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Clinical assessment of Optivate®[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Anna Dmoszynska, Kazimierz Kuliczkowski, Andrzej Hellmann, Jacek Treslinski, Janusz Kloczko, Trevor Baglin, Charles Hay, Denise O'Shaughnessy, Rukhsana Begum Shaikh-Zaidi, Clive H Dash

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Clinical assessment of Optivate®, a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.



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Keywords:	Factor VIII, haemophilia A, safety, efficacy, plasma derived concentrates

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1. Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

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Running titleClinical assessment of Optivate[®] in patients with haemophilia A.**Keywords**

Factor VIII; haemophilia A; safety; efficacy; plasma-derived concentrates

2. Abstract

Factor VIII concentrates have revolutionised the treatment of patients with haemophilia A. Concerns over the transmission of viral infections through these products have been addressed through stringent, donor-screening procedures and robust antiviral manufacturing steps. BPL has developed a high-purity FVIII product with von Willebrand factor (VWF), Optivate[®]. Its safety, tolerability and efficacy as prophylaxis and treatment of bleeds has been established in long term studies. Seventy previously treated patients with severe haemophilia A, with ≥ 20 exposure days (ED), were recruited into two long-term, multicentre, open-label studies. The protocols were virtually identical. Patients received Optivate[®] either prophylactically or on-demand. A mean of 159.0 EDs were experienced over 11,320 infusions. Under both conditions, Optivate[®] was well tolerated. Only 10% of patients experienced a treatment-related adverse event (AE); the most commonly reported were headache (4% of patients) and dizziness (3% of patients). The mean number of bleeds/patient over the 2 year treatment period was 23.5 during prophylactic use and 70.4 during on-demand use. In patients treated prophylactically, clinical responses to breakthrough bleeds were rated by physician as excellent or good and as very helpful or helpful by patients in 95% of bleeds. Clinical responses by physicians in on-demand patients were rated as excellent

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4 or good and helpful or very helpful by the patients for 91% of bleeds. There were no
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6 viral transmissions or inhibitors. The studies confirm the clinical efficacy and safety of
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8 Optivate[®] in both prophylactic and on-demand management of patients with
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10 haemophilia A.
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13 14 15 16 **3. Main body of text**

17 18 **Introduction**

19
20 It is well known that factor VIII (FVIII) concentrates have revolutionised the treatment
21
22 of patients with haemophilia, with considerable improvements in patients' quality of life
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24 [1,2]. The transmissions of hepatitis A (HAV), B (HBV), non-A-non-B hepatitis[3,4]
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26 and HIV[5,6] were significant setbacks. Many preventative measures were implemented
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28 to reduce the risk of viral transmission by transfusion and plasma products, including
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30 donor screening virucidal procedures[5,6,7,8,9] and virus eradication steps in
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32 manufacturing. For example, in 1985, BPL introduced an intermediate-purity
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34 FVIII/VWF concentrate (8Y) manufactured using a dry heat-treatment at 80°C for 72
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36 hours[10,11,12], which is known to have broad anti-viral effect[10,13]. Over the last 20
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38 years, 8Y has been well-tolerated in the treatment of haemophilia A and VWD, without
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40 any transmission of hepatitis A, B or C or HIV, and with a low incidence of
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42 inhibitors[14,15,16].
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52 A new high purity product, Optivate[®], has been developed, which includes a novel
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54 chromatographic purification step to remove unnecessary proteins, such as fibrinogen
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56 and fibronectin. In addition, the specific and well-established solvent-detergent step is
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58 included, to minimise transmission of enveloped viruses, including West Nile[17,18].
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4 The dry heating (80⁰C for 72 hours) process, used in 8Y, and known to inactive SARS
5 virus[19], has been retained. The two specific virucidal steps taken in the manufacture
6 of Optivate[®] are considered to be effective against enveloped and non-enveloped viruses
7 (e.g. HAV and parvovirus B19). The normal pharmacokinetics of Optivate[®] have been
8 reported elsewhere in patients with haemophilia A[20] and in patients with VWD[21].
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19 Nowadays, the development of inhibitor antibodies remains a concern with new FVIII
20 products. In the late 1980s and early 1990s two outbreaks of inhibitors amongst PTPs
21 treated with new concentrates showed that changes in manufacturing processes could
22 result in the formation of neoantigens leading to inhibitor formation. [22,23,24,25].
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26 Since then, it has been essential to evaluate all new FVIII concentrates in previously
27 treated patients (PTPs) to establish whether they are unusually antigenic.
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35 This paper reports consolidated clinical data, collected prospectively, over a follow-up
36 period of two years, from two studies conducted to assess the safety and efficacy of
37 Optivate[®] in patients with severe haemophilia A.
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45 **Materials and Methods**

46 *Study design*

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50 Two studies (called PK and SE) were conducted; as their designs were virtually
51 identical, the long-term clinical data have been combined in this report. The major
52 difference between the studies was that one of them (PK) additionally provided
53 pharmacokinetic profiles of the patients' previous FVIII and of Optivate[®]. These PK
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4 data are reported elsewhere[20]. Both studies were multicentre, international,
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6 open-label, non-randomised, prospective studies compliant with Committee for
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8 Medicinal Human Products (CHMP) guideline[26]. Ethics committee approval and
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10 written informed consent were obtained.
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16 Clinical assessments and the visit schedules were identical in both studies: a pre-study
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18 screening (2 weeks prior to Optivate[®] being given) ; a first dose assessment, followed by
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20 3 months of home therapy; a second dose assessment at the end of this period, followed
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22 by a further 21 months of home therapy; with regular check-up by phone throughout
23
24 and 3-monthly reviews at the haemophilia centre.
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28 29 30 *Patients*

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32 Patients were eligible for inclusion if they were male (≥ 12 years old), had haemophilia
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34 A (<2% basal FVIII activity at the time of diagnosis) without inhibitors, with at least 20
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36 exposure days (ED; but > 150 for SE study). Exclusion criteria were: history of
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38 inhibitors; international normalised ratio (INR) >1.5; thrombocytopenia (platelets <50 x
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40 $10^9/L$), clinically significant renal disease (creatinine >200 $\mu\text{mol/L}$); clinically
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42 significant liver disease (alanine transaminase (ALT) levels > three times the upper
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44 normal limit); participation in another clinical trial within 30 days before study entry.
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47 In the SE study patients needed to have CD4 lymphocyte counts of >0.4 x $10^9/L$.
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Treatments

Optivate[®] was used prophylactically or on-demand, according to preference. No specific medications were prohibited during the study, with the except other FVIII products.

Outcome variables

Safety was assessed by monitoring viral markers (anti-parvovirus B19, HIV, HBV, HCV, and HAV) at specified times. FVIII inhibitor screens (3 monthly), routine biochemistry and haematology, and adverse events (AEs). Factor VIII inhibitor screens were performed using standard APTT incubation techniques, as recommended by UK Haemophilia Centre Doctors' Organization (UKHCDO)[26,27,28]. If a screening test was positive, a Bethesda/Nijmegen quantitation assay was performed.

The extent of exposure was also determined. Efficacy was assessed by the number, type, and severity of bleeds as a new bleed (break-through bleed) or ongoing bleed (bleed requiring additional Optivate[®] doses). Subjective assessments of haemostasis were made by the clinician and the patients. .

Statistical methods

The sample sizes chosen for each study were in excess of CHMP guidance[26]. Descriptive statistics are presented and subdivided into prophylactic and on-demand use. As these modalities of treatment were not randomized, no formal, comparative, statistical tests were used. Prophylaxis was defined as least 2 prophylactic doses per week

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Results

Patients studied

A total of 70 patients were enrolled (15 in the PK study; 55 in the SE study). All, except one African-Caribbean patient, were Caucasian. Of the 70 patients, 11 were treated prophylactically and 59 on-demand (Figure 1).

Figure 1 near here

Out of the 59 on-demand patients, 47 administered intermittent prophylactic doses, mostly before increased physical activity. Consolidated baseline demographics of the participants are shown in Table 1.

Table 1 near here

Efficacy

Duration and infusions

Patients received Optivate[®] for a mean period of 92.9 weeks (Table 2).

Table 2 near here

There was no significant difference in the mean duration of treatment per patient between the two Optivate[®] usage groups. However, because of the different numbers of patients in these two subgroups the mean treatment period was considerably higher in patients on prophylaxis than those using Optivate[®] on-demand ; 97.3 weeks and 92.1 weeks respectively. Overall mean experience in the study was 124.6 patient.years.

Altogether 11,320 infusions of Optivate[®] were used.

Table 3 near here

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4 The study recorded a mean of 159.0 exposure days (Table 3), which included in the
5 patients on prophylaxis 2789 doses prophylactically and 408 infusions to treat a bleed
6 and those on-demand using 5580 infusions to treat a bleed, 2205 doses for intermittent
7 prophylaxis (Table 4).
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14 **Table 4 near here**
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17 Overall, the mean number of infusions administered per patient was 161.7. The Polish
18 subjects had fewer EDs per patient than the UK patients (Table 5).
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21 **Table 5 near here**
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26 *Doses of Optivate®*
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31 When a bleed occurred in patients on prophylaxis, the mean dose/patient used for a new
32 bleed was 25.0 IU/kg and the mean total for an ongoing bleed was 53.6 IU/kg/patient.
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34 In comparison the on-demand patients used slightly lower doses for new bleeds
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36 (Table 6).
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41 **Table 6 near here**
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46 As well as the 11 patients in the prophylactic group, 47 on-demand patients
47 administered intermittent prophylactic doses. Overall the mean prophylactic dose was
48 13.7 IU/kg/patient: 17.6 IU/kg in the prophylactic group; 13.0 IU/kg in the on-demand
49 group (Table 7). Patients in the UK administered more frequent prophylactic doses and
50 used a higher dose per infusion than those in Poland; 1.63 and 0.54 prophylactic doses
51 per week/patient respectively (Table 8).
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60 **Table 7 & 8 near here**

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Treatment of spontaneous bleeds during the study

The mean number of bleeds/patient was 23.5 for patients using Optivate[®] prophylactically (mean 0.24 new bleeds per week/patient) compared to 70.4 for on-demand patients (mean 0.75 new bleeds per week/patient). The UK patients had a mean bleed rate of 0.49 bleeds/week/patient, whereas the Polish patients had 0.72 bleed/week/patient (Table 9).

Table 9 near here

Overall 78% of the bleeds were into the joints, 11% were muscle bleeds and 9% were open/other bleeds and for the remaining 1% location was not specified (Table 6).

The objective outcome of the bleeding episodes was assessed by the clinicians for 84.2% of bleeds and in 97.4% of bleeds by patients. For patients treated prophylactically the clinicians' rated Optivate[®] therapy as excellent or good in 95% of the bleeding episodes. The patients reported clinical responses of helpful or very helpful in controlling bleeding episodes in 95% using prophylaxis and in 91% of those using Optivate[®] on-demand (Table 10).

Table 10 near here

Safety

Table 11 near here

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Consolidated adverse events (AEs)

In the prophylactic group, one patient (9%) reported 5 treatment-related AEs. In the on-demand group, 6 patients (10%) reported an AE (17 events). Overall 22 treatment-related AEs occurred in seven patients (10%). Headache was the most frequent AE which occurred in three (4%) patients, then dizziness, reported by two (3%) patients (Table 11). Overall, one AE occurred in every 894 infusions.

Other safety variables

All patients had negative screens for inhibitors to FVIII throughout the studies, no virus transmissions occurred, and there were no significant changes in laboratory values.

Discussion

The aim of the studies was to evaluate the FVIII and VWF concentrate (Optivate®) in PTPs. Although the data originate from formal clinical studies, the outcomes represent usual clinical practice, for example, the doses were given to the nearest whole (500 IU) vial.

Combined safety and efficacy data from two similar studies of Optivate® are included in this report. In both of these studies, the use of Optivate® was analysed by prophylactic use and on-demand use but, as the patients were not randomized, a comparison is not appropriate. However, the standard management of patients with severe haemophilia A can involve either one of these treatment modalities, and therefore the inclusion of both

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4 treatment regimens in the studies allows the clinical utility of Optivate[®] to be
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6 established comprehensively.
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11 Prophylaxis is mainly used in children and young adults. The patients studied with
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13 Optivate[®] used prophylactically did not differ in age to those using it on-demand,
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15 although only a minority (11/70; 15.7%) were using it prophylactically. Overall, the
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17 on-demand patients tended to use lower doses than those in the prophylactic group both
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19 to treat a bleed and as intermittent prophylaxis.
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26 The patients who used Optivate[®] prophylactically experienced about a third of the
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28 number of bleeds as those on-demand, with a bleed rate of 0.24 bleeds/week/patient and
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30 0.75 bleeds/week/patient respectively. The outcome is in accord with that when the two
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32 treatment modalities have been compared [29]. As expected, the majority of Polish
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34 patients were treated on-demand and so consumed less factor VIII product, compared
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36 with the those treated in the UK [30].
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42 The efficacy of Optivate[®] was explored qualitatively by assessing the impact of
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44 prophylactic and on-demand treatment on the subjective outcomes of spontaneous
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46 bleeds. Physician and patient based assessments of response yielded similar positive
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48 results.
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54 The data collected on spontaneous bleeding cannot provide evidence of the efficacy of
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56 Optivate[®] relative to other FVIII products, since this was not a comparative study. The
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4 results of this study, however, indicate that prophylactic use of Optivate[®] is effective
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7 with fewer bleeds than with on-demand use.
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11 The use of Optivate[®] was well tolerated in patients. There were no safety concerns with
12 the use of Optivate[®] either prophylactically or on-demand. Only seven patients (10%)
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14 experienced treatment-related AEs at some time in the long-term follow-up. The
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16 number of AEs reported was not unusually high and the types of AEs were comparable
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18 to other high-purity products[31]. The most commonly reported treatment-related AEs
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20 were headache (4%) and dizziness (3%). Patients using Optivate[®] prophylactically
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22 experienced fewer AEs than those using it on-demand. The only treatment-related AE
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24 experienced by both treatment groups was headache. Since the formation of inhibitors
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26 currently represents a major obstacle to successful treatment in some patients with
27
28 haemophilia A, the absence of inhibitors in these trials with Optivate[®] further supports
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30 its use in clinical practice, although all patients were PTPs. The VWF content of
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32 Optivate[®] may have contributed to this outcome.
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42 **Conclusions**

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44 These findings confirm the clinical safety and efficacy of Optivate[®] in both the
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46 prophylactic management and on-demand treatment of bleeds in patients with severe
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48 haemophilia A. Furthermore, no concerns emerged regarding FVIII inhibitors.
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53 **4. Acknowledgements**

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4 We thank the patients who agreed to participate in BPL's Optivate® studies and all the
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9
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11
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13
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15
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20 (BPL), Elstree, UK.
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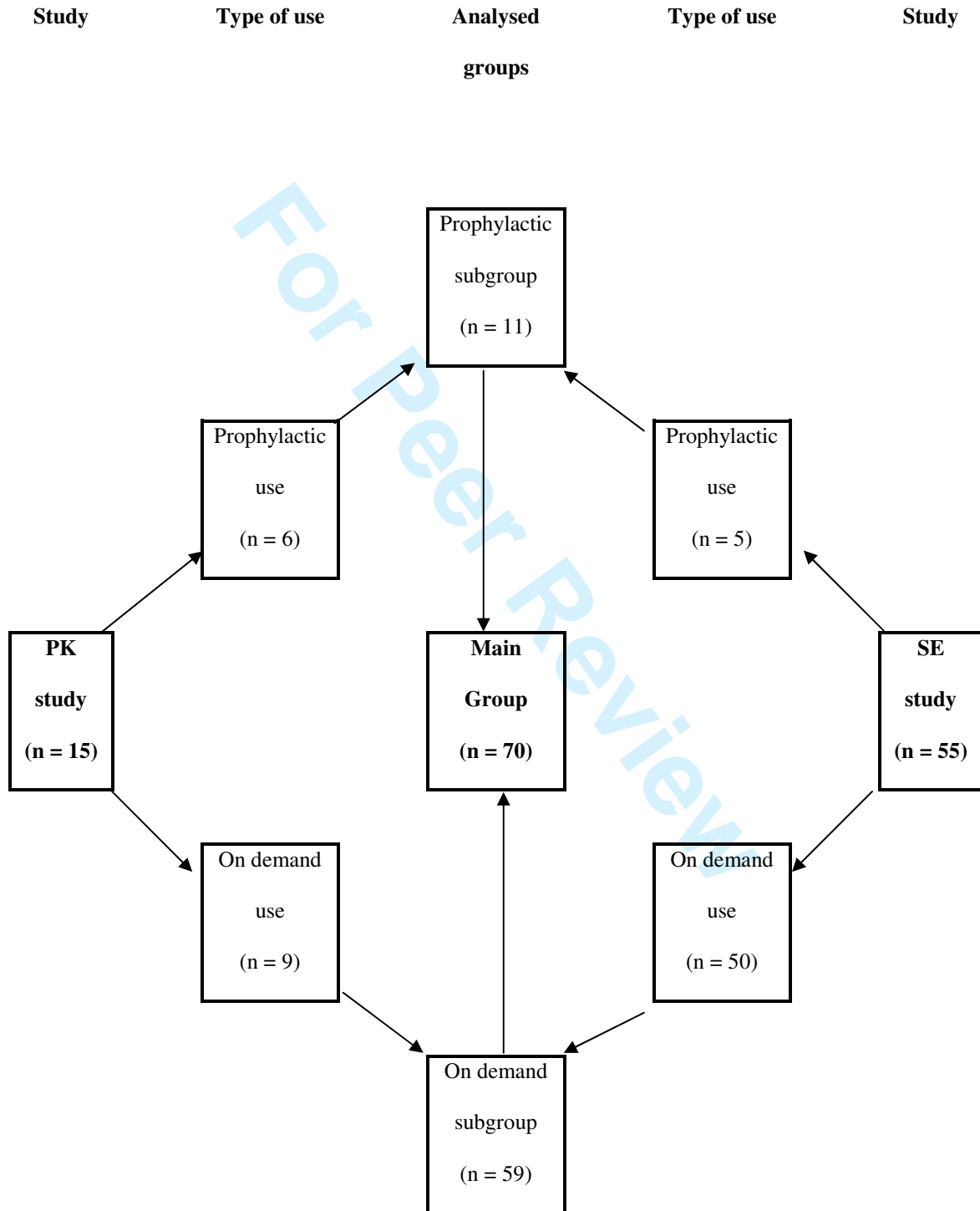
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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Figure 1 : Flow of participants in the studies to the analysed groups



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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 1: Consolidated Patient Demographics

	Prophylactic Use	On-demand Use	Overall
	N=11	N=59	N=70
Age (years)	Variable/stats	Variable/stats	Variable/stats
Mean	33.5	30.5	30.9
Range	20-48	12-65	12-65
Weight (kg)	Variable/stats	Variable/stats	Variable/stats
Mean	78.5	70.8	72.0
Range	55-100	32-106	32-106
Duration of FVIII treatment (years)	Variable/stats	Variable/stats	Variable/stats
Mean	21.6	13.9	14.8
Range	8-37	3-50	3-50

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 2: Duration of Optivate[®] therapy

	Prophylactic group	On-demand group	Overall
Mean duration in weeks (Min, Max)	97.3 (93.1, 104.7)	92.1 (10.1, 109.9)	92.9 (10.1, 109.9)
patient.years	20.5	104.1	124.6

Min = minimum, Max = Maximum

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 3: Overall exposure-days to Optivate[®] and for prophylactic and on-demand subgroups.

Number of exposure days#	Prophylactic sub-group (n = 11)	On-demand sub-group (n = 59)	Overall (n = 70)
To treat a bleed			
Mean	33.9	93.7	84.3
(95% CI)	(10.24;57.58)	(78.77;108.58)	(70.36;98.21)
Prophylactically			
Mean	253.4	37.3	71.2
(95% CI)	(221.18;285.55)	(23.38;51.16)	(48.62;93.84)
Overall*			
Mean	289.6	134.7	159.0
(95% CI)	(243.12;336.15)	(117.70;151.62)	(138.39;179.64)

CI = confidence interval

*including bolus doses at recovery assessments

#An exposure-day = a day when the patient received at least one infusion, whether it was administered as prophylaxis or on-demand for a bleed

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 4: Overall number of Optivate[®] infusions for prophylactic and on-demand subgroups.

Number of infusions	Prophylactic sub-group (n = 11)	On-demand sub-group (n = 59)	Overall (n = 70)
To treat a bleed			
Total	408	5580	5988
Mean	37.1	94.6	85.5
(95% CI)	(10.13;64.05)	(79.45;109.70)	(71.42;99.67)
Prophylactically			
Total	2789	2205	4994
Mean	253.6	37.4	71.3
(95% CI)	(221.29;285.80)	(23.35;51.39)	(48.67;94.02)
Overall*			
Mean	295.8	136.7	161.7
(95% CI)	(247.45;344.18)	(119.38;154.04)	(140.56;182.87)

CI = confidence interval

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 5 Exposure* days for all subjects – UK vs Poland

	n	No. of exposure days	Mean	95% LCL	95% UCL
Exposure* days per subject for UK	13	2727	209.8	138.84	280.70
Exposure *days per subject for Poland	57	8402	147.4	127.70	167.17

* including bolus doses at recovery assessment

LCL = Lower Confidence Interval, UCL = Upper Confidence Interval

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 6: Duration of bleeds and doses of Optivate[®] needed to control bleeding episodes

All bleeds	<i>Prophylactic group</i>	<i>On demand group</i>	Overall
Total No. bleeds	258	4151	4409
Mean/patient	23.5	70.4	63.0
Mean duration/patient (hrs)*	9.5 (CI: 4.90;14.12)	13.7 (CI: 10.72;16.73)	13.1 (CI: 10.43;15.66)
Median duration/patient (hrs)*	9.00	10.81	10.13
Mean dose per infusion/patient IU/kg	41.5 (CI: 14.44;68.46)	26.0 (CI: 22.15; 29.90)	28.5 (CI: 23.38;33.52)
Bleeds/week/patient	0.24 (CI:0.08;0.40)	0.75 (CI:0.65;0.86)	0.67 (CI:0.57;0.78)
New bleeds	<i>Prophylactic group</i>	<i>On demand group</i>	Overall
Mean dose IU/kg	25.0 (CI: 15.67;34.35)	18.2 (CI: 16.66;19.78)	19.3 (CI: 17.37;21.20)
Ongoing bleeds	<i>Prophylactic group</i>	<i>On demand group</i>	Overall
Mean dose IU/kg	53.6 (CI: -8.11; 115.36)	26.4 (CI: 21.15; 31.55)	29.9 (CI: 21.71;38.15)
Joint Bleeds#	<i>Prophylactic group</i>	<i>On demand group</i>	Overall
Total No. bleeds	*220	*3233	*3453
Mean dose IU/kg	30.4 (CI: 21.22;39.49)	26.0 (CI:22.17;29.74)	26.6 (CI: 23.16;30.02)
Muscle Bleeds#	<i>Prophylactic group</i>	<i>On demand group</i>	Overall
Total No. bleeds	*16	*470	*486
Mean dose IU/kg	30.9 (CI: 16.81;44.94)	25.6 (CI: 21.13;30.09)	26.2 (CI: 22.11;30.38)
Open/other#	<i>Prophylactic group</i>	<i>On demand group</i>	Overall
Total No. bleeds	*21	*386	*407
Mean dose IU/kg	52.6 (CI: -20.90;126.18)	30.8 (CI: 22.74; 38.78)	32.8 (CI: 24.10;41.47)

*dataset not normally distributed

#For 63 bleeds location was not specified

CI = confidence Interval

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 7: Prophylactic use of Optivate[®].

	<i>Prophylactic group</i>	<i>On demand group</i>
Total number of infusions	2789	2205
Mean dose per subject administered IU/kg	17.6	13.0
95% CI	13.05;22.13	10.64;15.38
Mean number of doses	253.6	37.37
Range	197-343	0-197
95% CI	221.29; 285.80	23.35;51.39
Mean number of doses per week per subject	2.6	0.4
Range	2.06-3.66	0-1.96

CI = confidence interval

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 8 Prophylactic doses summary for all subjects – UK vs Poland

	n	No. of infusions	Mean	95% LCL	95% UCL
No. of infusions per week per subject for UK	13	2018	1.63	0.79	2.46
Dose (IU/kg) per infusion for UK			18.6	18.31	18.98
No. of infusions per week per subject for Poland	57	2976	0.54	0.35	0.73
Dose (IU/kg) per infusion for Poland			14.4	14.13	14.59

LCL = Lower Confidence Interval, UCL = Upper Confidence Interval

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 9 Treatment of all Bleeds for UK vs Poland

	n	no. of bleeds	Mean	95% LCL	95% UCL
No. of bleeds per week per subject for UK	13	593	0.49	0.23	0.76
Dose per bleed (IU/kg) for UK			24.9	23.68	26.05
No. of bleeds per week per subject for Poland	57	3816	0.72	0.60	0.83
Dose per bleed (IU/kg) for Poland			24.8	23.99	25.51

LCL = Lower Confidence interval, UCL = Upper Confidence Interval

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 10: Response rates assessed by clinicians and patients for bleeding episodes in patients managed with Optivate[®] given prophylactically or on-demand.

Overall		
	Prophylactic	On-demand
Clinician's assessment		
Excellent	39 (53%)	1151 (32%)
Good	31 (42%)	2134 (59%)
Moderate	3 (4%)	336 (9%)
None	0 (0%)	17 (0%)
Not available	185	513
Patients' assessment		
Very helpful	124 (50%)	1272 (31%)
Helpful	110 (45%)	2418 (60%)
Helped a little	10 (4%)	327 (8%)
Did not help	2 (1%)	30 (1%)
Not available	12	104

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Clinical assessment of Optivate[®], a high-purity concentrate of factor VIII (FVIII) with von Willebrand factor (VWF), in the management of patients with haemophilia A.

Table 11 Summary of treatment-related AEs

	Number (%) of patients					
	Prophylactic Use N=11		Spontaneous Use N=59		Overall N=70	
	No. (%) of patients reporting AEs	No of events	No. (%) of patients reporting AEs	No of events	No. (%) of patients reporting AEs	No of events
Total no.	1 (9%)	5	6 (10%)	17	7 (10%)	22
Type of Adverse Events (AEs)						
Headache	1 (9%)	2	2 (3%)	5	3 (4%)	7
Vertigo	0 (0%)	0	2 (3%)	4	2 (3%)	4
Musculoskeletal stiffness	1 (9%)	3	0 (0%)	0	1 (1%)	3
Infusion site erythema	0 (0%)	0	2 (3%)	2	2 (3%)	2
Oedema peripheral	0 (0%)	0	1 (2%)	1	1 (1%)	1
Pyrexia	0 (0%)	0	1 (2%)	1	1 (1%)	1
Rigors	0 (0%)	0	1 (2%)	1	1 (1%)	1
Somnolence	0 (0%)	0	1 (2%)	1	1 (1%)	1
Contusion	0 (0%)	0	1 (2%)	1	1 (1%)	1
Pruritus generalised	0 (0%)	0	1 (2%)	1	1 (1%)	1