	2	Gastrointestinal	03/31/2003	39.5						ETAMSILATE	TA	
3	2	Epistaxis	04/01/2003	39.5	1					ETAMSILATE	TA	
3	2	Gastrointestinal	04/01/2003	39.5	1					ETAMSILATE	TA	
3	3	Gastrointestinal	04/04/2003	26.3						WB	ETAMSILATE	TA
3	3	Gastrointestinal	04/05/2003	26.3						ETAMSILATE		

3	3	Gastrointestinal	04/06/2003	26.3						ETAMSILATE		
3	3	Gastrointestinal	04/07/2003	26.3						ETAMSILATE		
3	3	Gastrointestinal	04/08/2003	26.3						ETAMSILATE		
3	3	Gastrointestinal	04/09/2003	26.3						ETAMSILATE		
3	3	Gastrointestinal	04/10/2003	26.3	1					ETAMSILATE		
3	3	Gastrointestinal	06/18/2003	39.5						WB	ETAMSILATE	TA
3	3	Gastrointestinal	06/19/2003	39.5						WB	ETAMSILATE	TA
3	3	Gastrointestinal	06/20/2003	39.5						WB	ETAMSILATE	TA
3	3	Gastrointestinal	06/21/2003	39.5						WB	ETAMSILATE	TA
3	3	Gastrointestinal	06/22/2003	39.5						ETAMSILATE	TA	
3	3	Gastrointestinal	06/23/2003	39.5						ETAMSILATE	TA	
3	3	Gastrointestinal	06/24/2003	26.3	1					ETAMSILATE	TA	
3	2	Epistaxis	07/07/2003	39.5						ETAMSILATE	TA	
3	2	Epistaxis	07/08/2003	39.5						ETAMSILATE	TA	
3	2	Epistaxis	07/09/2003	26.3						ETAMSILATE	TA	
3	2	Epistaxis	07/10/2003	26.3	3					ETAMSILATE	TA	
3	3	Gastrointestinal	09/10/2003	26.3								
3	3	Gastrointestinal	09/10/2003	26.3								
3	3	Gastrointestinal	09/11/2003	26.3						WB		
3	3	Gastrointestinal	09/11/2003	26.3	3					WB		
3	3	Gastrointestinal	09/16/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/16/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/17/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/17/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/18/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/18/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/19/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/20/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/20/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/21/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/22/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/22/2003	6.6						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/22/2003	19.7						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/23/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/24/2003	26.3						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	09/25/2003	26.3	2					AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	10/02/2003	13.2						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	10/03/2003	13.2	3					AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	10/07/2003	13.2						AMINOMIX	WB	CRYOPPT
3	3	Gastrointestinal	10/08/2003	13.2	2					AMINOMIX	WB	CRYOPPT
3	2	Gastrointestinal	10/15/2003	13.2						WB		
3	2	Gastrointestinal	10/16/2003	13.2	1							
3	3	Epistaxis	11/30/2003	52.6								
3	3	Epistaxis	12/01/2003	52.6						WB	ETAMSILATE	
3	3	Epistaxis	12/02/2003	52.6						WB	ETAMSILATE	
3	3	Epistaxis	12/03/2003	52.6						WB	ETAMSILATE	
3	3	Epistaxis	12/04/2003	52.6	1					ETAMSILATE		

**TMAE-104: Bleeding Episode by Individual Patient: Ctr 1 - Pt (b)(6)**

03/28/2002 The patient had been admitted to hospital due to GI bleeding episode (gastric ulcer). After confirmation of diagnosis (gastroscopy) of GI bleeding therapy with Vitale RBC transfusion, omeprazole i.v. and tranexamic acid i.v. was started. Improvement has been noticed on 23rd (no dark stools and higher level of hemoglobin after RBC transfusion on 22nd of Mar.). 03/28/2002. On 27th the 2nd gastroscopy was performed and confirmed that bleeding is stopped. Patient discharged on 28th of March 2002. 04/12/2002: Due to hemataesis patient had been admitted to hospital. Gastroscopy revealed angiodysplasia of duodenum. Patient did not need RBC transfusion. The dosage of Vitale increased. 04/12/2002 Bleeding episode stopped on 12.04.02 (started on 11.04.02). Gastroscopy performed on Apr. 17th 02 confirmed recovery. Patient was discharged on Apr. 19th, 2002. 05/28/2002: additional lab test: Hgb 11.3 g/dl, hct 35.3 %, WBC 4.0x10e3/µl, platelet 275.0x10e3/µl. 06/12/2002 On 29th of May and on 11th of June episodes of hematemesis occurred. After injections of Vitale bleeding stopped. On the previous day, she received 300 ml of RBC transfusion. On 6/12/02 Hgb 11.2 g/dl. 06/12/2002 Patient refused to be hospitalized. General condition is good on June 12th, 02. Patient has been given 12000 µg of Vitale for home treatment. 06/12/2002 Patient does not have any documentation of RBC transfusion on 06/12/02. 09/09/2002: Visit after 6 months. On Aug. 7th, 8th and Sep. 3rd and 4th patient received blood transfusion for anemia due to menorrhagia. On Aug. 10th she received also blood transfusion after episode. 09/09/2002: GI GI bleeding (hematemesis). Patient had not been hospitalized and does not possess any documentation. All data concerning blood transfusion and other concomitant medications has been entered. 09/09/2002. Info at visit after 6 months. The general condition of patient is good. 12/10/2002: (Planned visit after 9 months). on Sep. 13th, 2002 patient received blood transfusion to treat anemia due to GI bleeding episode (patient not hospitalized; blood transfusion given in hospital in Poznań). On Oct. GI patient started to receive oral contraceptive for menorrhagia (Mircilon). Tranexamic acid was given for GI bleeding and during menstruations (September '02, Oct. '02, Nov. '02). Omeprazole was given for GI bleeding. 12/27/2002. On Dec. 27th patient was been admitted to study site due to GI bleeding (melena and hematemesis). She received Vitale, blood transfusion, omeprazole, tranexamic acid. Gastroscopy and colonoscopy did not reveal site of bleeding. She was discharged on Dec. 31st, 2002 on her demand. 03/11/2003: Control visit. The general condition is good. Between Jan. 3th, 2003 and Jan. 8th, 2003 was receiving azithromycin due to pharyngitis. On Feb. 19th, 2003 received 600 ml of blood due to anemia after melena. She was not hospitalized on that day, with these lab data: Hgb 13.0 g/dl, Hct:

39.4 %. 06/16/2003 Control visit. The general condition is good. On Apr. 9th (600 ml), Apr. 10th (300 ml), May 19th (300 ml) and June 15th (300 ml) patient received blood transfusion due to GI bleeding episodes (melena) 06/18/2003 Patient was not hospitalized. 05/19/2003 Control visit (13 months visit). On July 19th, 2003 and on Sept. 11th, 2003 she received blood transfusion due to anemia after GI bleeding (melena). 01/14/2005. On Dec. 20th, 2004 the patient received Immunate for nose bleeding because she did not have the study product at home. The same happened on 11th and 12th Jan., 2005 when she injected herself Immunate. 01/14/2005 For GI bleeding. 05/29/2006 Visit no. 17 in the "efficacy study" on May 29th, 2006. On the same day she was included into "PK study" (29.30.31.05.2006) For PK she received 2500 iu of Vitale. 10/20/2006. On Aug. 11th, 2006 severe bleeding episode occurred - melena. Patient infused 5 doses of 1MAC-104 without good effect - she continued to bleed. She received blood transfusion for anemia (No blood tests results available since she was treated in another hospital) as well as tranexamic acid and 3 infusions of Immunate. 01/19/2007. On Jan. 17th, 2007 PK (2nd) analysis. Final visit on Jan. 19th, 2007. Due to a shortage of Vitale, the patient treated bleeding in Dec. 2006 with Fandhi (on: 05.12.06, 06.12.06, 13.12.06, 14.12.06, 15.12.06, 22.12.06, 23.12.06 each time 3000 iu (total 21000 iu)).

VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -I	VF-1	F8 2	VF-2	Concomitant Medications		
3	2	Gynaecologic, menorrhagia	03/14/2002	37.7	1					TA		
3	3	Gastrointestinal	03/21/2002	56.6								
3	3	Gastrointestinal	03/22/2002	37.7	4					RBC, CONCENTRATED	TA	
3	3	Gastrointestinal	03/23/2002	37.7	1					TA		
3	3	Gastrointestinal	04/11/2002	18.9								
3	3	Gastrointestinal	04/11/2002	37.7	1							
3	3	Gastrointestinal	04/12/2002	56.6						TA		
3	3	Gastrointestinal	04/12/2002	56.6	1					TA		
3	1	Gynaecologic	05/12/2002	37.7	2					TA		
3	3	Gastrointestinal	05/18/2002	56.6						TA		
3	3	Gastrointestinal	05/19/2002	56.6	2					TA		
3	2	Gastrointestinal	05/29/2002	56.6						TA		
3	2	Gastrointestinal	05/30/2002	56.6	2					TA		
3	2	Gastrointestinal	06/11/2002	75.5	2					WB	TA	
3	2	Gastrointestinal	06/12/2002	37.7	2					TA		
3	2	Gastrointestinal	06/19/2002	56.6	2					TA		
3	2	Gastrointestinal	06/25/2002	56.6	2					TA		
3	2	Gynaecologic, menorrhagia	07/08/2002	37.7	2					WB	TA	
3	2	Gastrointestinal	07/13/2002	56.6						WB	TA	
3	2	Gastrointestinal	07/14/2002	56.6	2					WB	TA	
3	3	Gynaecologic, menorrhagia	08/07/2002	37.7						WB	TA	
3	3	Gynaecologic, menorrhagia	08/08/2002	37.7	3					WB	TA	
3	2	Gastrointestinal	08/10/2002	56.6	2					WB	TA	
3	2	Gynaecologic, menorrhagia	09/03/2002	37.7	3					WB	TA	
3	3	Gastrointestinal	09/12/2002	56.6						TA		
3	3	Gastrointestinal	09/13/2002	56.6	2					WB	TA	
3	2	Gynaecologic, menorrhagia	10/01/2002	75.5	2					TA		
3	2	Gastrointestinal	12/18/2002	9.4						WB	TA	
3	2	Gastrointestinal	12/18/2002	47.2	2					WB	TA	
3	3	Gastrointestinal	12/23/2002	56.6						WB	TA	
3	3	Gastrointestinal	12/24/2002	37.7	4					WB	TA	
3	3	Gastrointestinal	12/27/2002	47.2						WB	TA	
3	3	Gastrointestinal	12/28/2002	47.2						WB	TA	
3	3	Gastrointestinal	12/29/2002	47.2	2					WB	TA	
3	3	Gastrointestinal	02/19/2003	56.6	2					WB	TA	
3	3	Gastrointestinal	04/08/2003	75.5						EXACYL		
3	3	Gastrointestinal	04/09/2003	16.6						WB	EXACYL	
3	3	Gastrointestinal	04/10/2003	56.6	2					WB	EXACYL	
3	3	Gastrointestinal	05/19/2003	56.6	2					WB	EXACYL	
3	3	Gastrointestinal	06/15/2003	56.6	2					WB	EXACYL	
3	3	Gastrointestinal, melena	07/19/2003	56.6	2					WB	TA	
3	3	Gastrointestinal, melena	09/11/2003	56.6	2					WB	TA	
3	2	Gastrointestinal	10/17/2003	56.6	2					TA		
3	2	Gastrointestinal	11/30/2003	56.6	2					TA		
3	2	Gastrointestinal, (black colour of the stool)	01/08/2004	56.6	2					WB	TA	
3	2	Gastrointestinal, (black colour of the stool)	02/16/2004	56.6						WB	TA	

3	2	Gastrointestinal, (black colour of the stool)	02/17/2004	37.7	2					WB	TA
3	3	Gastrointestinal	03/31/2004	56.6	2					TA	
3	3	Gastrointestinal	04/04/2004	56.6						WB	TA
3	3	Gastrointestinal	04/05/2004	56.6						TA	
3	3	Gastrointestinal	04/06/2004	56.6						WB	TA
3	3	Gastrointestinal	04/07/2004	18.9						TA	
3	3	Gastrointestinal	04/08/2004	75.5						TA	
3	3	Gastrointestinal	04/09/2004	75.5						WB	TA
3	3	Gastrointestinal	04/10/2004	75.5	2					WB	TA
3	3	Gastrointestinal, gastric haemorrhagic	04/15/2004	75.5						WB	TA
3	3	Gastrointestinal, gastric haemorrhagic	04/17/2004	75.5						TA	
3	3	Gastrointestinal, gastric haemorrhagic	04/18/2004	75.5						TA	
3	3	Gastrointestinal, gastric haemorrhagic	04/19/2004	56.6						WB	TA
3	3	Gastrointestinal, gastric haemorrhagic	04/20/2004	56.6						WB	TA
3	3	Gastrointestinal, gastric haemorrhagic	04/21/2004	37.7	2					WB	TA
3	3	Gastrointestinal	05/02/2004	75.5	2					WB	TA
3	3	Gastrointestinal	06/01/2004	75.5	2					TA	
3	3	Gastrointestinal, melena	08/09/2004	56.6	2					WB	TA
3	3	Gastrointestinal, melena	09/28/2004	56.6						TA	
3	2	Gastrointestinal, melena	09/29/2004	56.6						WB	TA
3	3	Gastrointestinal, melena	09/30/2004	56.6	2					WB	TA
3	3	Gastrointestinal	10/18/2004	56.6	2					WB	TA
3	3	Gastrointestinal	11/25/2004	56.6	2					WB	TA
3	3	Gastrointestinal	01/20/2005	56.6						WB	TA
3	3	Gastrointestinal	01/21/2005	56.6						WB	TA
3	3	Gastrointestinal	01/22/2005	56.6						TA	
3	2	Gastrointestinal	01/23/2005	56.6						TA	
3	3	Gastrointestinal	01/24/2005	56.6						TA	
3	3	Gastrointestinal	01/25/2005	75.5						WB	TA
3	3	Gastrointestinal	01/25/2005	75.5						WB	TA
3	3	Gastrointestinal	01/26/2005	75.5						WB	TA
3	3	Gastrointestinal	01/26/2005	75.5						WB	TA
3	3	Gastrointestinal	01/27/2005	37.7						WB	TA
3	3	Gastrointestinal	01/27/2005	75.5	1					WB	TA
3	3	Gastrointestinal	03/14/2005	18.9						WB	TA
3	3	Gastrointestinal	03/14/2005	56.6	2					WB	TA
3	3	Gastrointestinal	05/06/2005	75.5						WB	TA
3	3	Gastrointestinal	05/07/2005	75.5						WB	TA
3	3	Gastrointestinal	05/08/2005	37.7	2					WB	TA
3	3	Gastrointestinal	05/30/2005	75.5						TA	
3	3	Gastrointestinal	05/31/2005	75.5	2					WB	TA
3	3	Gastrointestinal, melena	06/29/2005	75.5						TA	
3	3	Gastrointestinal, melena	06/29/2005	75.5	2					TA	
3	3	Gastrointestinal, melena	07/14/2005	75.5						TA	
3	3	Gastrointestinal, melena	07/15/2005	56.6						RBC	TA
3	3	Gastrointestinal, melena	07/15/2005	18.9						RBC	TA
3	3	Gastrointestinal, melena	07/16/2005	75.5	2					RBC	TA
3	3	Gastrointestinal, melena	08/01/2005	37.7	4					RBC	TA
3	3	Gastrointestinal	02/15/2006	75.5						WB	TA

3	3	Gastrointestinal, melena	02/19/2006	75.5						WB	TA
3	3	Gastrointestinal, melena	02/20/2006	75.5						TA	
3	3	Gastrointestinal, melena	02/21/2006	56.6	3					WB	TA
3	3	Gastrointestinal, melena	02/27/2006	75.5						TA	
3	3	Gastrointestinal, melena	02/28/2006	75.5	2					WB	
3	3	Gastrointestinal, melena	04/03/2006	75.5						TA	
3	3	Gastrointestinal, melena	04/04/2006	75.5	2					WB	TA
3	3	Gastrointestinal, melena	08/11/2006	75.5						WB	TA
3	3	Gastrointestinal, melena	08/12/2006	75.5						TA	
3	3	Gastrointestinal, melena	08/13/2006	75.5						WB	TA
3	3	Gastrointestinal, melena	08/14/2006	75.5						WB	TA
3	3	Gastrointestinal, melena	08/15/2006	37.7	4					WB	TA
3	3	Gastrointestinal, melena	11/13/2006	56.6						WB	TA
3	3	Gastrointestinal, melena	11/14/2006	56.6						WB	TA
3	3	Gastrointestinal, melena	11/15/2006	56.6	2					WB	TA
3	3	Gastrointestinal, melena	12/02/2006	56.6						WB	TA
3	3	Gastrointestinal, melena	12/03/2006	75.5						WB	TA
3	3	Gastrointestinal, melena	12/04/2006	75.5	4					WB	TA

TMAE-104: Bleeding Episode by Individual Patient: Ctr 1 - PKmg											
01/24/2007 PK study or 24.01.2007 (2000 mg of wilotin 5420051817)											
VWD type	S	Bleeding Site	Date	Dose IU/kg	R	IF -1	VF -1	IF -2	VF -2	Concomitant Medications	
3	1	Ankle, right	05/01/2003	20	2						
3	1	Ankle, right	06/06/2003	20							
3	1	Ankle, right	06/07/2003	20	2						
3	2	Ankle, right	06/22/2003	20							
3	2	Ankle, right	06/23/2003	20							
3	2	Ankle, right	06/24/2003	20							
3	2	Ankle, right	06/25/2003	40	2						
3	1	Ankle, right	07/04/2003	40	2						
3	1	Ankle, right	08/28/2003	20	2						
3	1	Joint, left elbow	09/03/2003	40	3						
3	1	Ankle, right	09/16/2003	20	2						
3	1	Ankle, right	09/29/2003	40							
3	1	Ankle, right	09/30/2003	20	3						
3	1	Ankle, right	10/15/2003	20	3						
3	1	Ankle, right	10/17/2003	20	3						
3	1	Ankle, right	10/20/2003	20	2						
3	1	Ankle, right	11/06/2003	40	2						
3	2	Ankle, right	11/12/2003	20							
3	2	Ankle, right	11/13/2003	40							
3	2	Ankle, right	11/14/2003	20	2						
3	1	Ankle, right	11/24/2003	20	2						
3	1	Ankle, right	11/27/2003	20	2						
3	1	Ankle, right	12/13/2003	20							
3	1	Ankle, right	12/14/2003	20	2						
3	1	Ankle, right	01/01/2004	40							
3	1	Ankle, right	01/02/2004	20	2						
3	1	Ankle, right	01/26/2004	20	2						
3	1	Ankle, right	01/29/2004	20	2						
3	2	Ankle, right	05/04/2004	40							
3	2	Ankle, right	05/05/2004	40							















type	S	Bleeding Site	Date	IU/kg	R	-1	1	2	-2	Concomitant Medications
3	1	Epistaxis	08/11/2003	14.7	1					
3	2	Other, subcutaneous	12/29/2003	22.1	2					
3	2	Oral	01/07/2004	22.1	2					
3	2	Oral	05/31/2004	22.1	2					

TMAE-104: Bleeding Episode by Individual Patient: Ctr 3 - P(b)(6)										
12/21/2005 Drug dispensing, all substitutive treatments were done in hospital so that the patient did not take any medication at home.										
VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VI 1	F8 -2	VF -2	Concomitant Medications
1	2	Gynaecologic	06/03/2004	23.1						EACA
			06/03/2004					57.2	95	
			06/03/2004					66.4	95	
			06/03/2004			13.8	63	57.7	95	
1	2	Gynaecologic	06/04/2004	23.1	2					EACA
			06/04/2004					107.4	95	
			06/04/2004			74	63	107.4	95	
1	2	Gynaecologic	07/19/2004	23.1	2					EACA

TMAE-104: Bleeding Episode by Individual Patient: Ctr 5 - P(b)(6)										
No notes on patients in Center 5										
VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VI 1	F8 -2	VF -2	Concomitant Medications
3	2	Oral	12/19/2002	32.3	1					
3	2	Joint	01/11/2003	32.3	1					
3	2	Joint	01/16/2003	32.3	1					
3	2	Joint	01/29/2003	32.3	1					
3	2	Joint	01/31/2003	32.3						
3	2	Joint	02/01/2003	32.3	1					
3	2	Joint	02/05/2003	32.3						
3	2	Joint	02/07/2003	32.3	1					
3	2	Joint	02/22/2003	32.3						
3	2	Joint	02/23/2003	32.3	1					
3	1	Joint	04/28/2003	30.3						
3	1	Joint	04/29/2003	30.3	1					
3	1	Joint	05/07/2003	30.3	1					
3	1	Joint	05/31/2003	30.3	1					
3	1	Joint	07/12/2003	30.3	1					
3	1	Joint	07/28/2003	30.3	1					
3	2	Joint	10/12/2003	29.4	1					
3	2	Joint	12/19/2003	29.4	1					
3	2	Joint	12/31/2003	29.4						
3	2	Joint	01/02/2004	29.4	1					
3	1	Joint	01/15/2004	29.4	1					
3	2	Joint	01/25/2004	29.4						
3	2	Joint	01/26/2004	29.4						
3	2	Joint	01/27/2004	29.4	2					
3	2	Joint	01/30/2004	29.4						
3	2	Joint	02/01/2004	29.4	2					
3	1	Joint	02/19/2004	29.4	1					
3	1	Joint	02/22/2004	29.4	1					
3	1	Muscle	05/09/2004	27.4	1					
3	1	Joint	06/06/2004	27.4	1					
3	1	Joint	06/22/2004	27.4	1					
3	1	Joint	06/25/2004	28.6	1					
3	2	Joint	09/02/2004	29.6	1					
3	2	Joint	10/26/2004	27.8	1					
3	2	Joint	11/08/2004	27.8	1					
3	2	Joint	11/15/2004	27.8	1					
3	1	Joint	11/24/2004	27.8	1					
3	1	Joint	01/06/2005	25.6	1					
3	1	Joint	02/05/2005	25.6						
3	1	Joint	02/06/2005	12.8						
3	1	Joint	02/06/2005	12.8	1					
3	1	Joint	03/23/2005	25.6	1					
3	2	Joint	05/02/2005	25.6	1					
3	1	Joint	06/12/2005	25.6	1					
3	2	Muscle	06/17/2005	25.6						











2	3	Gastrointestinal	03/25/2004	12.5						KONAKION	TA	
2	3	Gastrointestinal	03/26/2004	25	2					KONAKION	TA	
2	2	Gastrointestinal	04/30/2004	25	2					KONAKION	TA	
2	2	Gastrointestinal	05/12/2004	25	2					KONAKION	TA	

**TMAE-104: Bleeding Episode by Individual Patient: Ctr 6 - PI(b)(6)**

12/09/2004: Patient 602 is a woman born in 1956. She has von Willebrand's disease in a severe form but is otherwise healthy. She has had previous bleeds due to von Willebrand's disease and developed arthropathy. Her main problems regarding von Willebrand's disease has otherwise been nose bleeds with increasing problems during the last years. This is sometimes related to stress. Due to increased problems with nose bleeds prophylaxis with Haemate started in December 2003. The patient was willing to participate in the Wiale clinical trial and after informed consent she was included on 22nd of March 2004. She started with one weekly injection. The dose was increased on May 3 to two weekly injections. Extra treatment was given in case of bleeding. The patient was on home treatment but in some cases she needed help with injections. She was used to take one or in some cases 2 injections (the day of bleeding and the day after) of factor concentrate in case of bleeding. Most often one injection with factor concentrate is enough for stopping the bleeding. She experienced with Wiale that the effect on bleeding seemed to be slower than she previously had noted with Haemate. Decision of withdrawal from study was taken 16th of August 2004.

VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VF- 1	F8 -2	VF -2	Concomitant Medications
3	2	Epistaxis, nose	05/03/2004	28.6	2					TA
3	3	Epistaxis, nose	07/08/2004	28.6						TA
3	3	Epistaxis, nose	07/09/2004	28.6						TA
3	3	Epistaxis, nose	07/10/2004	28.6						TA
3	3	Epistaxis, nose	07/11/2004	28.6						TA
3	3	Epistaxis, nose	07/12/2004	28.6	2					TA

**TMAE-104: Bleeding Episode by Individual Patient: Ctr 7 - PI(b)(6)**

02/16/2004: The patient has been on prophylaxis every 2nd day. The patient is included after contract with Octapharma 05/12/2004. The GI symptoms were somewhat less than e.g. one year previously, but he felt no difference during the 3 weeks on Wiale than the previous 3 weeks on Haemate. 08/17/2004: Principally unchanged condition, maybe less pronounced GI symptoms with irregular motility on Lanzo. The patient stopped the treatment with Wiale since it was suggested from Octapharma to continue on named patient basis. However, since he did not find any advantage with Wiale in comparison to Haemate he has continued with Haemate.

VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VF- 1	F8 -2	VF -2	Concomitant Medications
2	1	Gastrointestinal, blood just around the stool	04/04/2004	25.6	5					CYKLO
2	1	Gastrointestinal, blood just around the stool	04/20/2004	25.6	5					CYKLO
2	1	Gastrointestinal	05/23/2004	25.6	1					CYKLO
2	1	Gastrointestinal	06/20/2004	25.6	1					CYKLO
2	1	Gastrointestinal	08/03/2004	25.6						CYKLO
2	1	Gastrointestinal	08/04/2004	12.8	5					CYKLO
2	2	Gastrointestinal	09/05/2004	25.6						CYKLO
2	2	Gastrointestinal	09/06/2004	25.6	5					CYKLO
			09/12/2005					29.5	42	

**TMAE-104: Bleeding Episode by Individual Patient: Ctr 7 - PI(b)(6)**

The patient was on demand treatment but he has not required any Wiale. 08/29/2006: There were missing efficacy ratings throughout the CRFs, it is not possible to make a proper evaluation. Investigator did not know if the lesions are healed or not. 02/05/2007: It was agreed upon that the patient returns the medication to his local pharmacy. It will be sent to Vienna from there.

VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VF- 1	F8 -2	VF -2	Concomitant Medications
2	2	Gastrointestinal	02/03/2006	35.3						TA
2	2	Gastrointestinal	02/04/2006	23.5	5					TA
2	2	Gastrointestinal	02/08/2006	47.1						RBC
2	2	Gastrointestinal	02/09/2006	47.1						RBC
2	2	Gastrointestinal	02/10/2006	47.1						TA
2	2	Gastrointestinal	02/11/2006	23.5						TA
2	2	Gastrointestinal	02/12/2006	47.1						TA
2	2	Gastrointestinal	02/13/2006	23.5						TA
2	2	Gastrointestinal	02/14/2006	23.5						TA
2	2	Gastrointestinal	02/15/2006	23.5	5					TA
2	3	Gastrointestinal	02/20/2006	47.1						TA
2	3	Gastrointestinal	02/21/2006	47.1						TA
2	3	Gastrointestinal	02/22/2006	47.1						TA
2	3	Gastrointestinal	02/23/2006	47.1						TA
2	3	Gastrointestinal	02/24/2006	47.1						TA
2	3	Gastrointestinal	02/25/2006	47.1						TA

2	3	Gastrointestinal	02/26/2006	23.5						TA	TA	
2	3	Gastrointestinal	02/27/2006	23.5						TA	TA	
2	3	Gastrointestinal	02/28/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/01/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/02/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/03/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/04/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/05/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/06/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/07/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/08/2006	35.3						TA	TA	
2	3	Gastrointestinal	03/09/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/10/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/11/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/12/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/13/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/14/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/15/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/16/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/17/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/18/2006	35.3						RBC	TA	TA
2	3	Gastrointestinal	03/19/2006	11.8						TA	TA	
2	3	Gastrointestinal	03/19/2006	23.5						TA	TA	
2	3	Gastrointestinal	03/20/2006	35.3	5					TA	TA	
			05/02/2006			38.5	28					
			08/28/2006			36	14					
			12/11/2006			30.5	14					

**TMAE-104: Bleeding Episode by Individual Patient: Ctr 8 - Pt (b)(6)**

No patient notes available.

VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VF -1	F8 -2	VF -2	Concomitant Medications
2	2	Epistaxis	05/25/2005	26	2					
2	3	Epistaxis	06/08/2005	26						
2	3	Epistaxis	06/08/2005	25	1					
2	1	Epistaxis	06/23/2005	26	1					
2	2	Epistaxis	07/11/2005	26						
2	2	Epistaxis	07/11/2005	26	1					
2	1	Epistaxis	07/27/2005	25	1					
2	2	Epistaxis	08/29/2005	28.1	1					
2	2	Epistaxis	09/01/2005	39.1	1					TA

**TMAE-104: Bleeding Episode by Individual Patient: Ctr 9 - Pt (b)(6)**

07/13/2004: VWD diagnosed in childhood (type 2a); precise date of diagnosis unknown, DDAVP administered in 1990's. Precise date unknown. Non-responder. Has had long term treatment with VWF concentrates - exposure days runs into tens of thousands. No efficacy assessment of 1st dose of White - as given as "prophylaxis" i.e. not actively bleeding. 01/14/2005: Patient elects to withdraw from study. No clinical concern re efficacy.

VWD type	S	Bleeding Site	Date	Dose IU/kg	R	F8 -1	VF -1	F8 -2	VF -2	Concomitant Medications
2	2	Gastrointestinal	07/18/2004	28.6						
2	2	Gastrointestinal	07/20/2004	28.6						
2	2	Gastrointestinal	07/21/2004	28.6						
2	2	Gastrointestinal	07/27/2004	28.6						
2	2	Gastrointestinal	07/28/2004	28.6						
2	2	Gastrointestinal	07/29/2004	28.6	1					
2	1	Gastrointestinal	08/13/2004	28.6						
2	1	Gastrointestinal	08/14/2004	28.6						
2	1	Gastrointestinal	08/15/2004	28.6	1					
2	2	Gastrointestinal	08/27/2004	28.6						
2	2	Gastrointestinal	08/28/2004	28.6						
2	2	Gastrointestinal	09/29/2004	28.6						
2	2	Gastrointestinal	09/30/2004	28.6	1					
2	1	Gastrointestinal	09/11/2004	28.6						
2	1	Gastrointestinal	09/12/2004	28.6						
2	2	Gastrointestinal	10/01/2004	28.6						
2	2	Gastrointestinal	10/02/2004	28.6						
2	2	Gastrointestinal	10/03/2004	28.6						
2	2	Gastrointestinal	10/04/2004	28.6						
2	2	Gastrointestinal	10/05/2004	28.6	1					









3	3	Joint	06/30/2005	8.3	2					CYKLO		
3	2	Joint	07/01/2005	16.7						CYKLO		
3	2	Joint	07/01/2005	8.3	3					CYKLO		
3	2	Epistaxis	07/03/2005	16.7						CYKLO		
3	2	Epistaxis	07/03/2005	8.3	3					CYKLO		
3	3	Epistaxis	07/04/2005	16.7						CYKLO		
3	3	Epistaxis	07/04/2005	8.3						CYKLO		
3	3	Epistaxis	07/05/2005	16.7						CYKLO		
3	3	Epistaxis	07/05/2005	8.3						CYKLO		
3	3	Epistaxis	07/06/2005	16.7						CYKLO		
3	3	Epistaxis	07/06/2005	8.3	4					CYKLO		
3	3	Joint	07/08/2005	16.7						CYKLO		
3	3	Joint	07/08/2005	8.3	3					CYKLO		
3	3	Epistaxis	07/10/2005	16.7						CYKLO		
3	3	Epistaxis	07/10/2005	8.3						CYKLO		
3	3	Epistaxis	07/11/2005	16.7						CYKLO		
3	3	Epistaxis	07/11/2005	8.3						CYKLO		
3	3	Epistaxis	07/12/2005	16.7						CYKLO		
3	3	Epistaxis	07/12/2005	8.3	3					CYKLO		
3	3	Joint	07/13/2005	16.7						CYKLO		
3	3	Joint	07/13/2005	8.3						CYKLO		
3	3	Joint	07/14/2005	16.7						CYKLO		
3	3	Joint	07/14/2005	8.3						CYKLO		
3	3	Joint	07/15/2005	16.7						CYKLO		
3	3	Joint	07/15/2005	8.3	2					CYKLO		
3	2	Joint	07/19/2005	16.7						CYKLO		
3	2	Joint	07/19/2005	8.3	3					CYKLO		
3	2	Epistaxis	07/20/2005	16.7						CYKLO		
3	2	Epistaxis	07/20/2005	8.3	3					CYKLO		
3	1	Epistaxis	07/21/2005	16.7						CYKLO		
3	1	Epistaxis	07/21/2005	8.3	2					CYKLO		
3	3	Joint	07/24/2005	16.7						CYKLO		
3	3	Joint	07/24/2005	8.3	2					CYKLO		
3	2	Epistaxis	07/26/2005	16.7						CYKLO		
3	2	Epistaxis	07/26/2005	8.3	3					CYKLO		
3	2	Joint	07/27/2005	8.3						CYKLO		
3	2	Joint	07/27/2005	16.7	3					CYKLO		
3	1	Epistaxis	07/31/2005	16.7						CYKLO		
3	1	Epistaxis	07/31/2005	8.3	2					CYKLO		
3	1	Epistaxis	08/02/2005	16.7						RBC	CYKLO	
3	1	Epistaxis	08/02/2005	8.3	2					RBC	CYKLO	
3	2	Oral	08/05/2005	16.7						CYKLO		
3	2	Oral	08/05/2005	8.3	2					CYKLO		
3	2	Epistaxis	08/09/2005	16.7						CYKLO		
3	2	Epistaxis	08/09/2005	8.3	2					CYKLO		
3	2	Oral	08/10/2005	16.7						CYKLO		
3	2	Oral	08/10/2005	8.3	3					CYKLO		
3	2	Epistaxis	08/12/2005	16.7						CYKLO		
3	2	Epistaxis	08/12/2005	8.3	2					CYKLO		
3	2	Epistaxis	08/13/2005	16.7						CYKLO		
3	2	Epistaxis	08/13/2005	8.3	2					CYKLO		
3	3	Joint	08/18/2005	33.3	2					CYKLO		
3	3	Epistaxis	08/20/2005	33.3	2					CYKLO		
3	2	Joint	08/24/2005	33.3	2					CYKLO		
3	2	Joint	09/03/2005	16.7	2					CYKLO		
3	2	Joint	09/06/2005	16.7	2					CYKLO		
3	3	Joint	09/13/2005	33.3	2					CYKLO		
3	3	Muscle	09/14/2005	33.3	2					CYKLO		
3	2	Joint	09/16/2005	16.7	2					CYKLO		
3	3	Joint	09/18/2005	33.3						CYKLO		
3	3	Joint	09/19/2005	33.3	2					CYKLO		
3	2	Joint	09/23/2005	25	2					CYKLO		
3	2	Epistaxis	09/24/2005	25	2					CYKLO		
3	3	Joint	09/26/2005	25	2					CYKLO		
3	2	Epistaxis	09/27/2005	25	2					CYKLO		
3	2	Joint	09/30/2005	25	2					CYKLO		
3	2	Joint	10/02/2005	25	3					CYKLO		
3	3	Joint	10/06/2005	25	2					CYKLO		
3	3	Muscle	10/07/2005	25	2					CYKLO		
3	2	Joint	10/08/2005	33.3	2					CYKLO		
3	2	Oral	10/12/2005	25	2					CYKLO		
3	2	Epistaxis	10/13/2005	16.7	2					CYKLO		



3	2	Epistaxis	02/14/2006	16.7	2						CYKLO		
3	2	Epistaxis	02/16/2006	16.7	2						CYKLO		
3	2	Epistaxis	02/19/2006	16.7	2						CYKLO		
3	2	Joint	02/21/2006	16.7							CYKLO		
3	2	Joint	02/22/2006	16.7	4						CYKLO		
3	2	Epistaxis	02/25/2006	16.7	4						CYKLO		
3	2	Epistaxis	02/27/2006	16.7							CYKLO		
3	2	Epistaxis	02/28/2006	16.7	4						CYKLO		
3	2	Epistaxis	03/01/2006	16.7							CYKLO		
3	2	Epistaxis	03/02/2006	16.7	4						CYKLO		
3	2	Epistaxis	03/04/2006	16.7							CYKLO		
3	2	Epistaxis	03/05/2006	16.7	4						CYKLO		
3	2	Epistaxis	03/07/2006	16.7	4						CYKLO		
3	2	Joint	03/09/2006	16.7	4						CYKLO		
3	2	Epistaxis	03/11/2006	16.7	3						CYKLO		
3	2	Epistaxis	03/13/2006	16.7							CYKLO		
3	2	Epistaxis	03/14/2006	16.7							CYKLO		
3	2	Epistaxis	03/15/2006	16.7	4						CYKLO		
3	2	Epistaxis	03/16/2006	16.7							CYKLO		
3	2	Epistaxis	03/17/2006	16.7	3						CYKLO		
3	2	Epistaxis	03/20/2006	16.7	4						CYKLO		
3	2	Joint	03/29/2006	16.7							CYKLO		
3	2	Oral, mouth	03/29/2006	16.7							CYKLO		
3	2	Joint	03/30/2006	33.3	3						CYKLO		
3	2	Oral, mouth	03/30/2006	33.3	3						CYKLO		
3	2	Joint	04/01/2006	33.3	3						CYKLO		
3	2	Epistaxis	04/03/2006	16.7	4						CYKLO		
3	2	Oral, mouth	04/03/2006	16.7	4						CYKLO		
3	2	Joint	04/04/2006	16.7	4						CYKLO		
3	2	Oral	04/06/2006	33.3							CYKLO		
3	2	Epistaxis	04/06/2006	33.3							CYKLO		
3	2	Joint	04/06/2006	33.3							CYKLO		
3	2	Oral	04/07/2006	33.3							CYKLO		
3	2	Epistaxis	04/07/2006	33.3							CYKLO		
3	2	Joint	04/07/2006	33.3							CYKLO		
3	2	Oral	04/08/2006	16.7	3						CYKLO		
3	2	Epistaxis	04/08/2006	16.7	3						CYKLO		
3	2	Joint	04/08/2006	16.7	3						CYKLO		
3	2	Gynaecologic	04/10/2006	16.7							CYKLO		
3	2	Epistaxis	04/10/2006	16.7							CYKLO		
3	2	Gynaecologic	04/11/2006	16.7	4						CYKLO		
3	2	Epistaxis	04/11/2006	16.7	4						CYKLO		
3	2	Epistaxis	04/13/2006	33.3							CYKLO		
3	2	Oral	04/13/2006	33.3							CYKLO		
3	2	Joint	04/13/2006	33.3							CYKLO		
3	2	Epistaxis	04/14/2006	16.7							CYKLO		
3	2	Oral	04/14/2006	16.7							CYKLO		
3	2	Joint	04/14/2006	16.7							CYKLO		
3	2	Epistaxis	04/15/2006	16.7	3						CYKLO		
3	2	Oral	04/15/2006	16.7	3						CYKLO		
3	2	Joint	04/15/2006	16.7	3						CYKLO		
3	2	Oral	04/17/2006	16.7	3						CYKLO		
3	2	Epistaxis	04/17/2006	16.7	3						CYKLO		
3	2	Oral	04/19/2006	16.7							CYKLO		
3	2	Epistaxis	04/19/2006	16.7							CYKLO		
3	2	Gynaecologic	04/19/2006	16.7							CYKLO		
3	2	Oral	04/20/2006	16.7	3						CYKLO		
3	2	Epistaxis	04/20/2006	16.7	3						CYKLO		
3	2	Gynaecologic	04/20/2006	16.7	3						CYKLO		
3	2	Joint	04/22/2006	16.7	3						CYKLO		
3	2	Oral	04/24/2006	16.7	3						CYKLO		
3	2	Epistaxis	04/24/2006	16.7	3						CYKLO		
3	2	Oral	04/26/2006	16.7							CYKLO		
3	2	Epistaxis	04/26/2006	16.7							CYKLO		
3	2	Joint	04/26/2006	16.7							CYKLO		
3	2	Oral	04/27/2006	33.3							CYKLO		
3	2	Epistaxis	04/27/2006	33.3							CYKLO		
3	2	Joint	04/27/2006	33.3							CYKLO		
3	2	Oral	04/28/2006	16.7							CYKLO		
3	2	Epistaxis	04/28/2006	16.7							CYKLO		
3	2	Joint	04/28/2006	16.7							CYKLO		
3	2	Oral	04/29/2006	33.3							CYKLO		





			<p>one can find all details (pat. No 05). On 01/25/2001, patient was discharge from hospital. Patient received TMAE-109 (20000 IU) for home treatment. He received totally 5000 IU of TMAE for treatment of GI bleeding (in hospital). Details concerning usage of TMAE to prevent bleeding during and post-operatively one can find in another part of CRF ("surgery" P. No 05) and in "treatment documentation" on page 11 of this CRF.</p> <p>04/04/2001: The "6 month visit" - the general physical condition was good. Blood was taken to determine Hgb, Ht, rbc. One more "adverse event report" form has been filled in (follow up of the anaemia due to GI bleeding episodes in the past - see page 16 copy 9).</p>
104	1	(b)(6)	<p>07/05/2002: On 06/29/02 patient underwent dental extraction. Details see crf surgery pat. No. 02</p> <p>12/10/2002: Due to melena (GI bleeding) patient was admitted to study center. Gastroscopy and colonoscopy have been performed. Colonoscopy revealed polyps (removed during colonoscopy). Gastroscopy revealed gastritis but no bleeding. The main source of bleeding was not revealed. Patient was treated with Wiloctin, tranexamic acid, omeprazol. But bleeding did not stop. Between 12 and 16 of Dec. 2002, epistaxis also occurred.</p> <p>01/08-12/2002: Patient received 2000 IU (of FVIII) of cryoprecipitate and he stopped to bleed. On 01/17/03 patient was discharged.</p> <p>10/16/2003: Due to episodes of syncope (in July 2003), patient was hospitalized in (b)(6) and underwent electrophysiologic heart testing. Patient was also examined by neurologist. Since no cardiac disease had been diagnosed, patient underwent EEG, which revealed some pathological changes (mild). Patient to receive lamictal (lamotrigine) on 08/18/03 - prescribed by Neurologist. The general condition of the patient was now good.</p> <p>01/09/2004: In investigator's opinion, patient should assess the efficacy of the treatment with Wiloctin not after every injection of the study drug, but in case of severe bleeding demanding many infusions of F-VIII/VWF concentrate - after a few administrations. Sometimes to stop the bleeding episodes patient must receive the concentrate injections for two, three or even more consecutive days.</p> <p>03/22/2004: Admission to hospital due to GI bleeding episode and discharged on 03/31/2004.</p> <p>10/07/2004: On 09/12/04 patient was admitted to hospital due to GI bleeding episode. During hospitalization, patient used 62000 IU of Wiloctin. Discharged on 10/07/04.</p> <p>03/14/2005: Between 02/01/05 and 02/16/05 the patient was hospitalized at the Inst. of Hematology, and had blood transfusion in Warsaw due to GI bleeding episode. On 03/14/05, he was admitted again to the hospital because of the next GI bleeding episode. Despite intensive replacement therapy with Wiloctin, hemorrhage was not stopped, and the patient underwent surgery (partial resection of the bowel) on 04/13/05. On the following day, bleeding complications occurred after surgery and it was necessary to reoperate the patient. FVIII level before the procedure was 224%. During second procedure performed a few hours after the first one, the surgery evacuated 2500 ml of blood from the peritoneal cavity. The patient developed renal insufficiency (anuria), hypotension, respiratory failure. Mechanical ventilation was applied. The patient received dopamine and dobutamine to optimize the flow to organs and to keep the blood pressure on appropriate level. Intravenous fluids (5% glucose, electrolytes, etc), furosemide for oliguria, antibiotics, blood transfusion, FFP, transfusions of platelets and cryoprecipitate, corticosteroids.</p> <p>04/20/2005: The patient died at 05:30 a.m. The cause of death was attributed to be multiorgan dysfunction caused by bleeding complications following surgery for GI hemorrhage in patient with VWD and angiodysplasia. The FVIII level before, during and after surgery was normalized by Wiloctin replacement therapy. The bleeding was probably the consequence of dispersed angiodysplastic lesions in the bowel. The surgical procedure, presumably, caused the intensification of bleed.</p> <p><u>Note from Surgery CRF:</u> During surgery (04/18/2005) hemostasis was said to be very good. The partial resection of small bowel (with source of bleeding) was done. After surgery - hypotension, oliguria, respiratory failure. Blood transfusion, mechanical ventilation, intravenous fluids were administered. The patient needed reoperation. The second surgical procedure showed blood in the abdominal cavity. The evacuation of the blood did not cause the improvement of the general condition of the patient. The oliguria, respiratory failure and hypotension persisted. Mechanical ventilation had to be applied. The FVIII level before, during and after surgery was normalized after Wiloctin administration. On 4/19/05 the hemostatic disturbances were complex (fibrinogen 1.0 g/l, PT 70 sec., APTT 65 sec., FVIII C 74%, FV C 5%, FVII C 12%, FX C 21%). Patient died on (b)(6).</p>
			(b)(6) (female subject; VWD Type 1; birth year 1968)
105	1		06/02/2000: The patient agreed to participate in TMAE-109
109	2		09/12/2000: The patient returned 2 broken vials x 1000 IU and 3 intact vials.
			09/12/2000: ODAVP not being registered in Bulgaria. There were no adverse events on 09/12/00 at 12:00, 11:30 h, 14:00 h, 17:00 h, 23:00 h.
			(b)(6) (female subject; VWD Type 2B; birth year 1945)
105	1		06/15/2000: The patient agreed to participate in TMAE-109
109	2		08/15/2000: ODAVP not being registered in Bulgaria
			09/21/2000: There were no adverse events on 09/20/00 at 10:05 h, 12:35 h, 15:25 h
			02/28/2001: The follow up sample was taken much later than 2 weeks post-injection
			(b)(6) (male subject; VWD Type 3; birth year 1976)
105	1	(b)(6)	06/05/2000: All of patient's bleeding episodes were from gums and nose. The patient agreed to participate in TMAE-109
109	2		02/19/2001: There were no any adverse events 19:02, 01:00 h, 12:30 h, 15:30 h, 21:30 h
			04/02/2001: Blood sample taken 6 weeks post last injection. The patient could not come to the centre 7-14 days post injection
			(b)(6) (female subject; VWD Type 1; birth year 1986)
105	1		07/15/2000: The patient agreed to participate in TMAE-109
109	2		09/12/2000: ODAVP not being registered in Bulgaria. There were no any adverse events at 12:00, 11:40 h, 14:10 h, 17:10 h, 23:00 h
			09/13/2000: There was hemolysis in the sample
			03/05/2001: Blood sample taken much later than 2 weeks post injection

			(b)(6) (female subject; VWD Type 2B; birth year 1937)
105	1		02/22/2000: Risperidone (25 mg oral) for subcutaneous implantation. Prophylactic Wiloclin administration to cover the subcutaneous application of the estradiol implant. There was hemolysis in the blood sample taken, and tests could not be performed. 06/15/2000: The patient agreed to participate in TMAE-109
109	2		08/15/2000: DDAVP not being registered in Bulgaria. 09/21/2000: There were no adverse events on 09/20/00 at 10:05 h, 12:35 h, 15:25 h. 02/28/2001: The follow up sample was taken much later than 2 weeks post-injection
			(b)(6) (male subject; VWD Type 3; birth year 1958)
105	2	(b)(6)	01/12/2000: Patient took 20x500 IU for home treatment. 08/14/2000: Patient returned 20x500 IU (didn't use TMAE-105 between 7/12/00 and 8/14/00) 08/14/2000: Patient has been included into TMAE-109 study.
109	1		04/11/2001: After injection with TMAE-109 (for hemarthrosis - right knee), the patient felt a numb sensation in his both hands and both legs. It lasted for a few minutes. This was the last - 6 month visit. The general physical condition was good.
			(b)(6) (male subject; VWD Type 3; birth year 1953)
109	1		11/06/2000: 1) Patient was hospitalized in hospital in (b)(6) between 09/22/00 and 10/04/00 because of gastrointestinal bleeding. He was treated with Immunate stim plus, cryoprecipitate and drugs listed in crf (concomitant medication) page 8. All relevant data have been entered in "International adverse event report" form on page 16. 2) The second episode of GI bleeding took place on 10/10/00. Patient was not hospitalized. Increased dosage of study drug has stopped bleeding. 3) On 10/30/00 prolonged and massive epistaxis caused anemia (Hgb 8.9 g/dl). Epistaxis stopped after injection of 1000 IU of TMAE-109. 4) Due to pharyngitis patient started antibiotic with complete recovering and resolving on 10/28/00. 02/06/2001: Dental extraction on 02/06/01 (see crf-surgery, no 2). Hgb 10.8 g/dl. Ferrous sulfate was started. See adverse event form (copy 6) page 16. (Patient stopped to use this drug - despite investigator's advice - on 12/01/00). For surgery 4000 IU of TMAE-109 was used. 05/03/2001: Patient had been hospitalized at his regional hospital between 03/28/01 and 04/30/01 due to GI bleeding. was discharged on 04/30/01 but didn't stop to bleed. (see page 16, copy no 7). On this day, patient came to study center to complete - according to protocol - the study. Because he had not stopped to bleed (Hgb 6.0 g/dl), the patient was admitted to hospital. The admission, however is out of Protocol, since he completed the study before admission. On Page 16, copy no 8 - re follow-up - anemia - is described. Concomitant medication (including hospitalization at Patient's regional hospital) one can find on page 10 of this CRF. During hospitalization at his regional hospital patient received other blood products: Cryoprecipitate, RBC, etc.
104	1	(b)(6)	03/04/2002: On 02/27/02 Efficacy assessment after injection with Wiloclin was performed. Because suspicion of GI bleeding (low Hgb level) patient was hospitalized until 03/04/02. During hospitalization he received in total 9000 IU of Wiloclin (together for efficacy assessment and prophylaxis). He has been prescribed for treatment at home: tranexamic acid, omeprazole and ferrous sulfate. 04/03/2002: The investigator was informed by phone that patient has been admitted to hospital in (b)(6) due to GI bleeding. His physician increased the dose of Wiloclin. RBC transfusion was needed. 06/05/2002: Investigator was informed that patient had been admitted to hospital in (b)(6) due to GI bleeding. 20000 IU of Wiloclin was sent to hospital in (b)(6) for treatment. 07/09/2002: Patient came to center for 1st visit after inclusion to TMAE-104. Blood was drawn and some blood assays performed. Hgb 8.15 g/dl - anemia (see re copy 4). Patient received Wiloclin for home treatment. Patient refused to be hospitalized. 07/25/2002: Patient was admitted to hospital of the study center due to anemia (Hb 7.71 g/dl) and suspicion of GI bleeding. Between 7/13-27/02 patient had been hospitalized in hospital in (b)(6) (GI bleeding and epistaxis). 07/30/2002: Patient underwent dental extraction. All data concerning the procedure one may find in crf surgery part. No (b)(6). 08/06/2002: Patient hospitalized since 7/25/02 at the surgical department of Inst. Hematology due to GI bleeding episode. On 7/30/02 patient underwent dental extraction. No bleeding complications occurred during surgery and postoperatively. During hospitalization patient was receiving injections of Wiloclin for GI bleeding and on page 6 of this crf, all injections between 7/27 and 8/6 were documented. Patient still hospitalized and waiting for diagnostic procedures to localize precisely the site of GI bleeding. 08/16/2002: Despite many tests (gastroscopy, colonoscopy, radiography of the small bowel) cause of bleeding in GI tract has not been found. At the time being patient's Hgb is satisfactory. Patient was discharged on 8/16/02. Patient received Wiloclin for home treatment. 08/27/2002: On 8/24/02, patient was admitted to hospital in (b)(6) due to GI bleeding. 10/22/2002: Visit no 2. The general condition was good. No bleeding episodes occurred since 10/5/02. Hgb 11.2 g/dl. 01/20/2003: Due to GI bleeding, patient had been hospitalized at the city hospital in (b)(6) between 12/22/02 and 1/10/03. Patient received Wiloclin, blood transfusion, Kocate Jva, and other drugs. (See control visit 3 and SAE four). Since 12/22/02 patient started to receive antihypertensive drug captopril 3x50 mg/day p.o. 02/20/2003: On 2/20/03 patient admitted to study site for dental extraction (4 teeth). During hospitalization epistaxis treated with Wiloclin on 02/24/03 and 02/26/03. 02/26/2003: On 3/4/03 dental extraction (4 teeth) upper left 4, 5, 6 and lower left 6. Before extraction patient received 3500 IU Wiloclin. No bleeding complication after surgery occurred. Some changes in concomitant medication - instead of captopril patient started to receive enalapril 5 mg/day. Discharge on 03/07/03. 06/18/2003: Patient hospitalized at (b)(6). Patient's daughter picked up concentrates (40x500 IU) for treatment at the hospital. After discharge patient will come to study center. 06/30/2003: Visit no 04. According to schedule, this visit is delayed approx. 50 days. Between March 31st and June 29th patient had been hospitalized 4 times at (b)(6). On this day, the general condition was good. Blood samples were drawn, and patient received 20000 IU Wiloclin for home treatment. 09/08/2003: Since 09/4/03, patient has been hospitalized at the Inst. of haemat. and blood transfused. Due to

		<p>suspicion of GI bleeding. Between 9/1-9/4/01 patient had been hospitalized in (b)(6) due to GI bleeding. Since patient did not have Wilfactin at (b)(6) he received Immune (see intern. Serious adverse event report - copy no 115).</p> <p>04/06/2004 Visit no. 6. Due to protocol violation (patient has not come regularly for control visits) and at the patient request the patient was withdrawn from the study. Blood was drawn on (virology tests). During the whole study period Wilfactin efficacy was not always sufficient. Due to limited product at home/hospital patient received on many occasions other FVIII/VWF concentrates.</p>
		(b)(6) (male subject; VWD Type 3; birth year 1981)
105	1	06/01/2000: All of his bleedings were from gums and nose. The patient will be included in TMAE-109.
109	2	02/20/2001: There were no any adverse events from drug administration at 9-45 h, 12-15 h, 15-10 h.
		(b)(6) (female subject; VWD Type 3; birth year 1972)
105	1	06/14/2000: All of her bleeding episodes were from gums and menstrual bleedings. The patient will participate in TMAE-109.
109	2	12/05/2000: The patient has menorrhagia since previous evening. She came for administration of the product at the site of the hospital. Her visit coincided with the time for her control visit after 3 months. No adverse events after study drug administration the previous day at 10-10 h, 12-40 h, 15-40 h.
		02/12/2001: 10 vials of 1000 IU, were stolen from the car of the patient on 12/7/00.
		03/05/2001: The sample was taken much later than 8 weeks post injection.

(b)(4)



Page 149 redacted for the following reason  
.....  
(b)(1)

(b)(4)

**E. Efficacy Ratings by Patients/Investigators in VWD Bleeding Episodes with More Than One Infusion**

Analysis of Bleeding Episodes with More Than One Infusion of Wilate																		
Study	Ctr	PI	PrtID	Lpt	Severity	Site	First Infusion		Efficacy Rating for Infusion									
							Date	Date	1	2	3	4	5	6	7	8	9	10









104	1
104	1
104	1
104	1
104	1
104	1
104	1
104	1

104	1
104	1
104	1

109	1
109	1
109	1
104	1

104	1
104	1
104	1

104	1
104	1
104	1

104	1
104	1
104	1

104	1
104	1
104	1

104	1
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104	1

104	1
104	1
104	1

104	1
104	1
104	1

105	1
105	1
105	1

105	1
105	1
109	2

104	11
104	11
104	11

105	2
109	1
109	1

104	1
104	1
104	1

104	1
104	1
104	1

104	1
104	1
104	1

104	1
104	1
104	1

104	1
104	1
104	1

68	minor	joint	10/20/2004	18.9	G	E													
70	minor	epistax	11/18/2004	28.3	G	E													
71	sev	GI	12/27/2004	28.3	N	N	N	N	G	G	E	E							
72	sev	GI	01/17/2005	47.2	N	N	N	N	G	E	N	N	N	N	N	N	N	M	M
73	sev	GI	01/27/2005	47.2	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
74	sev	GI	02/17/2005	47.2	N	N	N	N	N	M	E								
75	sev	GI	03/03/2005	47.2	N	N	N	N	N										
76	sev	GI	03/14/2005	37.7	N	N	N	N	M	G									
77	sev	GI	04/03/2005	18.9	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

1	mod	epistax	12/23/2004	23.8	G	G													
23	minor	other	06/17/2006	35.7	G	E	E												
76	mod	joint	07/09/2006	17.9	E	G													

2	sev	GI	09/10/2000	45.5	N	N	N	N											
3	sev	GI	10/10/2000	45.5	G	E	E	E	E										
5	sev	GI	03/27/2001	60.6	N	N	M	M	M	M	M	M	M	M	M	N	N	N	N
1	sev	GI	03/29/2002	52.6	N	N	M	M	M	M	M	M	M	M	M				

2	sev	GI	06/03/2002	39.5	G	G													
4	minor	epistax	07/09/2002	19.7	G	G	G	G	G	G	G	G	G	G	G				
6	sev	GI	07/31/2002	26.3	G	G	G	G	G	G	G	G	G	G	G				

7	mod	GI	08/13/2002	26.3	G	G	G	G	G										
8	sev	GI	08/19/2002	26.3	G	G	G	G	G										
9	sev	GI	08/29/2002	39.5	G	G	G	G	G										

10	mod	epistax	10/07/2002	26.3	G	G	G	G	G										
11	sev	GI	12/21/2002	26.3	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
13	sev	other	02/10/2003	26.3	M	M	M	M	M	M	M	M	M	M	M				

14	minor	epistax	02/24/2003	19.7	E	E													
16	mod	epistax	03/14/2003	32.9	G	G	G												
17	sev	epistax	03/27/2003	39.5	M	M	M	M	G	E									

20	sev	GI	04/04/2003	26.3	M	M	M	M	M	E	E								
21	sev	GI	06/18/2003	39.5	N	N	N	M	M	G	E								
22	mod	epistax	07/07/2003	39.5	M	M	M	M											

23	sev	GI	09/10/2003	26.3	N	N	M	M											
24	sev	GI	09/16/2003	26.3	M	M	G	G	E	E	E	E	E	F	N	N	N	N	N
25	sev	GI	10/02/2003	13.2	M	M													

26	sev	GI	10/07/2003	13.2	G	G													
27	mod	GI	10/15/2003	13.2	G	F													
28	sev	epistax	11/30/2003	52.6	G	E	E	E	F										

7	mod	other	04/07/2000	26.7	E	E													
13	mod	other	06/21/2000	26.7	E	F	F												
14	mod	other	07/03/2000	40	C	E	E												

15	mod	other	07/10/2000	26.7	E	E													
16	mod	other	07/24/2000	13.3	E	E													
6	mod	other	09/26/2000	26.3	G	E	E	E											

6	sev	other	10/02/2004	21.3	E	E													
16	mod	other	03/05/2006	18.9	E	E													
17	minor	epistax	04/25/2006	18.9	E	E													

19	mod	oral	07/27/2006	18.9	N	N	E	E	E	E	E	E	E	E	E				
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2	minor	joint	06/28/2000	28.6	G	E	E												
2	minor	joint	08/09/2000	42.9	E	E													
3	minor	joint	09/09/2000	42.9	E	E													

2 01	mod	joint	03/08/2002	42.9	M	G													
8	mod	joint	10/12/2002	42.9	M	G	G												
9	mod	joint	10/26/2002	42.9	G	G													

9 01	mod	joint	10/30/2002	21.4	C	C													
12	minor	joint	12/05/2002	14.3	F	E	E												
13	minor	joint	12/10/2002	21.4	F	E													

15	minor	joint	02/03/2003	28.6	E	E													
19	minor	joint	02/17/2003	14.3	E	E													
21	mod	joint	02/26/2003	42.9	E	E	E												

22	mod	joint	03/25/2003	35.7	G	G	G												
23	minor	joint	03/31/2003	28.6	E	E													
28	minor	joint	04/28/2003	42.9	N	G	E												

30	minor	joint	05/21/2003	42.9	G	E													
38	minor	joint	07/23/2003	42.9	G	E													

[illegible]

3	mod	epistax	04/21/2005	33.3	G	M	G											
5	mod	oral	04/27/2005	33.3	G	G	N	C	N	N	N	N	N	N	N	N	N	M
9	mod	epistax	05/22/2005	25	G	G	G	G										
12	mod	epistax	05/30/2005	25	G	G												
14	mod	epistax	06/04/2005	25	G	G	C	G										
18	mod	oral	06/16/2005	8.3	G	G												
19	mod	epistax	06/22/2005	8.3	G	G	G	G										
21	mod	epistax	06/28/2005	8.3	C	G	G	C	M	M	M	M	N	N	N	N	N	N
29	mod	joint	07/19/2005	9.3	M	M	M	M	G	G								
32	sev	joint	07/24/2005	8.3	G	G	M	M	M	M								
35	minor	epistax	07/31/2005	8.3	C	G	G	G										
37	mod	oral	08/05/2005	8.3	G	G												
38	mod	epistax	08/09/2005	3.3	G	G	M	M	G	G	G	G						
47	sev	joint	08/18/2005	33.3	G	G												
47	sev	joint	09/13/2005	33.3	G	G	G	N	G									
51	mod	joint	09/23/2005	25	G	G	G	C										
55	mod	joint	09/30/2005	25	G	M												
57	sev	joint	10/06/2005	25	G	G	G											
60	mod	oral	10/12/2005	25	G	G	G	M	N	G	G	G	M	M	M	M	M	M
79	mod	joint	11/14/2005	25	M	M	G	M	N	M	M	M	M	M	M	M	M	M
95	mod	joint	12/20/2005	16.7	G	G	G	M	M	M	M	M	M					
103	mod	epistax	01/10/2006	16.7	G	E	M	N	N	N	N	N	M	M	M			
112	mod	joint	01/29/2006	16.7	M	G												
114	sev	epistax	02/04/2006	16.7	N	N												
116	mod	epistax	02/10/2006	16.7	N	C	M	G	G									
121	mod	epistax	02/19/2006	16.7	C	N	N											
123	mod	epistax	02/25/2006	16.7	N	N	N	N	N	N	N	N	N	M	N	N	N	N
133	mod	joint	03/29/2006	16.7	M	M	M	N	N	N	N	M	N	N	M	M	M	M
177	mod	epistax	05/23/2006	16.7	N	N	M	M	N	N	N	M	N					

1	mod	joint	07/07/2005	14.3	G	C	G	G
2	mod	joint	09/07/2005	14.3	G	C	G	G
3	mod	joint	09/23/2005	14.3	G	C	G	G
4	mod	joint	09/06/2005	14.3	G	C	G	G
5	mod	joint	09/23/2005	14.3	G	C	G	G
6	mod	joint	10/20/2005	14.3	G	C	G	G
7	mod	joint	03/05/2006	14.3	G	C	G	-
8	mod	joint	03/10/2006	14.3	G	C	G	-
9	sev	joint	05/19/2005	14.3	G	C	G	G
10	sev	joint	05/25/2005	14.3	G	C	G	G
11	sev	joint	06/06/2005	14.3	G	C	G	G
12	sev	joint	06/14/2005	14.3	G	C	G	G
13	mod	joint	07/17/2006	14.3	G	C	G	-
15	mod	joint	10/19/2005	14.3	G	C	G	-



(b)(5)

157

[illegible]

Pages 159 through 198 redacted for the following reasons:

(b)(4)

(b)(4) - FOIA