CLINICAL STUDY REPORT

An Open Multi-centre Study in Patients with von Willebrand Disease to Investigate the Pharmacokinetics, Efficacy and Safety of OPTIVATE®, a High Purity, Dual Inactivated Factor VIII and von Willebrand Factor Concentrate

Protocol Number: 8VWF01

EudraCT Number:	2006-000663-28
Kendle Study Number:	BT-2528
Investigational Medicinal Product:	OPTIVATE®
Indication:	von Willebrand Disease
Phase:	III
Design:	An open, multi-centre study in patients with von Willebrand Disease (VWD).
Study Initiation Date:	14 Feb 2007
Study Completion Date:	24 Oct 2008
Co-ordinating Investigator:	Charles RM Hay MD, FRCP, FRCPath, Consultant Haematologist, Haemophilia Comprehensive Care Centre, University Department of Haematology, Manchester Royal Infirmary, Manchester, UK
Sponsor:	Bio Products Laboratory (BPL) Dagger Lane, Elstree Hertfordshire WD6 3BX UK
GCP Statement:	This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.
Date of Report:	21 Aug 2009
Status of Report:	Final

CONFIDENTIAL

1 Study Synopsis

Name of Sponsor/Company:	Bio Products Laboratory
Name of IMP:	OPTIVATE®
Name of Active Ingredient:	Factor VIII (FVIII) and associated von Willebrand Factor (VWF)
Title of Study: An Open Multi-centre Study in Patients with von Willebrand Disease to Investigate the Pharmacokinetics, Efficacy and Safety of OPTIVATE®, a High Purity, Dual Inactivated Factor VIII and von Willebrand Factor Concentrate.	
Co-ordinating Investigator: Charles RM Hay MD, FRCP, FRCPath, Consultant Haematologist, Haemophilia Comprehensive Care Centre, University Department of Haematology, Manchester Royal Infirmary, Manchester, UK.	
Study Centres: Eight sites (3 in the UK, 3 in Poland, 2 in Israel).	
Publication (Reference): None	
Studied Period: 14 Feb 2007 to 24 Oct 2008	**Phase of Development:** III
Objectives: The primary objective of the study was to assess the pharmacokinetics (PK) of OPTIVATE® after a single dose of 80 IU/kg von Willebrand Factor Ristocetin Cofactor Assay (VWF:RCo). The secondary objectives of the study were to assess efficacy and safety of OPTIVATE® in long-term use over at least 12 months.	
Methodology: This was an open, multi-centre study in patients with severe von Willebrand Disease (VWD) to assess the PK, efficacy and safety of OPTIVATE®, a viral dual-inactivated FVIII and VWF concentrate. Patients were screened up to 14 days before treatment. Eligible patients were required to undergo a 5-day washout period from their last dose of replacement factor concentrate or desmopressin (DDAVP) before the Baseline Visit (Visit 1). At the Baseline Visit (Visit 1) all patients were to receive an infusion dose of 80 IU/kg VWF: RCo OPTIVATE® (to the nearest 0.1 mL) and had blood samples taken at specific timepoints for a PK assessment. Following Visit 1, patients then were either supplied with OPTIVATE® to use at home, or they returned to the clinic to be treated with OPTIVATE® as required. All patients were supplied with diaries to complete. Patients who self-administered could do so prophylactically (defined as at least once a week), or to treat bleeds on-demand at a dose and treatment regimen according to the investigator's clinical judgement and patient choice. Patients could also have taken OPTIVATE® preventatively (*eg* before planned activity). At least 5 patients with Type 3 VWD were to be assigned to a prophylactic regimen. After 3 months of treatment either at home or at the clinic as required, patients returned to the clinic for their Visit 2 assessment. Patients then resumed home therapy or continued to return to the clinic to be treated with OPTIVATE® as required for a further 3 months. After 6 months at Visit 3, all patients with Type 3 VWD were to participate in a second PK assessment where a second infusion of 80 IU/kg VWF:RCo OPTIVATE® was to be administered. Patients with other types of VWD were to be invited to participate in this second PK assessment but it was not mandatory for them. Patients who participated were to undergo a second 5-day washout period from OPTIVATE® (and DDAVP, if appropriate) before dosing. Patients who elected not to participate in the second PK assessment were still to return to the clinic after 6 months for a Visit 3 assessment. Patients then resumed home therapy or continued to return to the clinic to be treated	

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with OPTIVATE® as required for a further 3 months.
After 9 months, patients returned to the clinic for their Visit 4 assessment and VWF and FVIII inhibitor screens. Patients then resumed home therapy or continued to return to the clinic to be treated with OPTIVATE® as required for a further 3 months.
After a minimum of 12 months, patients returned to the clinic for a final End-of-study Visit. The timing of this visit depended on whether the target of 10 bleeds treated with OPTIVATE® recorded in the patient population, of which at least five were major mucosal bleeds, was reached.
The sponsor was to review the status of the study and likelihood of reaching the target number of bleeds on an ongoing basis. A formal review was to occur when 50% of patients had had their Month 6 Visit (Visit 3) and then again when 50% of patients had reached their Month 9 Visit (Visit 4). If the review suggested that the 10 bleeds was not reached within the 12-month treatment period, the treatment period was to be extended by intervals of 3 months as required and additional visits will be necessary. Patients were to continue to receive home therapy or treatment at the clinic as required between visits. The End-of-study Visit was to take place after any additional study-extension visits. The number, location, severity and treatment of bleeds were also monitored on an ongoing basis to enable a decision to be made about extending the treatment period.
The investigator was required to follow-up adverse events (AEs) for 30 days after the last dose of OPTIVATE®. If a patient had a dose of OPTIVATE® within 30 days of the End-of-study Visit, a follow-up contact (by telephone or visit) was arranged.

Number of Patients (Planned and Analysed): It was anticipated that 26 patients with severe VWD (VWF: RCo <20%) of any type were to be recruited. At least 15 of the recruited patients were to have Type 1, 2A or 3 VWD. Of these 15 patients, at least eight patients were to have Type 3 VWD. Recruitment was slower than expected and after a formal review the sponsor indicated, on 04 Sep 2008, that this study should be terminated. Eleven patients were enrolled and 3 patients completed the study.

Diagnosis and Main Criteria for Inclusion: Patients aged 12 years or older, with severe VWD (VWF:RCo <20%) of known type (severity was to be confirmed by a current VWF:RCo result of <20%), who were known or expected to require a concentrate for management of VWD, who had had at least one spontaneous bleed in the last 12 months which required treatment with a FVIII and VWF concentrate, who had a known lack of, or poor response to, DDAVP, or for whom DDAVP was contraindicated, and who had a prothrombin time (PT) of not more than 3 seconds above the upper limit of the reference range. At the Baseline Visit (Visit 1), patients were to have had at least 5 days since their last infusion of replacement factor concentrate or DDAVP. Female patients of child-bearing potential were to have had a negative result on a human chorionic gonadotropin-based pregnancy test and if sexually active were to practice contraception using a method of proven reliability for the duration of the study.

Test Product, Dose and Mode of Administration, Batch Number: OPTIVATE® is a concentrate of human coagulation FVIII with associated VWF (the natural stabiliser for FVIII). OPTIVATE® is obtained from plasma from screened donors. OPTIVATE®

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contains a nominal 100 IU/mL human coagulation FVIII (European Pharmacopoeia [Ph.Eur.] chromogenic FVIII assay) when reconstituted in Sterilised Water for Injections Ph.Eur. The VWF Antigen (VWF: Ag) content is 200 to 320 IU/mL (enzyme linked immunosorbent assay antigen method) and VWF: RCo is 90 to 250 IU/ml. The ratio of FVIII to VWF is approximately 1 IU: 2.5 IU. OPTIVATE® was supplied by the sponsor as a powder for solution, containing a nominal 500 IU FVIII per vial (and approximately 1250 IU VWF: Ag), each to be reconstituted with 5 mL Sterilised Water for Injections Ph.Eur. OPTIVATE® was administered by intravenous infusion at a rate not exceeding 3 mL/min and within 1 h of reconstitution. For each PK assessment (at the Baseline Visit [Visit 1] and the Month 6 Visit [Visit 3]), a dose of 80 IU/kg VWF: RCo OPTIVATE® (to the nearest 0.1 mL) was to be administered at a rate not exceeding 3 mL/min. The dose was calculated by the investigator or site nurse using the body weight recorded at that visit. For all patients assigned to receive OPTIVATE® for at-home use and clinical dosing at unscheduled dosing visits, the dose for prophylactic or on-demand OPTIVATE® use throughout the rest of the study was decided on a patient-by-patient basis as per the investigator's clinical judgement and in discussion with the patient. Patients who were receiving OPTIVATE® on-demand and who self-administered OPTIVATE® at home were to decide with the investigator how much OPTIVATE® they self-administered when they had a bleed (rounded to the nearest whole vial) based on their needs. It was recognised that patients who were assigned to receive OPTIVATE® on-demand may have, on occasion, come to the study site to receive preventative doses *eg* in anticipation of planned activity which might have caused a bleed or may have self-administered such doses at home. Similarly, patients assigned to receive OPTIVATE® prophylactically may have, on occasion, administered OPTIVATE® in response to a bleed. These doses may have varied during the study according to the response to treatment. OPTIVATE® batch FVSN7227/C was used at Site 01 for Patient 005, Site 02 for Patient 008 and at Site 03 for Patients 001 (the patient had a change in the packaging of OPTIVATE® [changed from FVSN7227/C to FVSN7227/D] during at-home dosing) and 002; batch FVSN7090 was used at Site 10 for Patient 009 and at Site 12 for Patient 007; batch FVSN7375/A was used at Site 20 for Patients 016 and 019, Site 21 for Patient 012, and at Site 22 for Patients 017 and 018. Six (54.5%) patients received the on-demand treatment regimen (5 patients with Type 3 VWD and one patient with “other” type of VWD). Four (36.4%) patients, all with Type 3 VWD, received prophylactic treatment. One (9.1%) patient with “other” type of VWD received both treatment regimens (patient received both on-demand treatment and prophylactic treatment during the study).	
Duration of Treatment: Approximately 54 weeks in total, comprising a variable screening period (approximately 2 weeks) and a treatment period of at least 12 months. If the required number of bleeds (at least 10 bleeds treated with OPTIVATE®, of which at least 5 were major mucosal bleeds, in the patient population) had not been reached, the treatment period to individual patients may have been extended by intervals of 3 months as required.	

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Reference Therapy, Dose and Mode of Administration, Batch Number: None	
Criteria for Evaluation:	

Von Willebrand Factor Multimer Analysis: VWF multimer analyses and the interpretation of the results were performed by the sponsor using a validated assay. Blood samples for VWF multimer analyses were collected for all patients at the Baseline Visit (Visit 1) at the following timepoints: predose, 15 min (± 5 min), 6 h (± 15 min), 11 h (± 60 min) and 24 h (± 60 min) after the start of dosing. All patients who participated in the second PK assessment were also to have blood sample collections for multimer analysis at the second PK assessment, the Month 6 Visit (Visit 3), at the following timepoints: predose, 15 min (± 5 min), 6 h (± 15 min), 11 h (± 60 min) and 24 h (± 60 min) after the start of dosing. VWF multimer analyses were performed on plasma. Multimer analysis band patterns were scanned for a visual qualitative result, and densitometry was performed to provide quantitative results.

Efficacy: The primary efficacy endpoints were AUC(0-t), AUC(0-72 h), MRT(0-t) and MRT(0-72 h) for VWF:RCo at Baseline Visit (Visit 1) by VWD type and overall.

Due to sparsity of data it was realised that statistical analysis of Baseline Visit (Visit 1) and Month 6 Visit (Visit 3) PK data was not possible. There was also insufficient data to summarise the results at the Month 6 Visit (Visit 3). As a result, the secondary efficacy endpoints were modified and were defined in the statistical analysis plan (SAP) as:

1. AUC(0-∞), MRT(0-∞), T½el, Cmax, Cmax(obs), Tmax(obs), CL, Vd and incremental recovery for VWF: RCo at Baseline Visit (Visit 1) by VWD type and overall.
2. AUC(0-t), AUC(0-72 h), MRT(0-t) and MRT(0-72 h), MRT(0-∞), T½el, AUC(0-∞), Cmax, Cmax(obs), Tmax(obs), Vd, CL and incremental recovery for Factor VIII: coagulant activity (FVIII:C) at Baseline Visit (Visit 1) by treatment group, VWD type and overall.
3. VWF multimer data at the Baseline Visit (Visit 1) for all patients and at Month 6 Visit (Visit 3) for patients who participated in the second PK assessment.
4. Total dose (dose in IU/kg VWF:RCo and dose in IU/kg FVIII), total number of infusions and average dose per infusion by treatment group, VWD type, treatment regimen, OPTIVATE® type and overall.
5. Average monthly dose (dose in IU/kg VWF:RCo and dose in IU/kg FVIII) and average number of infusions per month by treatment group, VWD type, treatment regimen and overall.
6. Total dose to treat a bleed (dose in IU/kg VWF: RCo and dose in IU/kg FVIII) (including dose for new bleeds and ongoing bleeds), number of infusions used to treat bleeds, and dose per infusion on a per patient by treatment regimen, VWD type and overall.
7. Number of bleeds including severity, duration, location and cause per patient by VWD type and overall.
8. Patient's assessment of efficacy (all bleeds) and investigator's assessment of efficacy (major bleeds only) by VWD type and overall.
9. Investigator's overall assessment of efficacy by VWD type and overall.

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Safety: Safety was evaluated by monitoring AEs, laboratory parameters (haematology, clinical chemistry, PT and activated partial prothrombin time (APTT), viral serology, thrombogenicity and VWF and FVIII inhibitor screen), vital signs, infusion site observations and physical examination.

Statistical Methods: The planned statistical analyses of PK data, comparison of Visit 1 and Visit 4 data as defined in the protocol, were not appropriate given the early termination of this study and the sparse data available. As defined in the SAP, no statistical comparisons of the PK data were undertaken in this study, so descriptive summary statistics were presented.

Summary – Conclusions:

Pharmacokinetic Results: Peak plasma IU concentrations (Tmax(obs), median estimates) were attained consistently at 0.33 h after dosing (FVIII:C, VWF:Ag), and at 0.27 to 3.54 h (VWF:Collagen Binding Assay [VWF:CBA]) and 0.33 to 0.67 h (VWF:RCo) after dosing.

Mean apparent terminal elimination half life (T½el) was 27.43 h (FVIII:C), and 16.10 to 43.65 h (VWF:Ag), and 11.68 to 18.20 h (VWF:CBA) and 13.32 to 16.36 h (VWF:RCo).

Mean estimates of clearance (CL) and volume of distribution (Vd) for FVIII:C were 2.165 mL/h/kg and 97.69 mL/kg (Type 3 VWD only), respectively, and for VWF:RCo the estimates ranged from 3.927 to 4.397 mL/h/kg and 80.44 to 92.94 mL/kg for CL and Vd, respectively.

Incremental recovery estimates were comparable between the different assays; estimates ranged from 0.0172 to 0.0220 (FVIII:C), 0.0238 to 0.0242 (VWF:Ag), 0.0145 to 0.0171 (VWF:CBA) and 0.0174 to 0.0178 (VWF:RCo) IU/mL per IU/kg.

Systemic exposure to VWF:RCo was comparable between the different types of VWF (Types 1 to 3) and there was no appreciable difference in any of the other PK parameters reported for the different types of VWF. Systemic exposure to FVIII:C was higher in patients with Type 3 VWD compared to patients with “other” type of VWD, but no appreciable differences were reported in any of the other PK parameters reported. Systemic exposure to VWF:Ag and VWF:CBA was slightly lower in patients with Type 3 VWD compared to patients with “other” type of VWD; while T½el and MRT(0-∞) were longer in patients with “other” type of VWD compared to patients with Type 3 VWD.

In some patients with Type 3 VWD, a rapid decline in plasma IU concentration *vs* time profiles was noted, most obviously for FVIII:C IU concentrations, from approximately 24 h after dosing onwards.

Von Willebrand Factor Multimer Analysis Results: OPTIVATE® contains fewer high molecular weight VWF (78%) than is present in normal pooled plasma. When administered to patients with Type 3 VWD, the multimer profiles in the 15 min plasma samples were very similar to those of the infused OPTIVATE®. The 6 h samples showed some evidence of the loss of the highest molecular weight multimers.

After administration of OPTIVATE® to patients with Type 3 VWD, the high resolution multimer profiles showed that the triplet structures were similar to those of normal pooled plasma.

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Efficacy Results:

Total Dose, Total Number of Infusions and Average Dose per Infusion

Overall, the median total dose, total number of infusions and dose per infusion of VWF:RCo were lower in patients with Type 3 VWD (477.49 IU/kg, 7.0 infusions and 43.00 IU/kg, respectively) compared with patients with "other" type of VWD (2866.19 IU/kg, 75.0 infusions and 58.85 IU/kg, respectively).

Overall, the median total dose and total number of infusions of VWF:RCo were higher in patients who were managed on the prophylactic treatment regimen (553.74 IU/kg and 16.0 infusions, respectively) compared with patients managed on the on-demand treatment regimen (258.13 IU/kg and 6.0 infusions, respectively). However, the median dose per infusion of VWF:RCo was lower in patients managed on the prophylactic treatment regimen (35.75 IU/kg *vs* 59.05 IU/kg).

Within the patients managed on the on-demand treatment regimen, the median total dose and total number of infusions of VWF:RCo was higher in patients with Type 3 VWD (269.59 IU/kg and 6.0 infusions, respectively) compared with the one patient with "other" type of VWD (159.90 IU/kg and 2.0 infusions, respectively). However, the median dose per infusion of VWF:RCo was lower for patients with Type 3 VWD (44.90 IU/kg *vs* 80.00 IU/kg).

The total dose and total number of infusions of VWF:RCo were both higher for the one patient who received both treatment regimens (5572.48 IU/kg and 148.0 infusions, respectively) than the median total dose and total number of infusions of VWF:RCo for patients managed on the prophylactic or on-demand treatment regimens. However, the dose per infusion of VWF:RCo for this patient (37.70 IU/kg) was similar to the median dose per infusion of VWF:RCo for patients managed on the prophylactic treatment regimen and lower than the median dose per infusion of VWF:RCo for patients managed on the on-demand treatment regimen.

Average Monthly Dose and Average Monthly Infusions Used

Overall, the median monthly dose and number of infusions per patient per month for VWF:RCo were higher in patients with Type 3 VWD (301.80 IU/kg and 7.00 infusions, respectively) compared with patients with "other" type of VWD (159.55 IU/kg and 4.05 infusions, respectively).

Overall, the median monthly dose and number of infusions per patient per month for VWF:RCo were higher in patients who were managed on the prophylactic treatment regimen (355.50 IU/kg and 10.30 infusions, respectively) compared with patients managed on the on-demand treatment regimen (98.10 IU/kg and 2.20 infusions, respectively).

Within the patients managed on the on-demand treatment regimen, the median monthly dose and number of infusions per patient per month for VWF:RCo were higher in patients with Type 3 VWD (105.20 IU/kg and 2.30 infusions, respectively) compared with the one patient with "other" type of VWD (25.60 IU/kg and 0.30 infusions, respectively).

The monthly dose and number of infusions per patient per month for VWF:RCo were both lower for the one patient who received both treatment regimens (293.50 IU/kg and 7.80 infusions, respectively) compared with the median monthly dose and number of

infusions per patient per month for VWF:RCo for patients managed on the prophylactic treatment regimen, but higher compared with patients managed on the on-demand treatment regimen.

Total Dose and Number of Infusions Required to Treat a Bleed

Overall, the median total dose and dose per infusion required to treat a bleed per patient for VWF:RCo were lower in patients with Type 3 VWD (166.67 and 39.90 IU/kg, respectively) compared with the one patient with "other" type of VWD (234.24 and 46.80 IU/kg, respectively). However, the median number of infusions required to treat a bleed was similar for patients with Type 3 VWD and the one patient with "other" type of VWD (5.0 and 5.0 infusions, respectively).

Overall, the median total dose and dose per infusion required to treat a bleed per patient for VWF:RCo were both lower in patients who were managed on the prophylactic treatment regimen (134.76 and 33.70 IU/kg, respectively) compared with patients managed on the on-demand treatment regimen (254.37 and 41.45 IU/kg, respectively). However, the median number of infusions required to treat a bleed was similar for patients managed on the prophylactic and on-demand treatment regimens (4.0 and 5.0 infusions, respectively).

The total dose required to treat a bleed per patient for VWF:RCo was lower for the one patient who received both treatment regimens (234.24 IU/kg) compared with patients managed on the on-demand treatment regimen, and was higher than for patients managed on the prophylactic treatment regimen. The median number of infusions required to treat a bleed per patient for VWF:RCo was similar for each of the 3 treatment regimens (5.0 infusions for the patient who received both treatment regimens). The dose per infusion required to treat a bleed per patient for VWF:RCo for the one patient who received both treatment regimens (46.80 IU/kg) was higher than the median dose per infusion required to treat a bleed per patient for VWF:RCo for patients managed on the prophylactic treatment regimen and similar to patients managed on the on-demand treatment regimen.

Overall, the median total dose, dose per infusion and number of infusions required to treat a bleed per bleed for VWF:RCo were similar for patients with Type 3 VWD (37.51 IU/kg, 33.60 IU/kg and 1.0 infusion, respectively) and patients with "other" type of VWD (37.50 IU/kg, 37.50 IU/kg and 1.0 infusion, respectively).

Overall, the median total dose and dose per infusion required to treat a bleed per bleed for VWF:RCo were both lower in patients who were managed on the prophylactic treatment regimen (30.32 and 30.30 IU/kg, respectively) compared with patients managed on the on-demand treatment regimen (44.74 and 39.10 IU/kg, respectively). However, the median number of infusions required to treat a bleed per bleed was similar for patients managed on the prophylactic and on-demand treatment regimens (1.0 and 1.0 infusion, respectively).

The median total dose required to treat a bleed per bleed for VWF:RCo was lower for the one patient who received both treatment regimens (37.50 IU/kg) compared with patients managed on the on-demand treatment regimen, and was higher than for patients managed on the prophylactic treatment regimen. The median number of infusions required to treat a bleed per bleed for VWF:RCo was similar for each of the

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3 treatment regimens (1.0 infusion for the prophylactic, on-demand and both treatment regimens). The median dose per infusion required to treat a bleed per bleed for VWF:RCo for the one patient who received both treatment regimens (37.50 IU/kg) was higher than the median dose per infusion required to treat a bleed per bleed for VWF:RCo for patients managed on the prophylactic treatment regimen and similar to patients managed on the on-demand treatment regimen.

Number and Duration of Bleeds

In total, 77 bleeds were recorded for the 9 patients with Type 3 VWD (mean: 8.56 bleeds per patient) and 20 bleeds were recorded for the 2 patients with "other" type of VWD. The median duration of bleeds was longer for patients with Type 3 VWD (185.0 min) compared with patients with "other" type of VWD (5.0 min). However, it should be noted that 50.0% of the bleeds recorded for patients with "other" type of VWD had a missing duration.

In total, 17 bleeds were recorded for the 6 patients managed on the prophylactic treatment regimen and 60 bleeds were recorded for 4 patients managed on the on-demand treatment regimen. Overall, the proportion of bleeds was higher in the on-demand treatment regimen (60 [61.9%] bleeds) than the prophylactic treatment regimen (17 [17.5%] bleeds). The median duration of bleeds was higher for patients who were managed on the prophylactic treatment regimen (510.0 min) compared with patients managed on the on-demand treatment regimen (150.0 min).

In total, 20 bleeds were recorded for the one patient who received both treatment regimens. The median duration of bleeds was lower for the one patient who received both treatment regimens (5.0 min) compared with patients managed on the on-demand or prophylactic treatment regimens.

Overall, and within each VWD type, the most common location for a bleed was mucosal. The proportion of bleeds within each VWD type that were mucosal bleeds was similar between patients with Type 3 VWD (65 [84.4%] bleeds) and patients with "other" type of VWD (16 [80.0%] bleeds). The median duration of mucosal bleeds was higher for patients with Type 3 VWD (150.0 min) than for patients with "other" type of VWD (5.0 min). However, it should be noted that 45.0% of the mucosal bleeds recorded for patients with "other" type of VWD had a missing duration.

Overall, the median duration of bleeds was highest for joint bleeds (1530.0 min), which were reported only for patients with Type 3 VWD.

Overall, and within each VWD type, the most common cause for a bleed was spontaneous. The proportion of bleeds within each VWD type that were spontaneous bleeds was similar between patients with Type 3 VWD (72 [93.5%] bleeds) and patients with "other" type of VWD (19 [95.0%] bleeds). The median duration of spontaneous bleeds was higher for patients with Type 3 VWD (177.5 min *vs* 5.0 min). However, it should be noted that 50.0% of the spontaneous bleeds recorded for patients with "other" type of VWD had a missing duration.

The proportion of bleeds within each VWD type that were bleeds as a result of injury was similar between patients with Type 3 VWD (5 [6.5%] bleeds) and patients with "other" type of VWD (one [5.0%] bleed). The median duration of bleeds as a result of injury was higher for patients with Type 3 VWD than patients with "other" type of VWD

(300.0 min *vs* 20.0 min).

Overall, and within each VWD type, the most common severity of a bleed was minor. The proportion of bleeds within each VWD type that were minor and the median duration of minor bleeds were both higher in patients with Type 3 VWD (73 [94.8%] bleeds and 177.5 min, respectively) compared with patients with "other" type of VWD (10 [50.0%] bleeds and 5.0 min, respectively).

The proportion of bleeds within each VWD type that were major bleeds was lower for patients with Type 3 VWD (4 [5.2%] bleeds) compared with patients with "other" type of VWD (9 [45.0%] bleeds). However, the median duration of major bleeds was higher for patients with Type 3 VWD (1950.0 min) compared with patients with "other" type of VWD (390.0 min).

Patient's and Investigator's Assessment of Efficacy

Patients with Type 3 VWD assessed OPTIVATE® as "very helpful" (14 [45.2%] bleeds) or "helpful" (14 [45.2%] bleeds) in treating the majority of bleeds. Overall, patients with "other" type of VWD assessed OPTIVATE® as "very helpful" in treating all of the 4 (33.3%) bleeds assessed. No patient assessed OPTIVATE® as "did not help" in treating a bleed. Patients managed on the prophylactic treatment regimen assessed OPTIVATE® as "very helpful" for a higher proportion (6 [60.0%] bleeds) of bleeds than patients managed on the on-demand treatment regimen (8 [38.1%] bleeds). However, patients managed on the on-demand treatment regimen assessed OPTIVATE® as "helpful" for a higher proportion of bleeds (12 [57.1%] bleeds) than patients managed on the prophylactic treatment regimen (2 [20.0%] bleeds).

The investigator's assessment of efficacy for patients with Type 3 VWD was missing for 3 major bleeds and "excellent" for one major bleed. Overall, the investigator assessed the efficacy of OPTIVATE® to treat the 7 major bleeds for patients with "other" type of VWD as "excellent".

The investigator's assessment of the efficacy of OPTIVATE® to treat major bleeds was missing for all major bleeds experienced by patients managed on the on-demand treatment regimen. The investigator's assessment of the efficacy of OPTIVATE® to treat major bleeds was missing for one major bleed and "excellent" for the other major bleed experienced by patients managed on the prophylactic treatment regimen.

The investigator assessed the efficacy of OPTIVATE® to treat major bleeds as "excellent" for the 7 bleeds recorded for the one patient who received both treatment regimens. The patient assessed OPTIVATE® as "very helpful" in treating all 4 bleeds assessed.

Investigator's Overall Assessment of Efficacy

Overall, the most commonly recorded investigator's overall assessment of the efficacy of OPTIVATE® during the study was "good", recorded for both patients with "other" type of VWD and for 6 patients with Type 3 VWD. The investigator assessed the efficacy of OPTIVATE® during the study as "excellent" for one patient (Type 3 VWD).

The investigator's overall assessment of the efficacy of OPTIVATE® during the study was "good" for all 3 patients assessed who were managed on the prophylactic treatment regimen, for 4 of the 5 patients assessed who were managed on the on-demand treatment regimen, and for the one patient who received both treatment

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regimens. The investigator's overall assessment of the efficacy of OPTIVATE® during the study was "excellent" for one patient (managed on the on-demand treatment regimen).

Safety Results: There were no deaths and no patient was withdrawn from the study due to a treatment-emergent AE (TEAE).

Ten treatment-emergent serious AEs (SAEs) were reported for 2 (18.2%) patients. Appendicitis was reported as a treatment-emergent SAE for one patient with Type 3 VWD and one patient with "other" type of VWD had treatment-emergent SAEs of anaemia (2 events), gastrointestinal haemorrhage (3 events), melaena (2 events), intentional overdose (temazepam overdose), and hepatitis A antibody positive. No SAE was considered to be related to the investigational medicinal product (IMP).

Overall, 123 TEAEs were reported for 8 (72.7%) patients. A higher number of TEAEs were reported for patients with "other" type of VWD (101 TEAEs) compared with patients with Type 3 VWD (22 TEAEs). TEAEs were most commonly reported for patients in the General disorders and administration site conditions System organ class (SOC). No individual TEAE was reported for more than 2 (18.2%) patients overall. Abdominal discomfort, lethargy and depression were the only TEAEs reported for more than one patient within each VWD type (each reported for 2 [100%] patients with "other" type of VWD).

Five IMP-related TEAEs were reported for 2 (18.2%) patients, both of whom had Type 3 VWD. IMP-related TEAEs were most commonly reported in the General disorders and administration site conditions SOC. IMP-related TEAEs of infusion site erythema (2 events), drug ineffective, infusion related reaction, and hypersensitivity were each reported for one (9.1%) patient.

Eleven severe TEAEs were reported for 3 (27.3%) patients. A higher number of severe TEAEs were reported for patients with "other" type of VWD (10 severe TEAEs) compared with patients with Type 3 VWD (one severe TEAE). Severe appendicitis was reported for one patient with Type 3 VWD. One patient with "other" type of VWD had severe TEAEs of intentional overdose (temazepam overdose), gastrointestinal haemorrhage, anaemia and hepatitis A antibody positive; and one patient with "other" type of VWD had severe TEAEs of hot flush, arthritis, depression and pruritus generalised (2 events).

There were no notable overall median changes from baseline to the End-of-study Visit in haematology variables. Anaemia was reported as 11 TEAEs and 2 SAEs for one patient, and one further patient had a moderate TEAE of haemoglobin decreased. No other individual haematology result was considered clinically significant or reported as an AE.

There were no notable overall median changes from baseline to the End-of-study Visit in any biochemistry variable and no individual biochemistry result was considered clinically significant or reported as an AE.

No individual PT or APTT result was considered clinically significant or reported as an AE.

One patient had a negative hepatitis A virus antibody (gamma G immunoglobulin [IgG]) result at the Baseline Visit (Visit 1) but a positive result at the End-of-study Visit.

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Hepatitis A antibody positive was reported as an SAE for this patient and was considered unlikely to be related to the IMP. All other viral serology measurements were negative for this patient. No other patient had a change in viral serology result at the End-of-study Visit compared with baseline.

There were large median changes from baseline in thrombogenicity variables for patients with Type 3 VWD and patients with "other" type of VWD at the majority of timepoints. However, due to the large variability in the data, there was no evidence of a consistent trend over time. Thrombocytopenia was reported as a mild TEAE for one patient. No other thrombogenicity result was considered clinically significant or reported as an AE.

VWF and FVIII inhibitor screens were recorded as negative for all patients at all visits.

There were no notable overall median changes from baseline in supine systolic pressure, supine diastolic pressure, supine pulse, oral temperature or respiration rate. Two moderate AEs of hypertension were reported for one patient. No other vital sign result was considered clinically significant or reported as an AE.

One patient had change in physical examination in the musculoskeletal body system from normal at baseline to abnormal at the End-of-study Visit (worsening of arthritis in the left knee).

There was no notable median change from baseline to the End-of-study Visit in body weight for patients with Type 3 VWD. There was a median decrease of 4.20 kg from baseline to the End-of-study Visit in body weight for patients with other types of VWD (one patient with "other" type of VWD had an increase from baseline in body weight of 10.0 kg and one patient had a decrease in body weight of 1.6 kg).

No warmth, induration or tenderness were recorded at the infusion site for any patient at any timepoint during the study. One patient had mild erythema (definite pink) at each of the post dose timepoints to 11 h at the Baseline Visit and at the 6 h timepoint at the Month 6 Visit (Visit 3) and infusion site erythema was reported as a TEAE for this patient. Erythema was not recorded for any other patient during the study. Mild discomfort was reported for one patient at the 6 h timepoint at the Month 6 Visit (Visit 3) and infusion related reaction was reported as a TEAE for this patient. Discomfort was not recorded for any other patient during the study. One patient had a petechial rash at 15 min, and 1, 3, 6, 11, 24, 30, and 48 h post dose at the Baseline Visit.

Conclusion: The study was terminated early due to slower than expected recruitment therefore it was not possible to answer fully the study objectives. The number of patients with "other" type of VWD was low so comparisons with data for patients with Type 3 VWD should be interpreted with caution.

Pharmacokinetics

Tmax(obs) estimates indicated a rapid distribution of FVIII:C and VWF:Ag from the site of administration, but suggested some delay in distribution for VWF:CBA and VWF:RCo. The half life for VWF:RCo ranged from 13.32 h to 16.36 h. Based on terminal half life estimates (T½el), a return to baseline would likely be reached within 3 days for VWF:RCo. This is consistent with the VWF:RCo half life of 14.4 h reported for Fanhdi, another VWF/FVIII concentrate.

The VWD:RCo recovery ranged from 0.0174 to 0.0178 IU/mL per IU/kg. This is

comparable to the value of 0.019 IU/mL per IU/kg reported for Fanhdi.

Total systemic exposure (based on area under plasma activity *vs* time curves [AUCs] and Cmax(obs)) was greatest for FVIII:C followed by VWF:Ag, VWF:RCo and VWF:CBA in patients with Type 3 VWD. In contrast, for patients with "other" type of VWD (Types 1 and 2B) systemic exposure was greatest for VWF:Ag followed by VWF:CBA, VWF:RCo and FVIII:C, respectively.

Elimination of FVIII:C and VWF:RCo from the plasma would not likely be limited by plasma flow through the liver or the kidney. FVIII:C and VWF:RCo distributed readily beyond the central plasma compartment.

There was a consistent rapid decline in FVIII:C activity following the 24 h timepoint, particularly in 3 patients with Type 3 VWD. These observations were not readily explicable and as the FVIII inhibitor screen for all of these patients remained negative at Screening and at study completion, the effect was unlikely due to antibody formation.

There were insufficient data to perform the planned statistical comparison of Visit 3 and Visit 1 data. Since PK data were available for only 2 patients with "other" type of VWD, it is difficult to draw any firm conclusions on the comparative PK of OPTIVATE® in patients with Type 3 VWD *vs* those patients with "other" type of VWD.

The early termination of the study affected the overall dose consumption during the study. One patient, who received both treatment regimens, received a higher total dose of VWF:RCo and FVIII:C and had a higher number of exposure days to VWF:RCo and FVIII:C than the other patients in the study because this patient was the first patient enrolled in the study and therefore in the study longer. As a result of the early study termination, and the resulting difference in study duration for each patient (and therefore total dose consumption during the study), caution should be taken when making comparisons of study duration, number of exposure days and total dose received between patients.

Efficacy

Patients who were managed on the prophylactic treatment regimen required a similar number of infusions of VWF:RCo at a lower dose (*ie* a lower total dose) to treat a bleed (134.76 IU/kg and 4.0 infusions, respectively) compared with patients managed on the on-demand treatment regimen (254.37 IU/kg and 5.0 infusions, respectively).

Patients who were managed on the prophylactic treatment regimen had fewer bleeds (17 [17.5%] bleeds) compared with patients managed on the on-demand treatment regimen (60 [61.9%] bleeds).

Drug ineffective (lack of efficacy according to patient's self-reporting) was reported as a moderate IMP-related TEAE for one patient (Type 3 VWD; prophylactic treatment regimen).

Patients with Type 3 VWD assessed OPTIVATE® as "very helpful" or "helpful" in treating the majority of bleeds. Overall, patients with "other" type of VWD assessed OPTIVATE® as "very helpful" in treating all of the 4 bleeds assessed. No patient assessed OPTIVATE® as "did not help" in treating a bleed.

Patients managed on the prophylactic treatment regimen assessed OPTIVATE® as "very helpful" for a higher proportion (6 [60.0%] bleeds) of bleeds than patients managed on the on-demand treatment regimen (8 [38.1%] bleeds). However, patients

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managed on the on-demand treatment regimen assessed OPTIVATE® as "helpful" for a higher proportion of bleeds (12 [57.1%] bleeds) than patients managed on the prophylactic treatment regimen (2 [20.0%] bleeds).

The investigator's assessment of efficacy for patients with Type 3 VWD was missing for 3 major bleeds and "excellent" for one major bleed. Overall, the investigator assessed the efficacy of OPTIVATE® to treat the 7 major bleeds for patients with "other" type of VWD as "excellent".

The investigator's assessment of the efficacy of OPTIVATE® to treat major bleeds was missing for all major bleeds experienced by patients managed on the on-demand treatment regimen. The investigator's assessment of the efficacy of OPTIVATE® to treat major bleeds was missing for one major bleed and "excellent" for the other major bleed experienced by patients managed on the prophylactic treatment regimen.

The investigator assessed the efficacy of OPTIVATE® to treat major bleeds as "excellent" for the 7 bleeds recorded for the one patient who received both treatment regimens. The patient assessed OPTIVATE® as "very helpful" in treating all 4 bleeds assessed.

Overall, the most commonly recorded investigator's overall assessment of the efficacy of OPTIVATE® during the study was "good", recorded for both patients with "other" type of VWD and for 6 patients with Type 3 VWD. The investigator assessed the efficacy of OPTIVATE® during the study as "excellent" for one patient (Type 3 VWD).

The investigator's overall assessment of the efficacy of OPTIVATE® during the study was "good" for all 3 patients assessed who were managed on the prophylactic treatment regimen, for 4 of the 5 patients assessed who were managed on the on-demand treatment regimen, and for the one patient who received both treatment regimens. The investigator's overall assessment of the efficacy of OPTIVATE® during the study was "excellent" for one patient (managed on the on-demand treatment regimen).

Safety and Tolerability

There were no deaths and no patient was withdrawn from the study due to a TEAE. Two patients had SAEs; however none of the SAEs were considered to related to the IMP. The most commonly reported TEAEs were abdominal discomfort, lethargy and depression (each reported for both patients with "other" type of VWD). No individual TEAE was reported for more than 2 patients overall. OPTIVATE® was considered to be safe and well tolerated in the 11 patients in this study.