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Pharmacokinetics of Optivate®[®], a high-purity concentrate of Factor VIII (FVIII) with von Willebrand factor (VWF), in patients with severe haemophilia A.

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Pharmacokinetics of Optivate®, a high-purity concentrate of Factor VIII (FVIII) with von Willebrand factor (VWF), in patients with severe haemophilia A.



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6 **1** Pharmacokinetics of Optivate[®], a high-purity concentrate of Factor VIII (FVIII) with
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8 von Willebrand factor (VWF), in patients with severe haemophilia A.
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51 **Keywords**

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53 Factor VIII; haemophilia A; pharmacokinetics; plasma concentrations; recovery.
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2. Abstract

Optivate[®] is a high purity FVIII/VWF concentrate, which is manufactured using two antiviral processes: solvent/detergent and terminal dry heating (80⁰C for 72 hours). A multicentre, non-randomised open-label study in 15 patients was conducted to test the pharmacokinetics (PK) of Optivate[®]. PK variables were analysed for the patients' prior FVIII product (PK1), their first dose of Optivate[®] (PK2) and at 3 months therapy (PK3). Mean non-compartmental half-lives (h) were 14.1, 12.4 and 12.1 respectively (p = 0.45), mean clearances (mL/kg/h) were 3.6, 3.2 and 3.1 respectively (p= 0.051), MRTs (h) were 19.0, 17.3 and 17.4 respectively (p = 0.39) and mean AUC₀₋₄₈ (h.IU/mL) were 14.3, 15.4 and 16.6 respectively (p=0.051) and mean AUC_{0-∞} (h.IU/mL) were 15.9, 16.4 and 17.9 respectively (p = 0.18).

The recovery data from this PK study was aggregated with recovery data collected from another study, with similar design but devoid of the other PK measurements. A total of 309 recoveries were conducted in 70 patients, The overall mean recovery per subject across 27 Optivate[®] batches was 2.7 IU/dL per IU/kg.

There were no clinical differences between Optivate[®] and other FVIII products, and except for Vd, no statistically significant differences were seen with respect to any of the other PK variables, or in recovery between weeks 0 and 12. Therefore, the PK of FVIII is not affected by the processes used to manufacture Optivate[®], which can be expected to be effective in the management of patients with haemophilia A.

3. Main body of text

Introduction

Optivate® is a high purity FVIII/VWF concentrate. The FVIII:VWF:RCo ratio is 1:1.7. Two antiviral steps are included in the manufacturing process: solvent/detergent and dry heat (80°C for 72 hours). These processes have antiviral activity against both enveloped (HIV, HBV, HCV and West Nile Virus)[1,2, 3,4] and non-enveloped viruses [1,5]. These well-established virucidal processes have safely and individually been used on BPL products, such as Replenine-VF and 8Y[1,6,7,8,9,10]. However, to ensure that the FVIII pharmacokinetics is not affected when these two methods are used in combination, a comparative PK study was conducted to investigate the pharmacokinetics of Optivate® against other FVIII products.

The full clinical programme for Optivate® included a study to examine the safety and efficacy (SE) of Optivate® in patients with severe haemophilia A. In the PK study, recovery (incremental recovery), was assessed at the same time as the other PK measurements. In both studies, recovery was also assessed when patients changed Optivate® batches. This report includes recovery data from both studies[11].

Materials and Methods

Study design

Two studies were conducted in previously treated patients (PTPs): a PK study and a SE study. This paper presents the pharmacokinetic data from the PK study and recovery

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4 data from both studies. Safety and efficacy data from both studies are presented
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6 elsewhere [12].
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11 Both studies were multicentre, international, open-label, non-randomised, prospective
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13 studies compliant with guidelines for plasma-derived products [11]. Ethics committee
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15 approval and written informed consent were obtained.
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21 Clinical assessments, including recovery and visit schedules were identical in both
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23 studies, except for an additional PK profile using each patient's current FVIII (PK 1).
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28 The patients refrained from administering any FVIII at least 3 days (preferably 7 days),
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30 prior to each PK profiling.
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33 34 35 *Patients*

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37 Patients were included in the studies if they had haemophilia A (<2% basal FVIII
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39 activity at the time of diagnosis) and no inhibitors to FVIII. Exclusion criteria are given
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41 in full elsewhere [12], but included active bleeding, clinically significant renal disease
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43 (creatinine >200 $\mu\text{mol/L}$), liver disease (alanine transaminase [ALT] levels > 3 times
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45 the upper normal limit).
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50 51 52 *Treatments*

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54 For the three pharmacokinetic assessments, a dose of 50 IU/kg was infused at a rate of
55
56 10 mL/minute. Between each assessment, patients administered Optivate®
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4 prophylactically or on-demand, according to preference. No specific treatments were
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6 prohibited during the study, except other FVIII products.
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10 11 ***Factor VIII assays***

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13 All FVIII assays were carried out in the Haemostasis Unit, Department of Haematology,
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15 Addenbrooke's Hospital, Cambridge, UK. The FVIII assays were conducted using
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17 one-stage clotting method. Blood samples for the PK analyses were collected at 14
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19 specified intervals before and up to 48 hours post infusion and for recovery 3 samples
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21 within 1 hours post infusion, in accordance with International Society for Thrombosis
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23 and Haemostasis (ISTH) recommendations [13].
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30 31 ***Outcome variables***

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33 The primary pharmacokinetic outcome measures: the difference between the half-life
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35 (non-compartment) for the current FVIII and the first dose of Optivate®; and the
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37 difference between the half-life for the first dose of Optivate® and Optivate® dose at
38
39 12-weeks. Secondary variables were area under the concentration-time curve to 48
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41 hours (AUC_{0-48h}), AUC to infinity ($AUC_{0-\infty}$) clearance (Cl), mean residence time
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43 (MRT), volume of distribution (Vd) and half-life (non-compartmental; also two
44
45 compartmental models for alpha and beta half-life).
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52 Recovery calculated from the first infusion of Optivate® was compared with that
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54 calculated 12 weeks later. Recovery was also assessed if a patient changed batch.
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Statistical methods

All subjects with complete pharmacokinetic data at specified time points were included in the pharmacokinetic population (n=13). The half-life (non-compartmental) of the current FVIII (PK1), the first dose of Optivate® (PK2) and the Optivate® dose at 12-weeks (PK3) were compared using Analysis of Variance (ANOVA), with centre, patient within centre, and assessment timepoint as explanatory variables. Non-compartmental analysis was used to calculate AUC_{0-48h} , $AUC_{0-\infty}$ (using the linear/log trapezoidal method), Cl, MRT and Vd. All results were tested for normality using Shapiro-Wilk test. The secondary outcome variables (with the exception of recovery at each batch change) for PK1 were compared with PK2 and PK3 using three-way ANOVA, with centre, patient within centre, and assessment timepoint as explanatory variables.

The two-compartmental PK modeling was performed using WinNonLin Professional (Version 1.5. Scientific Consulting Inc, North Carolina, USA). The other parameters were calculated using SAS release 9.1.3.

The recovery population included subjects from both studies and was calculated by dividing the FVIII increment (IU/dL) in the first 1 hour post-infusion by the FVIII dose (IU/kg).

Descriptive statistics include mean, median, 95% confidence interval as appropriate.

Statistical significance for comparative analyses was set at $p \leq 0.05$.

Results

Patients studied

A total of 70 patients were enrolled: 15 in the PK study; 55 in the SE study. Consolidated demographics have been presented elsewhere in detail [12]. Briefly, ages ranged from 12 to 65 years and duration of prior FVIII treatment ranged from 3 to 50 years. The pharmacokinetic analyses were only conducted on 13 patients from the PK study, as two patients had incomplete data sets. Recovery was assessed on all 70 patients enrolled.

In the two studies combined, 11 patients were treated prophylactically and 59 patients were treated on-demand. The flow of participants through the study is shown in

Figure 1.

Figure 1 near here

Pharmacokinetic assessment

A total of six different FVIII products were used in PK1 (Czynnik VIII, 8Y, Baxter FVIII, Replenate, Fandhi and Kogenate). The mean plasma FVIII concentration–time profiles for PK1, PK2, and PK3 are shown in Figure 2.

Figure 2 near here

There was no statistically significant difference in the non-compartmental terminal half-life ($T_{1/2}$) between treatment groups (Table 1): prior FVIII, first dose of Optivate® and Optivate® dose at 12 weeks ($p=0.45$).

Table 1 near here

There was no statistically significant difference in non-compartmental AUC_{0-48h} ($p=0.051$), $AUC_{0-\infty}$ ($p=0.18$), Cl ($p=0.051$), or MRT ($p=0.39$) assessed at the three pharmacokinetic timepoints and, therefore, no statistically significant differences among treatments (Table 1). In the case of Vd the mean Vd for prior FVIII was statistically higher than the two Optivate® assessments ($p=0.18$ at PK2 and $p=0.001$ at PK3). Suggesting that lower FVIII peak values might be observed and so lower recoveries. However, there was no statistically difference noted in recoveries between prior FVIII or either of the Optivate® assessments and the confidence intervals for Vd for prior FVIII and consolidated Optivate® show some overlap. Therefore it can be concluded that the difference seen in the Vd may be a chance finding due to the small sample size.

The two-compartmental model was used to derive the alpha and beta half-lives. If the coefficient of variance was greater than 100%, these values were

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4 considered to be outliers and excluded from the analysis (Table 1). For this reduced
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6 sample size, mean alpha half-life (hours) at PK1, PK2 and PK3 was 2.9, 1.7 at and 2.8
7
8 respectively. The mean beta half-life (hours) was 13.2, 12.3, and 13.1. The treatment
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10 difference was not statistically significant ($p=0.76$).
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13 14 15 16 ***Incremental recovery data***

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18 The mean recoveries at PK1, PK2 and PK3 (Table 1) were not significantly different
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20 between treatments ($p=0.14$).
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25 A total of 27 batches of Optivate® was used in the studies. Recovery was evaluated on
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27 309 occasions across 70 patients. Overall the mean consolidated recovery, including
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29 batch changes, was 2.7 IU/dL per IU/kg.
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33 34 35 **Discussion**

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38 The pharmacokinetics of a FVIII product are regarded as surrogates for efficacy,
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40 therefore it is import to assess these markers during the clinical development of any new
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42 FVIII concentrate[14, 15].
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49 There are however growing concerns regarding the variability in the assessment of PK
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51 parameters [15,16]. Different assay techniques, such as standards used or methodology
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53 (one-stage, two-stage or chromogenic) can affect the outcomes[17,18]. For example,
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55 when comparing two different assays methods the chromogenic recovery value was
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57 reported to be 17-28% higher than the one-stage method [19].
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7 Other factors affecting PK outcomes include inter- and intra-patient variability, the type
8 of product being tested [14,16] and also the type analytical tools used to derive the
9 data[16,18,19,20,21]. Modern PK analytical computer programs allow
10 model-independent calculation of various PK parameters, and its use is supported by the
11 Scientific Standards Committee of the ISTH [15, 20].
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21 The overall evaluation of the PK of Optivate® in this study was in accordance with the
22 realisation which has been developing. The use of the model-independent analysis and
23 excluding half-life estimates with a coefficient of variance of greater than 100% from
24 the two-compartment model provided a clearer set of results.
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33 Moreover, in the PK study, a PK assessment was carried out on each patient's product
34 immediately before they transferred to Optivate®. The first PK assessment on Optivate®
35 was carried out 7 days afterwards, by which time all the previous product should have
36 been cleared from the body (> 6 half-lives), this was confirmed by the trough
37 concentration in each patient just before infusion of Optivate®. The pharmacokinetic
38 analysis for half-life, clearance, MRT and recovery conducted in this study, found no
39 clinical or statistically significant difference between the subjects' prior FVIII and
40 Optivate® using the assay techniques and PK analytical programs.
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54 Furthermore, the non-compartmental half-life of FVIII from Optivate® was similar at
55 the first and second pharmacokinetic assessments as were the other PK variables
56 assessed.
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7 The PK results for Optivate® were shown to be comparable with those reported by other
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9 researchers. Morfini *et al* [14] reported the results of the most significant
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11 pharmacokinetic parameters across several studies for different products. The terminal
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13 half-life across products ranged from 16.7 ± 9.8 hours (for Haemate P) to 10.5 ± 3.4
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15 hours (for Monoclate HT). Messori *et al* [22] published pharmacokinetic parameters for
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17 3 different products; they reported a mean FVIII clearance between 3.14 to 4.37
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19 mL/h/kg, a mean FVIII MRT of 14.9 to 15.5 hours across the three products. Bjorkman
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21 *et al* [23] also reviewed the pharmacokinetics properties of plasma-derived concentrated
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23 and found that the FVIII clearance ranged from 1.8 to 6 mL/h/kg and the FVIII half-life
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25 ranged from 8 to 23 hours. Nemes *et al* [24] conducted a PK study with Immunate
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27 (FVIII/VWF concentrate) in a small group of subjects and found that the mean FVIII
28
29 half-life was 12.0 hours, and ranged from 8.4 to 18.6 hours, the mean recovery was
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31 2.0 IU/dL per IU/kg and ranged from 1.1 to 3.0 IU/dL per IU/kg.
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40 Recovery data from two similar, long-term, clinical studies were also consolidated. This
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42 analysis was to assess the *in vivo* consistency of Optivate® and, thereby, act as an
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44 alternative surrogate to support efficacy. There were no statistically significant
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46 differences in recovery between treatments. Bjorkman *et al* [23] reported FVIII
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48 recovery values between 0.020 and 0.025 IU/mL per IU/kg. Nemes *et al* [24] showed
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50 Immunate had a mean FVIII recovery of 2.0 IU/dL per IU/kg which ranged from 1.1 to
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52 3.0 IU/dL per IU/kg. Later, in 2007, Bjorkman *et al* [25] reported mean FVIII recovery
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54 values ranging from 2.2 to 3.0 IU/dL per IU/kg for various FVIII products. Therefore
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56 the efficacy of Optivate® in the treatment of patients with haemophilia A can be
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4 reasonably assumed. Clinical results from the PK and SE studies are presented
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6 elsewhere [12] and support this assumption. It can be inferred from these results that the
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8 manufacturing process of Optivate® does not lead to any clinically significant or
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10 unexpected changes in the FVIII pharmacokinetics.
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16 In conclusion, the FVIII pharmacokinetics of Optivate® do not differ from those
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18 generally accepted from other FVIII products. The recovery data include evaluation of
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20 27 batches over a mean duration of 92.9 weeks. Altogether the data presented from
21
22 these studies support both the manufacturing process and the clinical efficacy of
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24 Optivate® and its use prophylactically or on-demand.
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5. References

1. Rizza CR, Fletcher ML, Kernoff PB. Confirmation of viral safety of dry heated Factor VIII concentrate (8Y) prepared by Bio Products Laboratory (BPL): A report on behalf of UK Haemophilia Centre Directors. *Br J Haematol* 1993; 84: 269-72.
2. Colvin BT, Rizza RC, Hill GH, Kernoff PBA, Bateman CJT, Bolton-Maggs et al. Effect of dry-heating of coagulation factor concentrates at 80 degrees C for 72 hours on transmission of non-A, non-B hepatitis. Study Group of the UK Haemophilia Centre Directors on Surveillance of Virus Transmission by Concentrates. *Lancet* 1988; 2: 814-6.
3. Kreil TR, Berting A, Kistner O, Kindermann J. West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. *Transfusion* 2003; 43: 1023-28.
4. Remington KM, Trejo SR, Buczynski G, Li H, Osheroff WP, Brown JP et al. Inactivation of West Nile virus, vaccine virus and viral surrogates for relevant and emergent viral pathogens in plasma-derived products. *Vox Sang* 2004; 87: 10-8.
5. Yee TT, Lee CA, Pasi KJ. Life-threatening human parvovirus B19 infection in immunocompetent haemophilia. *Lancet* 1995; 345: 794-5.
6. P.L. Roberts, C, Dunkerley. Effect of manufacturing process parameter on virus inactivation by solvent-detergent treatment in a high-purity factor IX concentrate. *Vox Sang* 2003; 84: 170-5.
7. Yee TT, Williams MD, Hill FG, Lee CA, Pasi KJ. Absence of inhibitors in previously untreated patients with severe haemophilia A after exposure to a single intermediate purity Factor VIII product. *Thromb Haemost* 1997; 78: 1027-9.

- 1
2
3
4 8. Brown SA, Dasani H, Collins PW. Long-term follow up of patients treated with
5 intermediate FVIII concentrate BPL 8Y. Haemophilia. 1998; 4(2): 89-93.
6
7
- 8
9 9. Pasi KJ, Hill FG. Safety trial of heated factor VIII concentrate (8Y). Arch Dis
10 Child 1989; 64(10): 1463-7.
11
12
- 13 10. Gascoigne EW, Dash CH, Harman C, Wilmot D. A retrospective survey on the
14 safety of Replene[®], a high purity factor IX concentrate. Pharmacoepidemiol
15 Drug Saf 2004; 13: 187-95.
16
17
- 18 11. Notes for guidance to assess efficacy and safety of human plasma derived
19 factor VIII:C and factor VIII:C products in clinical studies in haemophiliacs before
20 and after authorisation (CPMP/BPWG/198/95 rev.1).
21
22
- 23 12. Dmoszynska A, K.Kuliczkowski AK, Hellmann A, Robak T, Kloczko J, Baglin T
24 et al . Clinical assessment of Optivate, a new high-purity concentrate of factor VIII
25 (FVIII) with von Willebrand factor (VWF), in the management of patients with
26 haemophilia A. July 2010 submitted for publication.
27
28
- 29 13. Scientific and standardization committee communication. The design and analysis
30 of pharmacokinetic studies of coagulation factors, 21 Mar 2001.
31
32
- 33 14. Morfini M. Pharmacokinetics of factor VIII and factor IX. Haemophilia 2003; 9
34 (suppl 1); 9-100.
35
36
- 37 15. Lee M , Morfini M, Schulman S, Ingerslev J.. The design and analysis of
38 pharmacokinetic studies of coagulation factors. Factor VIII/IX SSC-ISTH
39 recommendations at <http://www.med.unc.edu/isth/fviiiipharco.htm>.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
- 54 16. Messori A, Longo G, Matucci M, Morfini M, Ferrini PLR. Clinical
55 Pharmacokinetics of Factor VIII in patients with classic haemophilia. Clin
56 Pharmacokinet 1987; 13: 365-80.
57
58
59
60

- 1
2
3
4 17. Cinotti S, Longo G, Messori A, Morfini M, Blomback M, Schimpf K et al.
5
6 Reproducibility of one-stage, two-stage and chromogenic assays of factor VIII
7
8 activity: A multi-centre study. *Thromb Res* 1991; 61: 385-93.
9
- 10
11 18. Rosen S. A rebuttal: Issues with the assay of Factor VIII activity in plasma and
12
13 Factor VIII concentrates. *Thromb Haemost* 2001; 86: 1132-33.
14
- 15
16 19. Lee C, Barrowcliffe T, Bray G, Gomperts E, Hubbard A, Kemball-Cook G et al.
17
18 Pharmacokinetics in vivo comparison using 1-stage and chromogenic substrate
19
20 assays with two formulations of Hemofil-M. *Thromb Haemost* 1996; 76 (6):
21
22 950-6.
23
- 24
25 20. Morfini M, Lee M, Messori A. The design and analysis of half-life and recovery
26
27 studies for factor VIII and factor IX. *Thromb Haemost* 1991; 66: 384-6.
28
- 29
30 21. Bjorkman S Carsson M, Berntorp E, Stenberg P. Pharmacokinetics of factor VIII
31
32 in humans obtaining clinically relevant data from comparative studies. *Clin*
33
34 *Pharmacokinet* 1992; 22(5): 385-395.
35
- 36
37 22. Messori A, Morfini M, Blomback M, Cinotti S, Longo G, Schimpf K et al.
38
39 Pharmacokinetics of Two Pasteurised factor VIII Concentrates by Different and
40
41 Multicenter Assays of FVIII Activity. *Thromb Res* 1992; 65: 699 – 708.
42
- 43
44 23. Bjorkaman S, Berntorp E. Pharmacokinetics of coagulation factors, clinical
45
46 relevance for patients with haemophilia. *Clin Pharm* 2001;40 (11): 815-832.
47
- 48
49 24. Nemes L, Lisstchikov T, Dobaczewsk G, Klukowska A, Kmorsk V,
50
51 Zimmermann R et al. Pharmacokinetics, Efficacy and Safety of IMMUNATE[®]
52
53 Solvent/ Detergent (IMMUNATE[®] S/D) in Previously Treated Patients with
54
55 Severe Hemophilia A: Results of a Prospective, Multicenter, Open-Label Phase III
56
57 Study. *Acta Haematologica* 2008; 119: 89-97.
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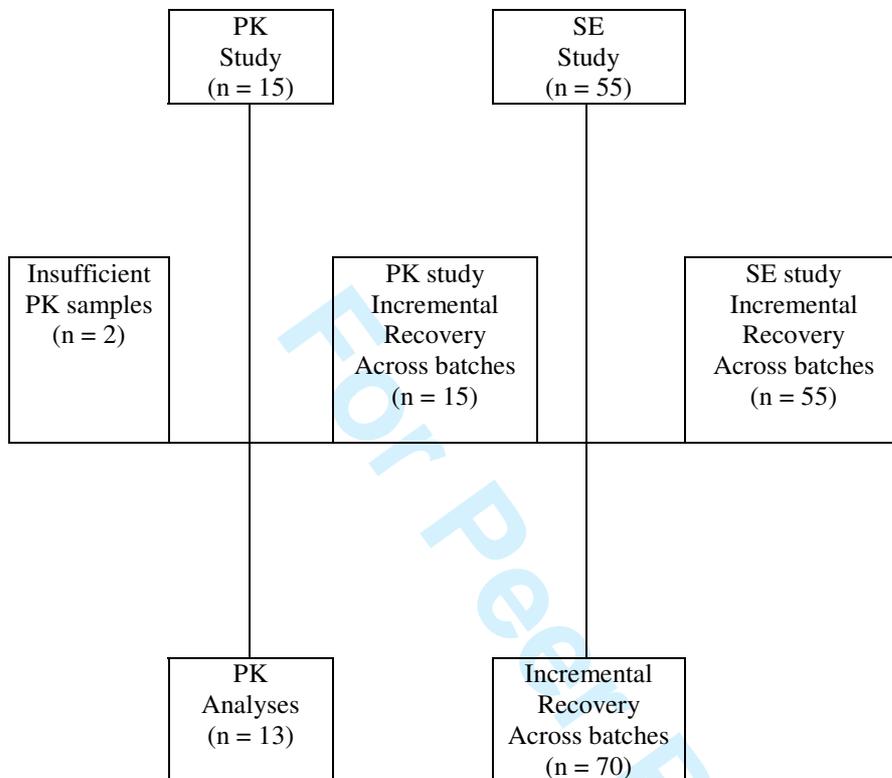
25. Bjorkaman S, Folkesson A, Berntorp E. In vivo recovery of factor VIII and Factor IX: intra- and inter-individual variance in a clinical setting. *Haemophilia* 2007; 12:2-8.

For Peer Review

BPLOptivatePK7Jul10

Pharmacokinetics of Optivate[®], a high-purity concentrate of Factor VIII (FVIII) with von Willebrand factor (VWF), in patients with severe haemophilia A.

Figure 1 : Flow of study patients (n=no. of patients)

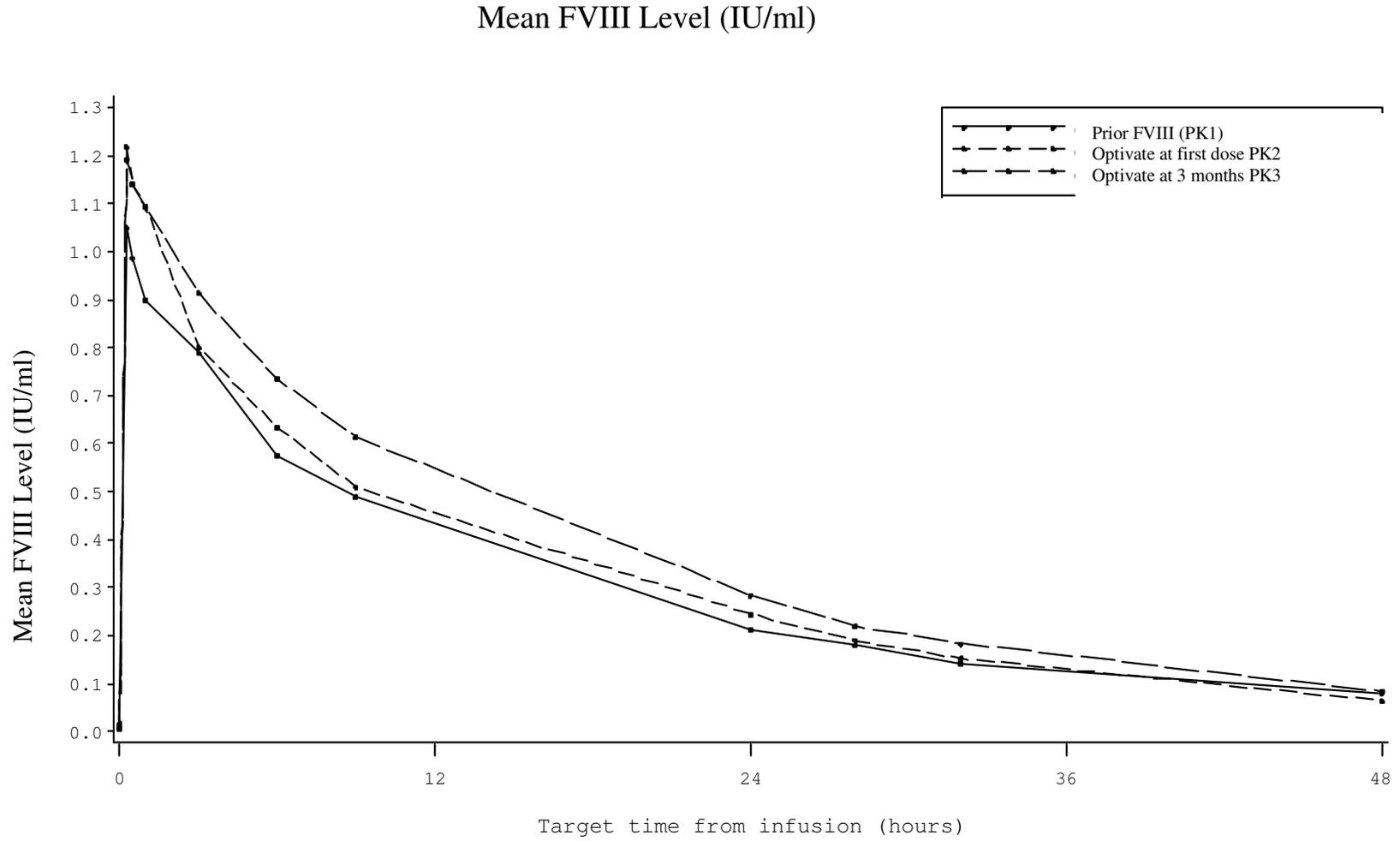


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Pharmacokinetics of Optivate[®], a high-purity concentrate of Factor VIII (FVIII) with von Willebrand factor (VWF), in patients with severe haemophilia A.

Figure 2: Plasma concentration–time profiles at PK1, PK2, and PK3



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Pharmacokinetics of Optivate[®], a high-purity concentrate of Factor VIII (FVIII) with von Willebrand factor (VWF), in patients with severe haemophilia A.**Table 1: Pharmacokinetic variables of FVIII in each of the three PK periods**

PK variable	Statistic	Prior FVIII PK1	First Optivate PK2	Second Optivate PK3	ANOVA Probability (for PK1, PK2, PK3)	Overall Optivate (PK2 and PK3)
$T_{1/2}$ (non-compartmental) (h)	n	13	13	13	$p = 0.45$	15
	Mean	14.1	12.4	12.1		12.4
	95%CI	9.81, 18.37	10.76, 14.09	10.25, 13.99		10.94, 13.83
AUC ₀₋₄₈ (h.IU/mL)	n	13	13	13	$p = 0.051$	15
	Mean	14.3	15.4	16.6		16.1
	95%CI	11.17, 17.38	13.44, 17.27	13.88, 19.38		13.97, 18.28
AUC _{0-∞} (h.IU/mL)	n	13	13	13	$p = 0.18$	15
	Mean	15.9	16.4	17.9		17.3
	95%CI	11.87, 19.93	14.41, 18.43	14.70, 21.16		14.98, 19.65
Clearance (mL/kg/h)	n	13	13	13	$p = 0.051$	15
	Mean	3.6	3.2	3.1		3.1
	95%CI	2.85, 4.43	2.80, 3.59	2.55, 3.54		2.71, 3.51
MRT (h)	n	13	13	13	$p = 0.39$	15
	Mean	19.0	17.3	17.4		17.5
	95%CI	14.50, 23.44	15.63, 19.05	15.34, 19.35		15.99, 18.92
Volume of distribution (mL/kg)	n	13	13	13	$p=0.003^{\text{®}}$	15
	Mean	63.7	55.2	51.1		53.4
	95%CI	53.21, 74.24	46.73, 63.60	44.98, 57.19		46.20, 60.52

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Pharmacokinetics of Optivate[®], a high-purity concentrate of Factor VIII (FVIII) with von Willebrand factor (VWF), in patients with severe haemophilia A.**Table 1(continued): Pharmacokinetic variables of FVIII in each of the three PK periods**

PK variable	Statistic	Prior FVIII PK1	First Optivate PK2	Second Optivate PK3	ANOVA Probability (for PK1, PK2, PK3)	Overall Optivate (PK2 and PK3)
Alpha-T _{1/2} (compartmental) (h)	n**	5	8	10		11
	Mean	2.9	1.7	2.8	N/A	2.2
	95%CI	1.59, 4.17	0.35, 3.00	1.20, 4.37		1.48, 2.88
Beta-T _{1/2} (compartmental) (h)	n**	14	12	15		15
	Mean	13.2	12.3	13.1	<i>p=0.76</i>	12.6
	95%CI	11.56, 14.81	11.58, 13.07	10.95, 15.18		11.33, 13.92
Incremental recovery in PK study (IU/dL per IU/kg)	n	15	14	15		15
	Mean	2.2	2.6	2.4	<i>p=0.14</i>	2.5
	95%CI	1.75, 2.65	2.18, 2.99	2.16, 2.59		2.22, 2.74
Incremental recovery across PK and SE study (IU/dL per IU/kg)	n	15	66*	68*		70
	Mean	2.2	2.7	2.6	N/A	2.7
	95%CI	1.75, 2.65	2.51; 2.86	2.40; 2.81		2.53, 2.79

** not all the patients data fit the two compartmental model (estimates with co-efficient of variance > 100% were excluded)

* recovery assessments across the two studies (PK and SE studies).

@ statistically significant

CI = confidence intervals, T_{1/2} = half-life